

Dissertation zur Erlangung des Doktorgrades  
der Fakultät für Chemie und Pharmazie  
der Ludwig-Maximilians-Universität München

**Synthesis and Biological Evaluation of Nipecotic Acid and  
Guvacine Derivatives with N-Allenic Spacers as Potential  
GABA Uptake Inhibitors**

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aus  
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## Erklärung

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## Eidesstattliche Versicherung

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This cumulative thesis is based on the following original publications and manuscripts:

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"Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes"

2019:

**Maren Schaarschmidt**, Georg Höfner, Klaus T. Wanner;

*ChemMedChem* **2019**, accepted manuscript.

"Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1"

2019:

**Maren Schaarschmidt**, Georg Höfner, Klaus T. Wanner;

Manuscript to be submitted.

"Synthesis and Biological Evaluation of Nipecotic Acid Derivatives as GABA Uptake Inhibitors with Terminally Double-Substituted Allenic Spacers"

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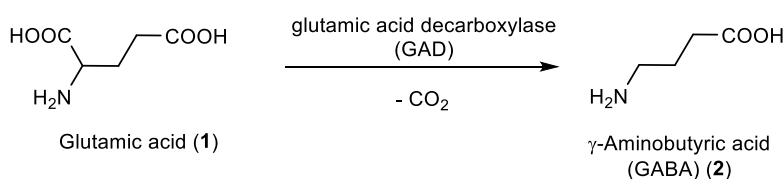
# 1 Introduction

The tight regulation of the biosynthesis, liberation, and removal of synaptically released  $\gamma$ -aminobutyric acid (GABA) is of fundamental importance for the maintenance of the brain function. Drugs targeting GABA transporters represent potential therapeutic tools for the treatment of several neurologic and psychiatric disorders that are associated with a dysfunction of the GABAergic system. Inhibitors of GABA transporters exert their beneficial effects by increasing the available GABA concentration at synaptic and extrasynaptic GABA receptors. To this point, a deeper understanding of the molecular biology, anatomical distribution, and regulation of GABA transporters will be necessary for the development of new classes of therapeutic agents. Thus, the design of novel compounds may add new insights into the structure–activity relationship of GABA transporter inhibitors and could therefore provide a promising starting point for the development of new CNS drugs.

## 1.1 CNS Diseases and GABA Transporters as Pharmacological Targets

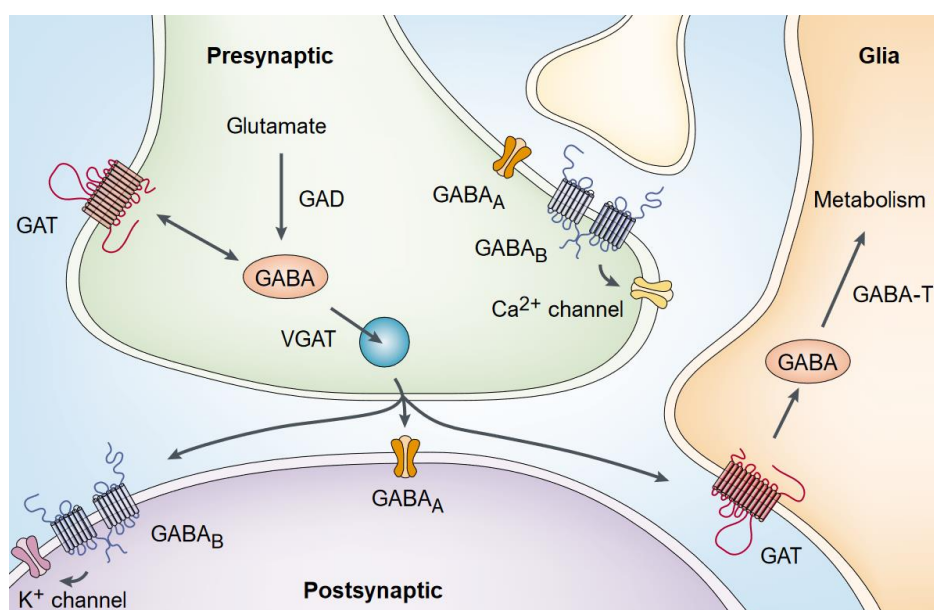
### 1.1.1 GABA Neurotransmission

$\gamma$ -Aminobutyric acid (GABA), the most abundant inhibitory neurotransmitter in the mammalian central nervous system, is essential for the overall balance between neurological excitation and inhibition. GABA is used by more than one third of the brain neurons for the synaptic communication.<sup>1</sup> The biosynthesis of GABA (**2**) includes the decarboxylation of glutamic acid (**1**) through the enzyme glutamic acid decarboxylase (GAD) with pyridoxal phosphate as cofactor (**Scheme 1**).



**Scheme 1:** Biosynthesis of GABA (**2**).

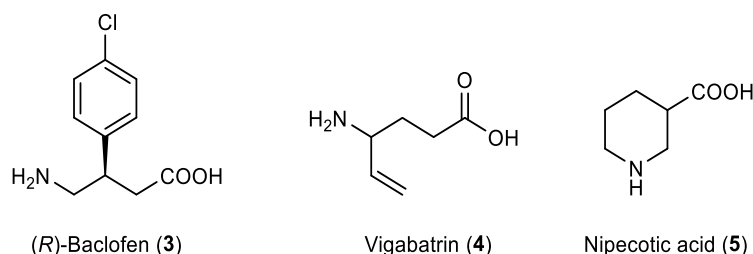
GABA is stored in synaptic vesicles by the vesicular neurotransmitter transporter VGAT and is liberated from nerve terminals into the synaptic cleft either by calcium-dependent exocytosis or release via transporter reversal (**Figure 1**). The effect of GABA is mediated by the activation of ionotropic or metabotropic receptors ( $GABA_A$ ,  $GABA_B$ ), which are localized pre- and postsynaptically (**Figure 1**). GABA acts at the ionotropic  $GABA_A$  receptors to increase the membrane chloride ion conductance, whereby chloride ions stream into the cell and hyperpolarize the resting membrane potential, which implicates a deactivation of the neuron. The binding of GABA to metabotropic  $GABA_B$  receptors causes presynaptic inhibition by suppressing the calcium influx reducing the neurotransmitter release, and achieves postsynaptic inhibition by inducing potassium currents that deactivate the cell through hyperpolarization. GABA signaling is terminated by the reuptake of GABA into nerve terminals and into surrounding glial cells via plasma-membrane bound high affinity GABA transporters (**Figure 1**).<sup>2</sup> Through sequential actions of GABA-transaminase (GABA-T) and succinic semialdehyde dehydrogenase (SSDH) GABA is finally metabolized to succinic acid.<sup>1</sup>



**Figure 1:** GABA neurotransmission according to Owens et al.<sup>2</sup>

### 1.1.2 Pathology and Therapy

GABA deficiency is associated with several neurological disorders, such as epilepsy,<sup>3</sup> schizophrenia,<sup>4</sup> Alzheimer's disease,<sup>5</sup> Huntington's chorea<sup>6</sup> and Parkinson's disease,<sup>7,8</sup> and psychiatric disorders like depression,<sup>9</sup> neuropathic pain,<sup>10</sup> panic, and mania.<sup>11</sup> Epileptic seizures for example are associated with an imbalance between excitatory and inhibitory synaptic activity. The latter is mediated by GABA and several currently approved antiepileptic drugs target components of the GABAergic synapse to compensate low GABAergic neurotransmission in the brain.<sup>12</sup> Due to its high polarity GABA itself is not able to cross the blood-brain barrier (BBB). A successful approach to increase GABA neurotransmission in the brain is the application of GABA derivatives that are capable of crossing the BBB and furthermore display complete functional activity. Hence, GABA analogues have been designed with regard to higher lipophilicity and structural rigidity, usually through implementing rings or enabling intramolecular hydrogen bond formation.<sup>1</sup>



**Figure 2:** GABA analogues.

The GABA analogue (*R*)-baclofen (**3**, **Figure 2**) for example, described as first selective GABA<sub>B</sub> receptor agonist, acts as muscle relaxant and antispastic agent.<sup>13</sup> Another mode of action is shown by vigabatrin (**4**, **Figure 2**) that specifically and irreversibly inhibits GABA-T, a catabolic enzyme involved in the degradation of GABA. The structural similarity to GABA allows vigabatrin (**4**) to interact with GABA-T and as a mechanism-based suicide substrate it is finally covalently bound via the vinyl moiety

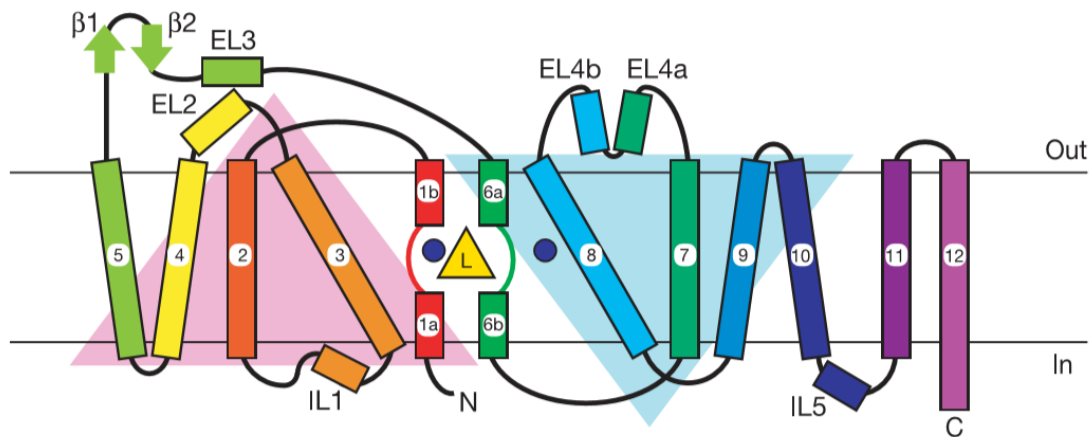


to the enzyme.<sup>14</sup> The inhibition of brain GABA-T results in elevated GABA levels whereby the probability of seizures is decreased. The rigid GABA analogue nipecotic acid (**5**, **Figure 2**) increases GABA levels by blocking the GABA reuptake through inhibition of the GABA transporters. Thus, nipecotic acid (**5**) is a useful tool for the investigation of GABA transport mechanisms.<sup>1</sup>

### 1.1.3 GABA Transporters

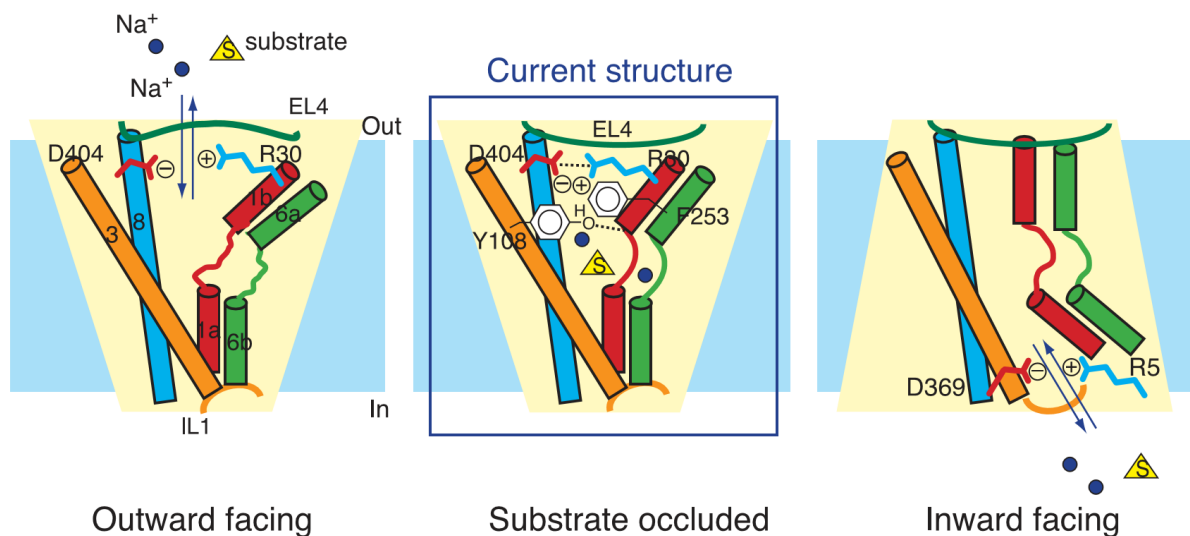
High affinity GABA transporters (GATs) in neurons and astrocytes are responsible for the removal of GABA from the synaptic cleft after a neuronal impulse. GATs are Na<sup>+</sup>/Cl<sup>-</sup>-dependent transporters which belong to the solute carrier family 6 (SLC-6).<sup>15,16</sup> Besides the already mentioned GABA transporters, the SLC6 transporter family includes the monoamine transporters and group I and II of amino acid transporters.<sup>16</sup> These neurotransmitter sodium symporters (NSS) are polytopic membrane proteins mediating the ion-coupled secondary active transport of their substrates across the membrane. The co-transport of Na<sup>+</sup> along its concentration gradient conveys the transport of the substrate GABA, against the concentration gradient into the cell.<sup>15</sup> For GABA transporters the stoichiometric ratio of substrate and co-transported ions is based on novel findings proposed as 3 Na<sup>+</sup>:1 Cl<sup>-</sup>:1 GABA.<sup>17</sup> Recent X-ray analysis of leucine transporter LeuT<sub>Aa</sub>, a bacterial homologue of the SLC6 transporters from *Aquifex aeolicus*, entailed deeper insights into the structure of this neurotransmitter transporter family.<sup>18</sup> LeuT<sub>Aa</sub> displays 20-25% sequence identity to its mammalian counterparts. X-ray revealed a dimeric protein whereat each of the protomers contains 12 transmembrane segments (TM) and a binding site for L-leucine in the center, called the S1 site (**Figure 3**).<sup>18</sup> Besides the S1 binding site a second substrate binding site (S2) located in the extracellular vestibule has been identified.<sup>19</sup> The substrate in S2

allosterically triggers intracellular release of  $\text{Na}^+$  and substrate from the primary site, thereby acting as a “symport effector”.<sup>19</sup>



**Figure 3:** Schematic representation of the transmembrane topology of the  $\text{Na}^+/\text{Cl}^-$ -coupled neurotransmitter transporter homologue from *Aquifex aeolicus* ( $\text{LeuT}_{\text{Aa}}$ ). The binding pocket for L-leucine (yellow triangle) and  $\text{Na}^+$  (dark blue dots) is formed by TM1 (red), TM3 (light orange), TM6 (green), and TM8 (light blue).<sup>18</sup>

During the transport of L-leucine and  $\text{Na}^+$  from the extracellular site into the cell, the transporter is assumed to adopt three states: the substrate occluded, the inward facing and the outward facing state. According to Yamashita et al. these three transporter states illustrated in **Figure 4** can be adopted by conformational changes of TM1 (red) and TM6 (green), which help to open and close the outward and inward gates.<sup>18</sup>



**Figure 4:** Postulated transport mechanism of  $\text{LeuT}_{\text{Aa}}$  according to Yamashita et al.<sup>18</sup>

Cloning of the GABA transporter genes has revealed the existence of the four GAT subtypes GAT1, GAT2, GAT3 and BGT1.<sup>20</sup> The four subtypes are termed as mGAT1, mGAT2, mGAT3, and mGAT4 when cloned from mouse brain, whereas according to the International Union of Basic and Clinical Pharmacology (IUPHAR) for the GABA transporters the nomenclature GAT1, BGT1, GAT2, and GAT3 is used irrespective of the species (**Table 1**).<sup>21</sup> All subtypes differ in their primary expression site resulting in differentially pronounced pharmacological significance. The subtypes GAT1 and GAT3 are exclusively found in the brain, whereas GAT2 and BGT1 are found in multiple other organs such as liver and kidney. GAT1 is expressed close to the GABAergic pathways, thus being widely distributed throughout the entire brain and primarily localized on presynaptic neurons in the synapse. Compared to GAT1, the localization of GAT3 is more restricted, being predominantly expressed on glial cells in direct contact with GABAergic neurons. Therefore, both transporter subtypes, GAT1 together with GAT3, are involved in the uptake and recycling of GABA and are consequently playing an important role in the termination of GABA neurotransmission. In contrast to GAT1 and GAT3, the expression of GAT2 and BGT1 in the brain is very limited, hence they appear to have a low level of influence on the control of seizure susceptibility.<sup>12,22-24</sup>

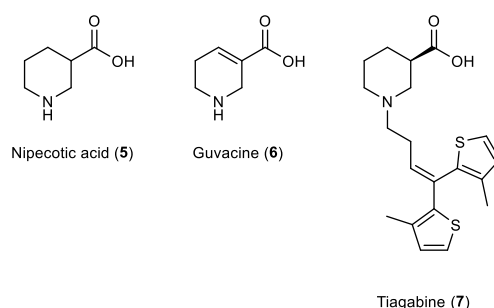
**Table 1:** GABA transporter nomenclature<sup>21</sup>

species	nomenclature			
human	hGAT-1	hBGT-1	hGAT-2	hGAT-3
mouse	mGAT1	mGAT2	mGAT3	mGAT4
IUPHAR	GAT1	BGT1	GAT2	GAT3

#### 1.1.4 Inhibition of GABA Transporters

Currently available antiepileptic drugs (AEDs) can be divided into three groups according to their mechanism of action. This includes the modulation of voltage-dependent ion-channels, the attenuation of excitatory neurotransmission and the

enhancement of inhibitory neurotransmission.<sup>12</sup> The latter mode of action can be achieved through the inhibition of GABA transporters whereby the extracellular GABA level is increased and the inhibitory GABAergic neurotransmission is facilitated. The first generation of *in vitro* inhibitors of GABA uptake includes cyclic analogues of GABA such as racemic nipecotic acid (**5**, **Figure 5**) and the areca nut alkaloid guvacine (**6**, **Figure 5**).<sup>25,26</sup> Although they exhibit reasonable inhibitory potency at mGAT1 (**5**:  $pI_{C_{50}} = 4.88 \pm 0.07$ ,  $pK_i = 4.24 \pm 0.10$ ; **6**:  $pI_{C_{50}} = 4.87 \pm 0.07$ ,  $pK_i = 3.75 \pm 0.09$ ),<sup>27</sup> one drawback of these compounds is their inability to cross the blood-brain barrier in significant amounts due to their polar and zwitterionic character.<sup>28,29</sup> This resulted in the development of nipecotic acid prodrugs and related compounds with possibly higher inhibitory potencies and selectivities. Upon N-substitution of parent compounds **5** and **6** with lipophilic aromatic residues the compounds are able to penetrate the blood-brain barrier and substantially improved potencies at and subtype selectivities for GAT1 are obtained. With the introduction of the GAT1 selective drug tiagabine (**7**, **Figure 5**), the therapeutic potential of GAT inhibition has been confirmed and GABA transporters, in particular GAT1, have been validated as interesting molecular targets for the development of antiepileptic drugs.<sup>12</sup>



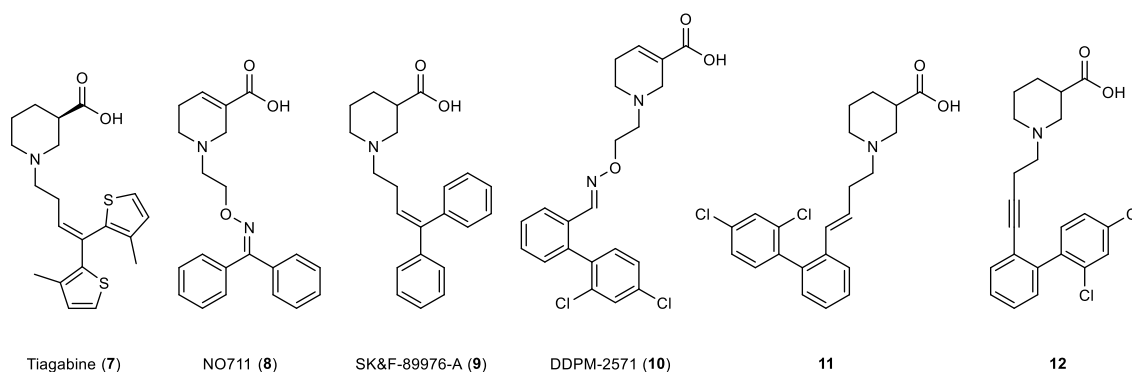
**Figure 5:** GAT inhibitors.

### 1.1.5 mGAT1 Selective Inhibitors

Nipecotic acid (**5**) and guvacine (**6**) have subsequently been used as lead structures in the efforts to synthesize potent mGAT1 inhibitors. The introduction of lipophilic aromatic residues like 4,4-diphenylbut-3-en-1-yl to the lead structures, such as nipecotic acid (**5**), resulted in compounds like SK&F-89976-A (**9**, **Table 2**), which is about 20 times more potent than the parent compound **5**.<sup>12</sup> To further improve the potency of GAT inhibitors, related compounds have been synthesized in which the length and electronegativity of the spacer was altered along with the attached di-aromatic domain. Two examples for such compounds are tiagabine (Gabitril®) (**7**, **Table 2**), a derivative of (*R*)-nipecotic acid which is used as add-on antiepileptic drug for the treatment of partial epileptic seizures, and NO711 (**8**, **Table 2**), a guvacine derivative representing an experimental drug. To improve the unfavorable pharmacokinetic properties of tiagabine (**7**) and to reduce the frequently observed side effects such as dizziness, asthenia, nervousness, tremor, and depression, several different structural elements of tiagabine (**7**) and related compounds have been varied in order to detect compounds with higher selectivities and potencies and hence possibly less side effects.<sup>30</sup> Structure-activity relationship (SAR) studies of Anderson et al.<sup>31</sup> indicated that a 2-biphenyl residue as aromatic moiety attached via a spacer to the amino nitrogen of nipecotic acid (**5**) or guvacine (**6**), might be advantageous regarding the inhibitory potency towards mGAT1. Later on, it was found that the most interesting lipophilic domain appears to be represented by a 2-biphenyl moiety carrying substituents, like for example chlorine, in 2' and 4' position of the terminal phenyl. The four- to five-carbon atom spacer between the polar head and the lipophilic aromatic domain has been modified through the introduction of alkenes, alkynes and hetero atoms. Guvacine derivative DDPM-2571 (**10**, **Table 2**) and nipecotic acid derivatives **11** and **12** (**Table 2**) are representatives for this new generation of mGAT1 selective

inhibitors, which are displaying inhibitory potencies up to 8.27 (**Table 2**). Regarding the stereochemistry of the polar nipecotic acid subunit, it is well known that the mGAT1 inhibition potency mainly resides in the (*R*)-configured isomer of the corresponding derivatives.

**Table 2:** Selection of highly potent and selective mGAT1 inhibitors



Compound	p <i>K</i> <sub>i</sub> <sup>a</sup>	p <i>C</i> <sub>50</sub> <sup>a</sup>			
	mGAT1 <sup>b</sup>	mGAT1 <sup>b</sup>	mGAT2 <sup>b</sup>	mGAT3 <sup>b</sup>	mGAT4 <sup>b</sup>
tiagabine (7)	7.43 ± 0.11 <sup>d</sup>	6.88 ± 0.12 <sup>c</sup>	52% <sup>c</sup>	64% <sup>c</sup>	73% <sup>c</sup>
NO711 (8)	7.50 ± 0.03 <sup>g</sup>	6.83 ± 0.06 <sup>c</sup>	3.20 ± 0.09 <sup>c</sup>	3.62 ± 0.04 <sup>c</sup>	3.07 ± 0.05 <sup>c</sup>
SK&F-89976-A (9)	6.73 ± 0.02 <sup>d</sup>	6.16 ± 0.05 <sup>c</sup>	3.43 ± 0.07 <sup>c</sup>	3.71 ± 0.04 <sup>c</sup>	3.56 ± 0.06 <sup>c</sup>
DDPM-2571 (10)	8.29 ± 0.02 <sup>e</sup>	8.27 ± 0.03 <sup>e</sup>	4.31 <sup>e</sup>	4.35 <sup>e</sup>	4.07 <sup>e</sup>
11	8.05 ± 0.13 <sup>d</sup>	7.28 ± 0.08 <sup>d</sup>	4.04 <sup>d</sup>	4.39 <sup>d</sup>	4.31 <sup>d</sup>
12	8.16 ± 0.04 <sup>f</sup>	7.26 ± 0.08 <sup>f</sup>	70% <sup>f</sup>	4.65 <sup>f</sup>	4.59 <sup>f</sup>

For the sake of comparability all listed functional inhibitory potencies (p*C*<sub>50</sub> values) and binding affinities (p*K*<sub>i</sub> values) are obtained from the biological testing in our research group.

<sup>a</sup> Data are the mean ± SEM. In case of low inhibitory potencies percentages are given that represent remaining GABA uptake in presence of 100 μM test compound.

<sup>b</sup> Results of [<sup>3</sup>H]GABA uptake assays performed with HEK cells stably expressing mGAT1-mGAT4 in our laboratory.

<sup>c</sup> Values from reference literature <sup>27</sup>.

<sup>d</sup> Values from reference literature <sup>32</sup>.

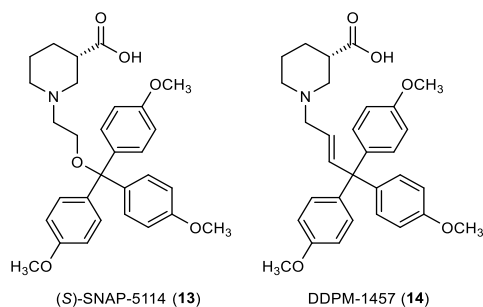
<sup>e</sup> Values from reference literature <sup>33</sup>.

<sup>f</sup> Values from reference literature <sup>34</sup>.

<sup>g</sup> Value from binding assay with [<sup>3</sup>H]NO711.

### 1.1.6 Inhibitors of mGAT4

mGAT4, the second most abundant transporter subtype in the brain, has gained increasing research interest as potential target for the development of antiepileptic drugs with improved pharmacological profile.<sup>35-37</sup> It differs from mGAT1 not only with regard to its localization, but also to its distribution in different brain regions. Although plenty of highly potent and subtype selective inhibitors are available for mGAT1, the lack of equivalent inhibitors for mGAT4 still retards the pharmacological elucidation of this transporter subtype. The first prototypic mGAT4 inhibitor with moderate potency and selectivity is represented by (S)-SNAP-5114 (**13**, **Table 3**).<sup>38</sup> However, the application of (S)-SNAP-5114 (**13**) *in vivo* is limited due to its low brain uptake and modest chemical stability.<sup>39</sup> In addition, its selectivity is not sufficiently pronounced to exclude effects on other GABA transporter subtypes. To improve the chemical stability of (S)-SNAP-5114 (**13**), which is easily undergoing side chain decomposition due to carbenium ion formation, the ether function of the spacer has been replaced by an alkene moiety, yielding the analogue DDPM-1457 (**14**, **Table 3**). Moreover, DDPM-1457 (**14**) displays the same or even slightly better subtype selectivity for mGAT4 over mGAT3 as compared to (S)-SNAP-5114 (**13**). Both compounds possess a triarylmethyl moiety as lipophilic anchor, whereby the aryl part is defined by a 4-methoxyphenyl group. In contrast to mGAT1 inhibitors, mGAT4 inhibition potency mainly resides in the (S)-configured isomer of the corresponding nipecotic acid derivatives. To further evaluate the physiological roles and therapeutic potential of this transporter subtype, the development of more potent and selective mGAT4 inhibitors is necessary.

**Table 3:** Selection of mGAT4 inhibitors

Compound	pIC <sub>50</sub> <sup>a</sup>			
	mGAT1 <sup>b</sup>	mGAT2 <sup>b</sup>	mGAT3 <sup>b</sup>	mGAT4 <sup>b</sup>
(S)-SNAP-5114 (13)	4.07 ± 0.09 <sup>c</sup>	63% <sup>c</sup>	5.29 ± 0.04 <sup>c</sup>	5.65 ± 0.02 <sup>c</sup>
DDPM-1457 (14)	4.40 ± 0.05 <sup>d</sup>	4.42 ± 0.11 <sup>d</sup>	5.47 ± 0.02 <sup>d</sup>	5.87 ± 0.08 <sup>d</sup>

For the sake of comparability all listed functional inhibitory potencies (pIC<sub>50</sub> values) are obtained from the biological testing in our research group.

<sup>a</sup> Data are the mean ± SEM. In case of low inhibitory potencies percentages are given that represent remaining GABA uptake in presence of 100 μM test compound.

<sup>b</sup> Results of [<sup>3</sup>H]GABA uptake assays performed with HEK cells stably expressing mGAT1-mGAT4 in our laboratory.

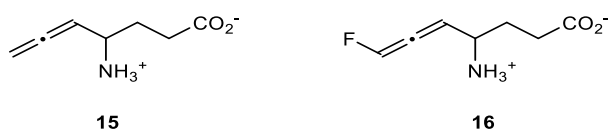
<sup>c</sup> Values from reference literature <sup>40</sup>.

<sup>d</sup> Values from reference literature <sup>41</sup>.



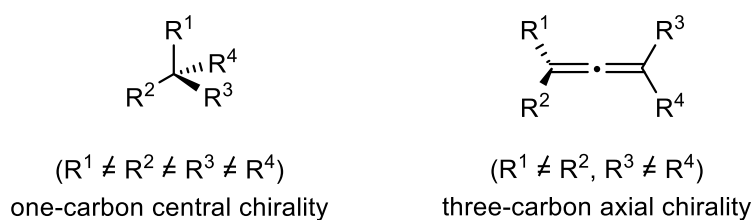
## 1.2 Allenes as Interesting Moiety in Pharmaceuticals

Allenes are important and useful building blocks in organic synthesis. Many natural products, molecular materials and pharmaceuticals with allene moiety are known.<sup>42-45</sup> Numerous allenic natural products display fascinating biological activities, which inspired to systematically introduce allene moieties in pharmacologically active compound classes such as steroids, prostaglandins, amino acids, and nucleosides.<sup>44</sup> Allenic derivatives of GABA, **15** and **16** (**Figure 6**), for example, have been synthesized as potential inhibitors of the pyridoxalphosphate-dependent enzyme GABA-aminotransferase.<sup>46,47</sup> However, experimental investigations regarding the biogenesis of allenes<sup>48,49</sup> and structure-activity relationships are rare, and due to this lacking evidence it is difficult to estimate the potential benefit of such cumulated double bond systems in pharmaceuticals.<sup>44</sup>



**Figure 6:** Allenic derivatives of GABA.

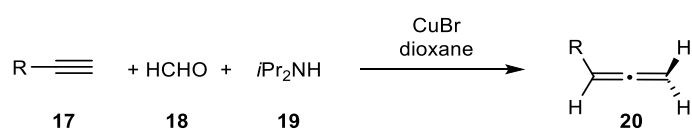
Allenes are the simplest class of cumulenes, possessing two contiguous C=C bonds.<sup>50</sup> Due to the prejudice that such systems are thought to be highly unstable, allenes have been regarded as chemical curiosities for a long period.<sup>44</sup> Properties like the intrinsic three-carbon axial chirality (**Figure 7**), sterically less demanding linear structure and high substituent-loading ability evoked a constantly growing interest in this moiety. As a result of their unique chemical properties, allenes show interesting reactivity patterns, which makes them an integral part of modern synthetic methods. Hence, efficient synthesis methods for allenes from simple and readily available starting materials are highly desirable.<sup>50</sup>



**Figure 7:** One-carbon central chirality vs. three-carbon axial chirality.<sup>51</sup>

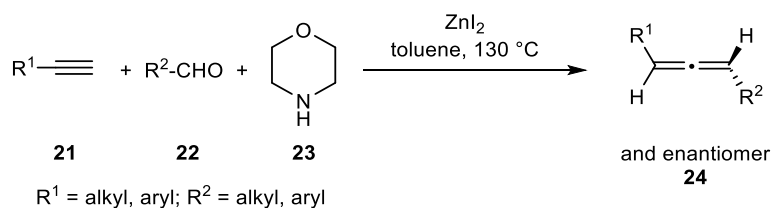
### 1.2.1 Synthesis of Allenes via Allenylation of Terminal Alkynes

Until now, many synthetic methods have been developed to access allenes.<sup>52</sup> One frequently employed method is the so called ATA reaction, the allenylation of terminal alkynes by their reaction with aldehydes or ketones and secondary amines in the presence of metal promoters like CuBr, CdI<sub>2</sub> and ZnI<sub>2</sub>.<sup>53-56</sup> The ATA reaction is based on the Crabbé homologation,<sup>53</sup> the generation of monosubstituted allenes **20** by a three-component reaction of terminal alkynes **17**, paraformaldehyde (**18**), and diisopropylamine (**19**) in the presence of substoichiometric amounts of CuBr (**Scheme 2**).



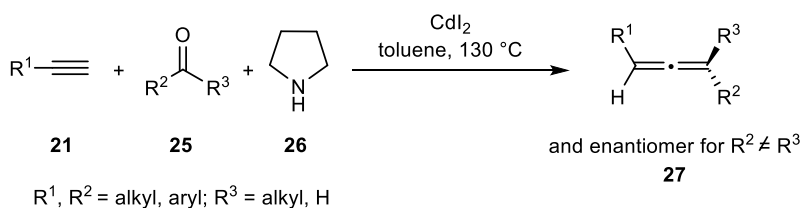
**Scheme 2:** Crabbé homologation.<sup>53</sup>

Several modifications of the Crabbé homologation have been reported until now. For example, Ma and coworkers reported a one-pot synthesis of 1,3-disubstituted allenes **24** from terminal alkynes **21**, aldehydes **22**, and morpholine (**23**) in the presence of ZnI<sub>2</sub> at elevated temperature (**Scheme 3**).<sup>56</sup>



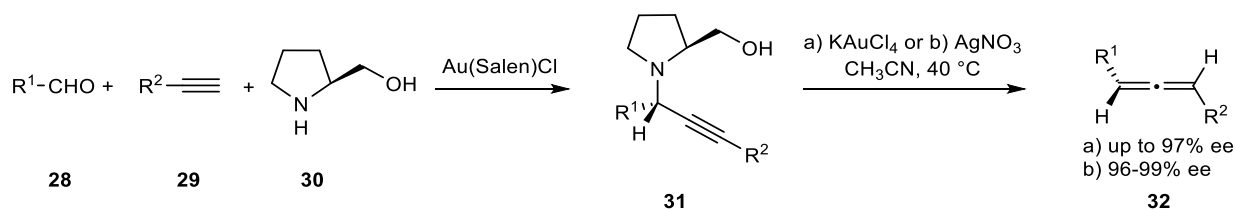
**Scheme 3:** One-pot synthesis of 1,3-disubstituted allenes from alkynes, aldehydes, and morpholine according to Ma and coworkers.<sup>56</sup>

In addition, Ma and coworkers developed an efficient  $\text{CdI}_2$ -mediated ATA reaction (**Scheme 4**) for the synthesis of 1,3,3-trisubstituted allenes **27** by applying ketones **25** instead of aldehydes and pyrrolidine (**26**) as amine.<sup>54</sup> One major advantage of the straight forward ATA reaction is that all the starting materials (terminal alkynes, amines, aldehydes, ketones) are common chemicals in any chemical laboratory.



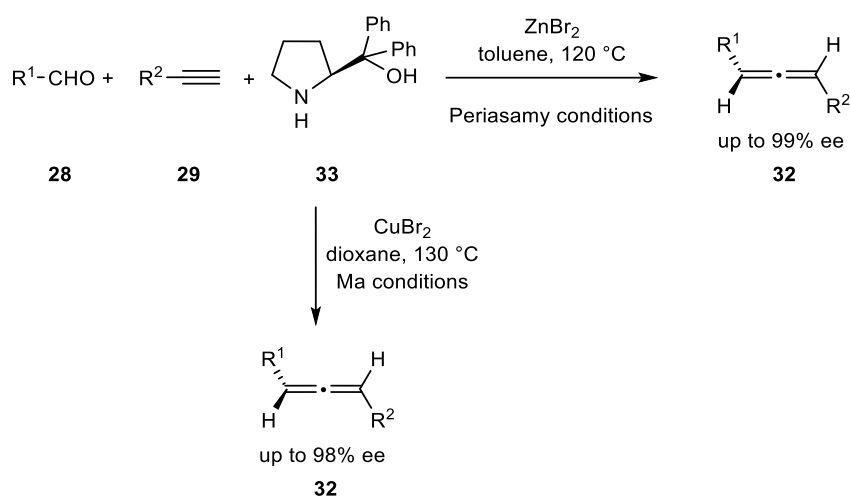
**Scheme 4:** Cadmium iodide-mediated allenylation of terminal alkynes with ketones according to Ma and coworkers.<sup>54</sup>

Later on, several groups developed asymmetric versions of this kind of reaction either by using chiral ligands in combination with Lewis acids<sup>57</sup> or by the application of chiral secondary amines<sup>58-60</sup> for the synthesis of chiral propargylic amines as precursors. Che and coworkers for instance described a two-step procedure for the synthesis of axially chiral allenes **32**, including first a gold(III)salen complex catalyzed synthesis of chiral propargylic amines **31** from chiral amine **30** followed by a  $\text{Au}^{3+}$  or  $\text{Ag}^+$  mediated rearrangement providing chiral allenes **32** under mild reaction conditions in high enantioselectivity (**Scheme 5**).<sup>61,62</sup>



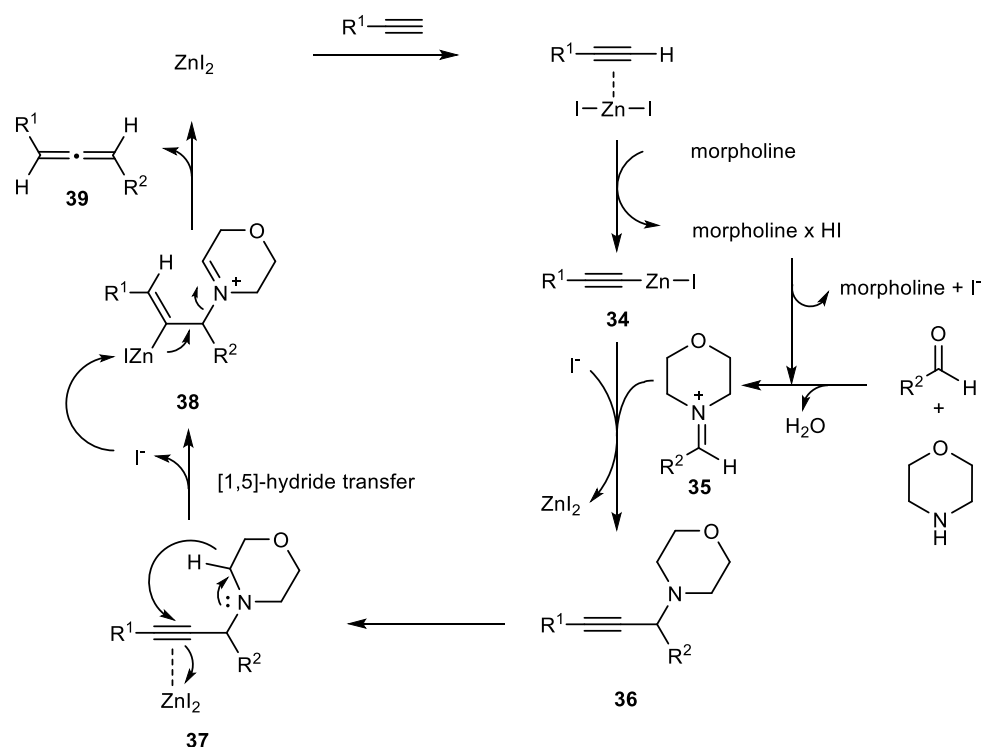
**Scheme 5:** Enantioselective synthesis of axially chiral allenes according to Che and coworkers.<sup>61,62</sup>

A one-step procedure to axially chiral 1,3-disubstituted allenes **32** mediated by chiral amine **33** has been reported by Periasamy et al.<sup>60</sup> as well as by Ma and coworkers<sup>58,63</sup> applying either ZnBr<sub>2</sub> or CuBr<sub>2</sub> as catalyst (**Scheme 6**).



**Scheme 6:** One-pot synthesis of axially chiral allenes according to Periasamy et al.<sup>60</sup> and Ma and coworkers.<sup>58,63</sup>

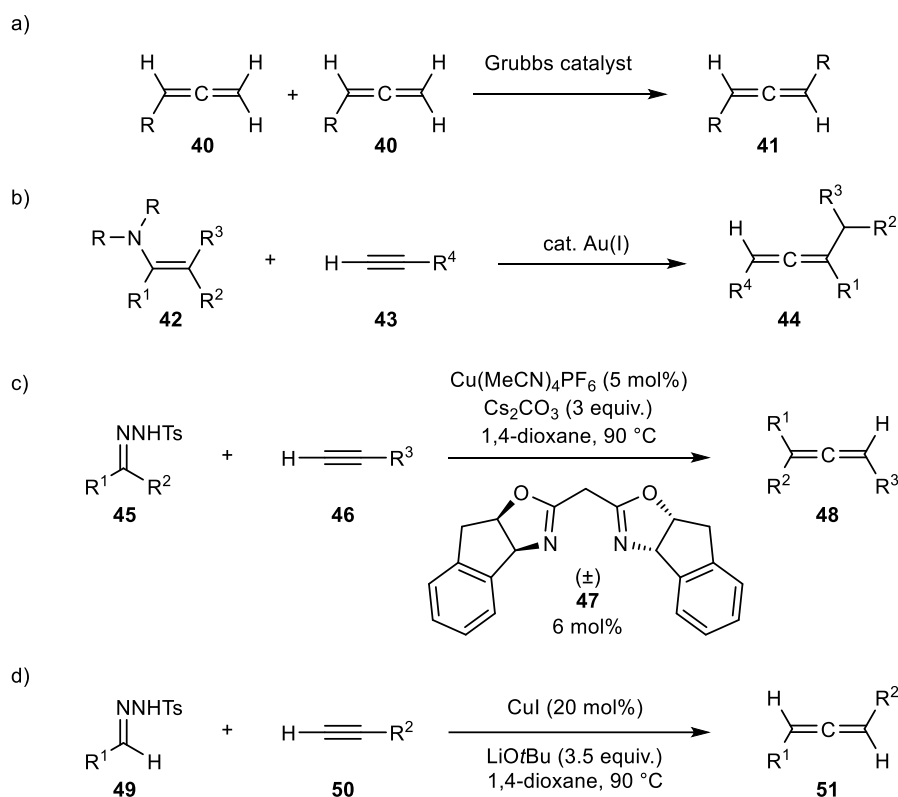
According to the reaction mechanism proposed by Ma and coworkers<sup>56</sup> in the ATA reaction at first propargylic amines are formed as precursors, which upon [1,5]-hydride transfer reaction and subsequent elimination of the thus formed iminium subunit yield the final allenes (**Scheme 7**). In detail, the alkynyl zinc species **34**, generated from a terminal alkyne in the presence of morpholine, reacts with the iminium ion **35** formed *in situ* out of aldehyde and morpholine, to give the corresponding precursor **36**. The carbon-carbon triple bond in **36** coordinates then to ZnI<sub>2</sub> to form complex **37**, which subsequently undergoes a [1,5]-hydride transfer and  $\beta$ -elimination to afford via **38** the corresponding 1,3-disubstituted allene **39** and to regenerate the Lewis acid catalyst.



**Scheme 7:** Postulated mechanism for the ATA reaction by Ma and coworkers.<sup>56</sup>

Since it is reported that the generation of the propargylic amine precursors from terminal alkynes, aldehydes, and secondary amines can be performed at room temperature,<sup>64,65</sup> it is reasonable to assume that the [1,5]-hydride transfer process described by Ma is the rate-determining step in the ATA reaction. Accordingly, this is the step which requires elevated temperature to proceed. To accelerate the [1,5]-hydride transfer reaction, Yu and coworkers<sup>64</sup> selected their employed amine on the criterion of the best hydride donating ability, resulting in tetrahydroisoquinoline as hydride donor, which delivered good yields in the synthesis of 1,3-disubstituted allenes.

## 1.2.2 Synthesis of Allenes via Cu(I)-Catalyzed Cross-Coupling of *N*-Tosylhydrazones or Diaryldiazomethanes with Terminal Alkynes

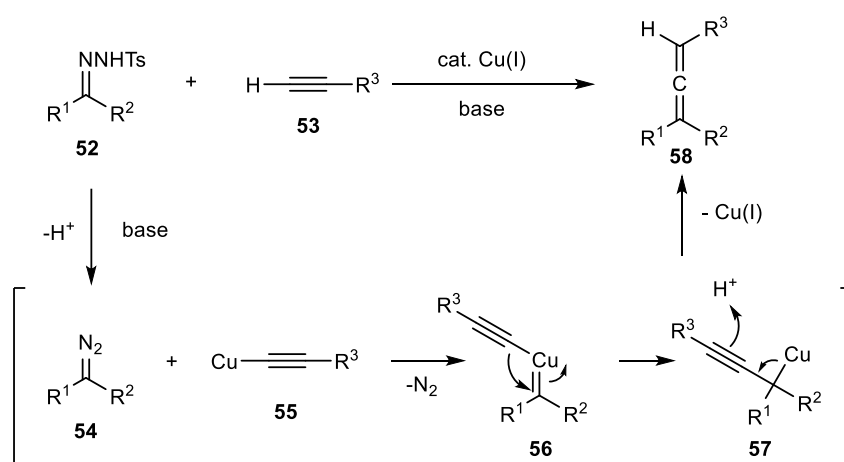


**Scheme 8:** a) Allene cross-metathesis, b) carbene/vinylidene cross-coupling, c) copper-catalyzed cross-coupling of *N*-tosylhydrazones with terminal alkynes to trisubstituted allenenes, d) copper-catalyzed cross-coupling of *N*-tosylhydrazones with terminal alkynes to disubstituted allenenes.

The direct coupling of two fragments mediated by a transition-metal catalyst is very attractive to generate allenenes due to efficiency and versatility. Examples for corresponding methods include allene cross-metathesis<sup>66</sup> (**Scheme 8a**), carbene/vinylidene cross-couplings<sup>67</sup> (**Scheme 8b**), the above described Crabbé homologation (**Scheme 2**) and its modifications (**Schemes 3-6**), and the cross-coupling of *N*-tosylhydrazones with terminal alkynes<sup>68,69</sup> (**Scheme 8c,d**). The latter method describes copper(I)-catalyzed cross-coupling reactions, which afford trisubstituted allenenes **48** using *N*-tosylhydrazones **45** derived from ketones (**Scheme 8c**) and disubstituted allenenes **51** applying aldehyde derived *N*-tosylhydrazones **49** (**Scheme 8d**) with high efficiency under mild reaction conditions. Besides the easily available

starting materials it is advantageous that the reaction tolerates various functional groups, such as esters and ethers.

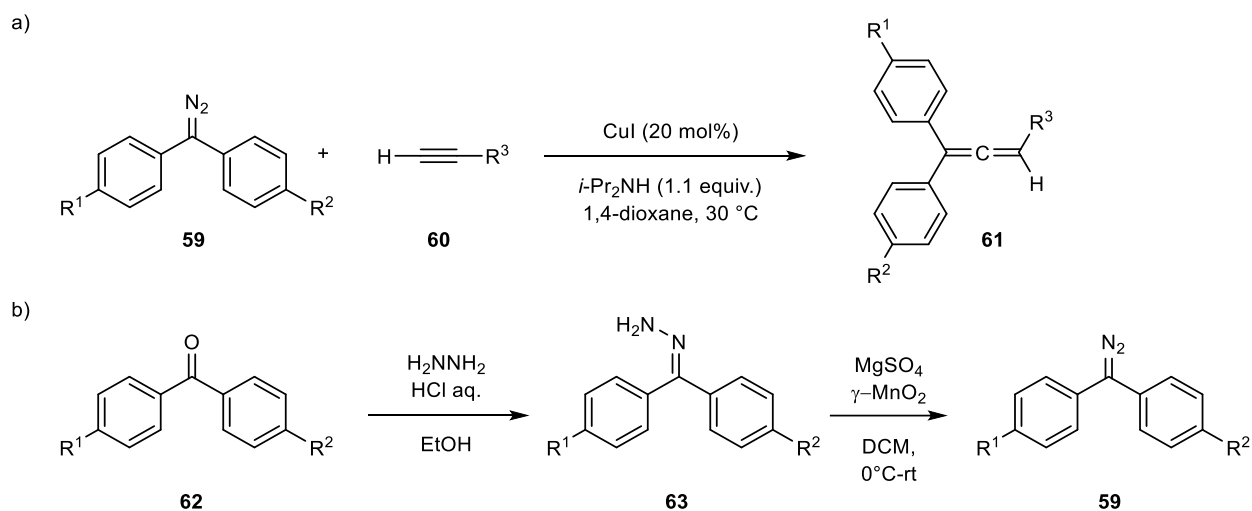
A possible mechanism for the Cu(I)-catalyzed cross-coupling of *N*-tosylhydrazones and terminal alkynes proposed by Wang and coworkers<sup>68,69</sup> is shown in **Scheme 9**. Copper acetylide **55** is formed from terminal alkyne **53** in the presence of a base and copper(I) salt. The diazo substrate **54**, which is generated *in situ* from *N*-tosylhydrazone **52** in the presence of a base, subsequently reacts with the copper acetylide **55** under release of nitrogen to form the copper-carbene species **56**. Migratory insertion of the alkynyl group to the carbenic carbon atom results in intermediate **57**, which is then protonated to form the allene **58** and to regenerate the Cu(I) catalyst. In this mechanistic pathway, the protonation occurs regioselectively at the triple bond carbon atom.<sup>68</sup>



**Scheme 9:** Cu-carbene migratory insertion process described by Wang and coworkers.<sup>68,69</sup>

Further developments of the Cu(I)-carbene migratory insertion process, concerning the synthesis of tri-aryl-substituted allenes **61**, led to the replacement of *N*-tosylhydrazones against diaryldiazomethanes **59** (**Scheme 10**).<sup>70</sup> The resulting improved reaction procedure outlined in **Scheme 10a** tolerates a wide substrate scope and can easily be carried out at relatively low temperature with CuI as a cheap catalyst. In contrast to the

coupling reaction via the *N*-tosylhydrazones (**Scheme 8c**), no additional ligand, such as **47**, is necessary. The applied diaryldiazomethanes **59** are accessible in two steps (**Scheme 10b**). First, the diarylmethanone hydrazones **63** are prepared in a general procedure applying hydrazine monohydrate and the commercially available ketones **62**. Next, through treatment with activated  $\gamma$ -MnO<sub>2</sub> and anhydrous MgSO<sub>4</sub> at 0 °C the hydrazones **63** are oxidized to obtain the purple-colored diaryldiazomethanes **59**.<sup>70</sup>

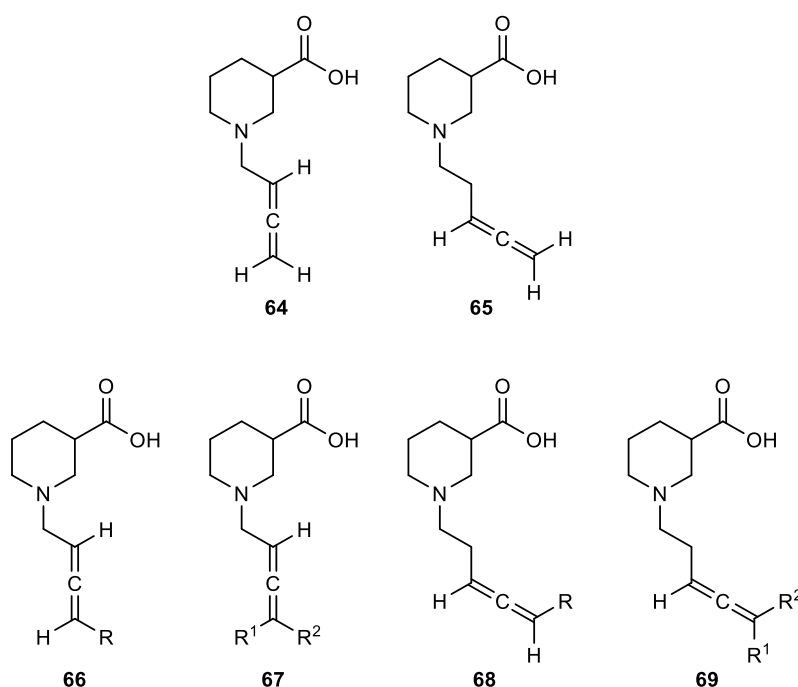


**Scheme 10:** a) *Cu(I)*-catalyzed cross-coupling of diaryldiazomethanes with terminal alkynes according to Wang and coworkers<sup>70</sup>, b) Synthesis route to diaryldiazomethanes.



## 2 Aims and Scope

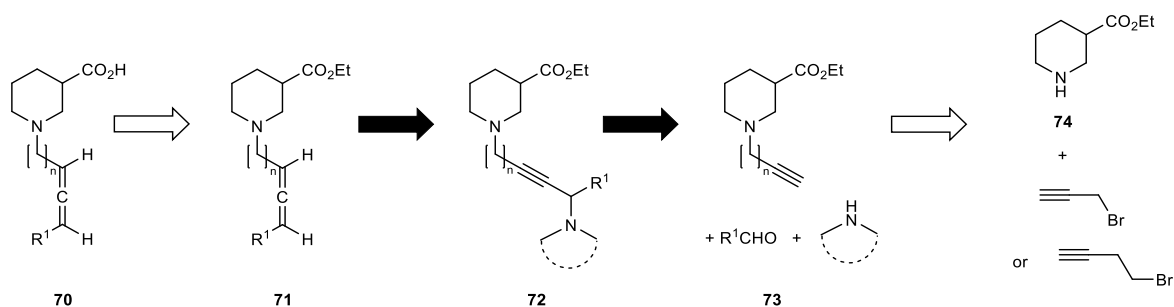
Within this thesis, a new compound class, clearly related to nipecotic acid derivatives **11** and **12** (**Table 2**), bearing an allene moiety containing spacer instead of an alkenyl and alkynyl spacer (**Figure 8**), should be synthesized and biologically evaluated with regard to their inhibitory activity at the GABA transporters mGAT1-4, with the preliminary aim to identify new highly potent and selective GAT inhibitors. In addition, this should allow to further explore the influence of the orientation of the ligands, resulting from the different geometry of the allenic spacer compared to other spacer types, on the biological activity. For this purpose, a suitable synthesis method for nipecotic acid derived allenes, including three different allene substitution patterns, i.e. terminal (**64**, **65**; **Figure 8**), 1,3-disubstituted (**66**, **68**; **Figure 8**) and 1,3,3-trisubstituted (**67**, **69**; **Figure 8**), should be developed.



**Figure 8:** Target compounds: nipecotic acid derived allenes possessing different substitution patterns and spacer lengths.

## 2.1 Method Development for the Synthesis of Nipecotic Acid Derivatives with N-Allenic Spacers

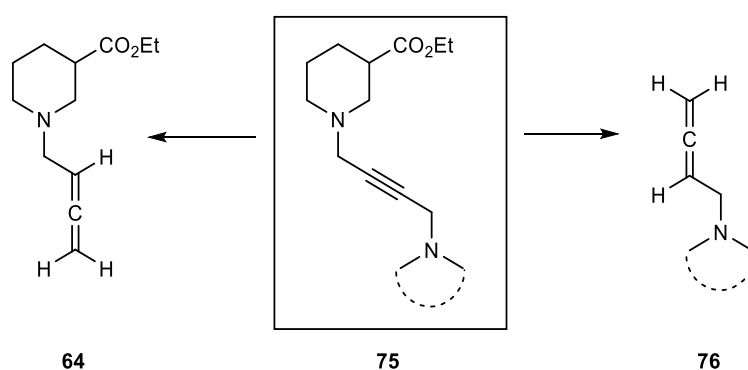
The key steps of the target synthesis route outlined in **Scheme 11** should be based on the ATA reaction modified by Ma and coworkers (Scheme 3,4) as known in literature.<sup>54,56</sup> N-alkylation of ethyl nipecotate (**74**) with 3-bromoprop-1-yne and 4-bromobut-1-yne, respectively, should deliver the terminal alkyne building block **73**, which should then be applied in an alkyne-aldehyde-amine coupling reaction (A<sup>3</sup> coupling) to get access to the intermediate propargylic amines **72**. With a suitable Lewis acid catalyst, the obtained precursors **72** should then be converted into the desired allenes **71** and subsequent hydrolysis should deliver the desired nipecotic acid derived allenes **70**.



**Scheme 11:** Retro synthesis of the target compounds. Key steps are labeled with solid black arrows.  $R^1 = H, \text{aryl, alkyl}; n = 1,2$ .

Parent compounds **64** and **65** (**Figure 8**), exhibiting a terminal allene moiety in the lipophilic N-substituent, should be synthesized in order to allow a comparison of the inhibitory potency of the latter with higher substituted nipecotic acid derived allenes (1,3-disubstituted and 1,3,3-trisubstituted at the allene moiety). Propargylic amine **75** (**Scheme 12**), an important intermediate in the intended synthesis route (**Scheme 11**), exhibits two amino groups in propargylic position. Thus, the [1,5]-hydride transfer process may deliver either the allenyl substituted amine **76** (**Scheme 12**) or the desired nipecotic acid derivative **64**, depending on the propensity of the introduced amino

function  $\text{NR}_2$  as compared to the nipecotic acid residue to serve as hydride donor. Therefore, amines  $\text{HNR}_2$  with distinctly better capabilities in mediating the allene formation than a nipecotic acid residue should be identified to exclude the latter to participate in the [1,5]-hydride transfer process. Within this method development, it should be studied how the nature of the hydride donor influences the formation of terminal and 1,3-disubstituted allenes. To this end, it is necessary to diverge from the frequently applied one-pot procedure and to perform the ATA reaction in two steps, which comprises the synthesis of the propargylic amine precursors and the separate rearrangement of the latter to the corresponding allenic products. The cyclic amines pyrroline and 1,2,5,6-tetrahydropyridine should serve as starting points for the method development. With the amino residue identified best suitable, nipecotic acid derivatives **64-69** (**Figure 8**) should be synthesized.

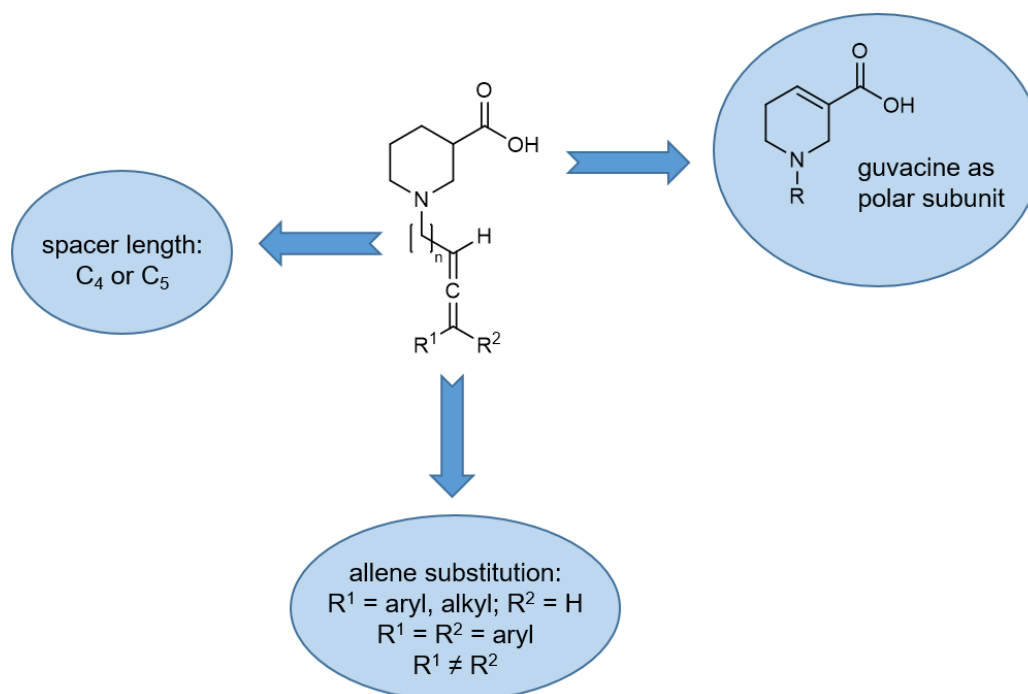


**Scheme 12:** Intramolecular competition reaction.

## 2.2 Variation of the Spacer Length, the Polar Subunit and the Allene Substitution Pattern

The developed synthesis method should be applied to introduce various lipophilic residues, such as alkyl, monoaryl, and biaryl groups, to generate a variety of 1,3-disubstituted allenes (**Figure 9**;  $\text{R}^1 = \text{aryl, alkyl}$ ;  $\text{R}^2 = \text{H}$ ). It should be examined whether the developed synthesis method is capable of accepting ketones instead of aldehydes

as substrates to generate 1,3,3-trisubstituted allenes (**Figure 9**;  $R^1 = R^2 = \text{aryl}$ ;  $R^1 \neq R^2$ ). The allenyl spacer should be varied with regard to length, including a four- and five-carbon atom spacer. In addition, guvacine should be implemented as polar subunit instead of nipecotic acid (**Figure 9**). For all synthesized nipecotic acid and guvacine derivatives, binding affinities for mGAT1 should be determined in MS Binding Assays with NO711 as native MS marker.<sup>71</sup> In addition, their functional activity should be characterized in [<sup>3</sup>H]GABA-Uptake-Assays on HEK293 cells stably expressing the individual mouse GABA transporters mGAT1-mGAT4.<sup>27</sup>



**Figure 9:** Variation points of the basic target structure.

## 3 Results and Discussion

### 3.1 First Publication: “Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes” (*J. Org. Chem.* 2017, 82, 8371-8388)

#### 3.1.1 Summary of the Results

Within this study the relative reactivities of several secondary amines serving as hydride donors in amino methylation products undergoing a [1,5]-hydride transfer (see **Scheme 7**) to yield the respective terminal and 1,3-disubstituted allenes have been examined.

Instead of the usually applied one-pot procedure, for this study a two-step procedure was employed, allowing the exclusive investigation of how the electronic nature, steric demand and conformational properties of different amines influence the [1,5]-hydride transfer process. The two-step procedure comprises the synthesis of amino methylation products from 4,4-diphenylbut-1-yne, paraformaldehyde and various secondary amines (e.g. morpholine, 1,2,5,6-tetrahydropyridine, allyl(*tert*-butyl)amine, diallylamine) in a Cu<sup>I</sup> catalyzed aldehyde-alkyne-amine coupling reaction, the product of which is subsequently subjected to a Lewis acid catalyzed rearrangement reaction, yielding the desired terminal allene. Among the various secondary amines employed, allyl(*tert*-butyl)amine was identified as the best hydride donor for the synthesis of terminal allenes. It has been found that the application of sterically demanding hydride donors, such as allyl(*tert*-butyl)amine, suppresses the reactivity limiting complexation of the hydride donor nitrogen by the Lewis acid catalyst, whereby the [1,5]-hydride transfer reaction could occur in significantly higher yields. Hence, besides the known influence of the electronic properties of the hydride donating amine, the steric demand of the latter was found to play an important role regarding the synthesis of terminal allenes. With allyl(*tert*-butyl)amine an amine was found, which due to its electronic and

steric characteristics is well suited for both, the synthesis of terminal and of 1,3-disubstituted allenes.

For the transformation of amino methylation products derived from aldehydes other than formaldehyde (such as **72** in **Scheme 11**,  $R^1 \neq H$ ) to the corresponding 1,3-disubstituted allenes, the steric encumbrance of the hydride donating amine was found to be less important for the reduction of the amino nitrogen complexation by the Lewis acid. This might be due to the additional residue  $R^1$ , introduced through the aldehyde, in the direct neighborhood to the amino nitrogen contributing to the steric shielding of the latter. Hence, in addition to allyl(*tert*-butyl)amine another high performing hydride donor with excellent electronic properties, that is 1,2,5,6-tetrahydropyridine, performed very well in the synthesis of 1,3-disubstituted allenes. In contrast to the synthesis of 1,3-disubstituted allenes applying allyl(*tert*-butyl)amine as hydride donor, the corresponding 1,2,5,6-tetrahydropyridine derived amino methylation products have been obtained in higher yields, due to the lower steric demand of 1,2,5,6-tetrahydropyridine as compared to allyl(*tert*-butyl)amine, what seems to be beneficial for the  $A^3$  coupling. In addition, the 1,2,5,6-tetrahydropyridine mediated [1,5]-hydride transfer reaction required shorter reaction times.

To demonstrate the applicability of the developed method for the synthesis of terminal allenes applying precursors equipped with allyl(*tert*-butyl)amine as hydride donor, alkynes exhibiting different functional groups, such as alkyl, halogen, nitrile, and ether, were shown to undergo the transformation to the corresponding allene in excellent yields (83–97%). Finally, with the developed procedure, nipecotic acid derivatives containing an *N*-allenyl substituent could be synthesized with good yields using either  $ZnI_2$  as catalyst for the preparation of terminal allenes or  $CdI_2$  for the synthesis of 1,3-disubstituted allenes.

### *3.1.2 Declaration of contributions*

The synthesis of all described compounds as well as the evaluation of the corresponding analytical data were accomplished by myself. I wrote the manuscript and generated all graphics and tables, supported by Prof. Dr. Klaus T. Wanner. The manuscript was corrected by Prof. Dr. Klaus T. Wanner.

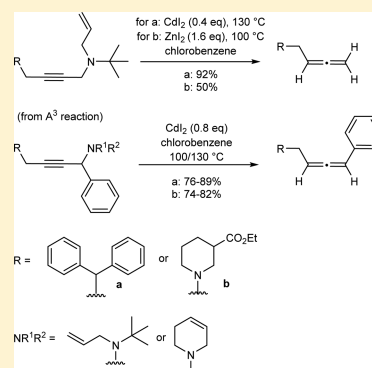
# Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes

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**S** Supporting Information

**ABSTRACT:** The relative reactivities of several secondary amines serving as hydride donors in propargylic amines undergoing a [1,5]-hydride transfer reaction to yield the respective terminal and 1,3-disubstituted allenes were studied. For this study, a two-step procedure was employed. At first, the synthesis of propargylic amines via the Cu<sup>I</sup>-catalyzed aldehyde-alkyne-amine reactions (A<sup>3</sup> coupling) was accomplished. The obtained propargylic amines were subsequently transformed to the desired allenes under CdI<sub>2</sub> or ZnI<sub>2</sub> catalysis. As a result, among the various secondary amines employed, differing in steric bulk, electronic nature, and conformational properties, allyl(*tert*-butyl)amine was found to be the best hydride donor for the synthesis of terminal allenes. For the synthesis of 1,3-disubstituted allenes, the propyne derivatives containing either a allyl(*tert*-butyl)amine or a 1,2,3,6-tetrahydropyridine unit in propargylic position performed best. Finally, with the developed procedure, nipecotic acid derivatives containing an *N*-allenyl substituent were synthesized with good yields using either ZnI<sub>2</sub> as catalyst for the preparation of 1-substituted or CdI<sub>2</sub> for the synthesis of 1,3-disubstituted allenes.



## INTRODUCTION

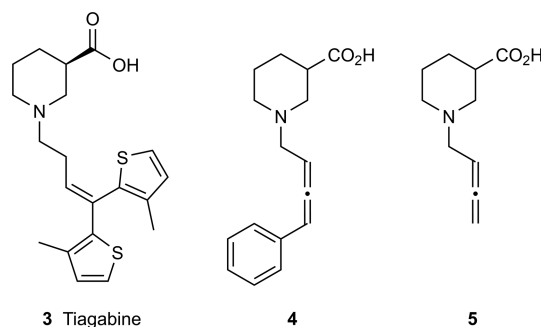
Allenes are important and useful building blocks in organic synthesis. Many natural products, molecular materials, and pharmaceuticals with an allene moiety are known.<sup>1–4</sup> For example, allenic derivatives of  $\gamma$ -aminobutyric acid (GABA) **1** and **2** have been synthesized as potential inhibitors of the pyridoxal phosphate-dependent enzyme GABA-aminotransferase (Scheme 1).<sup>5,6</sup>

**Scheme 1.** Allenic Derivatives of  $\gamma$ -Aminobutyric Acid



With GABA being the major inhibitory neurotransmitter in the mammalian central nervous system, a malfunction of its neurotransmission is involved in several diseases such as epilepsy,<sup>7</sup> Alzheimer's disease,<sup>8</sup> neuropathic pain,<sup>9</sup> and depression.<sup>10</sup> mGAT1 is considered to be the most important GABA transporter subtype for the regulation of neurotransmitter levels in the synaptic cleft.<sup>11</sup> Lipophilic derivatives of the nipecotic acid are known to inhibit the uptake of mGAT1. One example of such a nipecotic acid based drug is Tiagabine (Gabitril) (**3**), which is used as add-on therapy for epilepsy (Scheme 2, structure **3**).<sup>12</sup> It is known that nipecotic acid derivatives with a diaryl moiety attached via a spacer to the cyclic amino acid exhibit good inhibitory activities at mGAT1. Hence, it appears promising to synthesize similar nipecotic acid derivatives, for example by implementation of an allene moiety

**Scheme 2.** Tiagabine (**3**) and New Nipecotic Acid Derivatives with Allenyl Spacer (**4** and **5**)



in the spacer (Scheme 2, structure **4**) as new potential mGAT1 inhibitors. To be able to compare the inhibitory activity of nipecotic acid derivatives such as **4** with the nipecotic acid derivative containing solely an allenyl spacer, the parent compound **5** is of interest, too, as this would allow to analyze the contribution of the different subunits to the overall potencies of the final inhibitors.

Efficient synthetic methods for the preparation of terminal and 1,3-disubstituted allenes are of high interest in organic chemistry. Until now, many synthetic methods have been developed to access allenes.<sup>13,14</sup> One of these methods is the so-called ATA reaction, the allenylation of terminal alkynes by their reaction with aldehydes or ketones and secondary amines

Received: March 16, 2017

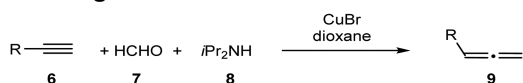
Published: July 12, 2017



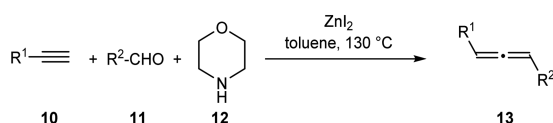
in the presence of metal promoters such as CuBr, CdI<sub>2</sub>, and ZnI<sub>2</sub>.<sup>15–18</sup> This method is based on the pioneering Crabbé homologation (Scheme 3), the generation of monosubstituted allenes **9** by a three-component reaction of terminal alkynes **6**, paraformaldehyde (**7**), and diisopropylamine (**8**) in the presence of substoichiometric amounts of CuBr.<sup>18</sup> Until now, several modifications of this reaction have been reported. For example, Ma and co-workers reported a one-pot synthesis of

### Scheme 3. Previous Works

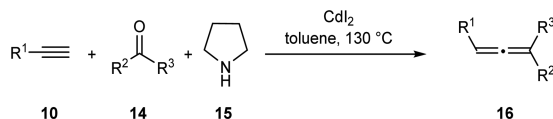
#### Crabbé homologation<sup>18</sup>



#### Ma and co-workers<sup>15,16,17,25,26</sup>

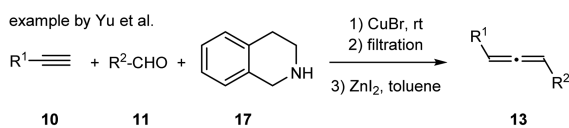


R<sup>1</sup> = alkyl, aryl; R<sup>2</sup> = alkyl, aryl



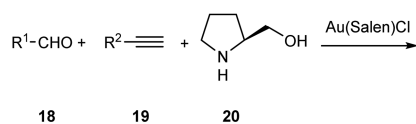
R<sup>1</sup>, R<sup>2</sup> = alkyl, aryl; R<sup>3</sup> = alkyl, H

#### Yu and co-workers<sup>34</sup>/ Ma and co-workers<sup>27</sup>



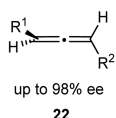
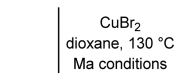
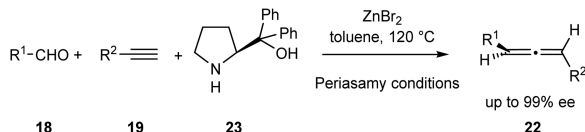
R<sup>1</sup> = alkyl, aryl; R<sup>2</sup> = alkyl, aryl

#### Che and co-workers<sup>23,24</sup>



#### Periasamy and co-workers<sup>21,22</sup>

#### Ma and co-workers<sup>20,27,28,29,30,31,32,33</sup>



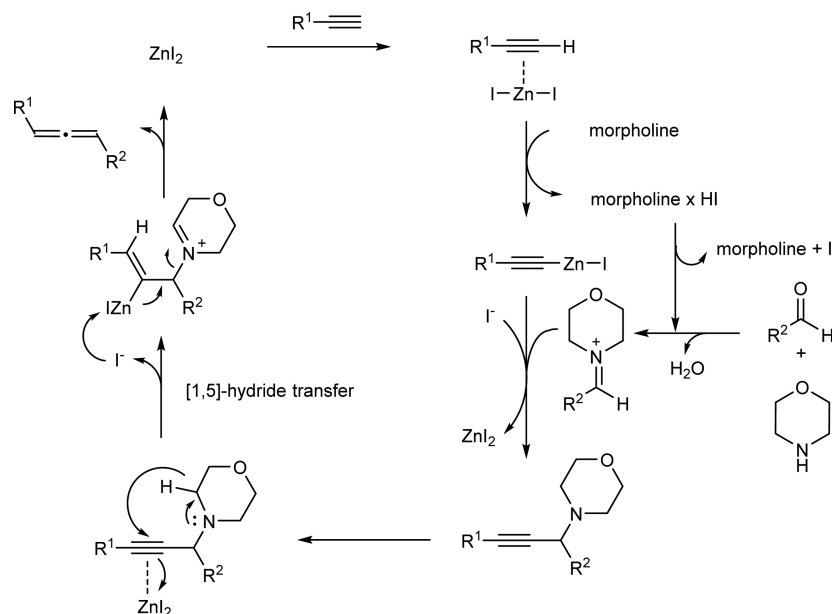
1,3-disubstituted allenes **13** from terminal alkynes **10**, aldehydes **11**, and morpholine (**12**) in the presence of ZnI<sub>2</sub> at elevated temperature (Scheme 3).<sup>17</sup> Later on, several groups developed asymmetric versions of this kind of reaction by using either chiral ligands in combination with Lewis acids<sup>19</sup> or chiral secondary amines (**20** and **23**)<sup>20–22,27–33</sup> for the synthesis of chiral propargylic amines as intermediates. Che and co-workers for instance described a two-step procedure for the synthesis of axially chiral allenes **22**, including first a gold(III)salen complex catalyzed synthesis of chiral propargylic amines **21** from chiral amine **20** followed by a Au<sup>3+</sup> or Ag<sup>+</sup> mediated rearrangement providing chiral allenes **22** in high enantioselectivity (Scheme 3).<sup>23,24</sup> A one-step procedure to axially chiral 1,3-disubstituted allenes was reported by Periasamy and co-workers<sup>21,22</sup> as well as by Ma and co-workers<sup>20,27–33</sup> (Scheme 3).

According to the reaction mechanism proposed by Ma et al.,<sup>15</sup> in the ATA reaction, at first propargylic amines are formed which, upon [1,5]-hydride transfer and subsequent elimination of the thus formed iminium subunit, yield the final allenes (Scheme 4). Because it is reported that the generation of propargylic amines from terminal alkynes, aldehydes, and secondary amines can be performed at room temperature,<sup>34,35</sup> it is reasonable to assume that the [1,5]-hydride transfer process described by Ma<sup>15</sup> is the rate-determining step<sup>34</sup> in the allene synthesis. Accordingly, this is the step which requires elevated temperature to proceed (Scheme 4). To accelerate the [1,5]-hydride transfer reaction, Yu and co-workers<sup>34</sup> selected their amine on the criterion of the best hydride donating ability (Scheme 3), but despite their good results with tetrahydroisoquinoline (THIQ, **17**) as hydride donor for the synthesis of 1,3-disubstituted allenes **13**, they were not able to perform the formation of terminal allenes **9** with paraformaldehyde and THIQ in noticeable yields. On the basis of this observation, we assumed that, besides the known electronic influence of the hydride donor, there might be some additional factors that could have an important impact on the allene formation. Hence, we were interested in studying how the nature of the hydride donor influences the formation of terminal and 1,3-disubstituted allenes. To this end, the ATA reaction should be performed in two steps, i.e. the synthesis of the propargylic amines, and the rearrangement of the latter to the corresponding allene derivatives.

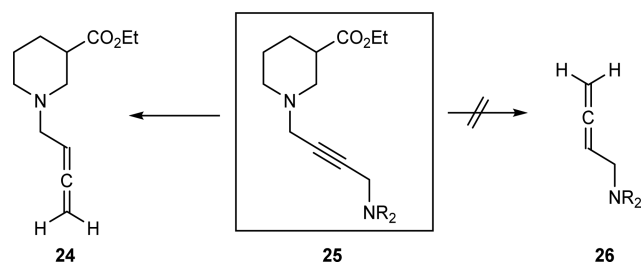
For the intended synthesis of allene substituted nipecotic acid derivatives such as **5** and related compounds by a [1,5]-hydride transfer process, alkyne derivatives such as **25** had to serve as starting materials. However, with two amino groups in propargylic position in **25**, the [1,5]-hydride transfer process may deliver either the allenyl substituted amine **26** or the desired nipecotic acid derivative **24** depending on the propensity of the amino function NR<sub>2</sub> as compared to the nipecotic acid residue to serve as hydride donor (Scheme 5). This study identifies amines with distinctly better capabilities in mediating the allene formation than a nipecotic acid residue to exclude the latter to participate in the [1,5]-hydride transfer process. With amino residues NR<sub>2</sub> suitable for this purpose, nipecotic acid derivatives **24** (Scheme 5) and **53a–e** (Table 5) containing an allene moiety in the spacer should be synthesized.

## RESULTS AND DISCUSSION

**Synthesis of Propargylic Amines.** To be able to study the [1,5]-hydride transfer process separately from the formation of the propargylic amines, a two-step procedure was followed, i.e. at first, the propargylic amines were synthesized and

Scheme 4. Postulated Mechanism for the ATA Reaction by Ma and Co-workers<sup>17</sup>

Scheme 5. Intramolecular Competition Reaction



subsequently subjected to a rearrangement reaction to give the corresponding allenes. The propargylic amines **29a–o** and **31a–o** required for this study were synthesized by  $A^3$  coupling from alkynes **27a**, **27b**, and **30**, and a set of different secondary amines and aldehydes (Scheme 6, Table S1, for the use of ketones in this reaction, see chapter 1 of the Supporting Information). The propargylic amines **29a–o** derived from 4,4-

diphenylbut-1-yne (**27a** and **b**) were intended to serve as test systems to study the [1,5]-hydride transfer process in the absence of a nipecotic acid residue. The substituents on the amino nitrogen were varied with respect to sterical demand, utilizing methyl, allyl, *i*Pr, and *t*-Bu residues, and with respect to electronic properties, introducing residues such as methyl, allyl, and *i*Pr as the hydride donating part of the amine.

**Effect of Different Hydride Donors on the Formation of Terminal Allene 32.** For the conversion of propargylic amines **29a–k** derived from formaldehyde as carbonyl component to terminal allene **32**, reaction conditions similar to a protocol established by Ma and co-workers were employed.<sup>15</sup> However, to improve the solubility of the reactants, chlorobenzene instead of toluene was used as solvent in the present experiments. Initial allene formation reactions were carried out with the propargylic amine **29a**, derived from the known hydride donor morpholine, also frequently used by Ma and co-workers<sup>17</sup> (Table 1, entry 1). This reaction and all other reactions listed in Table 1 were conducted by heating the

Scheme 6. Synthetic Route to Employed Propargylic Amines

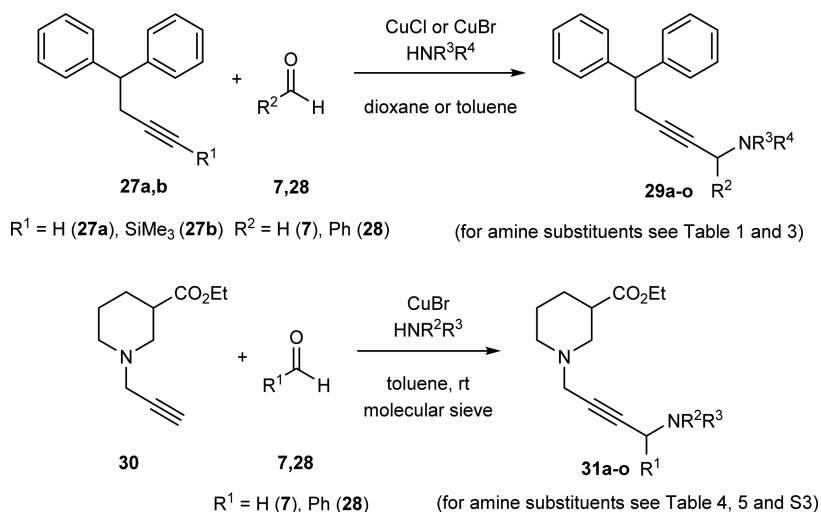
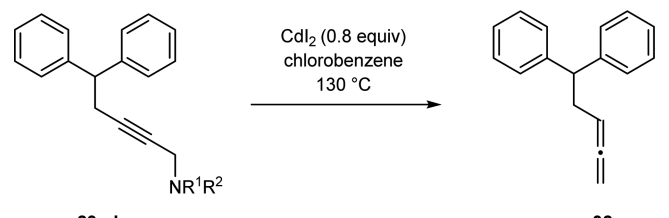


Table 1. Effect of Different Hydride Donors<sup>36</sup> on the Formation of Terminal Allene 32<sup>a</sup>


entry	starting material	NR <sup>1</sup> R <sup>2</sup>	t [h]	yield [%]
1 <sup>c</sup>	<b>29a</b>		3.75	2
2 <sup>c</sup>	<b>29b</b>		3.75	3
3 <sup>b</sup>	<b>29c</b>		2.00	29
4 <sup>c</sup>	<b>29d</b>		4.50	6
5 <sup>b</sup>	<b>29e</b>		2.00	88
6 <sup>b</sup>	<b>29f</b>		2.00	65
7 <sup>c</sup>	<b>29g</b>		3.50	24
8 <sup>c</sup>	<b>29h</b>		3.00	18
9 <sup>c</sup>	<b>29i</b>		4.00	21
10 <sup>b</sup>	<b>29j</b>		3.25	66
11 <sup>b</sup>	<b>29k</b>		1.25	82

<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and CdI<sub>2</sub> (0.8 equiv) at 130 °C in 4.0 mL of anhydrous chlorobenzene. <sup>b</sup>The reaction was stopped when all starting material was consumed (detection by TLC). <sup>c</sup>The reaction was stopped when no further transformation was observed (detection by TLC).

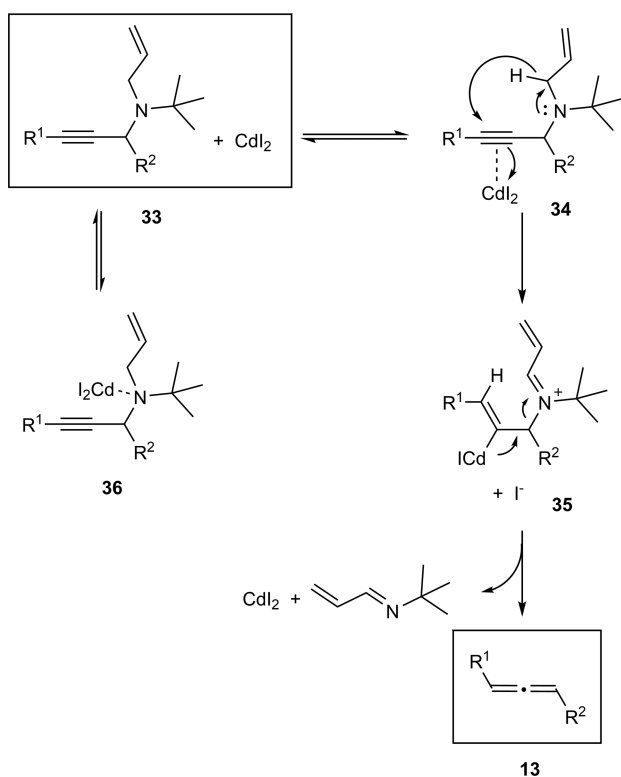
respective propargylic amine (**29a–k**) with 0.8 equiv of CdI<sub>2</sub> in chlorobenzene at 130 °C, conditions under which all compounds were found to undergo a transformation reaction. In each case, the reaction was run until all starting material had been consumed or, in the case of the less reactive hydride donors, until no further transformation was observed by TLC.

**Electronic Properties of Hydride Donors.** In case of **29a**, the yield of **32** was surprisingly low (2%, [Table 1](#), entry 1). Utilizing piperidine as hydride donor afforded a similar low yield of allene **32** (3%, [Table 1](#), entry 2), whereas the 1,2,3,6-tetrahydropyridine (THP) mediated allene conversion resulted in a significantly higher yield of 29% ([Table 1](#), entry 3). Similar to THIQ which, according to Yu et al.<sup>34</sup> is especially well suited as

hydride donor because of its electronic properties, also THP can be assumed to possess improved hydride donor capabilities. In addition to the ring structure, THP possesses two hydrogens in allylic position, adjacent to the amino group that should exhibit an increased propensity for the hydride shift reaction. This explains well the increased yield of allene **32** when utilizing the THP derivative **29c**.<sup>34</sup>

**Steric Properties of Hydride Donors.** With the electronic properties having clearly a positive effect on the [1,5]-hydrogen transfer reaction, next, allene formation reactions were studied, employing acyclic amines with an allyl group as hydride donating moiety for which the second amine substituent was varied with respect to the steric demand. With increasing steric demand of the second amine substituent, i.e. in the row from methyl to allyl to *i*Pr and *t*-Bu, the yields for allene **32** increased from 18 to 88% (Table 1, entries 5–8). As indicated in Scheme 7 depicting the reaction mechanism for the formation of the

Scheme 7. Proposed Mechanism for the Allene Formation

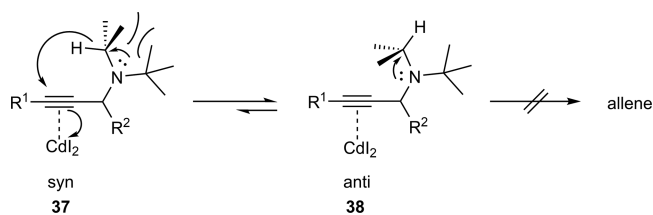


allenes, the Lewis acid,  $\text{CdI}_2$ , will promote the [1,5]-hydride transfer reaction by complexation of the alkyne moiety (**34**). This will initiate the hydride transfer to give the corresponding iminium ion **35**, which undergoes an elimination to give allene **13** as final product. Instead of complexing the triple bond, the Lewis acid may also complex the tertiary amino function present in the starting material (**36**).  $^1\text{H}$  NMR spectra obtained from mixtures of propargylic amine **29g** and  $\text{ZnI}_2$  in chlorobenzene- $d_5$  are in support of this assumption. In the presence of  $\text{ZnI}_2$ , signals arising from protons closest to the amino nitrogen experience a clear line broadening<sup>37</sup> and downfield shift compared to those in the  $^1\text{H}$  NMR spectrum of the pure amine **29g** (Figure S1). This may be best rationalized by the assumed complexation of the amino nitrogen of the propargylic amines by the Lewis acids (for more information, see the Supporting Information). Due to the

electron withdrawing effect of the Lewis acid when attached to the amino group, this species will not be able to undergo a [1,5]-hydride transfer reaction even if an additional molecule of Lewis acid was present at the triple bond. These three forms, the free starting material (**33**), the starting material complexing the  $\text{CdI}_2$  via the triple bond (**34**), and the starting material complexing the  $\text{CdI}_2$  via the amino function (**36**) will exist in an equilibrium (Scheme 7). The position of this equilibrium will depend on the steric demand of the amino subunit. With increasing steric demand, the amino function will be less capable of complexing the Lewis acid  $\text{CdI}_2$ . Accordingly, the equilibrium will shift toward the reactive species with the triple bond attached to the Lewis acid, resulting in an increased reaction rate for the desired rearrangement reaction. In line with this hypothetical model, the yields of the final product steadily increase with the steric demand of the second residue of the amino function in **29h–e**.

**Conformational Properties of Hydride Donors.** The data listed for the rearrangement reaction of **29e**, **29i**, and **29j** also allow a comparison of the influence the nature of the hydride donating residue has on the outcome of the reaction. All of these compounds contain the same inert *t*-Bu group but vary with regard to the hydride donating *N*-substituent, which is an allyl (**29e**), *i*Pr (**29i**), or methyl substituent (**29j**). Whereas the yield of the product decreases from 88% (Table 1, entry 5) to only 21% (Table 1, entry 9) when the allyl moiety is replaced by an *i*Pr residue, it raises to 66% (Table 1, entry 10) when a methyl group is present. With this trend not being in line with the electron donating ability of the varied residues (allyl, *i*Pr, methyl), the rearrangement must be governed by additional factors. For the [1,5]-hydride shift to occur, the hydride donating residue must place the migrating hydride in a syn orientation to the alkyne acceptor. In case of the isopropyl(*tert*-butyl)amino substituent in **29i**, the two major conformations given in Scheme 8 should exist in which the migrating hydride is

Scheme 8. Isopropyl(*tert*-butyl)amine as Hydride Donor



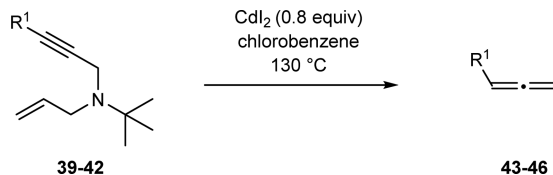
either oriented syn (**37**) or anti (**38**) to the alkyne acceptor. Because of severe steric interactions between the methyl groups of the *i*Pr residue with the bulky *t*-Bu group, the syn orientation of the hydride should be strongly disfavored and, as consequence thereof, also the [1,5]-hydride shift reaction, which nicely explains the low yield observed in this case.

**Best Performing Hydride Donor: A Comparison.** According to the results of the above-described experiments, the allyl group appears to possess the highest propensity to act as hydride donor, whereas the *t*-Bu residue is best suited as second *N*-substituent, due to its steric demand it hinders the formation of a complex between the amino function and the Lewis acid, that would hamper the desired rearrangement reaction. For comparison of the above-described results with those of Crabbé and co-workers utilizing diisopropylamine as hydride donor (Scheme 3),<sup>18</sup> in addition, transformation of the propargylic amine **29k** into allene **32** was studied (Table 1, entry 11). With

the diisopropylamine residue in **29k** as hydride donor, terminal allene **32** was obtained in a good yield of 82%. This is in line with the reasoning outlined above. For electronic reasons, the *iPr* residues should exhibit favorable hydride donating abilities, whereas the steric demand of the two *iPr* residues will lower the tendency of the amino nitrogen to form a complex with the Lewis acid that would negatively affect the transfer reaction. Obviously, there is also a subtle control of the reactive conformation. Whereas a *t*-Bu residue as second substituent in combination with an *iPr* as hydride donating moiety appears to disfavor the reactive conformation required for the hydride transfer reaction (Scheme 8), an *iPr* instead of an *t*-Bu residue is obviously compatible with it. Besides, also the influence of the amount of  $\text{CdI}_2$  on the formation of terminal allene **32** was studied, employing propargylic amine **29e** that had led to the highest yield of the rearrangement product **32** (Table 1, entry 5). Applying 0.4, 0.8, and 1.2 equiv of  $\text{CdI}_2$  under the same reaction conditions as for the reactions listed in Table 1, neither a trend nor a significant variation of the yield of allene **32** was observed (Table S2, entries 1–3, 88–93% yield).

**Scope of Terminal Alkynes.** To demonstrate the applicability of the developed method for the synthesis of terminal allenes applying allyl(*tert*-butyl)amine as hydride donor, additionally alkynes **39–42** exhibiting different residues were included in this study (Table 2). All substrates (**39–42**)

Table 2. Scope of Terminal Alkynes<sup>a</sup>



entry	R <sup>1</sup>	t [h]	yield [%]
1	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	3.00	94
2	Cl(CH <sub>2</sub> ) <sub>3</sub>	3.00	83
3	NC(CH <sub>2</sub> ) <sub>3</sub>	3.00	97
4	PhCH <sub>2</sub> OCH <sub>2</sub>	2.75	95

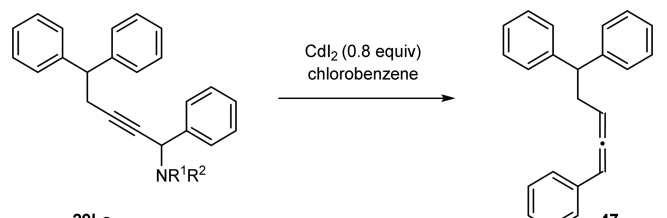
<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and  $\text{CdI}_2$  (0.8 equiv) at 130 °C in 4.0 mL of anhydrous chlorobenzene. The reaction was stopped when all starting material was consumed (detection by TLC).

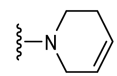
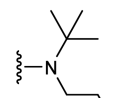
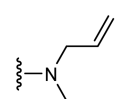
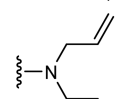
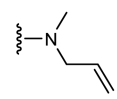
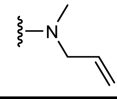
exhibiting either a pure alkyl residue or a halogen, nitrile, or ether functional group underwent transformation to the corresponding allene in excellent yields (83–97%, Table 2, entries 1–4).

**Effect of Different Hydride Donors on the Formation of 1,3-Disubstituted Allene 47.** In additional experiments, the suitability of some of the above-mentioned amino residues in [1,5]-hydride transfer reactions should be studied in which the substrate carries an additional substituent, i.e. a phenyl residue next to the amino group. For these experiments, THP, allyl(methyl)amine, allyl(*tert*-butyl)amine, and diallylamine with different steric and electronic properties were selected as hydride donors. In contrast to the less substituted starting materials **29c**, **29g**, and **29h** exhibiting the same, sterically less demanding amino residues, i.e. THP, diallylamine, and allyl(methyl)amine, due to this feature giving low yields of the rearrangement product **32** (18–29%), the corresponding phenyl derivatives performed significantly better. In the case of THP derivative **29l**, the yield rose from 29% (for **29c** → **32**) to

89% (for **29l** → **47**). Thereby, a temperature of only 100 °C (instead of 130 °C for **29c**) was sufficient to effect the desired transformation. For the diallylamine and allyl(methyl)amine derivatives **29n** and **29o**, the yields for the rearrangement product **47** were likewise substantially higher, 75% for the transformation of **29n** to **47** (Table 3, entry 4) and 43% for the transformation of **29o** in **47** (Table 3, entry 6) compared to those of the less substituted propargylic amines (Table 1, entry 7, **29g** → **32**, 24%; Table 1, entry 8, **29h** → **32**, 18%). However, for this transformation, again a reaction temperature of 130 °C was required, the yields at a temperature of 100 °C being in both cases with 10% of **47** much lower (Table 3, entries 3 and 5). As with the formation of terminal allene **32**, allyl(*tert*-butyl)amine performed well as hydride donor in the synthesis of 1,3-disubstituted allene **47** (**29m**, Table 3, entry 2), providing it in 76% yield, whereby the [1,5]-hydride transfer occurs already at a lower temperature of 100 °C. Diisopropylamine as well should be studied as a hydride donor in the formation of 1,3-disubstituted allene **47**. However, all attempts to synthesize the required propargylic amine from the corresponding alkyne **27a**, benzaldehyde (**28**), and diisopropylamine failed, indicating that this amine is not suitable for this purpose, which is most likely due to its high steric demand. Overall, the transformations of the propargylic amines **29l–o** to 1,3-disubstituted allene **47** appears to be less sensitive to the steric demand of R<sup>1</sup> and R<sup>2</sup> attached to the amino residue. This supports the assumption that complexation of the amino nitrogen by the Lewis acid, in competition with the complexation of the triple bond required for the induction of the rearrangement reaction, negatively affects the hydride donating ability of the respective alkyl amino subunit. With a phenyl residue in the direct neighborhood to the amino nitrogen contributing to the steric shielding of the latter, the steric encumbrance of the amino function provided by R<sup>1</sup> and R<sup>2</sup> becomes obviously less important for the reduction of the complexation of the amino nitrogen by the Lewis acid.

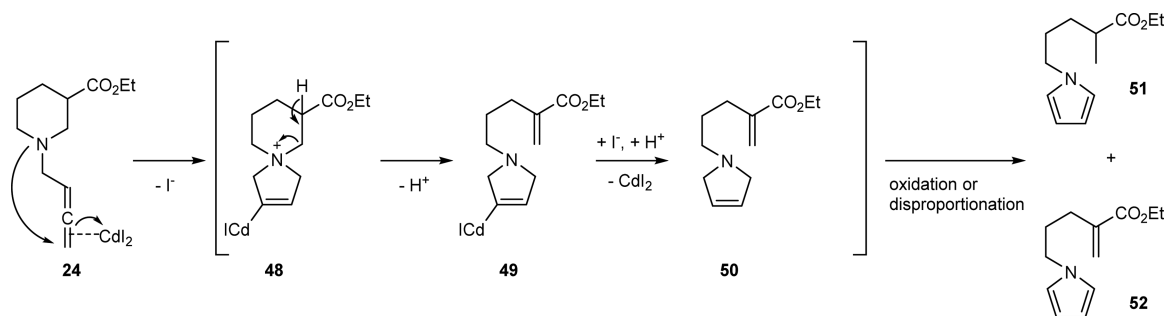
**Synthesis of Allene Substituted Nipecotic Acid Ester 24.** Based on the above-described results, the formation of the nipecotic acid derived allene **24** was undertaken with the propargylic amine **31a** exhibiting an allyl(*tert*-butyl)amino residue as hydride donor, which had performed well in the [1,5]-hydride transfer reaction independent of the substitution in propargylic position adjacent to the hydride donor. Using the same conditions as given in Table 1 for the preparation of **32**, i.e. treating **31a** in chlorobenzene with 0.8 equiv of  $\text{CdI}_2$  at 130 °C for 2 h, no terminal allene **24** but only side products **51** and **52** (Scheme 9) were obtained (Table 4, entry 1). It appeared likely that the desired allene **24** might have formed but underwent subsequent transformation reactions to give the two side products **51** and **52**. This assumption was supported by literature data, according to which buta-2,3-dienyl amines are prone to rearrangement reactions, giving rise to 2,5-dihydropyrroles, which may further easily undergo an oxidation reaction to give the corresponding pyrroles.<sup>38,39</sup> A reasonable reaction pathway for the formation of the pyrrole derivatives **51** and **52** from allene **24** is given in Scheme 9. As indicated in the first step, the Lewis acid causes the aminobutadiene subunit to form the dihydropyrrole ring **48** as part of a spirocyclic ring system. The latter undergoes a retro Michael reaction to give the *N*-monosubstituted dihydropyrrole derivative **49** which, after exchange of the metal substituent by a proton and either a subsequent oxidation or disproportionation, yields pyrrole derivatives **51** and **52**.

Table 3. Effect of Different Hydride Donors on the Formation of 1,3-Disubstituted Allene 47<sup>a</sup>


entry	starting material	NR <sup>1</sup> R <sup>2</sup>	temp [°C]	t [h]	yield [%]
1 <sup>b</sup>	<b>29I</b>		100	3.25	89
2 <sup>b</sup>	<b>29m</b>		100	4.25	76
3 <sup>c</sup>	<b>29n</b>		100	6.00	10
4 <sup>b</sup>	<b>29n</b>		130	4.50	75
5 <sup>c</sup>	<b>29o</b>		100	5.00	10
6 <sup>c</sup>	<b>29o</b>		130	4.00	43

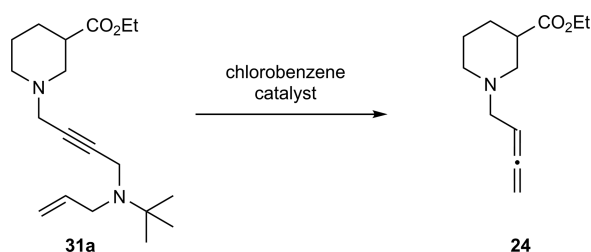
<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and CdI<sub>2</sub> (0.8 equiv) at 100/130 °C in 4.0 mL of anhydrous chlorobenzene. <sup>b</sup>The reaction was stopped when all starting material was consumed (detection by TLC). <sup>c</sup>The reaction was stopped when no further transformation was observed (detection by TLC).

Scheme 9. Proposed Mechanism for the Formation of Side Products 51 and 52 from Allene 24



**Optimization of the Reaction Conditions.** This led us to vary the reaction conditions to possibly be able to isolate **24** under milder reaction conditions. Indeed, when the reaction temperature was lowered to 100 °C after 2 h, minute amounts (<4%) of allene **24** together with 5% of the side products **51** and **52** were isolated (Table 4, entry 2). Lowering the temperature to 90 °C led to a slightly improved yield of 7% for **24** after 2 h (Table 4, entry 3) together with neglectable amounts of **51** and **52** (1%). However, when the reaction time was extended to 3.75 h, the desired product **24** was not detectable any longer, whereas the yield of the side products **51**

and **52** had increased to 10% (Table 4, entry 4). Lowering the reaction temperature to 70 °C neither met any success, leading only to **51** and **52** (11%), after an extended reaction time of 72 h required for a detectable conversion of small amounts of the starting material **31a** (Table 4, entry 5). With the subsequent reaction of allene **24** leading to the side products **51** and **52**, being quite fast compared to the formation of **24**, further attempts to optimize the reaction with CdI<sub>2</sub> as catalyst were considered futile. Interestingly, with 0.8 equiv of ZnI<sub>2</sub> instead of CdI<sub>2</sub> at 90 °C after 7.75 h, 25% of allene **24** was isolated, whereas only 1% of the side products **51** and **52** had formed

**Table 4. Optimization of Reaction Conditions for the Synthesis of Allene 24<sup>a</sup>**

entry	catalyst	equiv	temp [°C]	t [h]	yield [%]	side products 51/52 [%]
1	CdI <sub>2</sub>	0.8	130	2.00	<4	47
2	CdI <sub>2</sub>	0.8	100	2.00	<4	5
3 <sup>b</sup>	CdI <sub>2</sub>	0.8	90	2.00	7	1
4	CdI <sub>2</sub>	0.8	90	3.75		10
5 <sup>c</sup>	CdI <sub>2</sub>	0.8	70	72		11
6	ZnI <sub>2</sub>	0.8	130	4.75		36
7	ZnI <sub>2</sub>	0.8	100	4.75	37	
8 <sup>d</sup>	ZnI <sub>2</sub>	0.8	90	7.75	25	1
9	ZnI <sub>2</sub>	1.6	100	4.00	50	
10	ZnI <sub>2</sub>	0.4	100	4.50	29	

<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and catalyst in 4.0 mL of anhydrous chlorobenzene. <sup>b</sup>About 15% of starting material was covered. <sup>c</sup>Small amount of **24** was observed after 6.50 h; after 72 hours, all of **24** was transformed into **51/52**, and starting material was still present. <sup>d</sup>About 20% of starting material was covered.

(Table 4, entry 8). The yield of **24** was further increased to 37% when the reaction was conducted at 100 °C with no side products **51** and **52** being detectable (Table 4, entry 7). In this case, the reaction had been stopped after 4.75 h, when still some starting material was left, but no further conversion was observed by TLC. However, increasing the temperature to 130 °C was detrimental for the formation of the desired product: only the side products **51** and **52** (36%) but no allene **24** was isolated (Table 4, entry 6). To support the assumption according to which side products **51** and **52** are formed via allene **24**, additional experiments were performed. When allene **24** was treated either with 0.8 equiv of ZnI<sub>2</sub> or 0.8 equiv of CdI<sub>2</sub> (in chlorobenzene) at a reaction temperature from 80 to 100 °C, TLC analysis of the reaction mixture revealed that, with CdI<sub>2</sub> as catalyst, the formation of side products **51** and **52** started already at 80 °C, whereas with ZnI<sub>2</sub>, side product formation started at a distinctly higher temperature, i.e. 100 °C. Furthermore, up to 150 °C, barely any of the side product **51** and **52** formed when neither of the catalyst was present. Obviously, CdI<sub>2</sub> appears to affect the transformation of **24** into the side products **51** and **52** already at lower temperature compared to ZnI<sub>2</sub>, whereas the [1,5]-hydride transfer reaction seems to be faster under ZnI<sub>2</sub> compared to under CdI<sub>2</sub> catalysis. Hence, ZnI<sub>2</sub> is the more appropriate Lewis acid for the synthesis of allene **24** from propargylic amine **31a**.

**Effect of Different Hydride Donors on the Formation of Allene 24.** The yields for converting propargylic amines **31c–f** (Table S3, entries 5–8) bearing different hydride donors under optimized reaction conditions applying 0.8 equiv of ZnI<sub>2</sub> follow trends the same as those in the test system (Table 1). Whereas diisopropylamine (Table S3, entry 3, **31b**) as well as allyl(*tert*-butyl)amine (Table S3, entry 1, **31a**) as hydride donors afforded allene **24** in good yields, the starting materials with amino residues, which are less hindered (Table S3, entries 5–7,

THP **31c**, diallylamine **31d**, allyl(methyl)amine **31e**) or adopt a conformation less favorable for the [1,5]-hydride transfer reaction (Table S3, entry 8, isopropyl(*tert*-butyl)amine **31f**), afforded much lower yields of allene **24**. The generally lower yields compared to the test system **29** (Table 1) might be due to additional coordination of the catalyst to the nitrogen of the nipecotic acid subunit. But most notably, in none of the above-described transformations of **31a–f** was detected an alternative allene product resulting from the nipecotic acid residue serving as a hydride donor. This agrees with former results according to which the nipecotic acid residue appeared to be among the least suited hydride donors tested (Table 1, entry 4, **29d** → **32**, 6%).

**Effect of Amount of Lewis Acid.** Next, it was investigated how the amount of Lewis acid effects the outcome of the rearrangement reaction (Table 4). In contrast to the test system where the yields of allene **32** were not influenced by the catalyst loading (Table S2), the use of 1.6 equiv instead of 0.8 equiv of ZnI<sub>2</sub> increased the yield for the transformation of **31a** into allene **24** from 37% (Table 4, entry 7) to 50% (Table 4, entry 9). In line with this result, the yield of **24** decreased to 29% when only 0.4 equiv ZnI<sub>2</sub> was used (Table 4, entry 10). Similar to the allyl(*tert*-butyl)amino derivative **31a**, also **31b** (Table S3) containing the sterically demanding diisopropylamino residue gave upon treatment with 0.8 equiv of ZnI<sub>2</sub> a high yield of **24** (42%, Table S3, entry 3) which, in contrast to the transformation of **31a** in **24**, however, lowered to 12% when the amount of ZnI<sub>2</sub> was doubled (Table S3, entry 4). Hence, in the case of nipecotic acid derived propargylic amines, it depends on the hydride donor of what influence the catalyst loading has on the yield of allene **24**.

**Synthesis of Nipecotic Acid Ethyl Esters with 1,3-Disubstituted Allene Residues.** Finally, the two-step procedure comprising preparation of the respective propargylic amine and subsequent rearrangement to an allene was also used for the preparation of the nipecotic acid derivatives *rac*-(*R<sub>w</sub>R*)-**53a–e** and *rac*-(*R<sub>w</sub>S*)-**53a–e** exhibiting an *N*-allene substituent with a terminal aryl or alkyl residue (Table 5), employing the propargylic amines **31g–o** as starting materials (mixture of racemic diastereomers, ~1:1; for preparation, see Scheme 6 and Table S1). Propargylic amines **31g** exhibiting an allyl(*tert*-butyl)amino residue and **31h** equipped with a THP moiety gave good yields of the allene derivative mixture *rac*-(*R<sub>w</sub>R*)-**53a**/*rac*-(*R<sub>w</sub>S*)-**53a** (82 and 74%, respectively, Table 5, entries 1 and 2). This is in good line with the results obtained so far, the sterically demanding allyl(*tert*-butyl)amino moiety leading to good results independent of whether an additional residue in propargylic position adjacent to the amino function is present or not and the THP hydride donor only when, as in this case, a residue increasing the steric encumbrance of the amino nitrogen such as a phenyl group is nearby. An attempt to improve the yield for the transformation of **31h** into *rac*-(*R<sub>w</sub>R*)-**53a**/*rac*-(*R<sub>w</sub>S*)-**53a** by increasing the reaction temperature from 100 to 130 °C led to the opposite, the yield being lower (Table 5, entry 3). This is likely to be assigned to an instability inferred by the nipecotic acid moiety.

To explore the scope of aldehydes applicable in this method, furthermore propargylic amines **31i–o** derived from different aromatic (2-naphthaldehyde and biphenyl-2-carboxaldehyde) and aliphatic (butyraldehyde and isobutyraldehyde) aldehydes, allyl(*tert*-butyl)amine, and THP were employed as starting materials in this rearrangement reaction (Table 5, entries 4–11). When compounds with aryl residues were applied, both hydride donors allyl(*tert*-butyl)amine and THP performed well,

Table 5. Synthesis of 1,3-Disubstituted Allenes 53a–e<sup>a</sup>

$\text{rac-(R,R)/rac-(R,S) (~1:1)}$ 
 $\text{rac-(R}_{a},\text{R})/\text{rac-(R}_{a},\text{S}) (~1:1)$

entry	starting material <sup>b</sup>	NR <sup>1</sup> R <sup>2</sup>	R <sup>3</sup>	product	temp [°C]	t [h]	yield [%]
1	<i>rac-(R,S)</i> -31g <i>rac-(R,R)</i> -31g		phenyl	<i>rac-(R<sub>a</sub>,S)</i> -53a <i>rac-(R<sub>a</sub>,R)</i> -53a	100	3.75	82
2	<i>rac-(R,S)</i> -31h <i>rac-(R,R)</i> -31h		phenyl	<i>rac-(R<sub>a</sub>,S)</i> -53a <i>rac-(R<sub>a</sub>,R)</i> -53a	100	3.00	74
3	<i>rac-(R,S)</i> -31h <i>rac-(R,R)</i> -31h		phenyl	<i>rac-(R<sub>a</sub>,S)</i> -53a <i>rac-(R<sub>a</sub>,R)</i> -53a	130	1.25	51
4	<i>rac-(R,S)</i> -31i <i>rac-(R,R)</i> -31i		2-naphthyl	<i>rac-(R<sub>a</sub>,S)</i> -53b <i>rac-(R<sub>a</sub>,R)</i> -53b	100	2.75	76
5	<i>rac-(R,S)</i> -31j <i>rac-(R,R)</i> -31j		2-naphthyl	<i>rac-(R<sub>a</sub>,S)</i> -53b <i>rac-(R<sub>a</sub>,R)</i> -53b	100	1.50	75
6	<i>rac-(R,S)</i> -31k <i>rac-(R,R)</i> -31k		2-biphenyl	<i>rac-(R<sub>a</sub>,S)</i> -53c <i>rac-(R<sub>a</sub>,R)</i> -53c	100	4.00	63
7	<i>rac-(R,S)</i> -31l <i>rac-(R,R)</i> -31l		2-biphenyl	<i>rac-(R<sub>a</sub>,S)</i> -53c <i>rac-(R<sub>a</sub>,R)</i> -53c	100	1.75	86
8	<i>rac-(R,S)</i> -31m <i>rac-(R,R)</i> -31m		<i>n</i> -propyl	<i>rac-(R<sub>a</sub>,S)</i> -53d <i>rac-(R<sub>a</sub>,R)</i> -53d	100	2.50	51
9	<i>rac-(R,S)</i> -31n <i>rac-(R,R)</i> -31n		<i>n</i> -propyl	<i>rac-(R<sub>a</sub>,S)</i> -53d <i>rac-(R<sub>a</sub>,R)</i> -53d	100	1.50	90
10	<i>rac-(R,S)</i> -31n <i>rac-(R,R)</i> -31n		<i>n</i> -propyl	<i>rac-(R<sub>a</sub>,S)</i> -53d <i>rac-(R<sub>a</sub>,R)</i> -53d	100	2.50	76
11	<i>rac-(R,S)</i> -31o <i>rac-(R,R)</i> -31o		isopropyl	<i>rac-(R<sub>a</sub>,S)</i> -53e <i>rac-(R<sub>a</sub>,R)</i> -53e	100	1.50	84

<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and CdI<sub>2</sub> (0.8 equiv) at 100/130 °C in 4.0 mL of anhydrous chlorobenzene. The reaction was stopped when all starting material was consumed (detection by TLC). <sup>b</sup>Approximately a 1:1 mixture of both racemic diastereomers.

providing allenes **53b** and **53c** in yields of 63–86% (Table 5, entries 4–7). In the case of propargylic amines **31m** and **31n** with an alkyl residue present, i.e. an *n*-propyl substituent, the THP mediated allene formation (Table 5, entry 9) performed distinctly better than the allene formation based on propargylic amine **31m**, containing allyl(*tert*-butyl)amine as hydride donor (Table 5, entry 8). Compared to those of the THP-mediated allene formation, the allene formation mediated by allyl(*tert*-butyl)amine required longer reaction times. In a control experiment, the reaction time of THP containing propargylic

amine **31n** was extended from 1.5 to 2.5 h. This led to a decrease in yield from 90% to 76% (Table 5, entries 9 and 10), which is likely to be due to product instability. Therefore, the longer reaction time required for the complete consumption of **31m** might explain the lower yield with allyl(*tert*-butyl)amine as hydride donor as compared to the excellent yield of the faster THP-mediated allene formation. The synthesis of allene **53e** exhibiting an isopropyl residue could be performed only with propargylic amine **31o** exhibiting THP as the hydride donor (Table 5, entry 11), as attempts to synthesize the analogous



propargylic amine based on isobutyraldehyde and allyl(*tert*-butyl)amine failed, which is likely to be attributed to the high steric demand of these two components. Nonetheless, as indicated by these results, THP and allyl(*tert*-butyl)amine are well-suited hydride donors in [1,5]-hydride transfer reactions, allowing a broad range of substituents in propargylic position next to the aforementioned amino groups.

## CONCLUSION

Studying the synthesis of terminal and 1,3-disubstituted allenes from propargylic amines via [1,5]-hydride transfer reactions under  $\text{CdI}_2$  or  $\text{ZnI}_2$  catalysis gave insight of how the electronic, steric, and conformational properties of different secondary amines serving as hydride donors influence this reaction. In addition to the known influence of the electronic properties of the amines, steric demand was found to play an important role regarding the synthesis of terminal allenes. Through application of sterically demanding hydride donors such as allyl(*tert*-butyl)amine, the reactivity limiting complexation of the hydride donor nitrogen by the Lewis acid is suppressed, and the [1,5]-hydride transfer reaction can occur in significantly higher yields. With allyl(*tert*-butyl)amine, an amine was found which, due to its electronic and steric characteristics, is well suited for the synthesis of both terminal and 1,3-disubstituted allenes. With this herein reported method, terminal and 1,3-disubstituted allenes attached to a nipecotic acid building block were also accessible in good yields.

## EXPERIMENTAL SECTION

Unless otherwise noted, all reactions were performed in oven-dried glassware under moisture-free conditions and argon or nitrogen atmosphere. All commercially available reagents were used without further purification. Chlorobenzene was dried over  $\text{CaCl}_2$ , distilled under nitrogen atmosphere, and stored over molecular sieves (4 Å) under nitrogen atmosphere prior to use. For chromatographic purposes only, distilled solvents were used (EtOAc, PE 42–62 °C, DCM, MeOH). Flash column chromatography was performed using silica gel (grading 0.035–0.070 mm). Thin layer chromatography (TLC) was carried out on precoated silica gel  $\text{F}_{254}$  glass plates. NMR spectra were measured at 298.1 K on 400 MHz ( $^1\text{H}$  NMR: 400 MHz,  $^{13}\text{C}$  NMR: 101 MHz) and 500 MHz ( $^1\text{H}$  NMR: 500 MHz,  $^{13}\text{C}$  NMR: 126 MHz) spectrometers. These NMR spectrometers were also used for DEPT, HMQC, HMBC, and COSY experiments. The coupling constants were stated with an accuracy of 0.5 Hz. MestreNova was used for further analysis of the NMR data ( $s_{\text{br}}$  = broad singlet, hept = septet, Nip = nipecotic acid residue, dia = diastereomeric racemate;  $^{13}\text{C}$  signals separated by a slash are illustrating the slightly different ppm values of the diastereomeric racemates). IR spectra were recorded with an FT-IR spectrometer, and Spectrum v2.00 software was used for analysis. High-resolution mass spectrometry was performed with sector field mass spectrometer or LTQ FT Ultra mass spectrometer.

**Synthesis of Alkynes.** (4,4-Diphenylbut-1-yn-1-yl)-trimethylsilane (**27b**). To a Schlenk flask was added diphenylmethane (1.00 g, 5.94 mmol) in anhydrous THF (20 mL). After cooling to 0 °C in an ice bath, a 1.6 M solution of *n*-BuLi in hexane (3.71 mL, 5.94 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h. Then, 3-bromo-1-(trimethylsilyl)-1-propyne (1.09 mL, 6.54 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 20 h. The completion of the reaction was monitored by TLC (PE:DCM = 9:1). The reaction mixture was quenched with 40 mL of phosphate buffer (pH 7) and extracted 6 times with  $\text{Et}_2\text{O}$ . The combined organic phases were then dried over  $\text{MgSO}_4$  and concentrated under vacuum. The crude product was purified by column chromatography (PE:DCM = 9:1) to afford **27b** (1.59 g, 96%) as colorless viscous oil: TLC:  $R_f$  = 0.33 (PE:DCM = 9:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.04 (s, 9 H, Si( $\text{CH}_3$ )<sub>3</sub>), 2.91 (d,  $J$

= 7.6 Hz, 2 H,  $\text{CHCH}_2$ ), 4.21 (t,  $J$  = 7.6 Hz, 1 H,  $\text{CHCH}_2$ ), 7.16–7.25 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  -0.1, 26.9, 50.0, 86.9, 105.6, 126.4, 128.0, 128.3, 143.4; IR (neat) 3374, 3086, 3062, 3028, 2958, 2361, 2176, 1600, 1494, 1450, 1249, 1043, 842, 757, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{Si}$  278.1491, found 278.1471.

**4,4-Diphenylbut-1-yne (27a).** This compound is literature known.<sup>40</sup> Because of already synthesized compound **27b**, a simple deprotection reaction<sup>41</sup> instead of the procedure described in literature was performed. Analytical data obtained agreed with published data. To a solution of TMS protected alkyne **27b** (3.31 g, 11.9 mmol) in THF (55 mL) was added 1 M TBAF solution in THF (1.50 eq, 5.17 mL, 17.9 mmol), and the mixture was stirred at rt overnight. After evaporation, the residue was filtered through a pad of silica gel (PE:DCM = 9:1) to afford **27a** as pale yellow crystals (1.80 g, 73%): mp = 72.1 °C (lit. 73.0–73.5 °C); TLC:  $R_f$  = 0.29 (PE:DCM = 9:1).

**Ethyl 1-(Prop-2-yn-1-yl)piperidine-3-carboxylate (30).** Compound **30** was synthesized employing a synthesis route similar to a procedure described in literature.<sup>42</sup> Propargyl bromide solution (80 wt % in xylene, 1.00 equiv, 1.08 mL, 10.0 mmol) and ethyl nipecotate (1.20 equiv, 1.87 mL, 12.0 mmol) were dissolved in acetone (20 mL), and  $\text{Na}_2\text{CO}_3$  (2.50 equiv, 2.65 g, 25.0 mmol) and NaI (0.50 equiv, 749 mg, 5.00 mmol) were added. The reaction mixture was refluxed for 72 h, and the reaction was monitored by TLC. For quenching, DCM (50 mL) and water (50 mL) were added, and the product was extracted five times with DCM. The combined organic phases were then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude product was purified by column chromatography (PE:EtOAc = 8:2) to afford **30** as pale yellow oil (1.85 g, 95%): TLC:  $R_f$  = 0.60 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.26 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.44 (qd,  $J$  = 11.7/3.9 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.60 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.71–1.83 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.89–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.22 (td,  $J$  = 11.0/3.1 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.26 (t,  $J$  = 2.4 Hz, 1 H,  $\text{NCH}_2\text{CCH}$ ), 2.38 (t,  $J$  = 10.4 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.59 (ddt,  $J$  = 11.0/10.4/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.72–2.82 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.96–3.05 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.32 (d,  $J$  = 2.4 Hz, or AB,  $J$  = 17.2 Hz, 2 H,  $\text{NCH}_2\text{CCH}$ ), 4.14 (q,  $J$  = 7.1 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.5, 26.5, 41.9, 47.3, 52.2, 54.2, 60.4, 73.3, 78.7, 173.9; IR (neat) 3291, 2942, 2864, 2807, 1730, 1468, 1450, 1368, 1311, 1223, 1183, 1153, 1133, 1095, 1031, 1002, 900, 864, 791, 654  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{18}\text{NO}_2$  [M + H]<sup>+</sup> 196.1338, found 196.1332.

**Synthesis of Propargylic Amines. General Procedure 1.** To a Schlenk flask was added CuCl (1.5 equiv). Dioxane anhydrous (12.0 mL/mmol) was then added, followed by TMS-protected alkyne (1.0 equiv), paraformaldehyde (1.2 equiv), amine (1.2 equiv) and  $\text{BF}_3\cdot\text{OEt}_2$  (1.0 equiv). The reaction mixture was stirred at rt for 10 min and at 50 °C overnight. The completion of the reaction was monitored by TLC. After cooling to rt the reaction mixture was added to a 1:1 solution of saturated potassium sodium tartrate solution and saturated sodium hydrogen carbonate solution (44.0 mL/mmol) and extracted 5 times with EtOAc. The combined organic phases were then filtrated, dried over  $\text{MgSO}_4$ , and concentrated under vacuum. The crude product was purified by column chromatography to afford the corresponding propargylic amine.

**General Procedure 2.** To a Schlenk flask was added CuBr (0.15 equiv) and molecular sieve (4 Å). Toluene anhydrous (5.00 mL/mmol) was then added, followed by the addition of the corresponding aldehyde (1.80 equiv), amine (1.40 equiv), and alkyne (1.00 equiv). The reaction mixture was stirred at rt overnight. Completion of the reaction was monitored by TLC. The reaction mixture was then filtrated, washed with EtOAc, and concentrated under vacuum. The crude product was purified by column chromatography to afford the corresponding propargylic amine. This procedure was performed according to a procedure described by Ma et al.<sup>27,34</sup>

**4-(5,5-Diphenylpent-2-yn-1-yl)morpholine (29a).** GP1 was followed using **27b** (200 mg, 0.720 mmol), CuCl (107 mg, 1.08 mmol),  $\text{BF}_3\cdot\text{OEt}_2$  (213 mg, 0.720 mmol), morpholine (74.5  $\mu\text{L}$ , 0.864 mmol), and paraformaldehyde (27.3 mg, 0.864 mmol). Purification by column

chromatography (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>) afforded **29a** (162 mg, 74%) as yellow oil: TLC:  $R_f$  = 0.18 (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.24–2.32 (m, 4 H, NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>), 2.92 (dt,  $J$  = 7.8/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.10 (t,  $J$  = 2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.59–3.67 (m, 4 H, NCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>), 4.21 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 7.15–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 25.7, 47.5, 50.4, 52.1, 66.8, 76.5, 84.0, 126.5, 127.9, 128.4, 143.4; IR (neat) 3357, 3060, 3026, 2957, 2922, 2852, 2809, 1599, 1494, 1451, 1346, 1330, 1313, 1288, 1115, 1004, 860, 737, 699 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>21</sub>H<sub>24</sub>NO<sup>+</sup> [M + H]<sup>+</sup> 306.1858, found 306.1852.

**1-(5,5-Diphenylpent-2-yn-1-yl)piperidine (29b)**. GP1 was followed using **27b** (267 mg, 0.958 mmol), CuCl (142 mg, 1.44 mmol), BF<sub>3</sub>·OEt<sub>2</sub> (283 mg, 0.958 mmol), piperidine (115 μL, 1.15 mmol), and paraformaldehyde (36.3 mg, 1.15 mmol). Purification by column chromatography (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>) afforded **29b** (263 mg, 91%) as yellow oil: TLC:  $R_f$  = 0.15 (PE:EtOAc = 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.32 (s<sub>br</sub>, 2 H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.49 (p,  $J$  = 5.7 Hz, 4 H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.22 (s<sub>br</sub>, 4 H, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.92 (dt,  $J$  = 7.8/2.2 Hz, 2 H, NCH<sub>2</sub>CCCH<sub>2</sub>), 3.11 (t,  $J$  = 2.2 Hz, 2 H, NCH<sub>2</sub>CCCH<sub>2</sub>), 4.21 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>), 7.13–7.26 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 23.8, 25.7, 25.9, 47.9, 50.5, 52.9, 77.2, 83.3, 126.4, 128.0, 128.3, 143.6; IR (neat) 3085, 3060, 3026, 2932, 2852, 2796, 2753, 1945, 1878, 1800, 1748, 1600, 1494, 1466, 1451, 1384, 1367, 1340, 1325, 1308, 1298, 1275, 1251, 1187, 1155, 1116, 1104, 1081, 1037, 993, 958, 908, 858, 781, 738, 699, 613 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>22</sub>H<sub>26</sub>N<sup>+</sup> [M + H]<sup>+</sup> 304.2065, found 304.2060.

**1-(5,5-Diphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (29c)**. GP1 was followed using **27b** (557 mg, 2.00 mmol), CuCl (297 mg, 3.00 mmol), BF<sub>3</sub>·OEt<sub>2</sub> (591 mg, 2.00 mmol), 1,2,3,6-tetrahydropyridine (223 μL, 2.40 mmol), and paraformaldehyde (75.9 mg, 2.40 mmol). Purification by column chromatography (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>) afforded **29c** (439 mg, 73%) as yellow oil: TLC:  $R_f$  = 0.37 (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.04–2.14 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>), 2.37 (t,  $J$  = 5.7 Hz, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>), 2.78–2.86 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>), 2.92 (dt,  $J$  = 7.8/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.23 (t,  $J$  = 2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 4.20 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 5.53–5.72 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>), 7.13–7.21 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 25.7, 26.2, 46.9, 48.4, 50.4, 50.7, 76.9, 83.5, 124.6, 125.2, 126.4, 127.9, 128.4, 143.5; IR (neat) 3028, 2909, 2799, 1948, 1874, 1802, 1713, 1599, 1494, 1450, 1430, 1327, 1195, 1128, 1113, 1031, 1004, 970, 803, 738, 699 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>22</sub>H<sub>24</sub>N<sup>+</sup> [M + H]<sup>+</sup> 302.1909, found 302.1905.

***N,N*-Diallyl-5,5-diphenylpent-2-yn-1-amine (29g)**. GP1 was followed using **27b** (200 mg, 0.720 mmol), CuCl (107 mg, 1.08 mmol), BF<sub>3</sub>·OEt<sub>2</sub> (213 mg, 0.720 mmol), diallylamine (107 μL, 0.864 mmol), and paraformaldehyde (27.3 mg, 0.864 mmol). Purification by column chromatography (PE:EtOAc = 9:1, 1% NEt<sub>3</sub>) afforded **29g** (170 mg, 75%) as pale yellow oil: TLC:  $R_f$  = 0.21 (PE:EtOAc = 9:1); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 2.85 (dt,  $J$  = 6.6/1.3 Hz, 4 H, N(CH<sub>2</sub>CHCH<sub>2</sub>)<sub>2</sub>), 2.94 (dt,  $J$  = 7.8/2.1 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.23 (t,  $J$  = 2.1 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 4.21 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 5.02–5.10 (m, 4 H, N(CH<sub>2</sub>CHCH<sub>2</sub>)<sub>2</sub>), 5.66–5.78 (m, 2 H, N(CH<sub>2</sub>CHCH<sub>2</sub>)<sub>2</sub>), 7.15–7.23 (m, 2 H, ArH), 7.23–7.32 (m, 8 H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 25.7, 41.6, 50.6, 56.1, 76.1, 83.7, 117.8, 126.5, 127.9, 128.4, 135.5, 143.5; IR (neat) 3377, 3062, 3027, 2919, 2815, 1642, 1494, 1450, 1327, 1110, 921, 738, 698 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>23</sub>H<sub>26</sub>N<sup>+</sup> [M + H]<sup>+</sup> 316.2065, found 316.2061.

***N*-Allyl-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (29h)**. GP1 was followed using **27b** (557 mg, 2.00 mmol), CuCl (297 mg, 3.00 mmol), BF<sub>3</sub>·OEt<sub>2</sub> (591 mg, 2.00 mmol), allyl(methyl)amine (235 μL, 2.40 mmol), and paraformaldehyde (75.9 mg, 2.40 mmol). Purification by column chromatography (PE:EtOAc = 6:4, 1% NEt<sub>3</sub>) afforded **29h** (498 mg, 86%) as pale yellow oil: TLC:  $R_f$  = 0.61 (PE:EtOAc = 6:4); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.07 (s, 3 H, NMe), 2.79 (dt,  $J$  = 6.6/

1.3 Hz, 2 H, NMeCH<sub>2</sub>CHCH<sub>2</sub>), 2.93 (dt,  $J$  = 7.8/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.18 (t,  $J$  = 2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 4.21 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 5.00–5.11 (m, 2 H, NMeCH<sub>2</sub>CHCH<sub>2</sub>), 5.73 (ddt,  $J$  = 17.1/10.6/6.6 Hz, 1 H, NMeCH<sub>2</sub>CHCH<sub>2</sub>), 7.13–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 25.7, 41.3, 45.4, 50.5, 58.6, 76.4, 83.7, 117.7, 126.4, 127.9, 128.4, 135.5, 143.5; IR (neat) 3027, 2913, 2788, 2359, 1945, 1600, 1494, 1450, 1327, 1192, 1128, 1082, 1031, 996, 922, 836, 789, 737, 699 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>21</sub>H<sub>24</sub>N<sup>+</sup> [M + H]<sup>+</sup> 290.1909, found 290.1904.

***N,N*-Diisopropyl-5,5-diphenylpent-2-yn-1-amine (29k)**. GP1 was followed using **27b** (382 mg, 1.37 mmol), CuCl (203 mg, 2.06 mmol), BF<sub>3</sub>·OEt<sub>2</sub> (405 mg, 1.37 mmol), diisopropylamine (231 μL, 1.64 mmol), and paraformaldehyde (52.0 mg, 1.64 mmol). Purification by column chromatography (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>) afforded **29k** (269 mg, 61%) as pale yellow oil: TLC:  $R_f$  = 0.26 (PE:EtOAc = 1:1, 1% NEt<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 0.94 (d,  $J$  = 6.5 Hz, 12 H, N(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 2.89 (dt,  $J$  = 7.8/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 2.95 (h,  $J$  = 6.5 Hz, 2 H, N(CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>), 3.28 (t,  $J$  = 2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 4.18 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 7.14–7.21 (m, 2 H, ArH), 7.21–7.33 (m, 8 H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 20.4, 25.9, 34.1, 47.9, 50.4, 80.5, 81.7, 126.4, 127.9, 128.3, 143.7; IR (neat) 3086, 3062, 3027, 2966, 2928, 2873, 2613, 1945, 1875, 1802, 1600, 1494, 1451, 1380, 1362, 1326, 1202, 1176, 1117, 1081, 1032, 749, 737, 698 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>23</sub>H<sub>30</sub>N<sup>+</sup> [M + H]<sup>+</sup> 320.2378, found 320.2376.

**Ethyl 1-(5,5-Diphenylpent-2-yn-1-yl)piperidine-3-carboxylate (29d)**. GP2 was followed using **27a** (206 mg, 1.00 mmol), CuBr (21.5 mg, 0.150 mmol), ethyl nipecotate (0.23 mL, 1.4 mmol), and paraformaldehyde (56.9 mg, 1.80 mmol). Purification by column chromatography (PE:EtOAc = 1:1) afforded **29d** (333 mg, 89%) as pale yellow oil: TLC:  $R_f$  = 0.33 (PE:EtOAc = 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.26 (t,  $J$  = 7.1 Hz, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.20–1.36 (m, 1 H, NCH<sub>2</sub>CHCH<sub>2</sub>H<sub>ax</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.40–1.55 (m, 1 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>H<sub>eq</sub>H<sub>ax</sub>CH<sub>2</sub>), 1.56–1.67 (m, 1 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>H<sub>eq</sub>H<sub>ax</sub>CH<sub>2</sub>), 1.80–1.91 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>H<sub>ax</sub>CH<sub>2</sub>CH<sub>2</sub>H<sub>ax</sub>), 2.11 (t,  $J$  = 10.7 Hz, 1 H, NCH<sub>2</sub>CH<sub>2</sub>H<sub>ax</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.42–2.55 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>H<sub>ax</sub>), 2.81 (dd,  $J$  = 11.1/3.6 Hz, 1 H, NCH<sub>2</sub>CH<sub>2</sub>H<sub>ax</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.92 (dt,  $J$  = 7.8/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 3.17 (dt,  $J$  = 3.1/2.2 Hz, 2 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 4.09–4.17 (m, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.21 (t,  $J$  = 7.8 Hz, 1 H, CHCH<sub>2</sub>CCCH<sub>2</sub>N), 7.10–7.23 (m, 2 H, ArH), 7.20–7.35 (m, 8 H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 14.2, 24.5, 25.7, 26.4, 41.9, 47.6, 50.4, 51.8, 54.0, 60.3, 76.6, 83.8, 126.4, 127.9, 128.4, 143.5, 174.0; IR (neat) 3086, 3061, 3027, 2937, 2854, 2806, 1947, 1882, 1730, 1600, 1494, 1467, 1451, 1367, 1316, 1223, 1181, 1153, 1132, 1090, 1031, 1000, 979, 956, 906, 868, 790, 750, 700, 608 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>25</sub>H<sub>30</sub>NO<sub>2</sub><sup>+</sup> [M + H]<sup>+</sup> 376.2277, found 376.2271.

***N*-Allyl-*N*-(*tert*-butyl)-5,5-diphenylpent-2-yn-1-amine (29e)**. GP2 was followed using **27a** (598 mg, 2.90 mmol), CuBr (62.4 mg, 0.435 mmol), allyl(*tert*-butyl)amine (0.61 mL, 4.06 mmol), and paraformaldehyde (165 mg, 5.22 mmol). Purification by column chromatography (PE:EtOAc = 6:4) afforded **29e** (877 mg, 91%) as pale yellow oil: TLC:  $R_f$  = 0.82 (PE:EtOAc = 6:4); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.03 (s, 9 H, *t*-Bu), 2.90 (dt,  $J$  = 7.7/2.1 Hz, 2 H, NCH<sub>2</sub>CCCH<sub>2</sub>), 3.04 (d,  $J$  = 6.5 Hz, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>), 3.35 (t,  $J$  = 2.1 Hz, 2 H, NCH<sub>2</sub>CCCH<sub>2</sub>), 4.19 (t,  $J$  = 7.7 Hz, 1 H, NCH<sub>2</sub>CCCH<sub>2</sub>CH), 4.97–5.06 (m, 2 H, NCH<sub>2</sub>CHCH<sub>2</sub>), 5.70 (ddt,  $J$  = 16.7/10.1/6.5 Hz, 1 H, NCH<sub>2</sub>CHCH<sub>2</sub>), 7.15–7.24 (m, 2 H, ArH), 7.20–7.32 (m, 8 H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 25.8, 27.6, 36.3, 49.7, 50.4, 54.7, 79.8, 82.4, 116.7, 126.4, 127.9, 128.4, 137.4, 143.6; IR (neat) 3063, 3027, 2971, 2913, 1944, 1800, 1728, 1640, 1600, 1494, 1451, 1432, 1416, 1389, 1362, 1334, 1307, 1270, 1217, 1203, 1128, 1081, 1032, 1018, 994, 941, 917, 860, 826, 783, 748, 737, 699, 645, 617 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>24</sub>H<sub>30</sub>N<sup>+</sup> [M + H]<sup>+</sup> 332.2378, found 332.2376.

***N*-Allyl-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (29f)**. GP2 was followed using **27a** (237 mg, 1.15 mmol), CuBr (24.7 mg, 0.172 mmol), allyl(isopropyl)amine (160 mg, 1.61 mmol), and paraformaldehyde (65.4 mg, 2.07 mmol). Purification by column chromatography

(PE:EtOAc = 1:1) afforded **29f** (185 mg, 51%) as pale yellow oil: TLC:  $R_f = 0.58$  (PE:EtOAc = 1:1);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.93 (d,  $J = 6.5$  Hz, 6 H,  $\text{NCH}(\text{CH}_3)_2$ ), 2.66 (hept,  $J = 6.5$  Hz, 1 H,  $\text{NCH}(\text{CH}_3)_2$ ), 2.91 (dt,  $J = 7.8/2.2$  Hz, 2 H,  $\text{CHCH}_2\text{CCCH}_2\text{N}$ ), 2.94 (dt,  $J = 6.6/1.3$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.25 (t,  $J = 2.2$  Hz, 2 H,  $\text{CHCH}_2\text{CCCH}_2\text{N}$ ), 4.20 (t,  $J = 7.8$  Hz, 1 H,  $\text{CHCH}_2\text{CCCH}_2\text{N}$ ), 4.99–5.10 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 5.73 (ddt,  $J = 16.9/10.2/6.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ ), 7.12–7.22 (m, 2 H, ArH), 7.22–7.34 (m, 8 H, ArH);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  19.8, 25.8, 38.9, 50.5, 50.6, 52.6, 77.8, 82.8, 117.2, 126.4, 127.9, 128.4, 136.5, 143.6; IR (neat) 3062, 3027, 2964, 2927, 2811, 1944, 1733, 1641, 1600, 1494, 1450, 1382, 1362, 1325, 1253, 1171, 1140, 1115, 1081, 1032, 995, 949, 918, 876, 780, 737, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{28}\text{N}^+$  [M + H]<sup>+</sup> 318.2222, found 318.2218.

*N*-(*tert*-Butyl)-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (**29i**). GP2 was followed using **27a** (297 mg, 1.44 mmol), CuBr (31.0 mg, 0.216 mmol), isopropyl(*tert*-butyl)amine (0.32 mL, 2.02 mmol), and paraformaldehyde (81.9 mg, 2.59 mmol). Purification by column chromatography (PE:EtOAc = 9:1) afforded **29i** (363 mg, 76%) as white solid: TLC:  $R_f = 0.23$  (PE:EtOAc = 9:1); mp = 47.7 °C;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.95 (d,  $J = 6.6$  Hz, 6 H,  $\text{NCH}(\text{CH}_3)_2$ ), 1.04 (s, 9 H, *Nt*-Bu), 2.88 (dt,  $J = 7.7/2.1$  Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2$ ), 3.20 (hept,  $J = 6.6$  Hz, 1 H,  $\text{NCH}(\text{CH}_3)_2$ ), 3.31 (t,  $J = 2.1$  Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2$ ), 4.17 (t,  $J = 7.7$  Hz, 1 H,  $\text{CHCH}_2$ ), 7.13–7.20 (m, 2 H, ArH), 7.21–7.30 (m, 8 H, ArH);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  22.4, 25.9, 28.4, 31.7, 46.6, 50.4, 55.1, 80.0, 84.1, 126.3, 127.9, 128.3, 143.8; IR (neat) 3062, 3027, 2970, 2926, 1600, 1558, 1540, 1494, 1451, 1388, 1362, 1338, 1306, 1253, 1218, 1170, 1113, 1081, 1051, 1032, 923, 788, 737, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{32}\text{N}^+$  [M + H]<sup>+</sup> 334.2535, found 334.2533.

*N*-(*tert*-Butyl)-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (**29j**). GP2 was followed using **27a** (297 mg, 1.44 mmol), CuBr (31.0 mg, 0.216 mmol), methyl(*tert*-butyl)amine (0.25 mL, 2.02 mmol), and paraformaldehyde (81.9 mg, 2.59 mmol). Purification by column chromatography (PE:EtOAc = 1:1) afforded **29j** (423 mg, 96%) as pale yellow oil: TLC:  $R_f = 0.26$  (PE:EtOAc = 1:1);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.00 (s, 9 H, *Nt*-Bu), 2.17 (s, 3 H, *NMe*), 2.90 (dt,  $J = 7.7/2.1$  Hz, 2 H,  $\text{CHCH}_2$ ), 3.21 (t,  $J = 2.1$  Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2$ ), 4.20 (t,  $J = 7.7$  Hz, 1 H,  $\text{CHCH}_2$ ), 7.14–7.21 (m, 2 H, ArH), 7.21–7.31 (m, 8 H, ArH);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  25.9, 26.3, 34.9, 40.6, 50.3, 54.1, 79.7, 82.3, 126.4, 127.9, 128.3, 143.7; IR (neat) 3086, 3061, 3027, 2971, 2785, 1945, 1801, 1600, 1494, 1451, 1387, 1361, 1262, 1218, 1120, 1081, 1000, 947, 823, 750, 737, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{28}\text{N}^+$  [M + H]<sup>+</sup> 306.2222, found 306.2219.

*N*-Allyl-*N*-(*tert*-butyl)undec-2-yn-1-amine (**39**). GP2 was followed using 1-decyne (0.36 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 9:1) afforded **39** (477 mg, 90%) as colorless oil: TLC:  $R_f = 0.56$  (PE:EtOAc = 8:2);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 6.9$  Hz, 3 H,  $\text{CH}_2\text{CH}_3$ ), 1.17 (s, 9 H,  $\text{NC}(\text{CH}_3)_3$ ), 1.21–1.34 (m, 8 H,  $(\text{CH}_2)_4$ ), 1.34–1.43 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CC}$ ), 1.43–1.54 (m, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CC}$ ), 2.16 (t,  $J = 7.0/2.2$  Hz, 2 H,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CC}$ ), 3.28 (d,  $J = 6.6$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.46 (t,  $J = 2.2$  Hz, 2 H,  $\text{NCH}_2\text{CC}$ ), 5.09 (ddt,  $J = 10.0/2.3/1.2$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.23 (dq,  $J = 16.9/1.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.83 (ddt,  $J = 16.9/10.0/6.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.1, 18.8, 22.7, 27.7, 28.9, 28.9, 29.1, 29.3, 31.9, 36.6, 50.0, 54.9, 78.0, 84.4, 116.6, 137.6; IR (neat)  $\bar{\nu}$  2959, 2928, 2856, 1745, 1641, 1465, 1432, 1389, 1362, 1332, 1270, 1216, 1203, 1129, 1073, 1018, 993, 940, 915, 825  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{34}\text{N}^+$  [M + H]<sup>+</sup> 264.2691, found 264.2686.

*N*-Allyl-*N*-(*tert*-butyl)-6-chlorohex-2-yn-1-amine (**40**). GP2 was followed using 5-chloro-1-pentyne (0.22 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 9:1) afforded **40** (443 mg, 97%) as colorless oil: TLC:  $R_f = 0.34$  (PE:EtOAc = 8:2);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.16 (s, 9 H,  $\text{NC}(\text{CH}_3)_3$ ), 1.94 (p,  $J = 6.6$  Hz, 2 H,  $\text{ClCH}_2\text{CH}_2\text{CH}_2$ ), 2.37 (tt,  $J = 6.6/2.2$  Hz, 2 H,  $\text{ClCH}_2\text{CH}_2\text{CH}_2$ ), 3.27

(dt,  $J = 6.5/1.3$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.45 (t,  $J = 2.2$  Hz, 2 H,  $\text{NCH}_2\text{CC}$ ), 3.66 (t,  $J = 6.6$  Hz, 2 H,  $\text{ClCH}_2\text{CH}_2\text{CH}_2$ ), 5.10 (ddt,  $J = 10.0/2.3/1.3$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.23 (dq,  $J = 16.9/1.3$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.82 (ddt,  $J = 16.9/10.0/6.5$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  16.3, 27.7, 31.5, 36.5, 43.8, 50.1, 54.9, 79.3, 82.1, 116.6, 137.5; IR (neat)  $\bar{\nu}$  2972, 1716, 1642, 1433, 1416, 1390, 1362, 1333, 1290, 1270, 1218, 1203, 1128, 1073, 1019, 994, 940, 918, 859  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{23}\text{ClN}^+$  [M + H]<sup>+</sup> 228.1519, found 228.1515.

7-(Allyl(*tert*-butyl)amino)hept-5-ynenitrile (**41**). GP2 was followed using hex-5-ynenitrile (0.22 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 7:3) afforded **41** (408 mg, 94%) as pale yellow oil: TLC:  $R_f = 0.31$  (PE:EtOAc = 7:3);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.16 (s, 9 H,  $\text{NC}(\text{CH}_3)_3$ ), 1.85 (p,  $J = 7.0$  Hz, 2 H,  $\text{NCCH}_2\text{CH}_2\text{CH}_2$ ), 2.37 (tt,  $J = 7.0/2.2$  Hz, 2 H,  $\text{NCCH}_2\text{CH}_2\text{CH}_2$ ), 2.49 (t,  $J = 7.0$  Hz, 2 H,  $\text{NCCH}_2\text{CH}_2\text{CH}_2$ ), 3.27 (dt,  $J = 6.4/1.3$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.45 (t,  $J = 2.2$  Hz, 2 H,  $\text{NCH}_2\text{CC}$ ), 5.10 (ddt,  $J = 10.0/2.2/1.2$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.22 (dq,  $J = 16.9/1.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.82 (ddt,  $J = 16.9/10.0/6.4$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ );  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  16.2, 18.0, 24.7, 27.6, 36.5, 50.2, 54.9, 80.4, 81.1, 116.7, 119.2, 137.4; IR (neat)  $\bar{\nu}$  2972, 1640, 1454, 1431, 1390, 1363, 1333, 1311, 1269, 1216, 1203, 1128, 1110, 1074, 1019, 994, 939, 918  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{23}\text{N}^+$  [M + H]<sup>+</sup> 219.1861, found 219.1857.

*N*-Allyl-4-(benzyloxy)-*N*-(*tert*-butyl)but-2-yn-1-amine (**42**). GP2 was followed using [(prop-2-yn-1-yloxy)methyl]benzene (0.29 mL, 2.0 mmol), CuBr (43 mg, 0.30 mmol), allyl(*tert*-butyl)amine (0.43 mL, 2.8 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 8:2) afforded **42** (478 mg, 88%) as colorless oil: TLC:  $R_f = 0.57$  (PE:EtOAc = 7:3);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.19 (s, 9 H,  $\text{NC}(\text{CH}_3)_3$ ), 3.31 (d,  $J = 6.5$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.55 (t,  $J = 1.9$  Hz, 2 H,  $\text{NCH}_2\text{CC}$ ), 4.19 (t,  $J = 1.9$  Hz, 2 H,  $\text{OCH}_2\text{CC}$ ), 4.60 (s, 2 H, ArH), 5.11 (ddt,  $J = 10.0/2.3/1.2$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.25 (dq,  $J = 16.9/1.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.83 (ddt,  $J = 16.9/10.0/6.5$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ ), 7.23–7.43 (m, 5 H, ArH);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  27.7, 36.6, 50.2, 54.9, 57.7, 71.4, 79.8, 85.2, 116.8, 127.8, 128.1, 128.4, 137.3, 137.6; IR (neat)  $\bar{\nu}$  3065, 3030, 2972, 2500, 1809, 1641, 1496, 1454, 1428, 1416, 1389, 1362, 1332, 1268, 1203, 1101, 1070, 1026, 994, 940, 918, 735, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{26}\text{NO}^+$  [M + H]<sup>+</sup> 272.2014, found 272.2009.

Ethyl 1-(4-[Allyl(*tert*-butyl)amino]but-2-yn-1-yl)piperidine-3-carboxylate (**31a**). GP2 was followed using **30** (586 mg, 3.00 mmol), CuBr (64.6 mg, 0.450 mmol), allyl(*tert*-butyl)amine (0.63 mL, 4.20 mmol), and paraformaldehyde (171 mg, 5.40 mmol). Purification by column chromatography (PE:EtOAc = 1:1) afforded **31a** (898 mg, 93%) as pale yellow oil: TLC:  $R_f = 0.27$  (PE:EtOAc = 1:1);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.17 (s, 9 H, *Nt*-Bu), 1.25 (t,  $J = 7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J \approx 11.7/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.52–1.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.76 (dp,  $J \approx 13.2/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.89–2.06 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.19 (td,  $J \approx 11.1/3.9$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.34 (t,  $J \approx 10.5$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 2.58 (ddt,  $J \approx 11.7/10.5/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2$ ), 2.73–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99–3.08 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.29 (dt,  $J = 6.5/1.3$  Hz, 2 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.32 (t,  $J = 2.0$  Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{Nip}$ ), 3.51 (t,  $J = 2.0$  Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{Nip}$ ), 4.13 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.10 (ddt,  $J = 10.0/2.2/1.3$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.24 (ddt,  $J = 17.1/2.2/1.3$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.81 (ddt,  $J = 17.1/10.0/6.5$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 27.7, 36.5, 42.0, 47.8, 50.1, 52.4, 54.3, 54.9, 60.3, 78.8, 83.5, 116.7, 137.5, 174.0; IR (neat) 3076, 2973, 2805, 1733, 1641, 1467, 1451, 1390, 1364, 1322, 1270, 1217, 1203, 1181, 1152, 1133, 1095, 1046, 1031, 995, 940, 916, 866  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_2^+$  [M + H]<sup>+</sup> 321.2542, found 321.2540.

**Ethyl 1-[4-(Diisopropylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31b).** GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diisopropylamine (0.39 mL, 2.80 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM:MeOH = 9:1) afforded **31b** (586 mg, 95%) as yellow oil: TLC:  $R_f$  = 0.37 (DCM:MeOH = 9:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (d,  $J$  = 6.6 Hz, 12 H,  $\text{N}(\text{CH}(\text{CH}_3)_2)_2$ ), 1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.41 (qd,  $J$   $\approx$  11.8/3.7 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.52–1.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.76 (dp,  $J$   $\approx$  13.3/3.4 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.89–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.18 (td,  $J$  = 11.1/3.0 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.33 (t,  $J$   $\approx$  10.6 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.58 (ddt,  $J$   $\approx$  11.8/10.6/3.8 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.73–2.82 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.98–3.07 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.24 (hept,  $J$  = 6.6 Hz, 2 H,  $\text{N}(\text{CH}(\text{CH}_3)_2)_2$ ), 3.31 (t,  $J$  = 2.0 Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{N}$  (diisopropyl)), 3.48 (t,  $J$  = 2.0 Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{N}$  (diisopropyl)), 4.13 (q,  $J$  = 7.1 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 20.5, 24.6, 26.6, 34.3, 42.0, 47.8, 48.7, 52.4, 54.4, 60.3, 78.5, 83.7, 174.0; IR (neat) 3420, 2966, 2939, 2872, 2804, 1733, 1466, 1381, 1363, 1321, 1179, 1153, 1134, 1095, 1031, 867  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{33}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  309.2542, found 309.2539.

**Ethyl 1-[4-[3,6-Dihydropyridin-1(2H)-yl]but-2-yn-1-yl]piperidine-3-carboxylate (31c).** GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), 1,2,3,6-tetrahydropyridine (0.26 mL, 2.80 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM:MeOH = 9:1) afforded **31c** (540 mg, 93%) as yellow oil: TLC:  $R_f$  = 0.40 (DCM:MeOH = 9:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J$  = 11.5/3.9 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.66 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.76 (dp,  $J$  = 13.3/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.91–1.98 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.13–2.25 (m, 3 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.33 (t,  $J$   $\approx$  10.5 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.58 (ddt,  $J$   $\approx$  11.5/10.5/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.65 (t,  $J$  = 5.7 Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2$ ), 2.75–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.98–3.06 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.06–3.12 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2$ ), 3.31–3.36 (m, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{Nip}$ ), 3.42 (t,  $J$  = 2.0 Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{Nip}$ ), 4.07–4.20 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.63–5.72 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2$ ), 5.72–5.82 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.2, 26.6, 41.9, 47.0, 47.7, 48.9, 51.1, 52.5, 54.4, 60.4, 79.7, 80.2, 124.8, 125.1, 174.0; IR (neat) 3373, 3033, 2939, 2908, 2801, 1731, 1465, 1448, 1323, 1223, 1182, 1153, 1134, 1094, 1031, 1004, 867, 803, 654  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{27}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  291.2073, found 291.2068.

**Ethyl 1-[4-(Diallylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31d).** GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diallylamine (0.35 mL, 2.80 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 1:1) afforded **31d** (546 mg, 90%) as colorless oil: TLC:  $R_f$  = 0.21 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.43 (qd,  $J$  = 12.4/4.2 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.55–1.67 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.77 (dp,  $J$   $\approx$  13.4/3.7 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.92–2.03 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.21 (td,  $J$  = 11.2/3.1 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.37 (t,  $J$  = 10.5 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 2.59 (tt,  $J$   $\approx$  11.5/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.75–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.00–3.07 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.13 (dt,  $J$   $\approx$  6.5/1.2 Hz, 4 H,  $\text{N}(\text{CH}_2\text{CHCH}_2)_2$ ), 3.36 (t,  $J$  = 2.0 Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{N}$  (diallyl)), 3.40 (t,  $J$  = 2.0 Hz, 2 H,  $\text{NCH}_2\text{CCCH}_2\text{N}$  (diallyl)), 4.09–4.18 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.15 (ddt,  $J$   $\approx$  10.1/1.8/1.2 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}})_2$ ), 5.24 (dq,  $J$   $\approx$  17.0/1.8 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}})_2$ ), 5.84 (ddt,  $J$   $\approx$  17.0/10.1/6.5 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_{\text{trans}}\text{H}_{\text{cis}})_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 41.7, 42.0, 47.7, 52.4, 54.3, 56.5, 60.3, 79.8, 118.0, 135.4, 174.0; IR (neat) 3077, 2978, 2939, 2812, 1732, 1643, 1467, 1449, 1429, 1367, 1322, 1255, 1222, 1181, 1153, 1133, 1095, 1031, 996, 921, 850, 792

$\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{29}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  305.2229, found 305.2226.

**Ethyl 1-[4-[Allyl(methyl)amino]but-2-yn-1-yl]piperidine-3-carboxylate (31e).** GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), allyl(methyl)amine (0.27 mL, 2.80 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM:MeOH = 9:1) afforded **31e** (525 mg, 94%) as pale yellow oil: TLC:  $R_f$  = 0.68 (DCM:MeOH = 18:2);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.43 (qd,  $J$   $\approx$  11.5/4.0 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.67 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.77 (dp,  $J$   $\approx$  13.3/4.0 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.88–2.02 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.20 (td,  $J$   $\approx$  11.2/4.0 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.31 (s, 3 H, -NMe), 2.36 (t,  $J$   $\approx$  10.7 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 2.59 (ddt,  $J$   $\approx$  11.5/10.7/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.75–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99–3.07 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.06 (dt,  $J$   $\approx$  6.6/1.2 Hz, 2 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.32–3.38 (m, 4 H,  $\text{NCH}_2\text{CCCH}_2$ ), 4.09–4.18 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.15 (ddt,  $J$   $\approx$  10.1/1.8/1.2 Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.22 (dq,  $J$   $\approx$  17.0/1.8 Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.84 (ddt,  $J$   $\approx$  17.0/10.1/6.6 Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 41.7, 41.9, 45.5, 47.7, 52.4, 54.3, 59.1, 60.4, 79.9, 80.0, 118.0, 135.4, 174.0; IR (neat) 3404, 2941, 2793, 1732, 1644, 1558, 1450, 1321, 1222, 1181, 1153, 1133, 1095, 1031, 997, 922  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  279.2073, found 279.2068.

**Ethyl 1-[4-[tert-Butyl(isopropyl)amino]but-2-yn-1-yl]piperidine-3-carboxylate (31f).** GP2 was followed using **30** (391 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), isopropyl(tert-butyl)amine (0.44 mL, 2.80 mmol), and paraformaldehyde (114 mg, 3.60 mmol). Purification by column chromatography (DCM:MeOH = 9:1) afforded **31f** (596 mg, 93%) as colorless oil: TLC:  $R_f$  = 0.40 (DCM:MeOH = 9:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.13 (d,  $J$  = 6.6 Hz, 6 H,  $\text{NCH}(\text{CH}_3)_2$ ), 1.22 (s, 9 H,  $\text{N}t\text{-Bu}$ ), 1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.41 (qd,  $J$  = 12.2/4.5 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.52–1.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.75 (dp,  $J$   $\approx$  13.2/3.8 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.89–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.18 (td,  $J$  = 11.3/3.0 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.33 (t,  $J$  = 10.7 Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 2.58 (tt,  $J$   $\approx$  11.5/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.73–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99–3.07 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2$ ), 3.30 (t,  $J$  = 1.9 Hz, 2 H,  $\text{NipCH}_2\text{CCCH}_2$ ), 3.37 (hept,  $J$  = 6.6 Hz, 1 H,  $\text{NCH}(\text{CH}_3)_2$ ), 3.46–3.53 (m, 2 H,  $\text{NipCH}_2\text{CCCH}_2$ ), 4.13 (q,  $J$  = 7.1 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 22.5, 24.6, 26.6, 28.5, 31.9, 42.0, 47.0, 47.9, 52.5, 54.4, 55.7, 60.3, 77.3, 87.6, 174.0; IR (neat) 2971, 2940, 2869, 2802, 1734, 1465, 1389, 1362, 1309, 1253, 1218, 1173, 1152, 1134, 1114, 1095, 1047, 1031, 862, 794  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{35}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  323.2699, found 323.2696.

***N,N*-Diallyl-1,5,5-triphenylpent-2-yn-1-amine (29n).** GP2 was followed using **27a** (413 mg, 2.00 mmol), CuBr (43.0 mg, 0.300 mmol), diallylamine (0.35 mL, 2.80 mmol) and benzaldehyde (0.37 mL, 3.60 mmol). Purification by column chromatography (PE:EtOAc = 19:1) afforded **29n** (728 mg, 93%) as white solid: mp = 44.0 °C; TLC:  $R_f$  = 0.54 (PE:EtOAc = 19:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.62 (ddt,  $J$  = 14.1/8.2/1.0 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_2)_2$ ), 2.97 (ddt,  $J$  = 14.1/4.2/1.9 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_2)_2$ ), 3.08 (dd,  $J$  = 7.8/2.1 Hz, 2 H,  $\text{NCHCCCH}_2$ ), 4.29 (t,  $J$  = 7.8 Hz, 1 H,  $\text{NCHCCCH}_2\text{CH}$ ), 4.71 (t,  $J$  = 2.1 Hz, 1 H,  $\text{NCHCCCH}_2\text{CH}$ ), 5.00–5.07 (m, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_{\text{cis}}\text{H}_{\text{trans}})_2$ ), 5.07–5.15 (m, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_{\text{cis}}\text{H}_{\text{trans}})_2$ ), 5.71 (dddd,  $J$  = 17.1/10.1/8.2/4.2 Hz, 2 H,  $\text{N}(\text{CH}_2\text{CHCH}_2)_2$ ), 7.14–7.26 (m, 5 H, ArH), 7.27–7.34 (m, 8 H, ArH), 7.34–7.41 (m, 2 H, ArH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  25.8, 50.8, 53.1, 55.9, 77.3, 86.1, 117.0, 126.5, 127.0, 127.8, 128.0, 128.2, 128.5, 136.8, 139.6, 143.5; IR (neat) 3062, 3027, 2923, 2817, 1946, 1726, 1641, 1600, 1493, 1449, 1417, 1351, 1328, 1274, 1122, 1081, 1030, 995, 971, 918, 874, 841, 814, 782, 736, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{30}\text{N}^+$  [ $\text{M} + \text{H}$ ] $^+$  392.2378, found 392.2376.

***N*-Allyl-*N*-methyl-1,5,5-triphenylpent-2-yn-1-amine (29o).** GP2 was followed using **27a** (349 mg, 1.69 mmol), CuBr (36.4 mg, 0.254 mmol), allyl(methyl)amine (0.23 mL, 2.37 mmol) and benzaldehyde (0.31 mL, 3.04 mmol). Purification by column chromatography

(PE:EtOAc = 19:1) afforded **29o** (407 mg, 66%) as colorless resin: TLC:  $R_f$  = 0.18 (PE:EtOAc = 19:1);  $^1\text{H}$  NMR (400 MHz)  $\delta$  1.92 (s, 3 H, NMe), 2.79 (ddt,  $J$  = 13.4/7.5/1.1 Hz, 1 H,  $\text{NCH}_2\text{H}_b\text{CHCH}_2$ ), 2.88 (ddt,  $J$  = 13.4/5.5/1.6 Hz, 1 H,  $\text{NCH}_3\text{H}_b\text{CHCH}_2$ ), 3.07 (dd,  $J$  = 7.8/2.1 Hz, 2 H,  $\text{NCHCCCH}_2\text{CH}$ ), 4.29 (t,  $J$  = 7.8 Hz, 1 H,  $\text{NCHCCCH}_2\text{CH}$ ), 4.60 (t,  $J$  = 2.1 Hz, 1 H,  $\text{NCHCCCH}_2\text{CH}$ ), 5.01–5.16 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 5.78 (dddd,  $J$  = 17.4, 10.1, 7.5, 5.5 Hz, 1H,  $\text{NCH}_2\text{CHCH}_2$ ), 7.15–7.27 (m, 5 H, ArH), 7.27–7.39 (m, 10 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  25.8, 37.4, 50.7, 57.4, 59.1, 76.9, 86.6, 117.3, 126.5, 127.1, 127.9, 128.0, 128.4, 128.5, 136.4, 139.1, 143.5; IR (neat) 3061, 3027, 2977, 2913, 2876, 2845, 2814, 2788, 1947, 1802, 1642, 1600, 1493, 1449, 1349, 1324, 1272, 1195, 1155, 1127, 1081, 1019, 995, 962, 919, 874, 840, 782, 736, 698  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{28}\text{N}^+$  [ $\text{M} + \text{H}$ ] $^+$  366.2222, found 366.2219.

*rac*-[Ethyl (R)-1-[4-[3,6-dihydropyridin-1(2H)-yl]-4-phenylbut-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(R,S)-**31h**) and *rac*-[Ethyl (R)-1-[4-[3,6-dihydropyridin-1(2H)-yl]-4-phenylbut-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(R,R)-**31h**). GP2 was followed using **30** (293 mg, 1.50 mmol), CuBr (32.3 mg, 0.225 mmol), 1,2,3,6-tetrahydropyridine (0.20 mL, 2.10 mmol), and benzaldehyde (0.27 mL, 2.70 mmol). Purification by column chromatography (PE:EtOAc = 1:1) afforded **31h** as mixture of both diastereomeric racemates (341 mg, 62%) as yellow oil: TLC:  $R_f$  = 0.45 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.44 (qd,  $J$  = 11.6/4.0 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ), 1.53–1.70 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.73–1.84 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.89–1.99 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ), 2.06–2.22 (m, 2 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.27 (td,  $J$  = 11.0/3.1 Hz, 1 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.44 (t,  $J$  = 10.6 Hz, 1 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CHCH}_2$ ), 2.54–2.70 (m, 3 H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.77–2.86 (m, 1 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.01–3.15 (m, 3 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.45–3.51 (m, 2 H,  $\text{NCHPhCCCH}_2\text{N}$ ), 4.08–4.18 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.74 ( $s_{br}$ , 1 H,  $\text{NCHPhCCCH}_2\text{N}$ ), 5.66 (m, 1 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 5.72 (m, 1 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.22–7.30 (m, 1H, ArH), 7.30–7.38 (m, 2H, ArH), 7.56–7.63 (m, 2 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.5, 41.9, 46.3, 47.8, 49.0, 52.4, 54.4, 60.3, 61.2, 81.1, 82.4, 125.0, 125.6, 127.5, 128.1, 128.5, 138.4, 174.0; IR (neat) 3031, 2939, 2807, 1731, 1466, 1449, 1319, 1268, 1223, 1181, 1152, 1132, 1095, 1029, 999, 973, 950, 727, 697, 654, 626  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{31}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  367.2386, found 367.2386; stereochemistry has not been assigned.

1-(1,5,5-Triphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (**29l**). To a Schlenk flask was added CuBr (66 mg, 0.460 mmol). Then, dioxane anhydrous (12.0 mL/mmol) was added, followed by benzaldehyde (0.24 mL, 2.40 mmol), 1,2,3,6-tetrahydropyridine (0.22 mL, 2.40 mmol), **27b** (557 mg, 2.00 mmol), and  $\text{BF}_3\cdot\text{OEt}_2$  (591 mg, 2.00 mmol). The reaction mixture was stirred for 10 min at rt and at 50 °C for 25 h. Completion of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was added to a 1:1 solution of saturated potassium sodium tartrate solution and saturated sodium hydrogen carbonate solution (44.0 mL/mmol) and extracted 5 times with EtOAc. The combined organic phases were then filtrated, dried over  $\text{MgSO}_4$ , and concentrated under vacuum. The crude product was purified by column chromatography (PE:EtOAc = 9:1) to afford **29l** (203 mg, 27%) as colorless crystals: mp = 94.6 °C; TLC:  $R_f$  = 0.66 (PE:EtOAc = 9:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.95–2.14 (m, 2 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.29–2.43 (m, 2 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.75–2.92 (m, 2 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.05 (dd,  $J$  = 7.8/2.1 Hz, 2 H,  $\text{CHCH}_2\text{CC}$ ), 4.27 (t,  $J$  = 7.8 Hz, 1 H,  $\text{CHCH}_2\text{CC}$ ), 4.54 (t,  $J$  = 2.1 Hz, 1 H, NCHCC), 5.57 (m, 1 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 5.66 (m, 1 H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.15–7.26 (m, 5 H, ArH), 7.26–7.37 (m, 10 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  25.9, 26.5, 45.8, 48.6, 50.7, 61.0, 77.7, 86.3, 124.7, 125.7, 126.5, 127.2, 127.9, 128.0, 128.4, 128.5, 138.5, 143.5; IR (neat) 3417, 3060, 3028, 2910, 2811, 1949, 1600, 1493, 1449, 1028, 727, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{28}\text{H}_{28}\text{N}^+$  [ $\text{M} + \text{H}$ ] $^+$  378.2222, found 378.2222; synthesis based on the procedure of Ma et al.<sup>27,34</sup>

*N*-Allyl-*N*-(*tert*-butyl)-1,5,5-triphenylpent-2-yn-1-amine (**29m**). To a Schlenk flask was added CuBr (43.0 mg, 0.300 mmol). Toluene

anhydrous (5.00 mL/mmol) was then added, followed by benzaldehyde (0.37 mL, 3.60 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.80 mmol), **27b** (557 mg, 2.00 mmol), and  $\text{BF}_3\cdot\text{OEt}_2$  (591 mg, 2.00 mmol). The reaction mixture was stirred at rt for 27 h. The completion of the reaction was monitored by TLC. The reaction mixture was then filtrated over a short pad of silica gel and eluted with DCM. The crude product was purified by MPLC (PE, 5% EtOAc) on silica gel to afford **29m** as colorless resin (270 mg, 33%): TLC:  $R_f$  = 0.68 (PE:EtOAc = 19:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.11 (s, 9 H, *Nt*-*Bu*), 2.97–3.03 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2$ ), 3.05 (dd,  $J$  = 7.8/2.0 Hz, 2 H,  $\text{NCHCCCH}_2$ ), 4.28 (t,  $J$  = 7.8 Hz, 1 H,  $\text{CHCH}_2\text{CC}$ ), 4.57 (dq,  $J$   $\approx$  10.1/1.8 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{cis}\text{H}_{trans}$ ), 4.69 (dq,  $J$  = 17.2/1.8 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{cis}\text{H}_{trans}$ ), 4.87 ( $s_{br}$ , 1 H, NCHCC), 5.38 (ddt,  $J$  = 17.2/10.1/5.9 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2$ ), 7.10–7.25 (m, 5 H, ArH), 7.25–7.38 (m, 10 H, ArH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  26.0, 28.6, 48.5, 50.7, 53.0, 56.2, 81.4, 85.5, 112.6, 126.6, 126.6, 127.6, 128.1, 128.3, 128.6, 141.6, 142.1, 143.7; IR (neat) 3061, 3027, 2971, 2911, 1946, 1877, 1804, 1637, 1600, 1493, 1449, 1390, 1363, 1203, 910, 733, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{30}\text{H}_{34}\text{N}^+$  [ $\text{M} + \text{H}$ ] $^+$  408.2691, found 408.2695; synthesis based on the procedure of Ma et al.<sup>27,34</sup>

*rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]-4-phenylbut-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(R,S)-**31g**) and *rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]-4-phenylbut-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(R,R)-**31g**). To a Schlenk flask was added CuBr (21.5 mg, 0.150 mmol). Toluene anhydrous (5.0 mL/mmol) was then added, followed by benzaldehyde (0.18 mL, 1.80 mmol), allyl(*tert*-butyl)amine (0.21 mL, 1.40 mmol),  $\text{BF}_3\cdot\text{OEt}_2$  (296 mg, 1.00 mmol), and **30** (195 mg, 1.00 mmol). The reaction mixture was stirred at 50 °C for 20 h. The completion of the reaction was monitored by TLC. After cooling to rt, the reaction mixture was filtrated, washed with EtOAc, and concentrated under vacuum. The crude product was then purified by column chromatography (PE:EtOAc = 1:1) to afford **31g** as mixture of both diastereomeric racemates (118 mg, 30%) as yellow oil: TLC:  $R_f$  = 0.69 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.25 (s, 9 H, *Nt*-*Bu*), 1.37–1.53 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ), 1.55–1.71 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.73–1.85 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.91–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ), 2.29 (tt,  $J$  = 11.1/3.3 Hz, 1 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.40–2.51 (m, 1 H,  $\text{NCH}_{ax}\text{H}_{eq}\text{CHCH}_2$ ), 2.55–2.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$ ), 2.79–2.89 (m, 1 H,  $\text{-NCH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.05–3.14 (m, 1 H,  $\text{-NCH}_{ax}\text{H}_{eq}\text{CHCH}_2$ ), 3.26–3.33 (m, 2 H,  $\text{NCH}_2\text{CH} = \text{CH}_{trans}\text{H}_{cis}$ ), 3.41–3.54 (m, 2 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.14 (q,  $J$  = 7.1 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.63 (dq,  $J$  = 10.2/1.8 Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{trans}\text{H}_{cis}$ ), 4.79 (dq,  $J$  = 17.3/1.8 Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{trans}\text{H}_{cis}$ ), 5.08 ( $s_{br}$ , 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 5.41–5.56 (m, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 7.16–7.25 (m, 1 H, ArH), 7.25–7.33 (m, 2 H, ArH), 7.55–7.70 (m, 2 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 28.7, 42.0, 47.9, 48.8, 52.5, 53.1, 54.4, 56.3, 60.3, 82.0, 85.0, 112.9, 126.8, 127.6, 128.2, 141.3, 141.8, 174.0; IR (neat) 3061, 2973, 2941, 2802, 1947, 1732, 1637, 1600, 1491, 1467, 1449, 1415, 1391, 1365, 1322, 1255, 1217, 1203, 1181, 1152, 1133, 1096, 1068, 1046, 1030, 994, 911, 750, 731, 696  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{37}\text{N}_2\text{O}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  397.2855, found 397.2857; synthesis procedure based on a procedure published by Ma et al.,<sup>27,34</sup> and stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(R,R)-**31i**) and *rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(R,S)-**31i**). GP2 was followed applying CuBr (129 mg, 0.900 mmol, 0.3 equiv), toluene abs. (12 mL), 2-naphthaldehyde (843 mg, 5.40 mmol), allyl(*tert*-butyl)amine (0.63 mL, 4.2 mmol),  $\text{BF}_3\cdot\text{OEt}_2$  (0.66 mL, 3.0 mmol, instead of molecular sieve), and **30** (586 mg, 3.00 mmol) at 50 °C overnight. The crude product was purified by column chromatography (PE:EtOAc = 8:2) to afford **31i** as mixture of both diastereomeric racemates as pale yellow resin (278 mg, 21%): TLC:  $R_f$  = 0.21 (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.30 (s, 9 H,  $\text{NC}(\text{CH}_3)_3$ ), 1.41–1.54 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ), 1.60–1.73 (m, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.81 (dq,  $J$  = 14.8/3.6 Hz, 1 H,  $\text{NCH}_2\text{CH}_{ax}\text{H}_{eq}\text{CH}_2\text{CH}$ ), 1.92–2.05 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{ax}\text{H}_{eq}$ ),

2.29–2.41 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.47–2.58 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.60–2.71 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.84–2.95 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.16 (d<sub>br</sub>,  $J = 10.7$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.27–3.40 (m, 2 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.55 (s, 2 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.14 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.56 (dq,  $J = 10.2/1.7$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 4.77 (dq,  $J = 17.2/1.7$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.22 (s, 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 5.36–5.52 (m, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 7.40–7.49 (m, 2 H, ArH), 7.69–7.87 (m, 4 H, ArH), 8.09 (s, 1 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.4, 24.8, 26.8, 28.9, 42.1, 48.1, 48.8, 52.6/52.7, 53.4, 54.5/54.6, 56.6, 60.5, 82.4, 85.1, 113.1, 125.7, 125.9, 126.6, 127.3, 127.6, 128.2, 132.8, 133.2, 139.3, 141.4, 174.1; IR (neat)  $\bar{\nu}$  3057, 2972, 2940, 2869, 2805, 1731, 1634, 1602, 1506, 1467, 1451, 1416, 1391, 1364, 1325, 1275, 1239, 1217, 1201, 1182, 1152, 1133, 1095, 1031, 995, 910, 860, 814, 788, 735  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_2^+$  [M + H] $^+$  447.3012, found 447.3005; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-[4-[3,6-dihydropyridin-1(2H)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31j) and *rac*-[Ethyl (R)-1-[4-[3,6-dihydropyridin-1(2H)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31j). GP2 was followed applying CuBr (43 mg, 0.30 mmol), toluene abs. (8 mL), 2-naphthaldehyde (562 mg, 3.60 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol), and 30 (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE:EtOAc = 7:3) to afford 31j as mixture of both diastereomeric racemates as pale yellow resin (695 mg, 83%): TLC:  $R_f = 0.13$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.23 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.47 (qd,  $J = 11.8/3.5$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.59–1.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.76–1.83 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.96 (dq,  $J = 12.8/4.1$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.08–2.22 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CHCHCH}_2$ ), 2.31 (td,  $J = 11.0/3.1$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.49 (t,  $J = 10.6$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1 or dia 2), 2.50 (t,  $J = 10.6$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1 or dia 2), 2.58–2.73 (m, 3 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CHCHCH}_2$ ), 2.81–2.89 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.03–3.20 (m, 3 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CHCHCH}_2$ ), 3.48–3.57 (m, 2 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.10–4.17 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.88 (t,  $J = 1.3$  Hz, 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 5.60–5.79 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CHCHCH}_2$ ), 7.41–7.51 (m, 2 H, ArH), 7.72 (dd,  $J = 8.5/1.7$  Hz, 1 H, ArH), 7.77–7.90 (m, 3 H, ArH), 8.06 (s, 1 H, ArH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 26.6, 42.0, 46.3/46.4, 47.8, 49.3/49.3, 52.5, 54.5/54.5, 60.3, 61.4, 81.2/81.2, 82.8/82.8, 125.1, 125.7, 125.9, 126.0, 126.6, 127.3, 127.6, 127.8, 128.1, 133.0, 133.1, 136.2, 174.0; IR (neat)  $\bar{\nu}$  3029, 2937, 2805, 1729, 1601, 1507, 1465, 1449, 1366, 1349, 1316, 1223, 1181, 1152, 1130, 1095, 1028, 999, 975, 955, 902, 860, 824, 795, 781, 761, 736  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_2^+$  [M + H] $^+$  417.2542, found 417.2538; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-[4-([1,1'-biphenyl]-2-yl)-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31k) and *rac*-[Ethyl (R)-1-[4-([1,1'-biphenyl]-2-yl)-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31k). GP2 was followed applying CuBr (86 mg, 0.60 mmol), dioxane abs. (8.0 mL), [1,1'-biphenyl]-2-carbaldehyde (0.58 mL, 3.6 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.8 mmol), and 30 (391 mg, 2.00 mmol). After stirring for 1 h at rt, the mixture was heated to 50 °C,  $\text{BF}_3 \cdot \text{OEt}_2$  (0.51 mL, 2.00 mmol) was added, and the reaction mixture stirred at 50 °C overnight. The crude product was purified by flash column chromatography (PE:EtOAc = 7:3) to afford 31k as mixture of both diastereomeric racemates as pale yellow resin (200 mg, 21%): TLC:  $R_f = 0.32$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.74 (s, 9 H, *t*-Bu), 1.25 (t,  $J = 7.2$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 and dia 2), 1.44 (qd,  $J = 11.9/4.3$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.69 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.73–1.84 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.90–2.02 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.25 (ddt,  $J = 11.2/7.9/4.1$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.42 (t,  $J = 10.7$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.55–2.66 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.82 (d<sub>br</sub>,  $J = 11.4$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.01–3.21 (m, 2 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.33

(ddt,  $J = 17.2/5.5/1.8$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.37–3.49 (m, 2 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.14 (q,  $J = 7.2$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.51 (dq,  $J = 10.1/1.7$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 4.60 (dq,  $J = 17.3/1.7$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.06–5.18 (m, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 5.21 (t,  $J = 2.2$  Hz, 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 7.07–7.13 (m, 1 H, ArH), 7.22–7.44 (m, 7 H, ArH), 7.81 (dt,  $J = 7.3/2.1$  Hz, 1 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 26.6, 27.4, 42.0, 47.1, 48.0, 50.5, 52.5/52.6, 54.5, 56.2, 60.3, 81.8, 86.0, 112.1, 126.7, 126.8, 126.9, 127.7, 129.3, 129.4, 129.7, 130.1, 138.4, 140.8, 141.9, 142.9, 174.0; IR (neat)  $\bar{\nu}$  2956, 1732, 1475, 1439, 1390, 1364, 1309, 1281, 1252, 1214, 1199, 1182, 1152, 1133, 1095, 1071, 1031, 912, 753, 701  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{41}\text{N}_2\text{O}_2^+$  [M + H] $^+$  473.3168, found 473.3166; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-[4-([1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31l) and *rac*-[Ethyl (R)-1-[4-([1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31l). GP2 was followed applying CuBr (21.5 mg, 0.15 mmol), toluene abs. (5.00 mL), [1,1'-biphenyl]-2-carbaldehyde (0.29 mL, 1.8 mmol), 1,2,3,4-tetrahydropyridine (0.13 mL, 1.4 mmol), and 30 (195 mg, 1.00 mmol). The crude product was purified by column chromatography (PE:EtOAc = 8:2) to afford 31l as mixture of both diastereomeric racemates as colorless resin (373 mg, 84%): TLC:  $R_f = 0.23$  (PE:EtOAc = 8:2);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (t,  $J = 7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 and dia 2), 1.42 (qd,  $J = 11.3/3.5$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.66 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.75 (dp,  $J = 13.1/3.8$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.87–1.97 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.96–2.17 (m, 2 H,  $\text{NCH}_2\text{CH} = \text{CHCH}_2\text{CH}_2$ ), 2.22 (td,  $J = 11.0/3.0$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.34–2.49 (m, 2 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CH} = \text{CHCH}_2\text{CH}_2$ ), 2.52–2.68 (m, 2 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CH} = \text{CHCH}_2\text{CH}_2$ ), 2.76 (d<sub>br</sub>,  $J = 11.3$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.85–3.08 (m, 3 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CH} = \text{CHCH}_2\text{CH}_2$ ), 3.34–3.48 (m, 2 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.12 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 and dia 2), 4.52 (t,  $J = 1.9$  Hz, 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 5.55–5.72 (m, 2 H,  $\text{NCH}_2\text{CH} = \text{CHCH}_2\text{CH}_2$ ), 7.22–7.29 (m, 1 H, ArH), 7.29–7.42 (m, 5 H, ArH), 7.46–7.56 (m, 2 H, ArH), 7.72–7.81 (m, 1 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.5, 26.5/26.5, 41.9, 46.4, 47.7, 48.2, 52.4/52.4, 54.3, 58.1, 60.3, 81.7/81.7, 82.3/82.3, 124.8, 125.6, 126.8, 127.0, 127.4, 127.7, 129.2, 129.7, 130.3, 136.5, 141.1, 142.6, 174.0; IR (neat)  $\bar{\nu}$  3057, 3030, 2938, 2909, 2864, 2804, 1731, 1477, 1466, 1449, 1367, 1347, 1315, 1279, 1252, 1222, 1181, 1152, 1132, 1095, 1047, 1029, 1009, 998, 973, 948, 774, 750, 702, 654, 628, 617  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{29}\text{H}_{35}\text{N}_2\text{O}_2^+$  [M + H] $^+$  443.2699, found 443.2702; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl](R)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31m) and *rac*-[Ethyl (R)-1-[4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl](S)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31m). GP2 was followed applying CuBr (86 mg, 0.60 mmol), 0.30 equiv, dioxane abs. (8 mL), butyraldehyde (0.33 mL, 3.6 mmol), allyl(*tert*-butyl)amine (0.42 mL, 2.8 mmol), and 30 (391 mg, 2.00 mmol) at rt for 2 h. Then  $\text{BF}_3 \cdot \text{OEt}_2$  (0.44 mL, 2.0 mmol) was added, and the reaction mixture was heated to 50 °C for 3 h and was stirred at rt overnight. The crude product was purified by column chromatography (PE:EtOAc = 8:2) to afford 31m as mixture of both diastereomeric racemates as yellow oil (235 mg, 32%): TLC:  $R_f = 0.31$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.88 (t,  $J = 7.1$  Hz, 3 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.11 (s, 9 H,  $\text{N}(\text{CH}_3)_3$ ), 1.25 (t,  $J = 7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.35–1.52 (m, 5 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCHCH}_2\text{CH}_2\text{CH}_3$ ), 1.55–1.67 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.72–1.81 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.90–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.19 (tt,  $J = 11.2/2.9$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.34 (t,  $J = 10.5$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.54–2.64 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.77 (dt<sub>br</sub>,  $J = 11.2/3.5$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99–3.07 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.22–3.40 (m, 4 H,  $\text{NCHCCCH}_2\text{N}$  and  $\text{NCH}_2\text{CH} = \text{CH}_2$ ), 3.72 (t,  $J = 6.1$  Hz, 1 H,  $\text{NCHCCCH}_2\text{N}$ ), 4.14 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.92 (dd,  $J = 10.2/2.1$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.13 (dq,  $J = 16.4/2.1$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.87 (ddt,  $J = 16.4/10.2/5.3$  Hz, 1 H,  $\text{NCH}_2\text{CH} = \text{CH}_2$ );  $^{13}\text{C}$  NMR

(101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9, 14.4, 19.9, 24.7, 26.7, 28.3, 39.6, 42.1, 47.9, 48.1, 49.8, 52.5/52.5, 54.4/54.4, 56.0, 60.5, 78.6, 88.2, 112.9, 142.6, 174.2; IR (neat)  $\tilde{\nu}$  2958, 2871, 2804, 1734, 1643, 1467, 1453, 1391, 1365, 1309, 1242, 1218, 1202, 1182, 1152, 1133, 1094, 1031, 995, 910  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{39}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}]^+$  363.3012, found 363.3005; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]hept-2-yn-1-yl}-(R)-piperidine-3-carboxylate] (*rac*-(R,R)-31n) and *rac*-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]hept-2-yn-1-yl}-(S)-piperidine-3-carboxylate] (*rac*-(R,S)-31n). GP2 was followed using CuBr (32.3 mg, mmol, 0.225 equiv), toluene abs. (6 mL), butyraldehyde (0.25 mL, 2.7 mmol), 1,2,3,4-tetrahydropyridine (0.20 mL, 2.1 mmol), and **30** (293 mg, 1.50 mmol). The crude product was purified by column chromatography (PE:EtOAc = 8:2) to afford **31n** as mixture of both diastereomeric racemates as yellow oil (385 mg, 77%): TLC:  $R_f$  = 0.17 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94 (t,  $J$  = 7.3 Hz, 3 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.25 (t,  $J$  = 7.0 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.35–1.72 (m, 6 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.72–1.82 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.89–2.00 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.09–2.30 (m, 3 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.35 (t,  $J$  = 10.7 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.48–2.65 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_3$ ), 2.69–2.86 (m, 2 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.94–3.11 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2\text{CH}_3$ ), 3.11–3.24 (m, 1 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ ), 3.30–3.41 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{N}$ ), 3.45 (t,  $J$  = 7.5 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{N}$ ), 4.13 (q,  $J$  = 7.0 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.62–5.82 (m, 2 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8, 14.2, 20.0, 24.6, 26.5, 26.6, 35.7, 41.9, 46.6, 47.7, 48.5, 52.4/52.4, 54.3/54.3, 57.2, 60.3, 79.9, 83.0, 125.0, 125.5, 174.0; IR (neat)  $\tilde{\nu}$  3031, 2956, 2937, 2870, 2804, 1732, 1465, 1449, 1366, 1321, 1222, 1180, 1151, 1133, 1093, 1046, 1030  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{33}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}]^+$  333.2542, found 333.2534; stereochemistry has not been assigned.

*rac*-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-5-methylhex-2-yn-1-yl}-(R)-piperidine-3-carboxylate] (*rac*-(R,R)-31o) and *rac*-[Ethyl (R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-5-methylhex-2-yn-1-yl}-(S)-piperidine-3-carboxylate] (*rac*-(R,S)-31o). GP2 was followed applying CuBr (43 mg, 0.30 mmol), toluene abs. (8 mL), isobutyraldehyde (0.33 mL, 3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol), and **30** (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE:EtOAc = 7:3) to afford **31o** as mixture of both diastereomeric racemates as colorless resin (651 mg, 98%): TLC:  $R_f$  = 0.26 (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.98 (d,  $J$  = 6.6 Hz, 3 H,  $\text{NCH}(\text{CH}_3)_2$ ), 1.06 (d,  $J$  = 6.6 Hz, 3 H,  $\text{NCH}(\text{CH}_3)_2$ ), 1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (dq,  $J$  = 12.0/3.5 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.55–1.65 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.73–1.80 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.86 (dp,  $J$  = 9.8/6.6 Hz, 1 H,  $\text{NCH}(\text{CH}_3)_2$ ), 1.90–1.98 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_3$ ), 2.13–2.25 (m, 3 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.37 (t,  $J$  = 10.7 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.45 (dt,  $J$  = 11.3/5.7 Hz, 1 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ ), 2.59 (tt,  $J$  = 10.7/3.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$ ), 2.72 (dt,  $J$  = 11.3/5.7 Hz, 1 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ ), 2.75–2.83 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.94 (dt,  $J$  = 9.8/1.9 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$ ), 2.96–3.08 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ ), 3.09–3.17 (m, 1 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ ), 3.34–3.43 (m, 2 H,  $\text{NCH}_2\text{CH}_2\text{N}$ ), 4.13 (qd,  $J$  = 7.1/1.0 Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.62–5.78 (m, 2 H,  $\text{NCH}_2\text{CH}=\text{CHCH}_2\text{CH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.3, 20.0, 20.8, 24.7, 26.7, 26.7, 30.6, 42.1, 46.4, 47.8, 49.3, 52.5, 54.4/54.4, 60.5, 64.6, 80.2, 82.8, 125.1, 126.0, 174.2; IR (neat)  $\tilde{\nu}$  3032, 2955, 2868, 2806, 1732, 1637, 1466, 1450, 1381, 1366, 1321, 1260, 1222, 1181, 1152, 1133, 1095, 1031, 1001, 976, 956  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{33}\text{N}_2\text{O}_2^+ [\text{M} + \text{H}]^+$  333.2542, found 333.2534; stereochemistry has not been assigned.

**Synthesis of Allenes.** *General Procedure 3.* To a Schlenk tube was added  $\text{CdI}_2$  (0.8 equiv) under argon atm. The  $\text{CdI}_2$  was then heated with a heat gun under vacuum until the pale yellow solid turned to darker yellow. Chlorobenzene anhydrous (8.0 mL/mmol) was added, followed by the propargylic amine (1.0 equiv). The reaction

mixture was stirred at 100/130  $^\circ\text{C}$  until all starting material was consumed (detection via TLC). After cooling to rt, the crude product was purified by column chromatography to afford the corresponding allene.

*Penta-3,4-diene-1,1-diyldibenzene* (**32**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **29e** (166 mg, 0.500 mmol) at 130  $^\circ\text{C}$  for 2.00 h. The crude product was purified by column chromatography (PE:EtOAc = 9:1) to afford allene **32** (97.0 mg, 88%) as colorless resin: TLC:  $R_f$  = 0.83 (PE:EtOAc = 9:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.76 (ddt,  $J$  = 7.9/7.1/2.9 Hz, 2 H,  $\text{CHCH}_2\text{CHCCH}_2$ ), 4.04 (t,  $J$  = 7.9 Hz, 1 H,  $\text{CHCH}_2\text{CHCCH}_2$ ), 4.56 (dt,  $J$  = 6.8/2.9 Hz, 2 H,  $\text{CHCH}_2\text{CHCCH}_2$ ), 5.00 (p,  $J$  = 6.8 Hz, 1 H,  $\text{CHCH}_2\text{CHCCH}_2$ ), 7.12–7.19 (m, 2 H, ArH), 7.19–7.30 (m, 8 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  34.6, 51.2, 74.7, 88.2, 126.2, 128.0, 128.4, 144.2, 209.1; IR (neat) 3085, 3061, 3026, 2915, 1954, 1599, 1494, 1450, 1082, 1030, 845, 784, 751, 738, 699  $\text{cm}^{-1}$ ; HRMS (DEP/EI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{16}$  220.1252, found 220.1250.

*Undeca-1,2-diene* (**43**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **39** (132 mg, 0.500 mmol) at 130  $^\circ\text{C}$  for 3 h. The crude product was purified by column chromatography (PE, 5% EtOAc) to afford **43** (71.4 mg, 94%) as colorless oil: TLC:  $R_f$  = 0.73 (PE, 5% EtOAc); the analytical and spectroscopic data are consistent with those reported in literature.<sup>43</sup>

*6-Chlorohexa-1,2-diene* (**44**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **40** (114 mg, 0.500 mmol) at 130  $^\circ\text{C}$  for 3 h. The crude product was purified by column chromatography (PE) to afford **44** (48.2 mg, 83%) as colorless oil: TLC:  $R_f$  = 0.53 (PE, 4% EtOAc); analytical and spectroscopic data are consistent with those reported in literature.<sup>44</sup>

*Hepta-5,6-dienitrile* (**45**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **41** (109 mg, 0.500 mmol) at 130  $^\circ\text{C}$  for 3 h. The crude product was purified by column chromatography (DCM) to afford **45** (52 mg, 97%) as colorless oil: TLC:  $R_f$  = 0.55 (DCM); analytical and spectroscopic data are consistent with those reported in literature.<sup>45</sup>

*[(Buta-2,3-dien-1-yloxy)methyl]benzene* (**46**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **42** (136 mg, 0.500 mmol) at 130  $^\circ\text{C}$  for 2.75 h. The crude product was purified by column chromatography (DCM) to afford **46** (76 mg, 95%) as colorless oil: TLC:  $R_f$  = 0.63 (DCM); analytical and spectroscopic data are consistent with those previously reported in literature.<sup>45</sup>

*Penta-3,4-diene-1,1,5-triyltribenzene* (**47**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **29m** (204 mg, 0.500 mmol) at 100  $^\circ\text{C}$  for 4.25 h. The crude reaction mixture was purified by column chromatography (PE:DCM = 1:1) to afford allene **47** (113 mg, 76%) as colorless resin: TLC:  $R_f$  = 0.65 (PE, 5% EtOAc);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.83–2.97 (m, 2 H,  $\text{CHCH}_2\text{CHCCH}$ ), 4.12 (t,  $J$  = 7.8 Hz, 1 H,  $\text{CHCH}_2\text{CHCCH}$ ), 5.49 (q,  $J$  = 6.7 Hz, 1 H,  $\text{CHCH}_2\text{CHCCH}$ ), 6.03 (dt,  $J$  = 6.7/2.8 Hz, 1 H,  $\text{CHCH}_2\text{CHCCH}$ ), 6.91–7.03 (m, 2 H, ArH), 7.10–7.37 (m, 13 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  35.3, 51.2, 93.3, 94.75, 126.24, 126.28, 126.6, 126.7, 127.9, 128.1, 128.4, 128.5, 128.5, 134.5, 144.2, 205.8; IR (neat) 3083, 3060, 3027, 2908, 1949, 1598, 1494, 1450, 1265, 1176, 1072, 1028, 912, 875, 790, 772, 741, 699, 629  $\text{cm}^{-1}$ ; HRMS (DEP/EI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{20}$  296.1565, found 296.1558.

*Ethyl 1-(Buta-2,3-dien-1-yl)piperidine-3-carboxylate* (**24**). To a Schlenk tube was added  $\text{ZnI}_2$  (255 mg, 0.799 mmol). The  $\text{ZnI}_2$  was then heated with a heat gun under vacuum until the pale yellow solid turned to darker yellow. Chlorobenzene anhydrous (4.0 mL) was added, followed by **31a** (160 mg, 0.499 mmol). The reaction mixture was stirred at 100  $^\circ\text{C}$  for 4.00 h. After cooling to rt, the reaction mixture was directly purified by column chromatography (PE:EtOAc = 1:1) to afford allene **24** (52.6 mg, 50%) as pale yellow oil: TLC:  $R_f$  = 0.39 (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J$  = 7.1 Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.43 (qd,  $J$  = 11.9/4.1 Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.52–1.65 (m, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.74 (dp,  $J$  = 13.4/3.6 Hz, 1 H,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.91–1.99 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ), 2.04 (td,  $J$  = 11.2/2.9 Hz, 1 H,

$\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.19 (t,  $J = 10.9$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.56 (tt,  $J = 10.9/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.82 (dt,  $J = 11.2/4.1$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99–3.06 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.06 (dtd,  $J = 7.2/2.5/1.3$  Hz, 2 H,  $\text{NCH}_2\text{CHCCH}_2$ ), 4.13 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.71 (dt,  $J = 6.6/2.5$  Hz, 2 H,  $\text{NCH}_2\text{CHCCH}_2$ ), 5.16 (p,  $J \approx 7.0$  Hz, 1 H,  $\text{NCH}_2\text{CHCCH}_2$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2, 24.6, 27.0, 41.9, 53.2, 54.9, 57.7, 60.3, 74.8, 86.5, 174.2, 209.4; IR (neat) 3345, 2940, 2803, 1956, 1731, 1630, 1467, 1452, 1367, 1309, 1277, 1253, 1218, 1180, 1152, 1134, 1094, 1030, 844, 793  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{20}\text{NO}_2^+$  [M + H] $^+$  210.1494, found 210.1488.

*rac*-[Ethyl ( $R_{\text{p}}$ )-1-(4-phenylbuta-2,3-dien-1-yl)(*S*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}S$ )-**53a**) and *rac*-[Ethyl ( $R_{\text{p}}$ )-1-(4-phenylbuta-2,3-dien-1-yl)(*R*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}R$ )-**53a**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene anhydrous (4.0 mL), and **31g** (198 mg, 0.499 mmol) at 100 °C for 3.75 h. The crude reaction mixture was purified by column chromatography (PE:EtOAc = 1:1) to afford allene **53a** as mixture of both diastereomeric racemates (117 mg, 82%) as pale yellow oil: TLC:  $R_f = 0.44$  (PE:EtOAc = 1:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.26 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.39–1.52 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.53–1.68 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.71–1.82 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.92–2.01 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.07–2.17 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.27 (t,  $J = 10.3$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 2.29 (t,  $J = 10.3$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.53–2.65 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.82–2.92 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.04–3.10 (m, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 3.10–3.16 (m, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 3.16–3.26 (m, 2 H,  $\text{NCH}_2\text{CHCCH}$ ), 4.09–4.18 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.59 (q,  $J = 7.0$  Hz, 0.5 H,  $\text{NCH}_2\text{CHCCH}$ , dia 1 or dia 2), 5.61 (q,  $J = 7.0$  Hz, 0.5 H,  $\text{NCH}_2\text{CHCCH}$ , dia 1 or dia 2), 6.14–6.21 (m, 1 H,  $\text{NCH}_2\text{CHCCH}$ ), 7.15–7.24 (m, 1 H, ArH), 7.25–7.37 (m, 4 H, ArH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2/14.3, 24.6/24.7, 26.8/26.9, 41.9/42.0, 53.2/53.2, 54.9/55.0, 57.8, 60.3, 91.3/91.4, 94.6/94.7, 126.8, 126.9, 128.6, 134.3, 174.1/174.1, 206.1/206.1; IR (neat) 3406, 2940, 2798, 1949, 1730, 1597, 1495, 1459, 1366, 1311, 1218, 1181, 1152, 1134, 1094, 1029, 911, 875, 774, 719, 691  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{24}\text{NO}_2^+$  [M + H] $^+$  286.1807, found 286.1801; stereochemistry has not been assigned.

*rac*-[Ethyl ( $R_{\text{p}}$ )-1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl](*R*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}R$ )-**53b**) and *rac*-[Ethyl ( $R_{\text{p}}$ )-1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl](*S*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}S$ )-**53b**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL), and **31i** (223 mg, 0.500 mmol) at 100 °C for 2.75 h, and the crude product was purified by column chromatography (PE:EtOAc = 7:3) to afford **53b** as mixture of both diastereomeric racemates (128 mg, 76%) as pale yellow resin: TLC:  $R_f = 0.16$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.13 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 2), 1.15 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1), 1.31–1.43 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.43–1.57 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.60–1.72 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.83 (dt,  $J = 12.9/4.3$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.01–2.13 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.21 (t,  $J = 10.7$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 2.24 (t,  $J = 10.7$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.41–2.54 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.68–2.83 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.91–2.99 (m, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.99–3.07 (m, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 3.12 (dd,  $J = 7.2/2.4$  Hz, 2 H,  $\text{NCH}_2\text{CHCCH}$ ), 4.00 (qd,  $J = 7.1/0.6$  Hz, 1 H,  $\text{OCH}_2\text{CH}_3$ , dia 2), 4.03 (q,  $J = 7.1$  Hz, 1 H,  $\text{OCH}_2\text{CH}_3$ , dia 1), 5.59 (q,  $J = 6.8$  Hz, 1 H,  $\text{NCH}_2\text{CHCCH}$ ), 6.28 (dt,  $J = 6.3/2.4$  Hz, 1 H,  $\text{NCH}_2\text{CHCCH}$ ), 7.30–7.46 (m, 3 H, ArH), 7.58 (s, 1 H, ArH), 7.65–7.79 (m, 3 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  14.6/14.6, 25.3, 27.4, 42.6/42.6, 53.8/53.8, 55.6, 58.3/58.3, 60.7/60.8, 92.6/92.6, 95.3/95.3, 125.2, 126.0, 126.2, 126.8, 128.2, 128.2, 128.7, 132.7, 133.2, 134.3, 174.5, 207.0/207.0; IR (neat)  $\tilde{\nu}$  3054, 2940, 2796, 1946, 1730, 1628, 1598, 1558, 1540, 1508, 1466, 1450, 1366, 1351, 1308, 1271, 1216, 1180, 1152, 1134, 1094, 1030, 949, 893, 857, 819, 752, 732  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{26}\text{NO}_2^+$  [M

+ H] $^+$  336.1964, found 336.1958; stereochemistry has not been assigned.

*rac*-[Ethyl ( $R_{\text{p}}$ )-1-[4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl](*R*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}R$ )-**53c**) and *rac*-[Ethyl ( $R_{\text{p}}$ )-1-[4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl](*S*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}S$ )-**53c**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene abs. (4.00 mL), and **31i** (221 mg, 0.500 mmol) at 100 °C for 1.75 h, and the crude product purified by column chromatography (PE:EtOAc = 7:3) to afford **53c** as mixture of both diastereomeric racemates (156 mg, 86%) as pale yellow resin: TLC:  $R_f = 0.39$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.23 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.25 (t,  $J = 7.1$  Hz, 1.5 H,  $\text{OCH}_2\text{CH}_3$ , dia 1 or dia 2), 1.44 (qd,  $J = 11.8/3.8$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.52–1.65 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.70–1.81 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.87–2.02 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.02–2.14 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.25 (t,  $J = 10.7$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.52–2.63 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.79–2.89 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.08–3.01 (m, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1 or dia 2), 3.08–3.22 (m, 2.5 H,  $\text{NCH}_2\text{CHCCHPh}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1 or dia 2), 4.12 (q,  $J = 7.1$  Hz, 1 H,  $\text{OCH}_2\text{CH}_3$ , dia 1), 4.14 (q,  $J = 7.1$  Hz, 1 H,  $\text{OCH}_2\text{CH}_3$ , dia 2), 5.49–5.58 (m, 1 H,  $\text{NCH}_2\text{CHCCH}$ ), 6.19–6.26 (m, 1 H,  $\text{NCH}_2\text{CHCCH}$ ), 7.21–7.46 (m, 8 H, ArH), 7.50–7.56 (m, 1 H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  14.2/14.2, 24.6/24.6, 26.9/26.9, 42.0/42.0, 53.1/53.2, 55.0/55.0, 57.8/57.8, 60.3, 91.0/91.0, 92.8/92.8, 126.7, 127.1, 127.4/127.4, 127.5, 128.2, 129.7, 130.2, 131.7, 140.3/140.3, 140.8/140.8, 174.1/174.1, 206.5/206.6; IR (neat)  $\tilde{\nu}$  3428, 3057, 3024, 2939, 2855, 2796, 1947, 1730, 1596, 1480, 1466, 1450, 1435, 1366, 1342, 1309, 1217, 1181, 1151, 1133, 1095, 1047, 1030, 1008, 881, 770, 746, 702  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{28}\text{NO}_2^+$  [M + H] $^+$  362.2120, found 362.2118; stereochemistry has not been assigned.

*rac*-[Ethyl ( $R_{\text{p}}$ )-1-(hepta-2,3-dien-1-yl)(*R*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}R$ )-**53d**) and *rac*-[Ethyl ( $R_{\text{p}}$ )-1-(hepta-2,3-dien-1-yl)(*S*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}S$ )-**53d**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL), and **31n** (166 mg, 0.500 mmol) at 100 °C for 1.5 h, and the crude product was purified by column chromatography (PE:EtOAc = 7:3) to afford **53d** as mixture of both diastereomeric racemates (113 mg, 90%) as colorless oil: TLC:  $R_f = 0.25$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  0.84 (t,  $J = 7.4$  Hz, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ), 1.15 (t,  $J = 7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.28–1.39 (m, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$  and  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.45 (dddd,  $J = 13.0/11.6/10.7/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.58–1.66 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.77–1.84 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.86–1.98 (m, 3 H,  $\text{CH}_2\text{CH}_2\text{CH}_3$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.05 (t,  $J = 10.6$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 2.09 (t,  $J = 10.6$  Hz, 0.5 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.42 (dddd,  $J = 11.0/10.1/3.9/1.0$  Hz, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.63–2.72 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.84–2.96 (m, 3 H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 4.01 (qd,  $J = 7.1/0.8$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.92–5.10 (m, 2 H,  $\text{NCH}_2\text{CHCCH}$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  14.0, 14.6, 22.9/23.0, 25.2/25.2, 27.5/27.5, 31.4/31.4, 42.6/42.6, 53.7/53.8, 55.5/55.6, 58.9/59.0, 60.7, 88.1/88.1, 91.2/91.2, 174.6/174.6, 205.6/205.7; IR (neat)  $\tilde{\nu}$  2957, 2935, 2871, 2797, 1962, 1733, 1466, 1454, 1367, 1335, 1309, 1274, 1218, 1181, 1152, 1134, 1095, 1047, 1031, 995, 960, 877, 863, 795  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{26}\text{NO}_2^+$  [M + H] $^+$  252.1964, found 252.1957; stereochemistry has not been assigned.

*rac*-[Ethyl ( $R_{\text{p}}$ )-1-(5-methylhexa-2,3-dien-1-yl)(*R*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}R$ )-**53e**) and *rac*-[Ethyl ( $R_{\text{p}}$ )-1-(5-methylhexa-2,3-dien-1-yl)(*S*)-piperidine-3-carboxylate] (**rac**-( $R_{\text{p}}S$ )-**53e**). GP3 was followed applying  $\text{CdI}_2$  (146 mg, 0.399 mmol), chlorobenzene abs. (4 mL), and **31o** (166 mg, 0.500 mmol) at 100 °C for 1.5 h. The crude product was purified by column chromatography (PE:EtOAc = 7:3) to afford **53e** as mixture of both diastereomeric racemates (105 mg, 84%) as colorless oil: TLC:  $R_f = 0.24$  (PE:EtOAc = 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  1.01 (dd,  $J = 6.8/0.7$  Hz, 6 H,  $\text{CH}(\text{CH}_3)_2$ ), 1.22 (t,  $J = 7.1$  Hz, 1.8 H,  $\text{OCH}_2\text{CH}_3$ , dia 1), 1.23 (t,  $J = 7.1$  Hz, 1.2 H,  $\text{OCH}_2\text{CH}_3$ , dia 2), 1.34–1.47 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.47–1.59 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.66–1.75 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.84–1.95 (m, 1 H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),



2.03 (td,  $J = 11.1/3.0$  Hz, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.12 (t,  $J = 10.7$  Hz, 0.6 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 2.19 (t,  $J = 10.7$  Hz, 0.4 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.22–2.37 (m, 1 H,  $\text{NCH}(\text{CH}_3)_2$ ), 2.45–2.55 (m, 1 H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.71–2.81 (m, 1 H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.90–3.09 (m, 3 H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 4.09 (q,  $J = 7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.06–5.20 (m, 2 H,  $\text{NCH}_2\text{CHCCH}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  14.6, 22.9, 25.2/25.2, 27.5/27.5, 28.5/28.6, 42.5/42.6, 53.9, 55.6/55.7, 59.1/59.2, 60.7, 89.6/89.6, 98.9/99.0, 174.6/174.6, 203.9/204.0; IR (neat)  $\bar{\nu}$  2959, 2868, 2796, 1960, 1733, 1620, 1466, 1453, 1366, 1344, 1303, 1217, 1181, 1152, 1134, 1095, 1031, 995, 874  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{26}\text{NO}_2^+$  [ $\text{M} + \text{H}$ ] $^+$  252.1964, found 252.1957; stereochemistry has not been assigned.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00630.

Overview of the procedures applied for the propargylic amine synthesis, additional data for the influence of the catalyst loading on the allene formation, amine reactivity study with nipecotic acid derived propargylic amines,  $^1\text{H}$  NMR experiment to investigate  $\text{ZnI}_2$  coordination to **29g**, and copies of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ DEDICATION

Dedicated to Prof. Dr. Herbert Mayr with warmest wishes on the occasion of his 70th birthday.

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Supporting Information

# **Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes**

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## 1. General Procedures for the Propargylic Amine Synthesis

For the preparation of propargylic amines **29a-o**, **31a-o** and **39-42** different protocols, depending on the nature of the amine, the aldehyde and the presence of an existing trimethylsilyl protection group of the terminal alkyne, were applied (Scheme 6 and Table S1). Utilizing substoichiometric amounts of CuBr in the presence of molecular sieve in toluene at room temperature afforded the highest yields, especially for the reaction of 4,4-diphenylbut-1-yne (**27a**) with paraformaldehyde (**7**) or benzaldehyde (**28**) and even with sterically demanding amines, resulting in **29a-o** as well as for the synthesis of the propargylic amines **31a-o** derived from ethyl 1-(prop-2-yn-1-yl)piperidine-3-carboxylate (**30**) and propargylic amines **39-42**. For sterically less hindered amines instead of **27a**, TMS-protected alkyne **27b** could be employed when the reaction was performed in the presence of BF<sub>3</sub>·OEt<sub>2</sub> in addition to CuCl. This allows to save the deprotection step for the removal of the TMS group from 4,4-diphenyl(but-1-yn-1-yl)trimethylsilane (**27b**) which is a remnant from the synthesis of **27a** (Table S1). The removal of the TMS group from **27b** might be attributed to an interaction of

**27b** with CuCl<sup>1,2</sup> as a complex of the latter with BF<sub>3</sub> resulting in a direct transfer of the alkynyl residue to Cu<sup>(I)</sup> or might be mediated by fluoride originating from BF<sub>3</sub>·OEt<sub>2</sub>.<sup>3,4</sup>

KA<sup>2</sup> reactions (ketone-alkyne-amine coupling) have been attempted as well with ketones like cyclohexanone, cyclopentanone and benzylacetone in combination with 1-decyne and allyl(*tert*-butyl)amine, and 1-decyne and THP. Unfortunately, when applying the conditions of GP2 none of the desired propargylic amines could be obtained, which is most likely to be attributed to the lower reactivity of ketones as compared to aldehydes (Table S1), as for these KA<sup>2</sup> reactions obviously harsher reaction conditions, i.e. higher temperature, were required. Different literature procedures<sup>5,6</sup> that have been used for reactions with ketones have been applied, but none of them provided the desired propargylic amines in sufficient yield (merely 9-11%).

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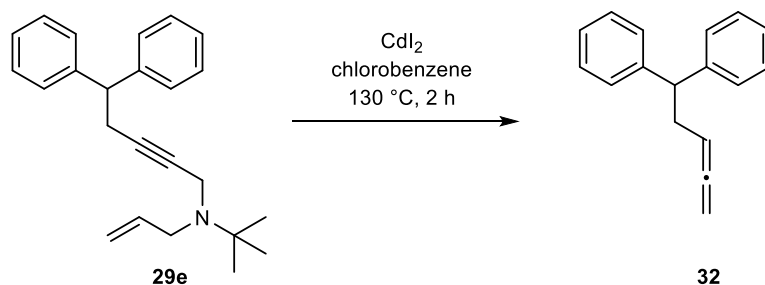
Table S1. Overview of synthesis protocols for propargylic amines **29a-o**, **31a-h** and **39-42**

entry	propargylic amine	alkyne	amine	aldehyde	yield [%]
1 <sup>a</sup>	<b>29a</b>	<b>27b</b>	morpholine	(CH <sub>2</sub> O) <sub>n</sub>	74
2 <sup>a</sup>	<b>29b</b>	<b>27b</b>	piperidine	(CH <sub>2</sub> O) <sub>n</sub>	91
3 <sup>a</sup>	<b>29c</b>	<b>27b</b>	THP	(CH <sub>2</sub> O) <sub>n</sub>	73
4 <sup>a</sup>	<b>29e</b>	<b>27b</b>	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	54
5 <sup>a</sup>	<b>29g</b>	<b>27b</b>	diallylamine	(CH <sub>2</sub> O) <sub>n</sub>	75
6 <sup>a</sup>	<b>29h</b>	<b>27b</b>	allyl(methyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	86
7 <sup>a</sup>	<b>29k</b>	<b>27b</b>	diisopropylamine	(CH <sub>2</sub> O) <sub>n</sub>	61
8 <sup>b</sup>	<b>29d</b>	<b>27a</b>	ethyl nipecotate	(CH <sub>2</sub> O) <sub>n</sub>	89
9 <sup>b</sup>	<b>29e</b>	<b>27a</b>	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	91
10 <sup>b</sup>	<b>29f</b>	<b>27a</b>	allyl(isopropyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	51
11 <sup>b</sup>	<b>29i</b>	<b>27a</b>	isopropyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	76
12 <sup>b</sup>	<b>29j</b>	<b>27a</b>	methyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	96
13 <sup>b</sup>	<b>29k</b>	<b>27a</b>	diisopropylamine	(CH <sub>2</sub> O) <sub>n</sub>	84
14 <sup>b</sup>	<b>31a</b>	<b>30</b>	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	93
15 <sup>b</sup>	<b>31b</b>	<b>30</b>	diisopropylamine	(CH <sub>2</sub> O) <sub>n</sub>	95
16 <sup>b</sup>	<b>31c</b>	<b>30</b>	THP	(CH <sub>2</sub> O) <sub>n</sub>	93
17 <sup>b</sup>	<b>31d</b>	<b>30</b>	diallylamine	(CH <sub>2</sub> O) <sub>n</sub>	90
18 <sup>b</sup>	<b>31e</b>	<b>30</b>	allyl(methyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	94
19 <sup>b</sup>	<b>31f</b>	<b>30</b>	isopropyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	93
20 <sup>b</sup>	<b>39</b>	1-decyne	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	90
21 <sup>b</sup>	<b>40</b>	5-chloro-1-pentyne	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	97
22 <sup>b</sup>	<b>41</b>	hex-5-yne nitrile	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	94
23 <sup>b</sup>	<b>42</b>	[(prop-2-yn-1-yloxy)methyl]benzene	allyl( <i>tert</i> -butyl)amine	(CH <sub>2</sub> O) <sub>n</sub>	88
24 <sup>c</sup>	<b>29l</b>	<b>27b</b>	THP	PhCHO	27
25 <sup>d</sup>	<b>29m</b>	<b>27b</b>	allyl( <i>tert</i> -butyl)amine	PhCHO	33
26 <sup>b</sup>	<b>29n</b>	<b>27a</b>	diallylamine	PhCHO	93
27 <sup>b</sup>	<b>29o</b>	<b>27a</b>	allyl(methyl)amine	PhCHO	66
28 <sup>e</sup>	<b>31g</b>	<b>30</b>	allyl( <i>tert</i> -butyl)amine	PhCHO	30
29 <sup>b</sup>	<b>31h</b>	<b>30</b>	THP	PhCHO	62
30	<b>31i</b>	<b>30</b>	allyl( <i>tert</i> -butyl)amine	2-naphthaldehyde	21
31 <sup>b</sup>	<b>31j</b>	<b>30</b>	THP	2-naphthaldehyde	83
32	<b>31k</b>	<b>30</b>	allyl( <i>tert</i> -butyl)amine	biphenyl-2-carboxaldehyde	21
33 <sup>b</sup>	<b>31l</b>	<b>30</b>	THP	biphenyl-2-carboxaldehyde	84
34	<b>31m</b>	<b>30</b>	allyl( <i>tert</i> -butyl)amine	butyraldehyde	32
35 <sup>b</sup>	<b>31n</b>	<b>30</b>	THP	butyraldehyde	77
36 <sup>b</sup>	<b>31o</b>	<b>30</b>	THP	isobutyraldehyde	98

<sup>a</sup> **GP1**: CuCl (1.5 equiv), alkyne (1.0 equiv), anhyd dioxane (12 mL/mmol), paraformaldehyde (1.2 equiv), amine (1.2 equiv), BF<sub>3</sub>OEt<sub>2</sub> (1.0 equiv), 50 °C, 20 h. <sup>b</sup> **GP2**: CuBr (0.15 equiv), molecular sieve (4Å), anhyd toluene (5.0 mL/mmol), aldehyde (1.80 equiv), amine (1.40 equiv), alkyne (1.00 equiv), rt, 20 h. <sup>c</sup> **GP4**: CuBr (0.23 equiv), anhyd dioxane (12 mL/mmol), benzaldehyde (1.20 equiv), amine (1.20 equiv), alkyne (1.00 equiv), BF<sub>3</sub>OEt<sub>2</sub> (1.00 equiv), 50 °C, 26 h. <sup>d</sup> **GP5**: CuBr (0.15 equiv), anhyd toluene (5.0 mL/mmol), benzaldehyde (1.80 equiv), amine (1.40 equiv), alkyne (1.00 equiv), BF<sub>3</sub>OEt<sub>2</sub> (1.00 equiv), rt, 27 h. <sup>e</sup> **GP6**: CuBr (0.15 equiv), BF<sub>3</sub>OEt<sub>2</sub> (1.00 equiv), anhyd toluene (5.0 mL/mmol), aldehyde (1.80 equiv), amine (1.40 equiv), alkyne (1.00 equiv), 50 °C, 20 h.

## 2. Effect of the Amount of Catalyst on the Formation of Allene **32**

**Table S2. Effect of the amount of catalyst on the formation of allene **32**<sup>a</sup>**

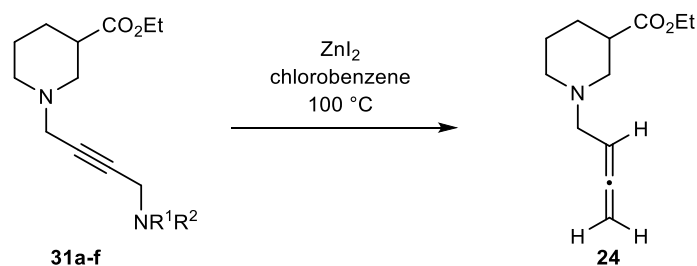


entry	$\text{CdI}_2$ (equiv)	t [h]	yield [%]
1	0.4	2.00	92
2	0.8	2.00	88
3	1.2	2.00	93

<sup>a</sup>The reaction was conducted using propargylic amine (0.5 mmol) and  $\text{CdI}_2$  at  $130\text{ }^\circ\text{C}$  in 4.0 mL of anhyd chlorobenzene. When the reaction was stopped, all starting material was consumed.

### 3. Effect of Different Hydride Donors on the Formation of Allene **24**

Table S3. Effect of different hydride donors on the formation of allene **24**<sup>a</sup>



entry	starting material	NR <sup>1</sup> R <sup>2</sup>	ZnI <sub>2</sub> (equiv)	t [h]	yield [%]
1	<b>31a</b>		1.6	4.00	50
2	<b>31a</b>		0.4	4.50	29
3	<b>31b</b>		0.8	1.50	42
4	<b>31b</b>		1.6	2.50	12
5	<b>31c</b>		0.8	2.00	19
6	<b>31d</b>		0.8	6.00	12
7	<b>31e</b>		0.8	3.00	6
8	<b>31f</b>		0.8	6.00	1

<sup>a</sup> The reaction was conducted using propargylic amine (0.5 mmol) and ZnI<sub>2</sub> at 100 °C in 4.0 mL of anhyd chlorobenzene. The reaction was stopped when all starting material was consumed or no further transformation could be observed (detection by TLC).

#### 4. NMR-Experiment: Coordination of $ZnI_2$ to the Hydride Donor Nitrogen of **29g**

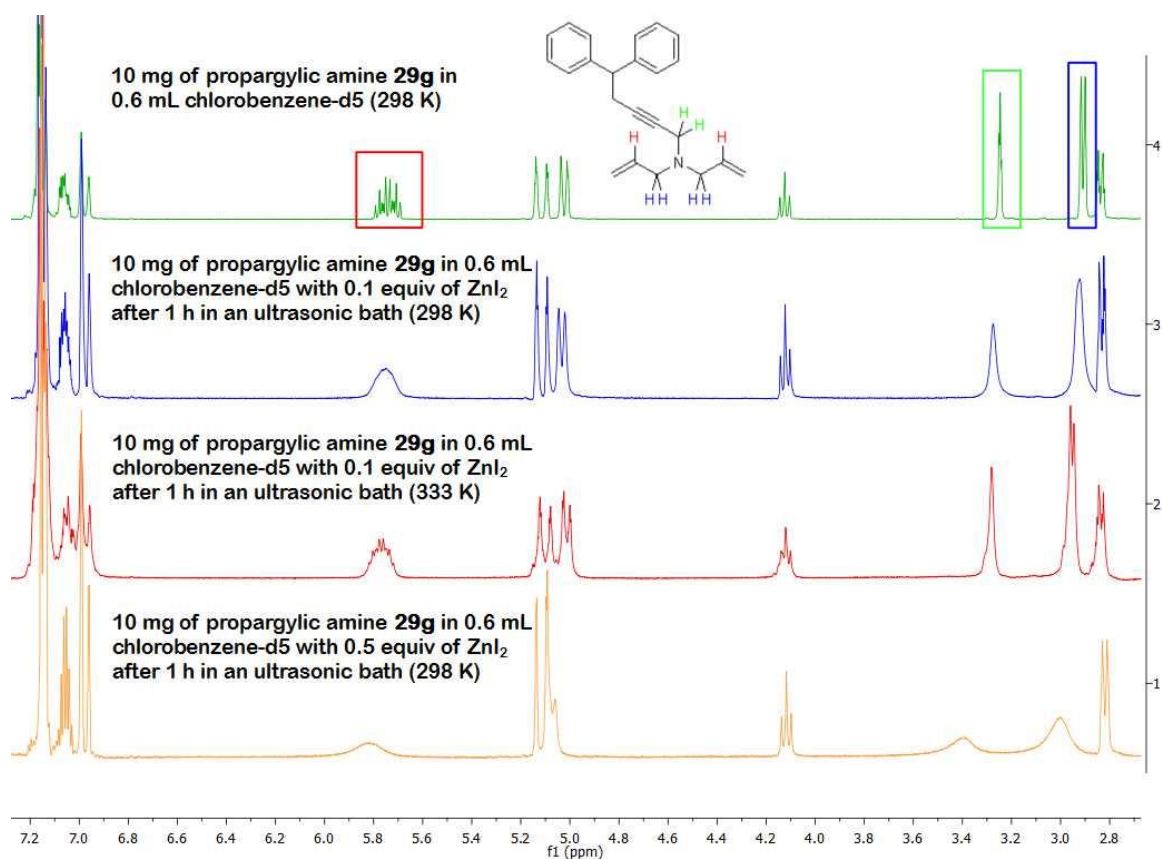
In additional experiments the coordination of the lewis acid to the nitrogen of the tertiary amino group was investigated by  $^1H$  NMR. Such studies are mainly hindered by the low solubility of the corresponding complexes in nonaqueous solvents.<sup>7</sup> Because of the better solubility in chlorobenzene this experiment was performed with  $ZnI_2$  instead of  $CdI_2$  as lewis acid. Propargylic amine **29g** was applied exhibiting diallylamine as hydride donor. First a  $^1H$  NMR spectrum of **29g** (10 mg) in chlorobenzene- $d_5$  (0.6 mL) was measured (green spectrum). Later on this NMR tube was charged with 0.1 equiv of  $ZnI_2$  and placed for 1 h in an ultrasonic bath, whereby the  $ZnI_2$  completely dissolved. Again a  $^1H$  NMR spectrum was measured (blue spectrum). As a consequence of the  $ZnI_2$  coordination to the tertiary nitrogen, the signals in the neighborhood of this nitrogen were now broadened and shifted downfield, whereas the signals with a greater distance to this nitrogen remained sharp and with unaltered chemical shifts compared to the spectrum without  $ZnI_2$ . The broadening of the signals is indicative for an exchange between free and coordinated amine molecules.<sup>7</sup> Measuring a  $^1H$  NMR spectrum at 333 K gave less broadened signals (red spectrum), indicating a faster exchange between amine and metal halide. In a second experiment the propargylic amine **29g** (10 mg) in chlorobenzene- $d_5$  (0.6 mL) was charged with 0.5 equiv of  $ZnI_2$  and kept again for 1 h in an ultrasonic bath, whereby the  $ZnI_2$  partly dissolved. The  $^1H$  NMR spectrum (orange) of this mixture exhibited an enhancement of broadening and shifting of the signals nearby the nitrogen. The signals with a greater distance to the nitrogen again appeared unaltered. These experiments indicate that the  $ZnI_2$  coordinates preferentially to the tertiary amino nitrogen as compared to the triple bond,

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<sup>7</sup> Chackalackal, S. M. Indian J. Chem. 1982, 21A, 667-669.



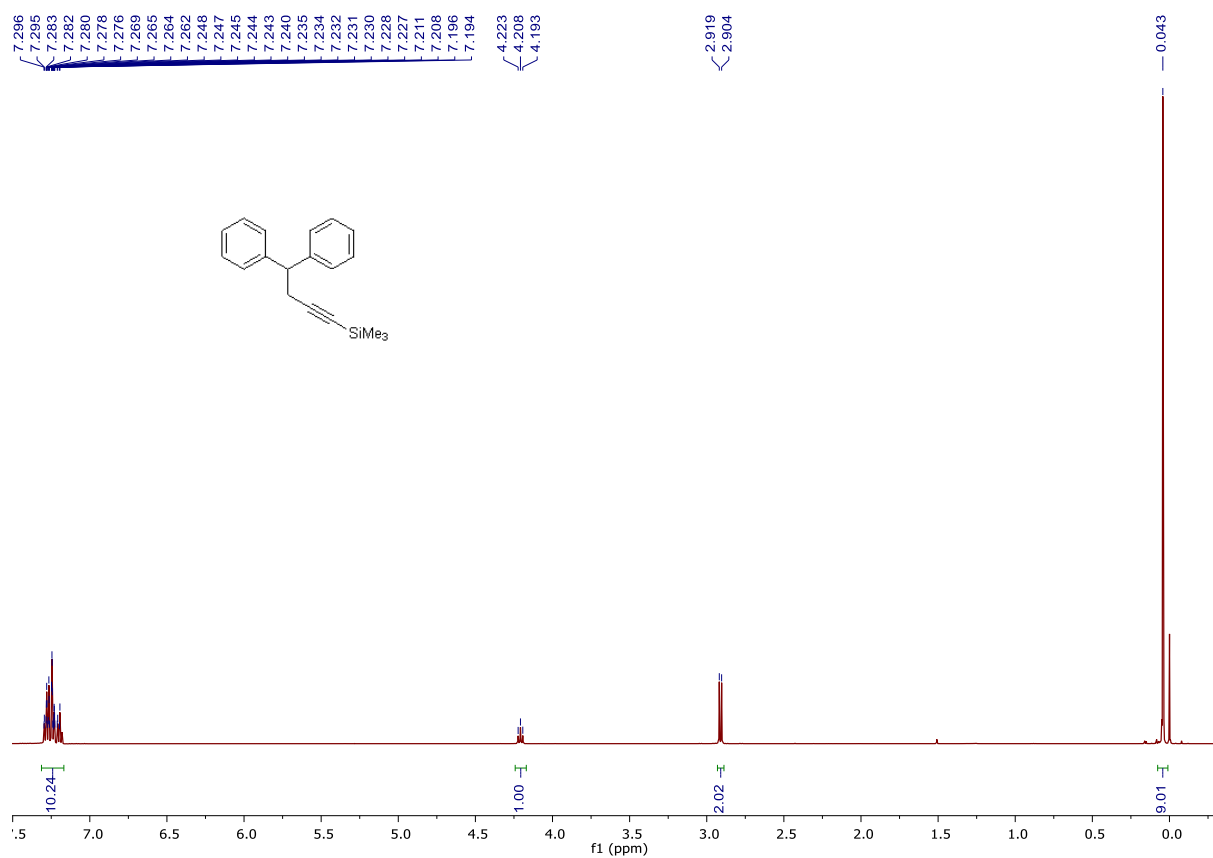
which is likely to lower the reactivity especially for sterically less hindered propargylic amines in the [1,5]-hydride transfer reactions.



**Figure S1:  $^1\text{H}$  NMR Experiment**

## 5. NMR Spectra: $^1\text{H}$ and $^{13}\text{C}$

**Figure S2:  $^1\text{H}$  NMR (4,4-diphenylbut-1-yn-1-yl)trimethylsilane (27b)**



**Figure S3:  $^{13}\text{C}$  NMR (4,4-diphenylbut-1-yn-1-yl)trimethylsilane (27b)**

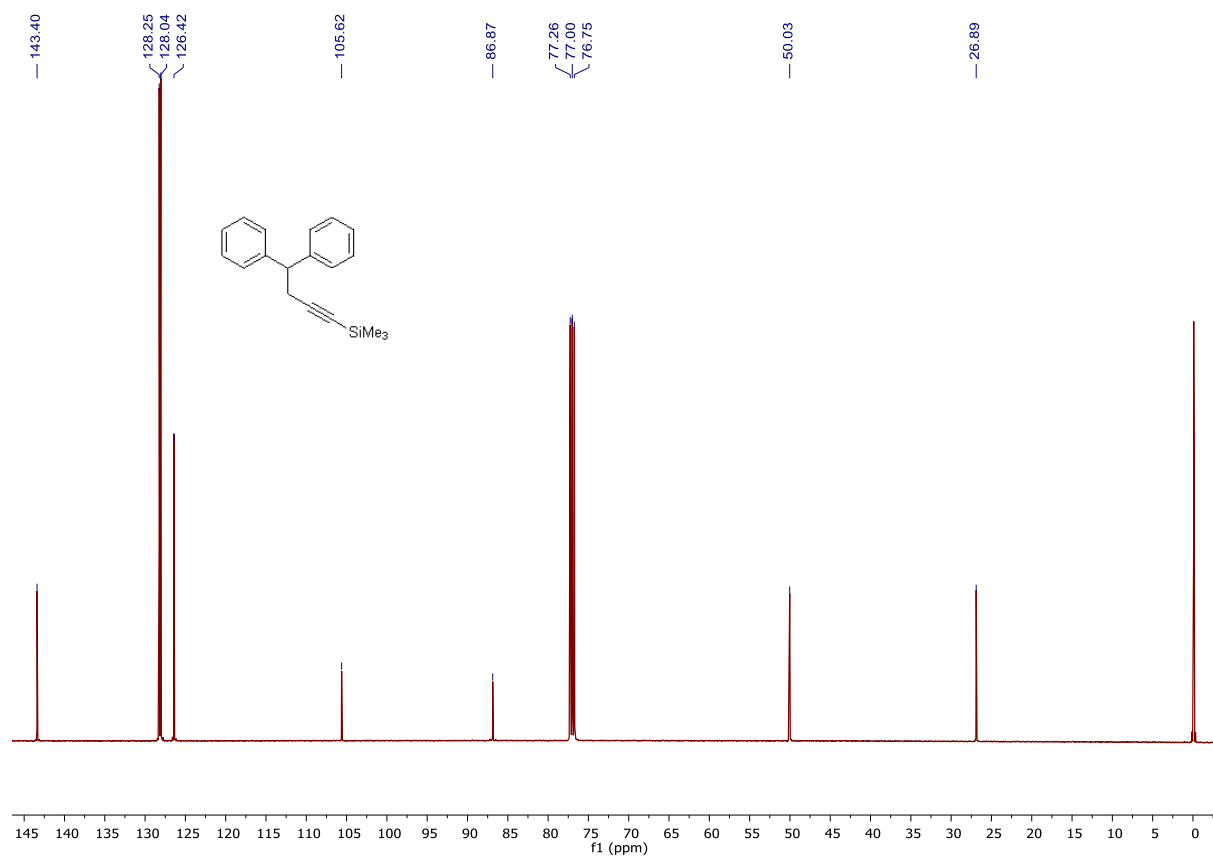


Figure S4: <sup>1</sup>H NMR 4,4-diphenylbut-1-yne (27a)

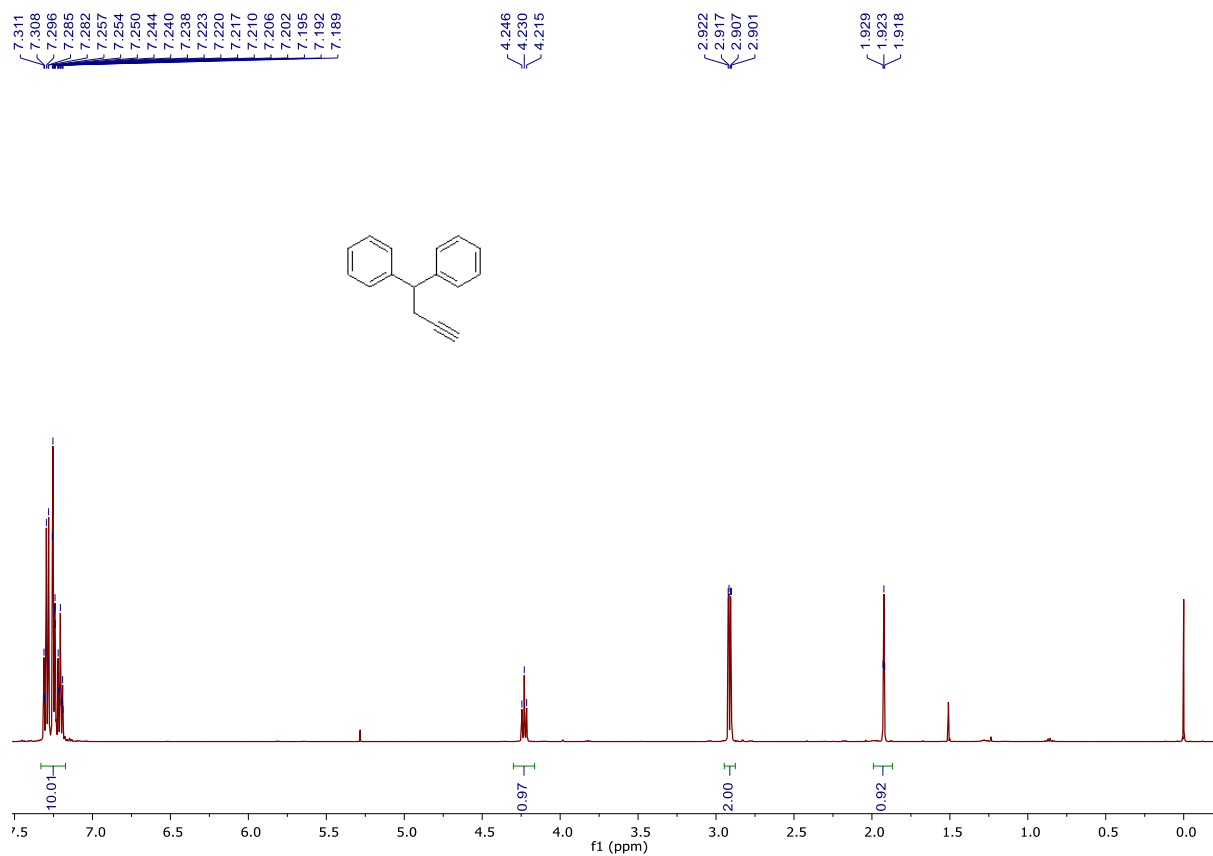


Figure S5: <sup>13</sup>C NMR 4,4-diphenylbut-1-yne (27a)

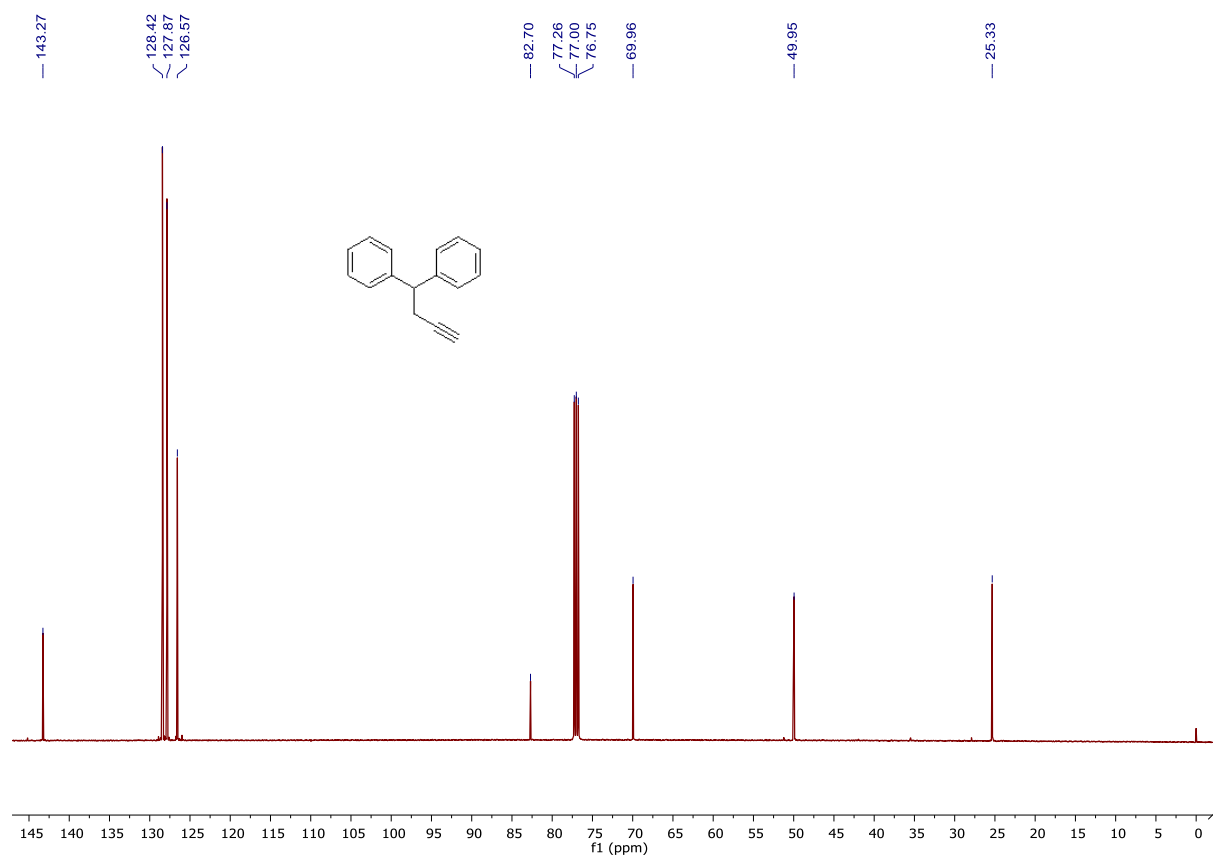


Figure S6: <sup>1</sup>H NMR ethyl 1-(prop-2-yn-1-yl)piperidine-3-carboxylate (30)

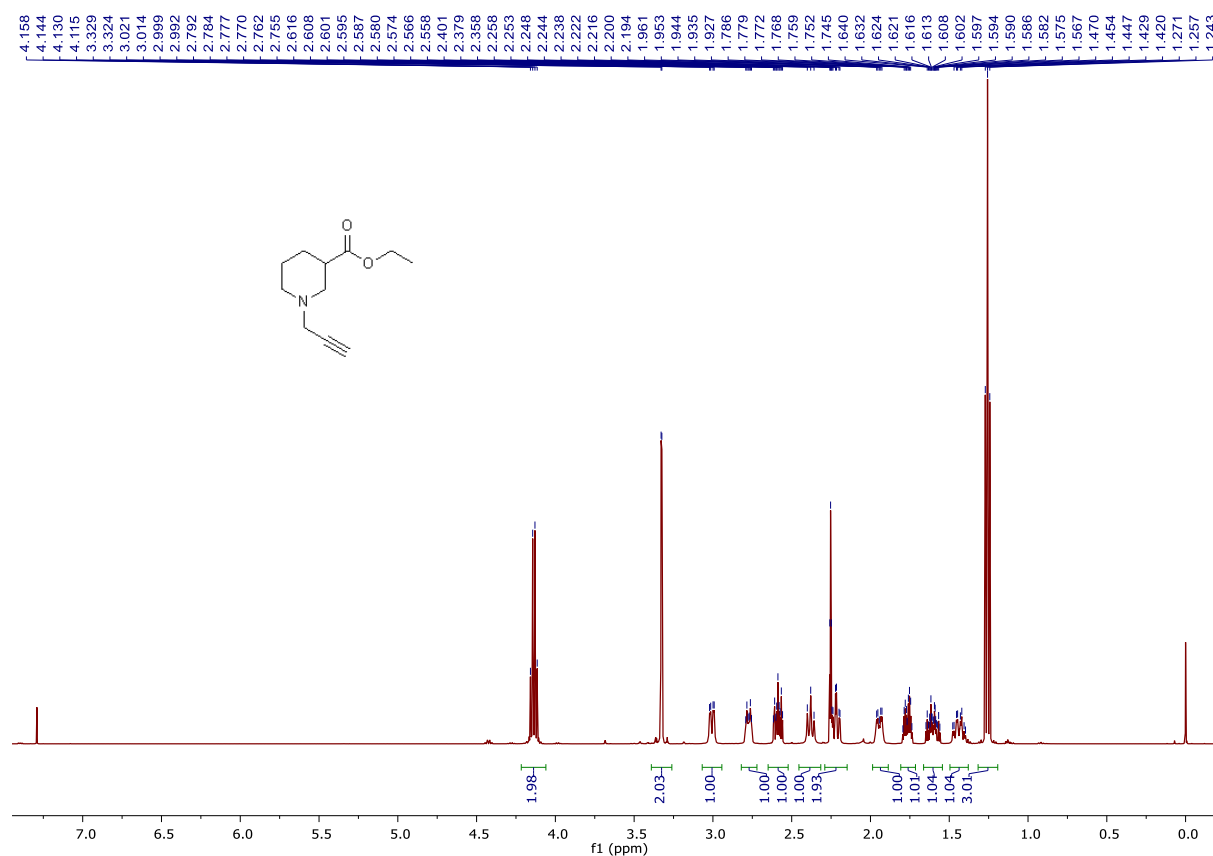
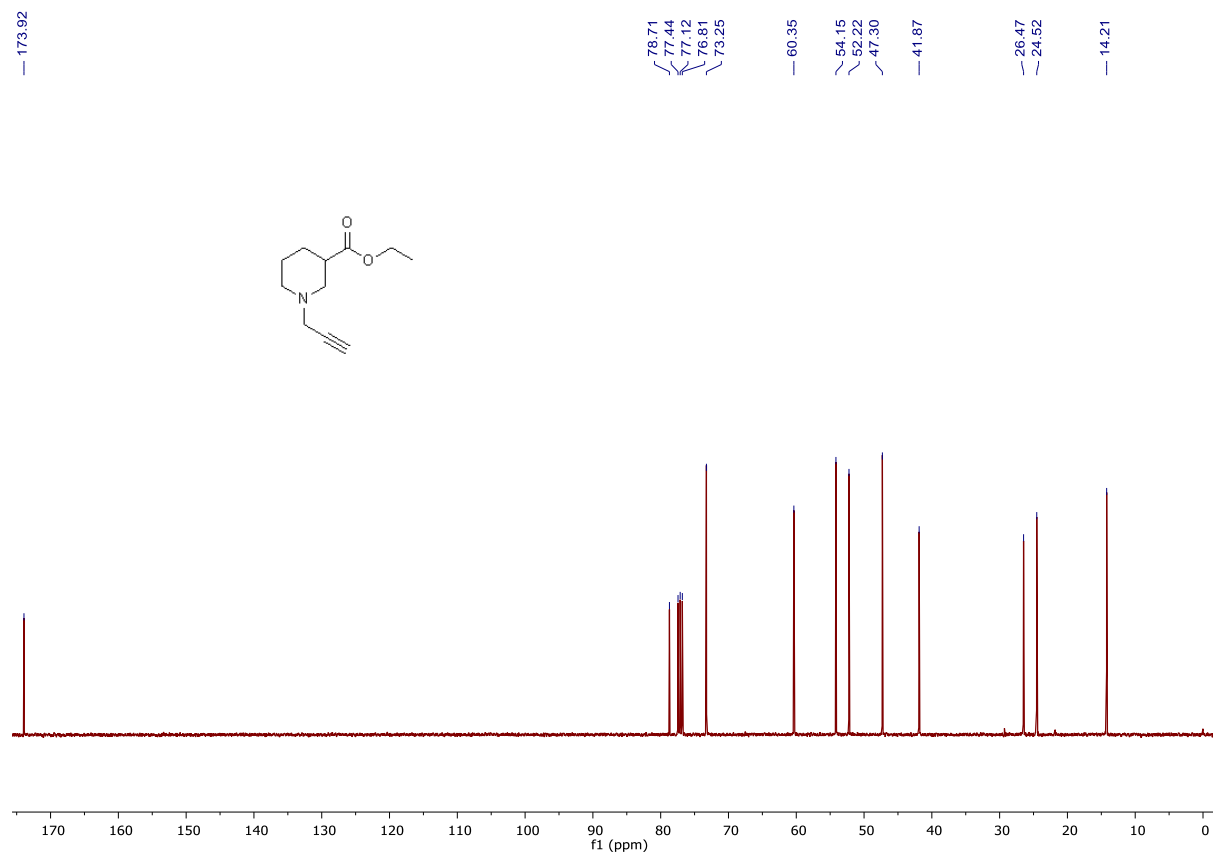
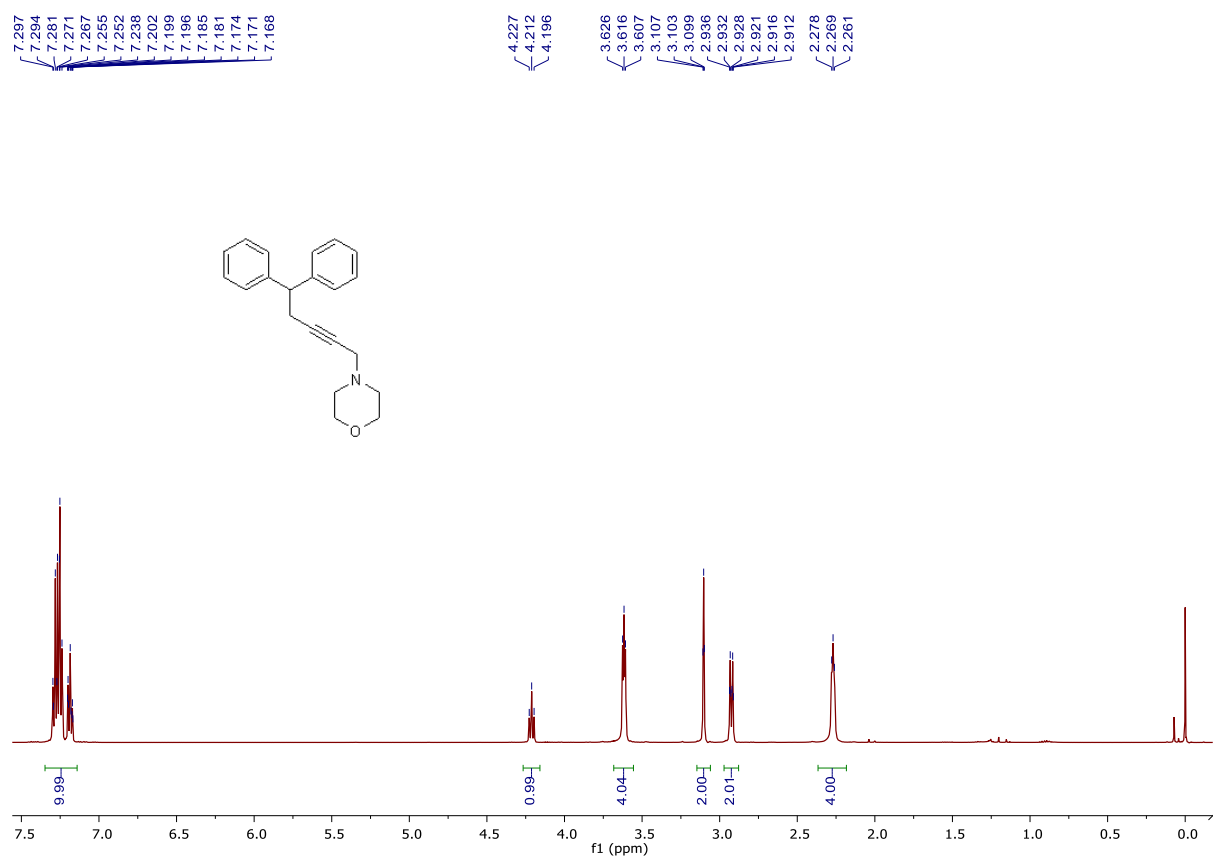


Figure S7: <sup>13</sup>C NMR ethyl 1-(prop-2-yn-1-yl)piperidine-3-carboxylate (30)



**Figure S8:  $^1\text{H}$  NMR 4-(5,5-diphenylpent-2-yn-1-yl)morpholine (29a)**



**Figure S9:  $^{13}\text{C}$  NMR 4-(5,5-diphenylpent-2-yn-1-yl)morpholine (29a)**

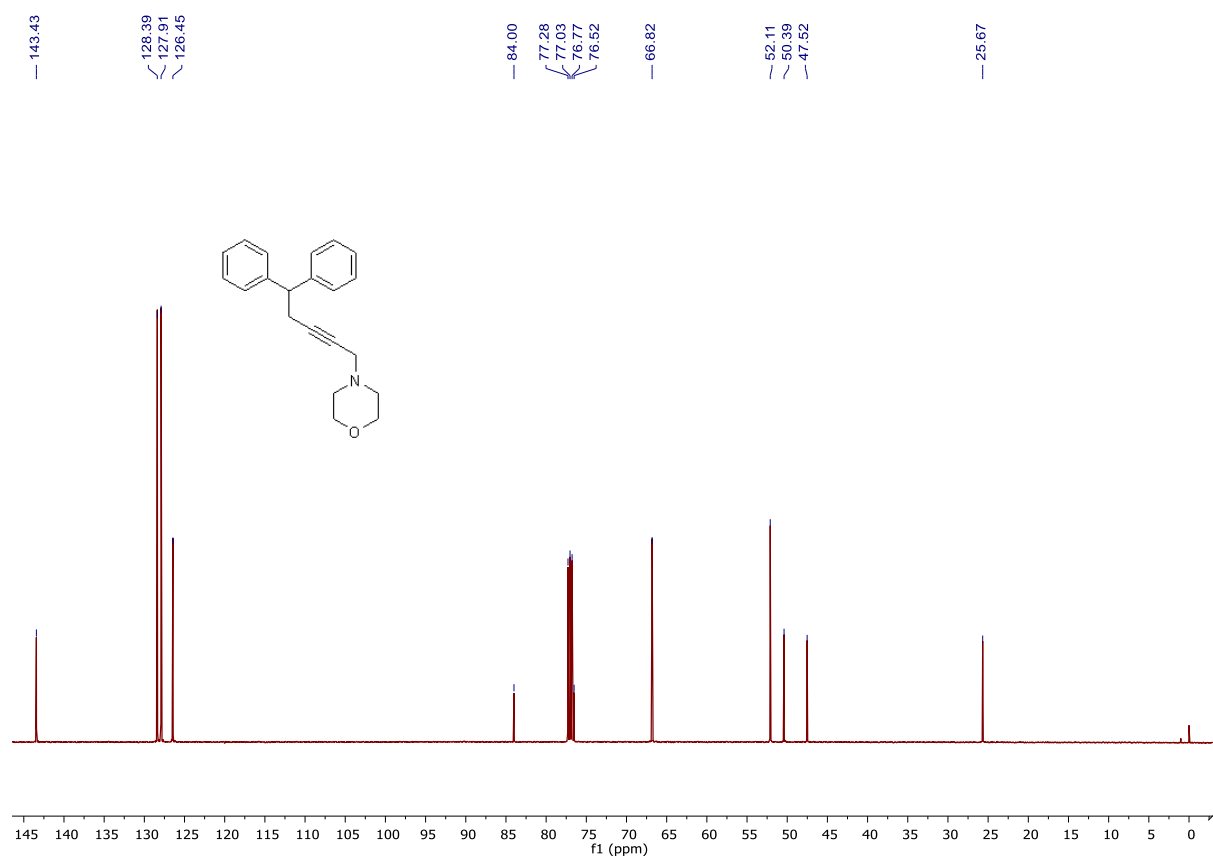


Figure S10: <sup>1</sup>H NMR 1-(5,5-diphenylpent-2-yn-1-yl)piperidine (29b)

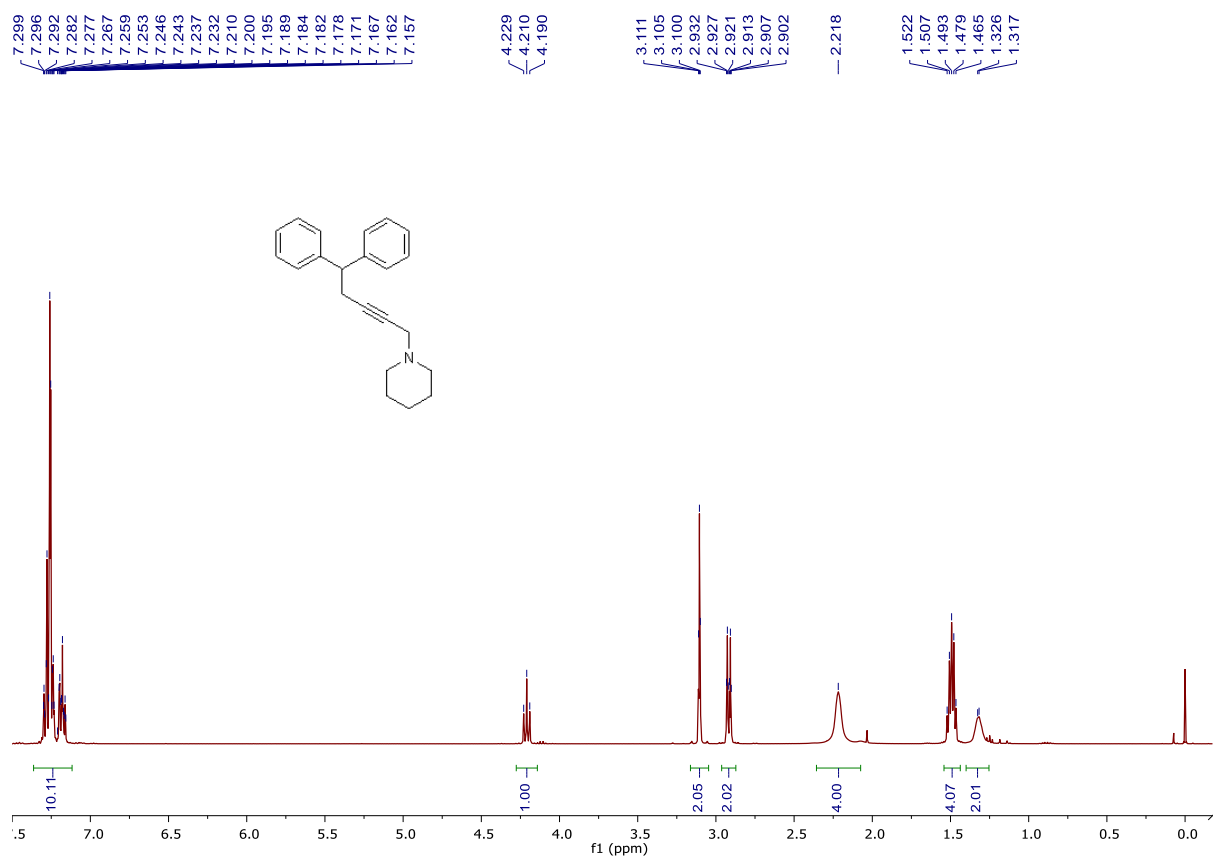


Figure S11: <sup>13</sup>C NMR 1-(5,5-diphenylpent-2-yn-1-yl)piperidine (29b)

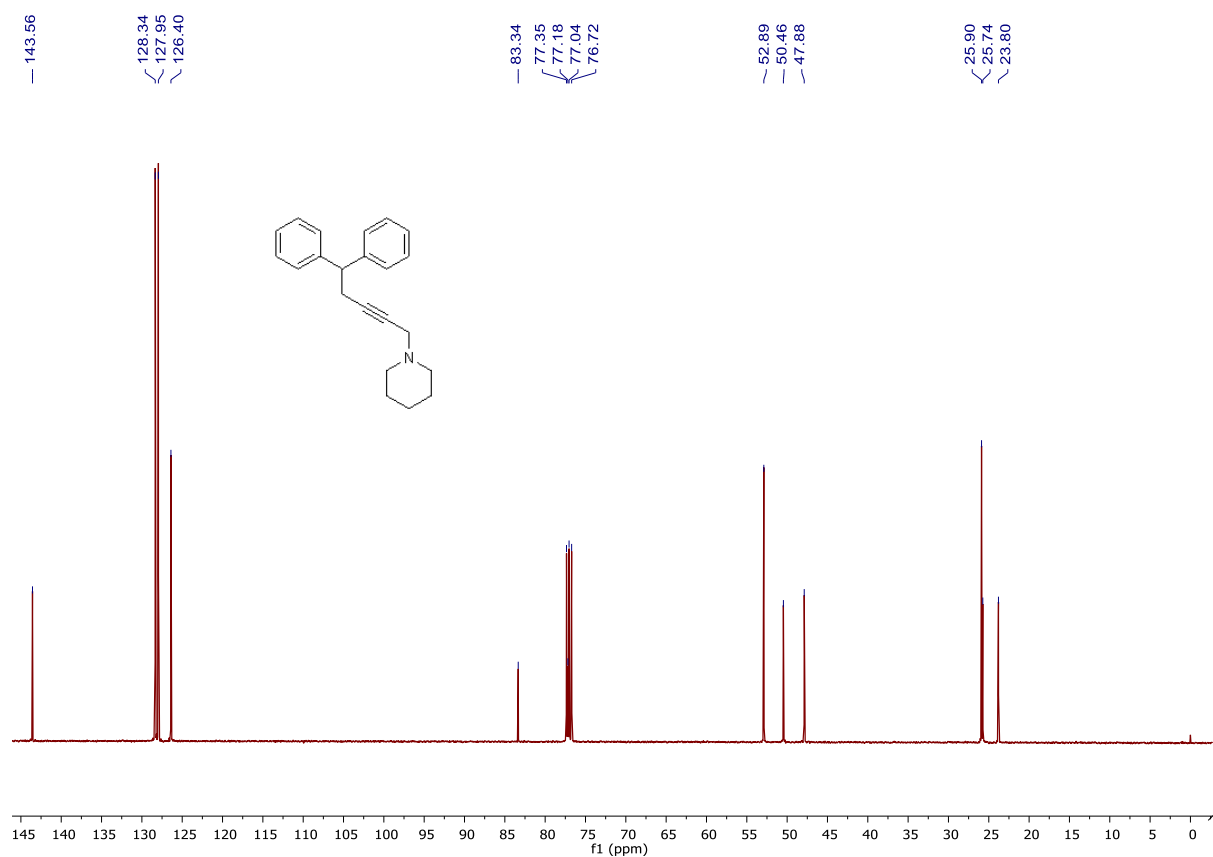


Figure S12: <sup>1</sup>H NMR 1-(5,5-diphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (29c)

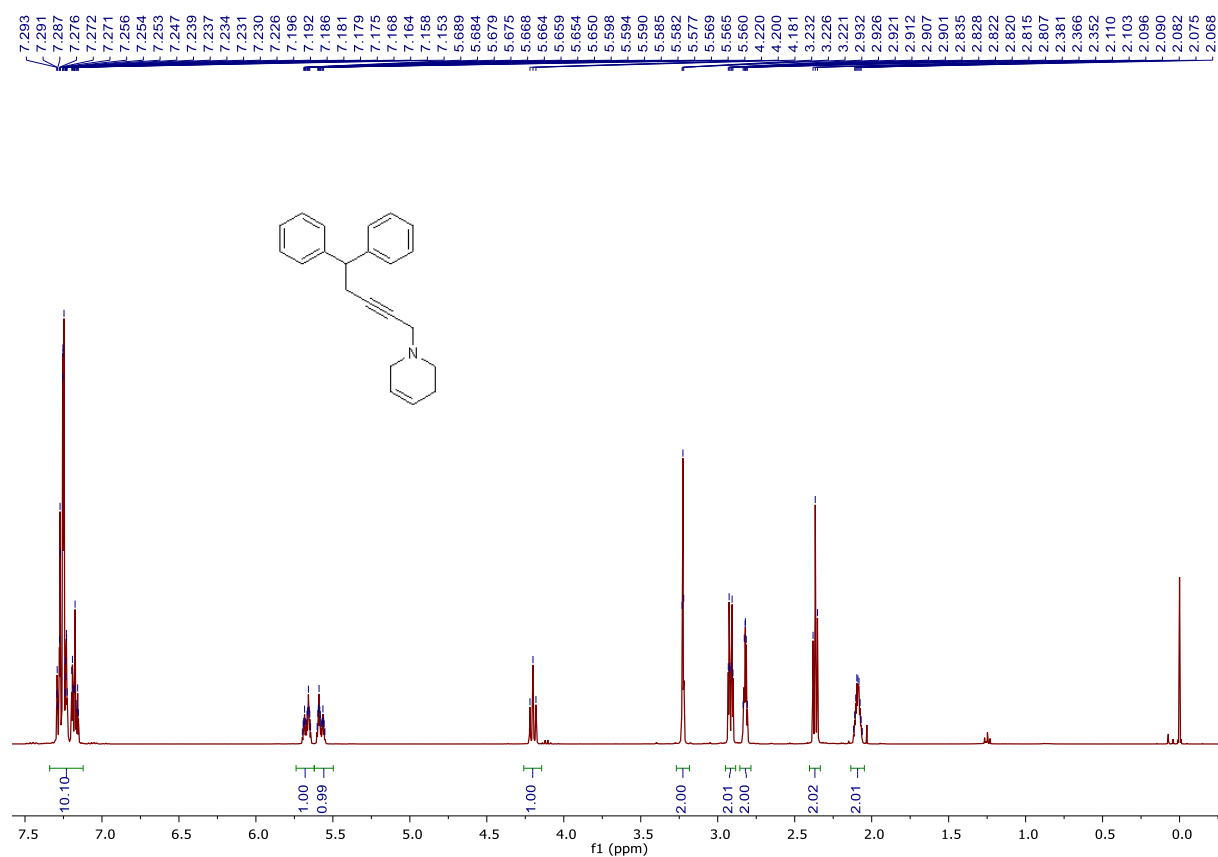


Figure S13: <sup>13</sup>C NMR 1-(5,5-diphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (29c)

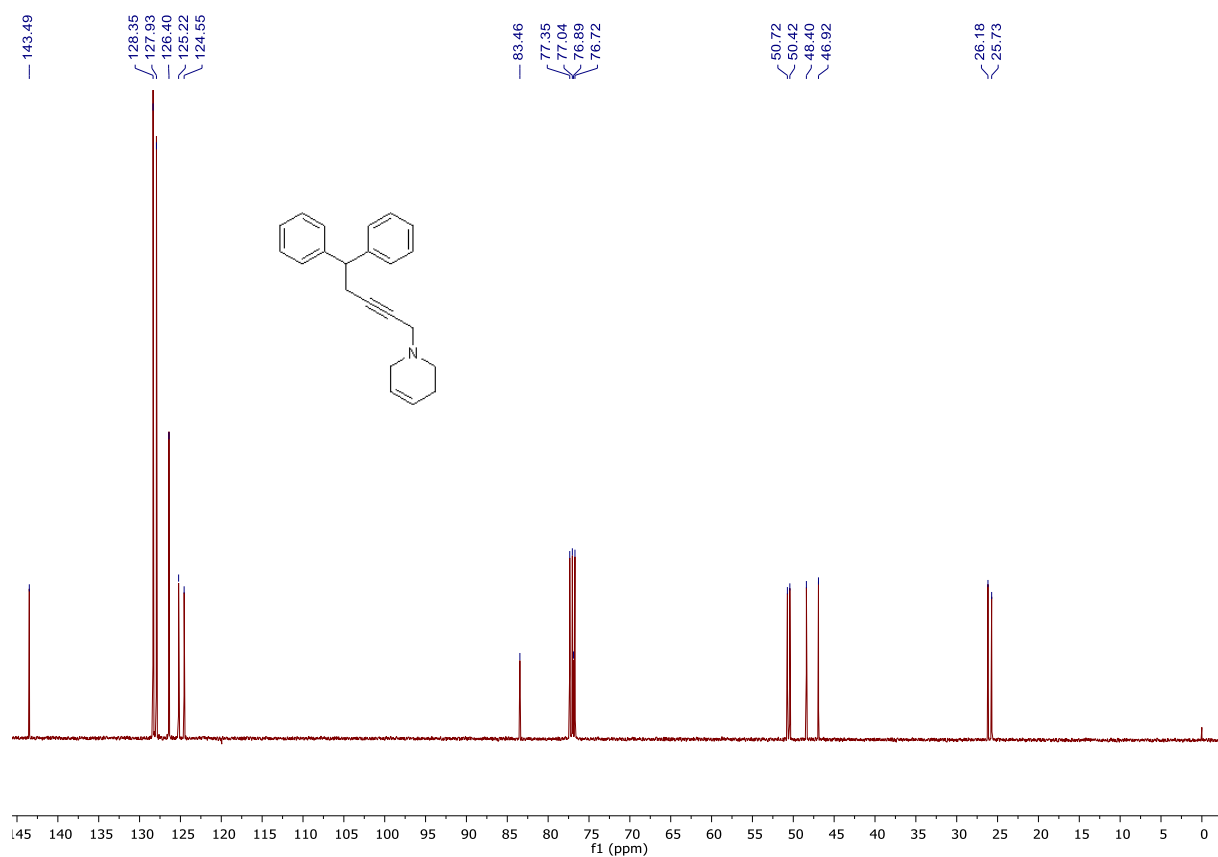


Figure S14: <sup>1</sup>H NMR ethyl 1-(5,5-diphenylpent-2-yn-1-yl)piperidine-3-carboxylate (29d)

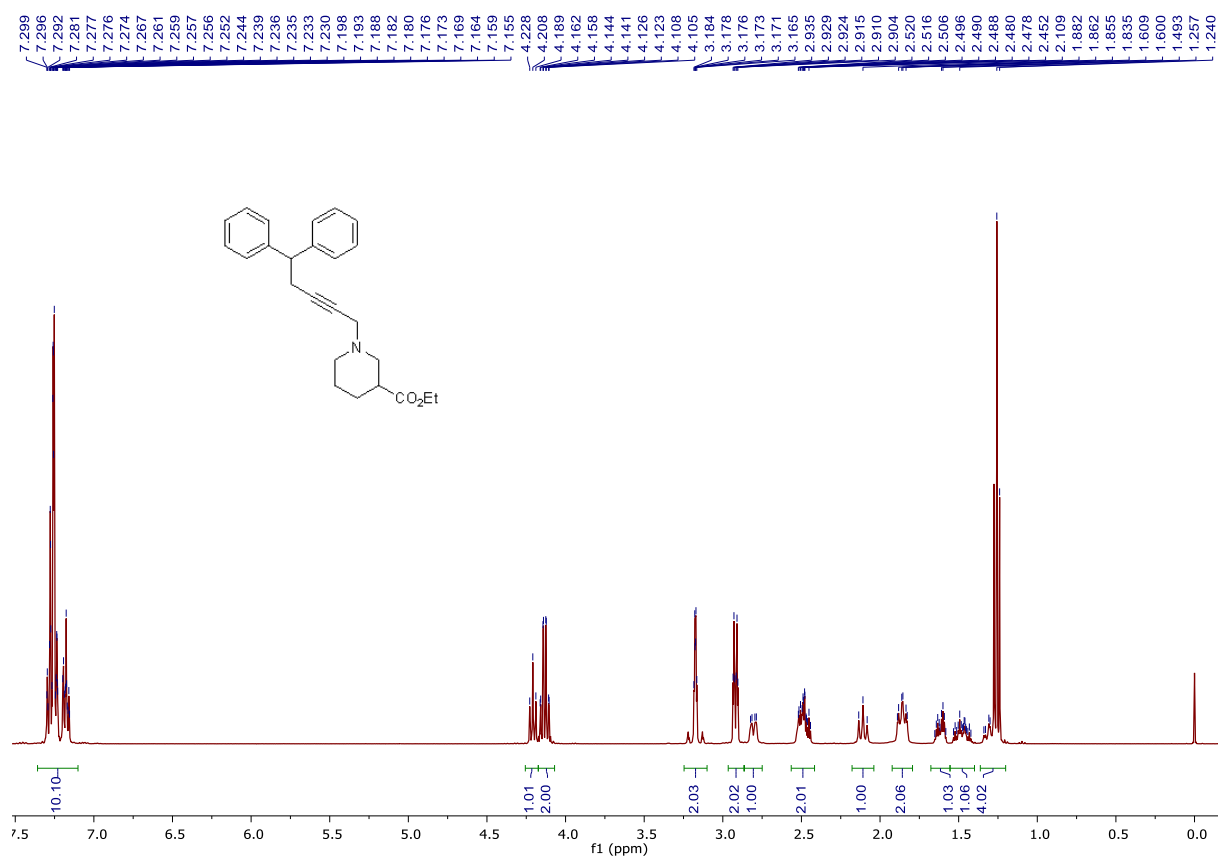


Figure S15: <sup>13</sup>C NMR ethyl 1-(5,5-diphenylpent-2-yn-1-yl)piperidine-3-carboxylate (29d)

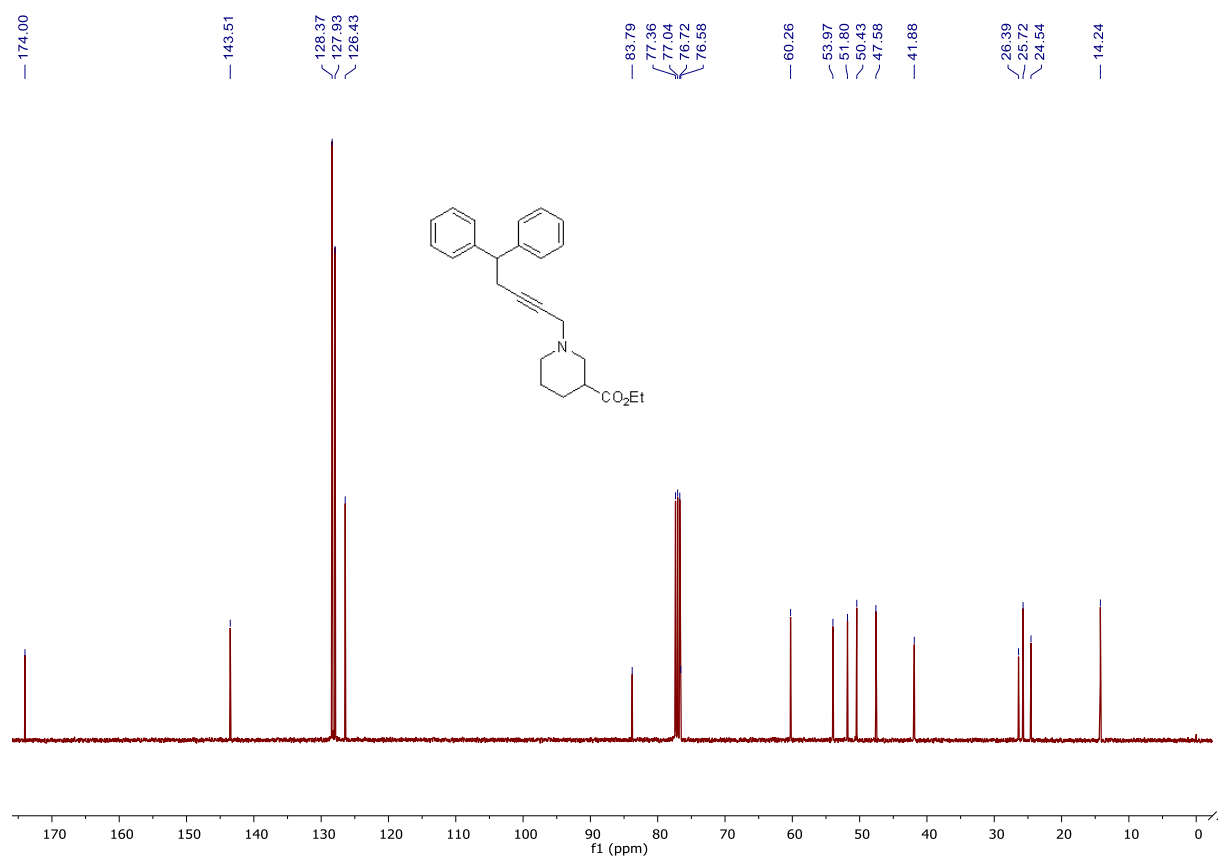




Figure S16: <sup>1</sup>H NMR *N*-allyl-*N*-(*tert*-butyl)-5,5-diphenylpent-2-yn-1-amine (29e)

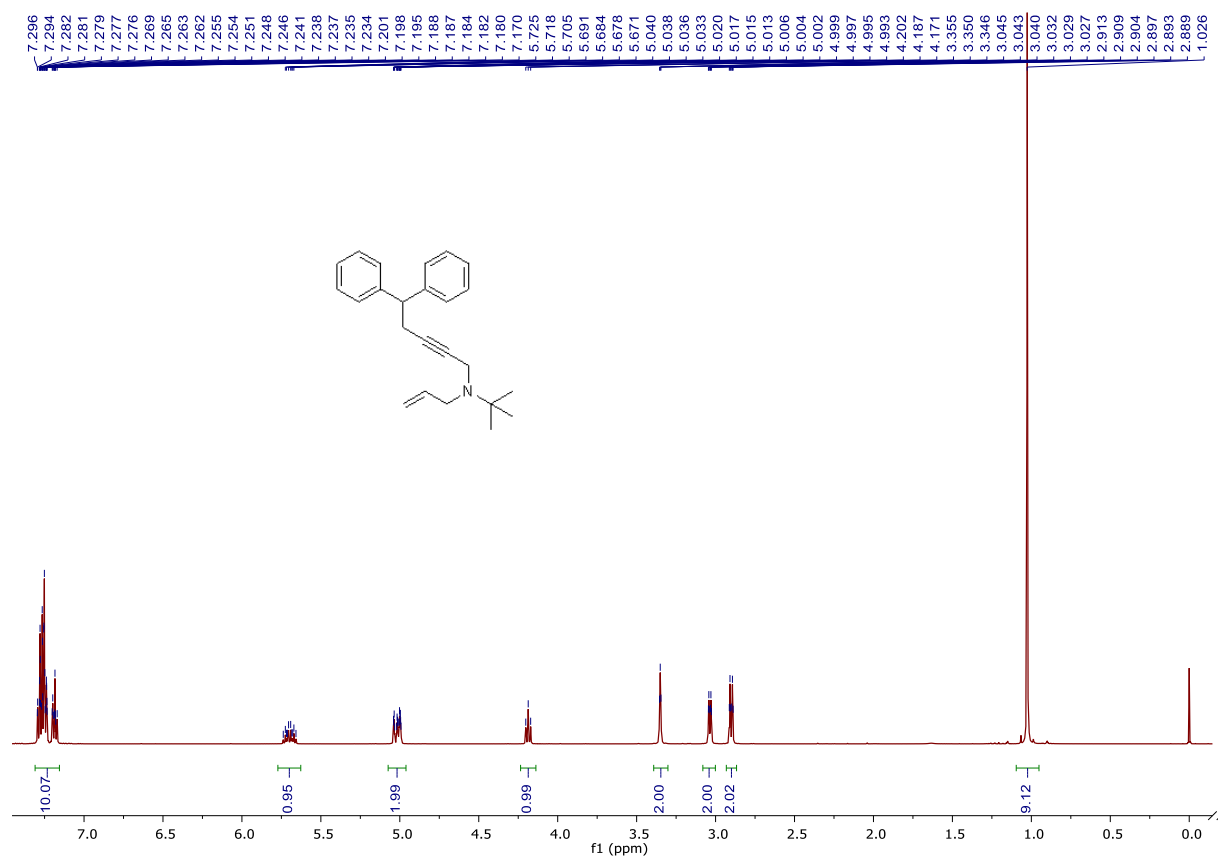


Figure S17: <sup>13</sup>C NMR *N*-allyl-*N*-(*tert*-butyl)-5,5-diphenylpent-2-yn-1-amine (29e)

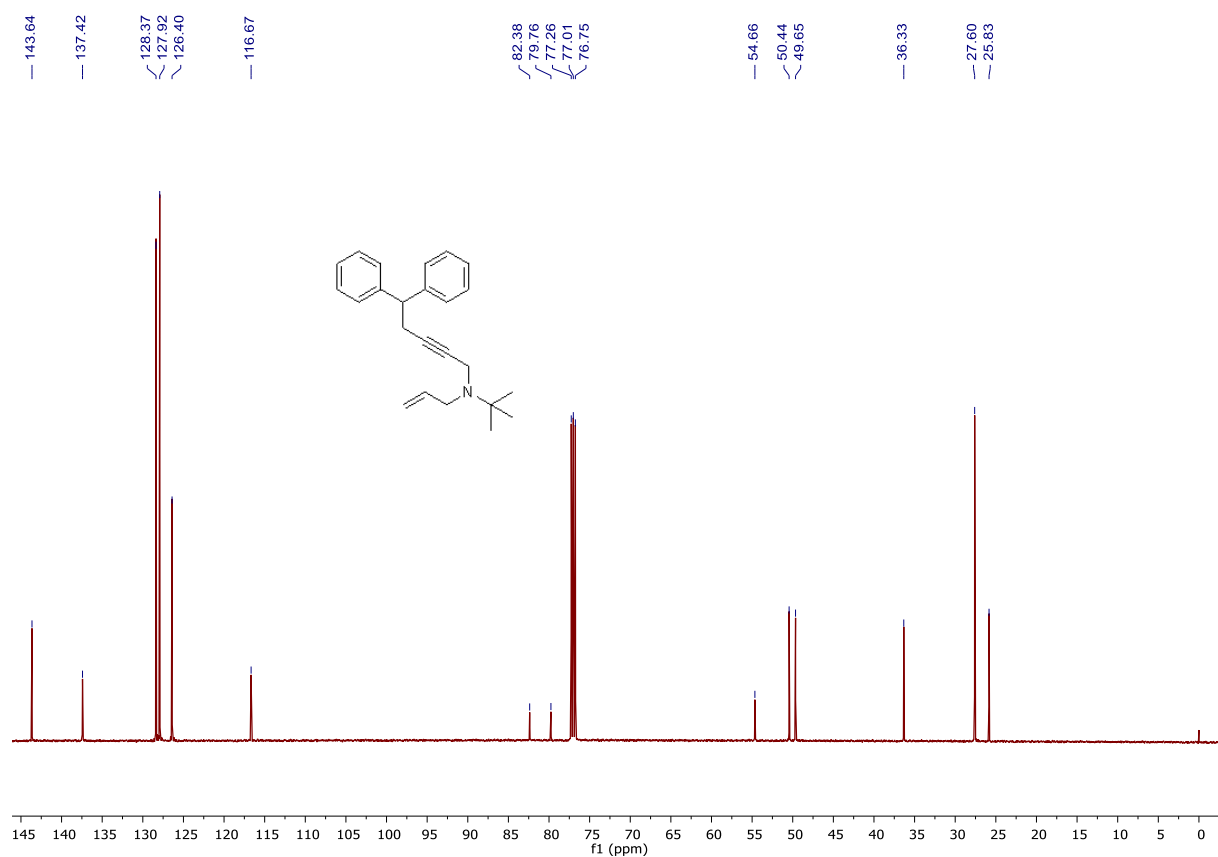


Figure S18: <sup>1</sup>H NMR *N*-allyl-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (29f)

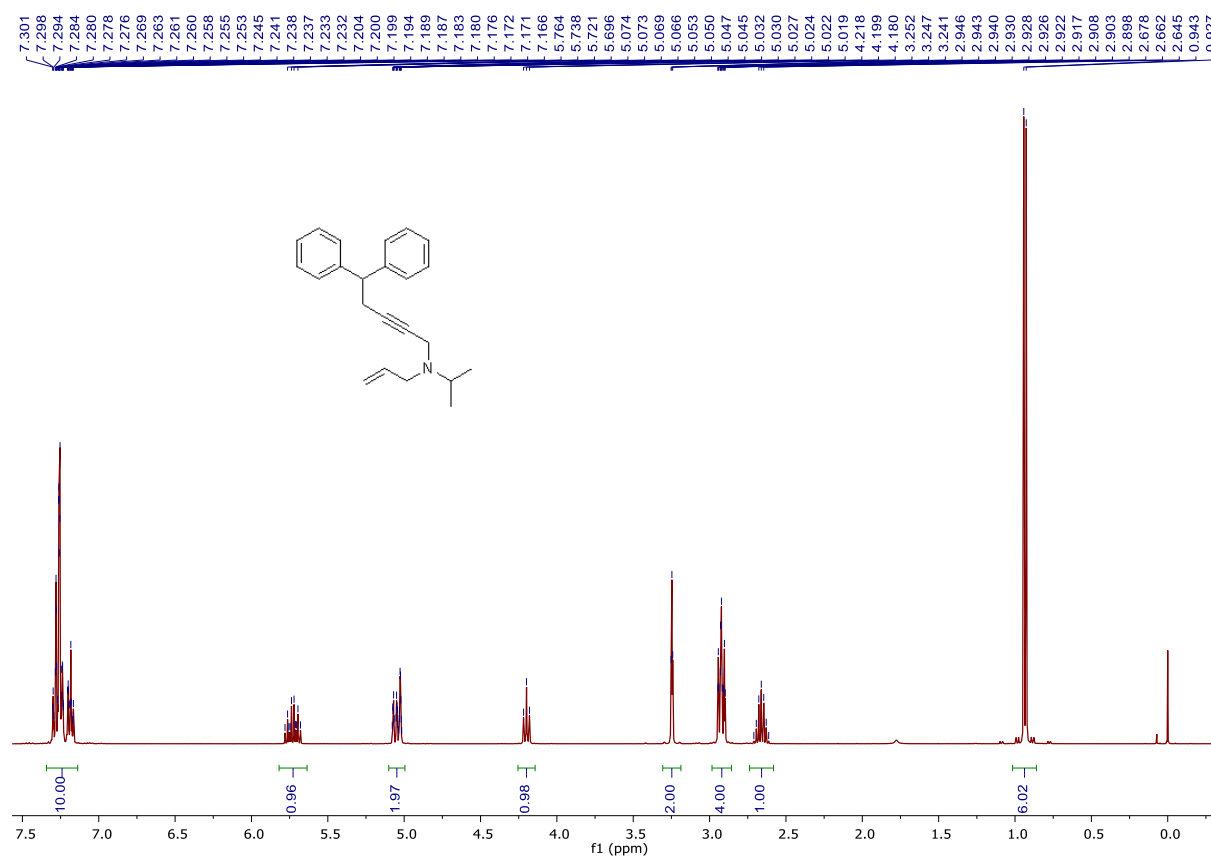


Figure S19: <sup>13</sup>C NMR *N*-allyl-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (29f)

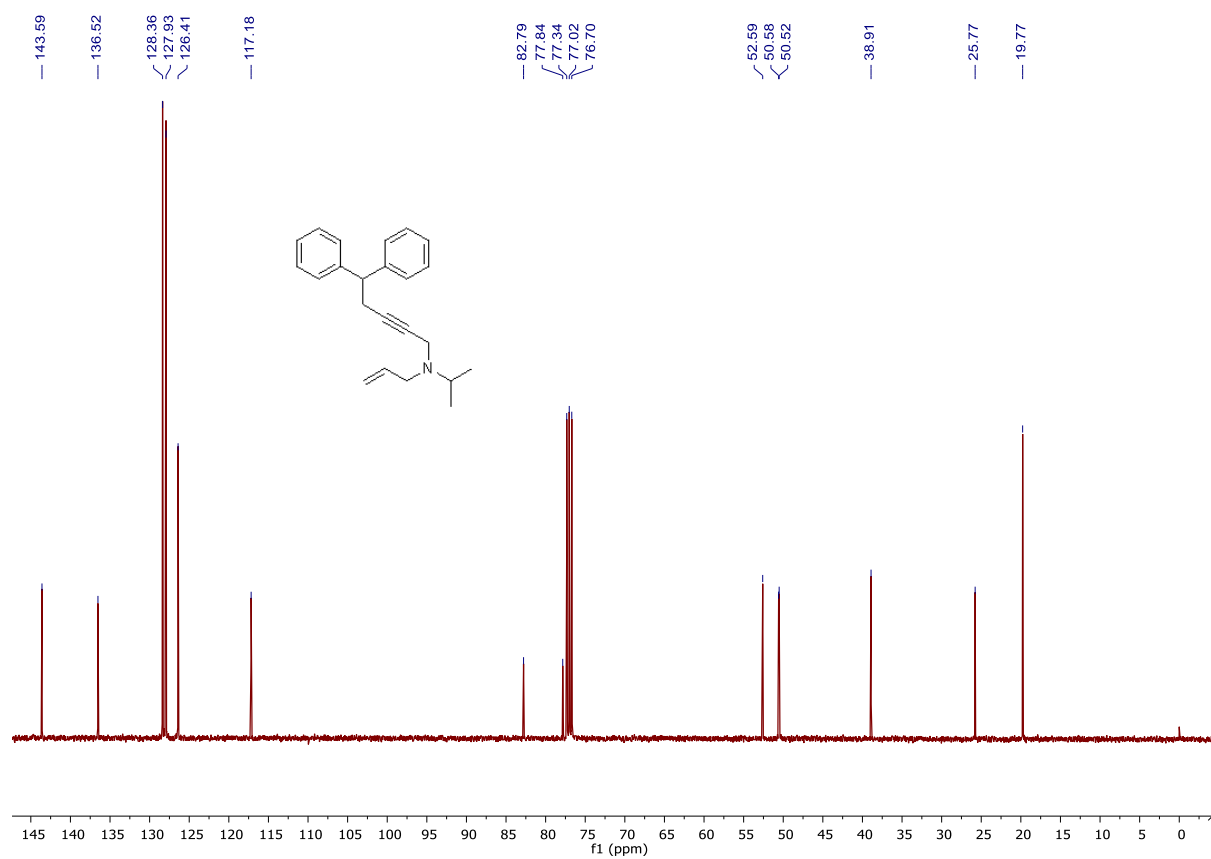


Figure S20: <sup>1</sup>H NMR *N,N*-diallyl-5,5-diphenylpent-2-yn-1-amine (29g)

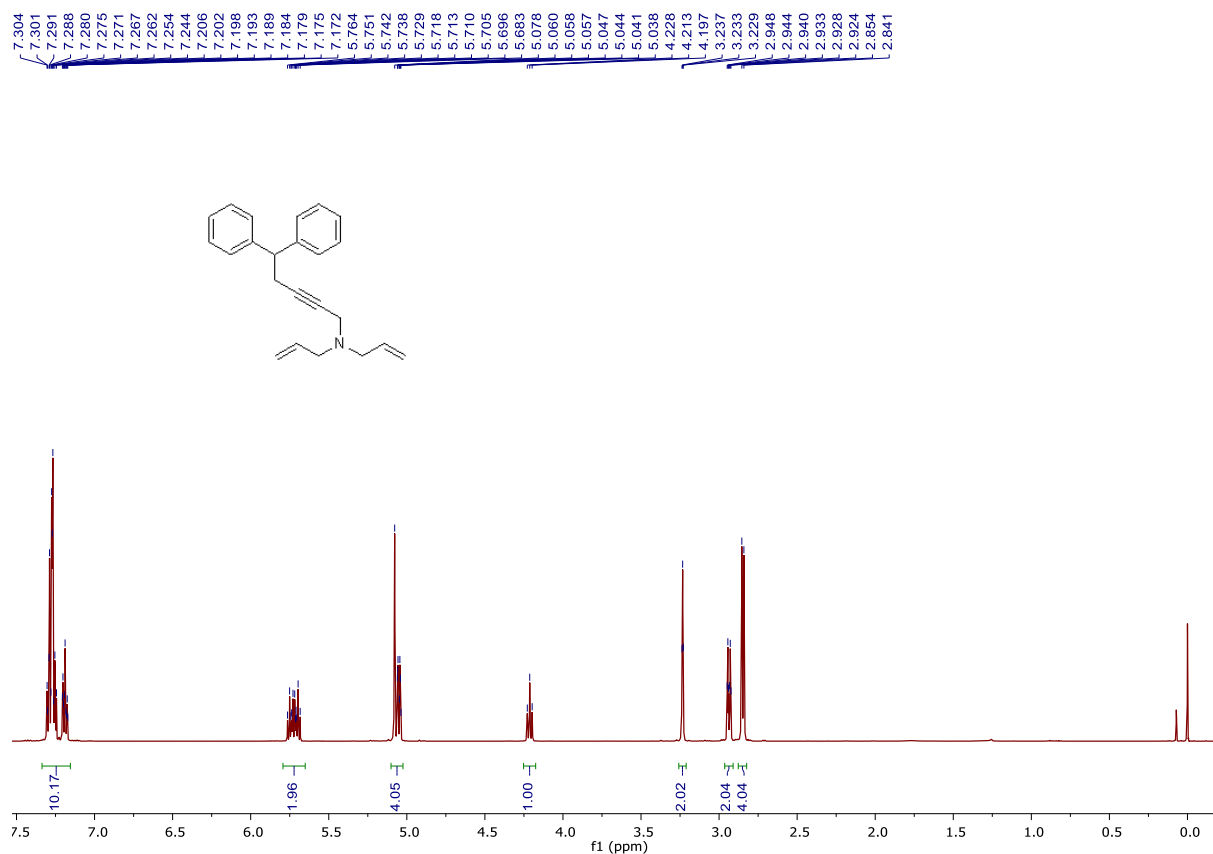


Figure S21: <sup>13</sup>C NMR *N,N*-diallyl-5,5-diphenylpent-2-yn-1-amine (29g)

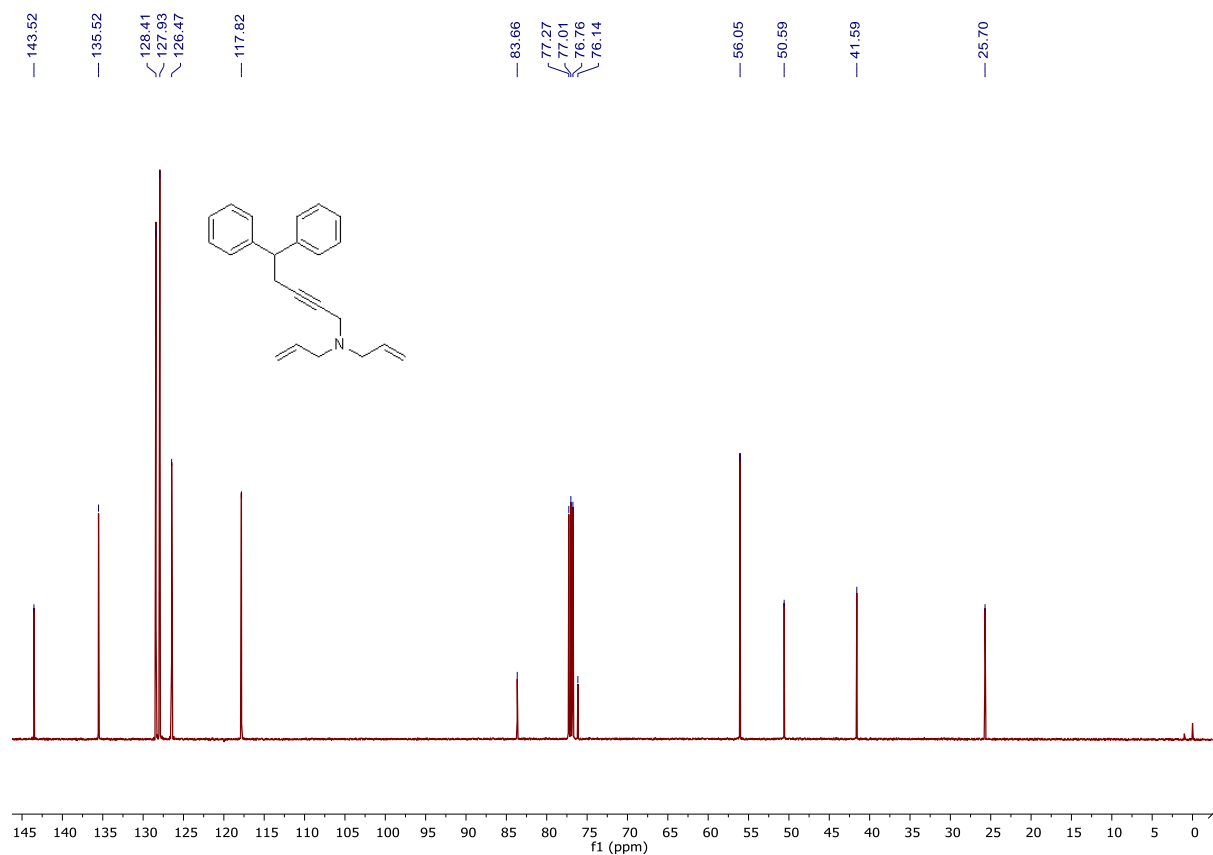


Figure S22: <sup>1</sup>H NMR *N*-allyl-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (29h)

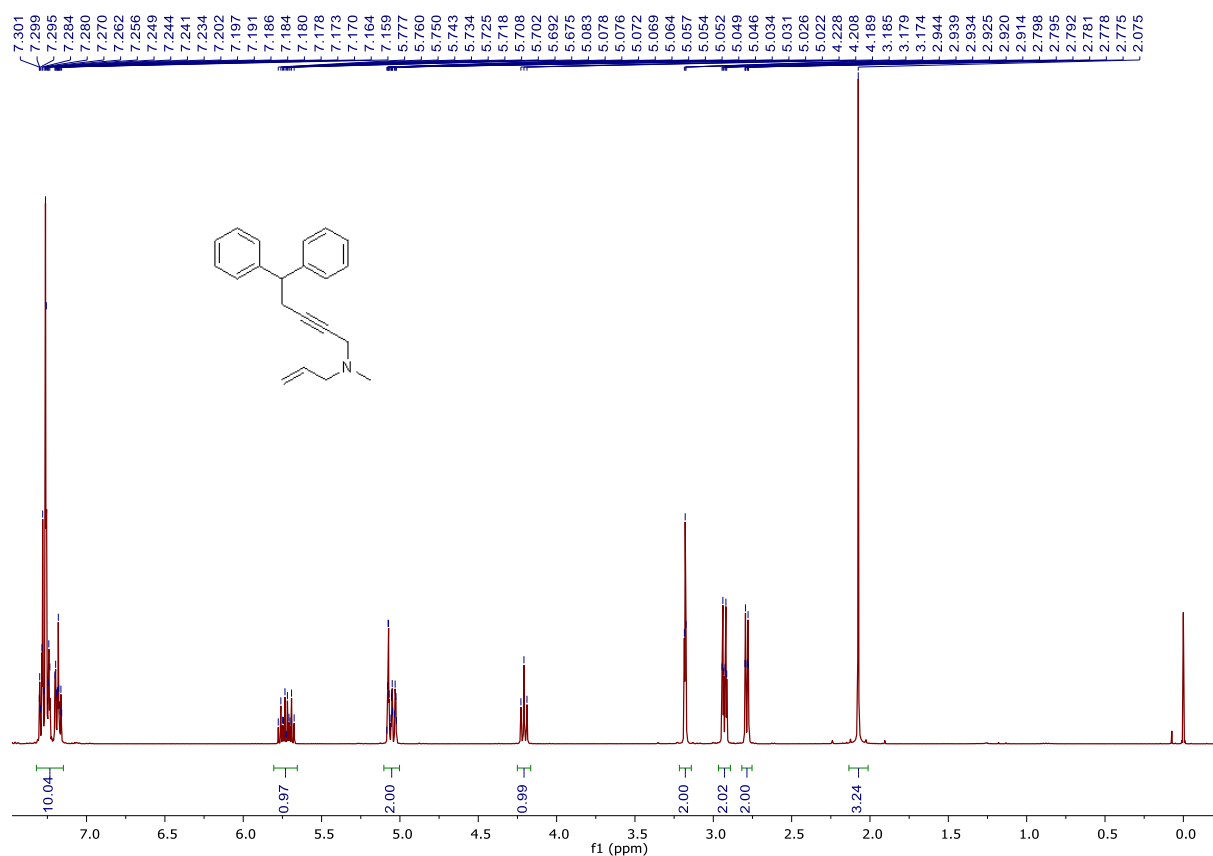


Figure S23: <sup>13</sup>C NMR *N*-allyl-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (29h)

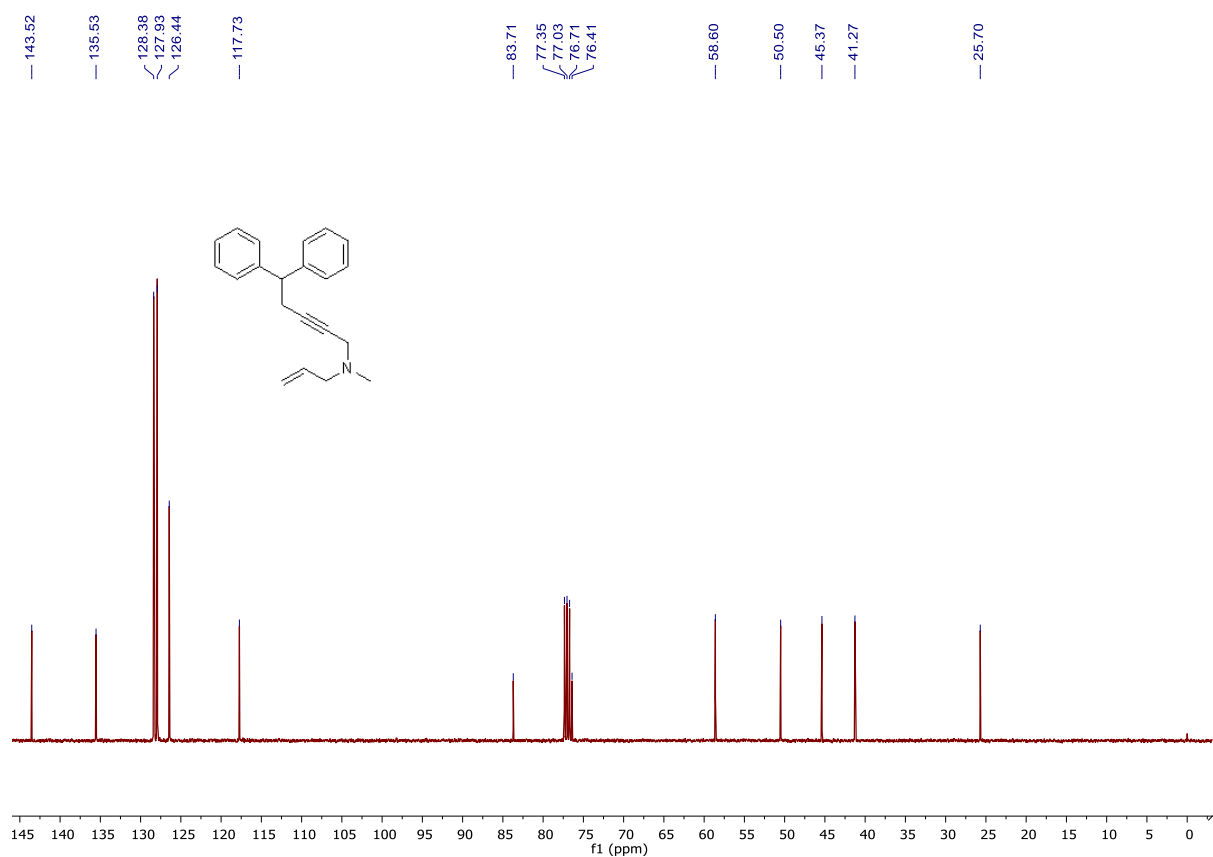


Figure S24: <sup>1</sup>H NMR *N*-(*tert*-butyl)-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (29i)

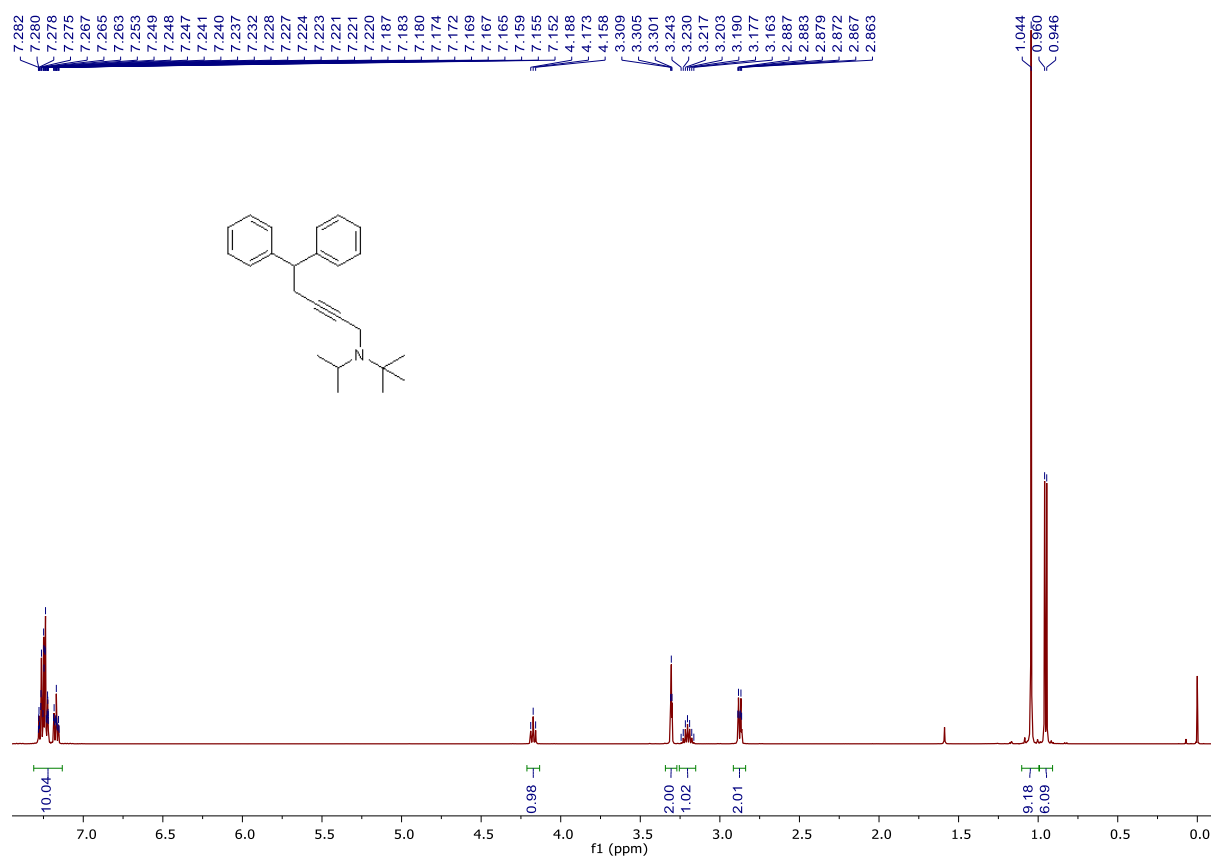


Figure S25: <sup>13</sup>C NMR *N*-(*tert*-butyl)-*N*-isopropyl-5,5-diphenylpent-2-yn-1-amine (29i)

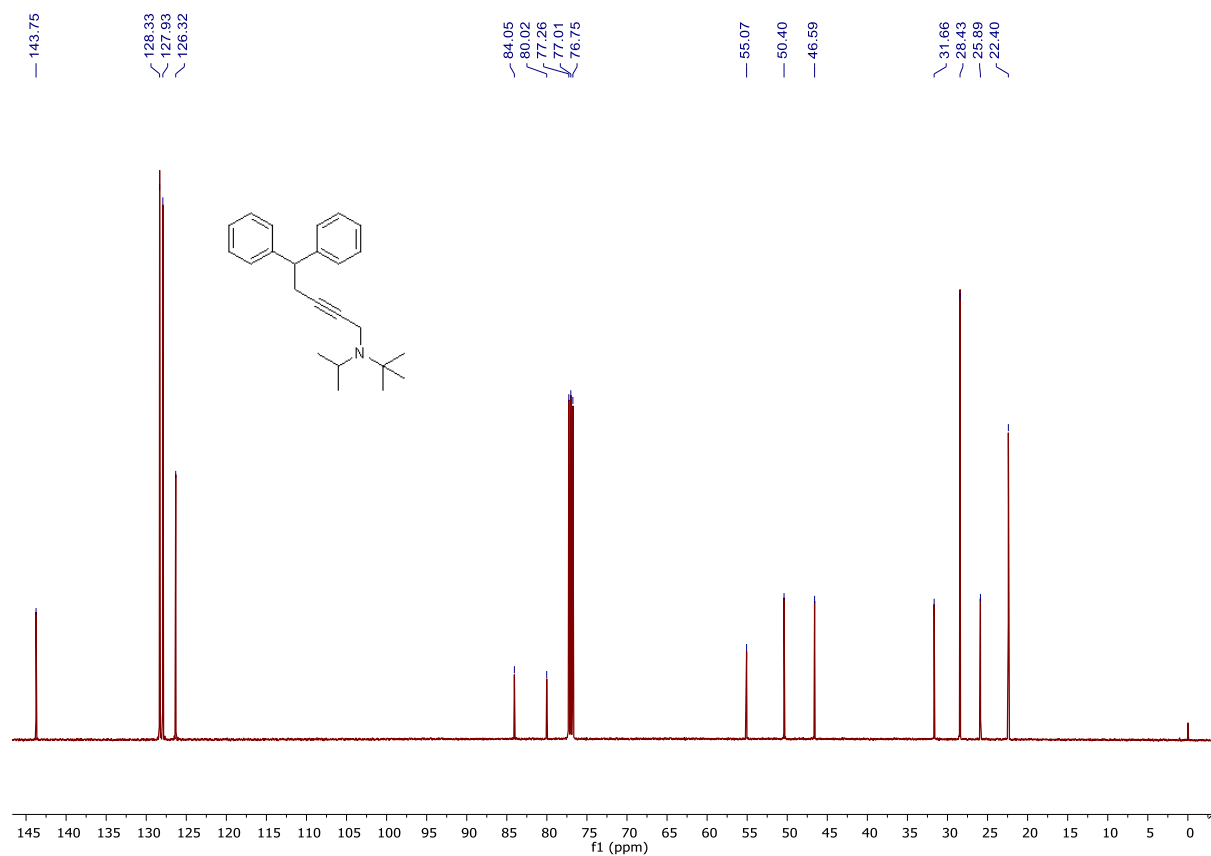


Figure S26: <sup>1</sup>H NMR *N*-(*tert*-butyl)-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (29j)

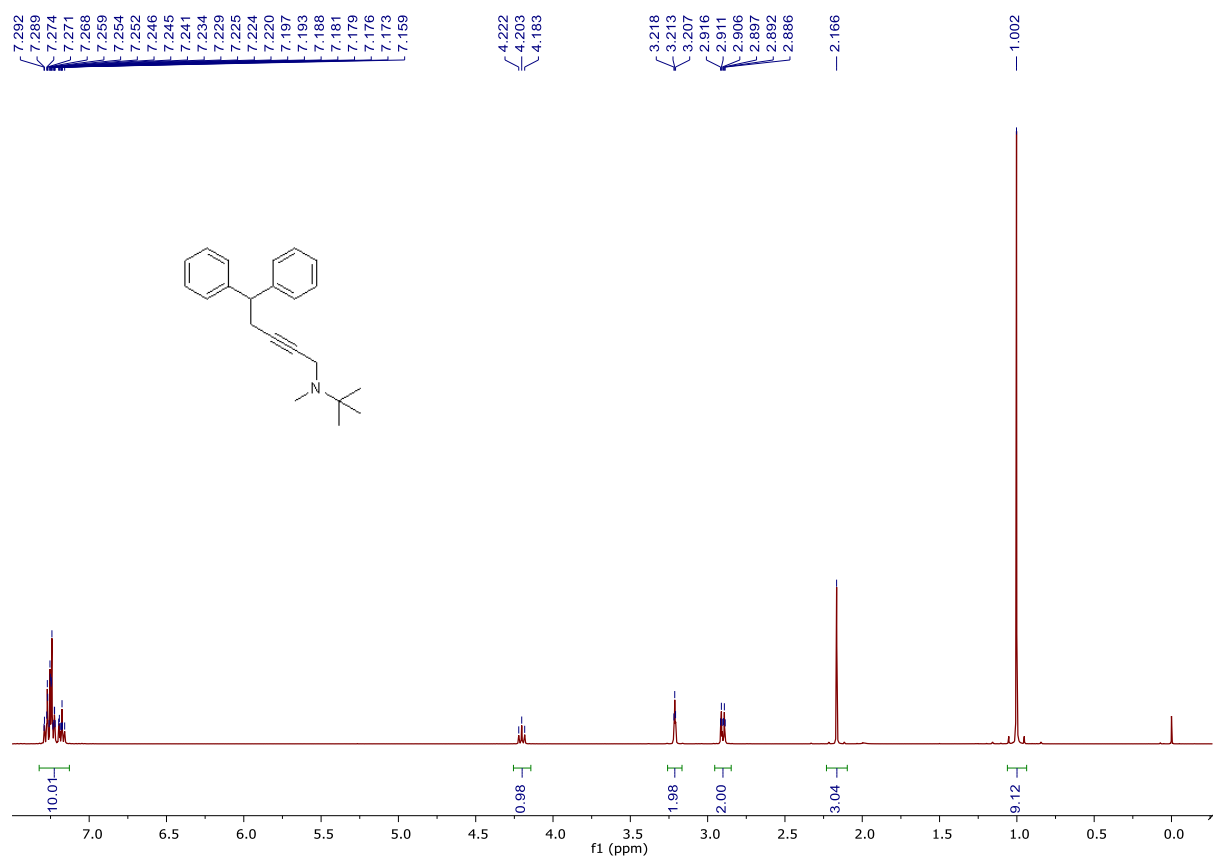


Figure S27: <sup>13</sup>C NMR *N*-(*tert*-butyl)-*N*-methyl-5,5-diphenylpent-2-yn-1-amine (29j)

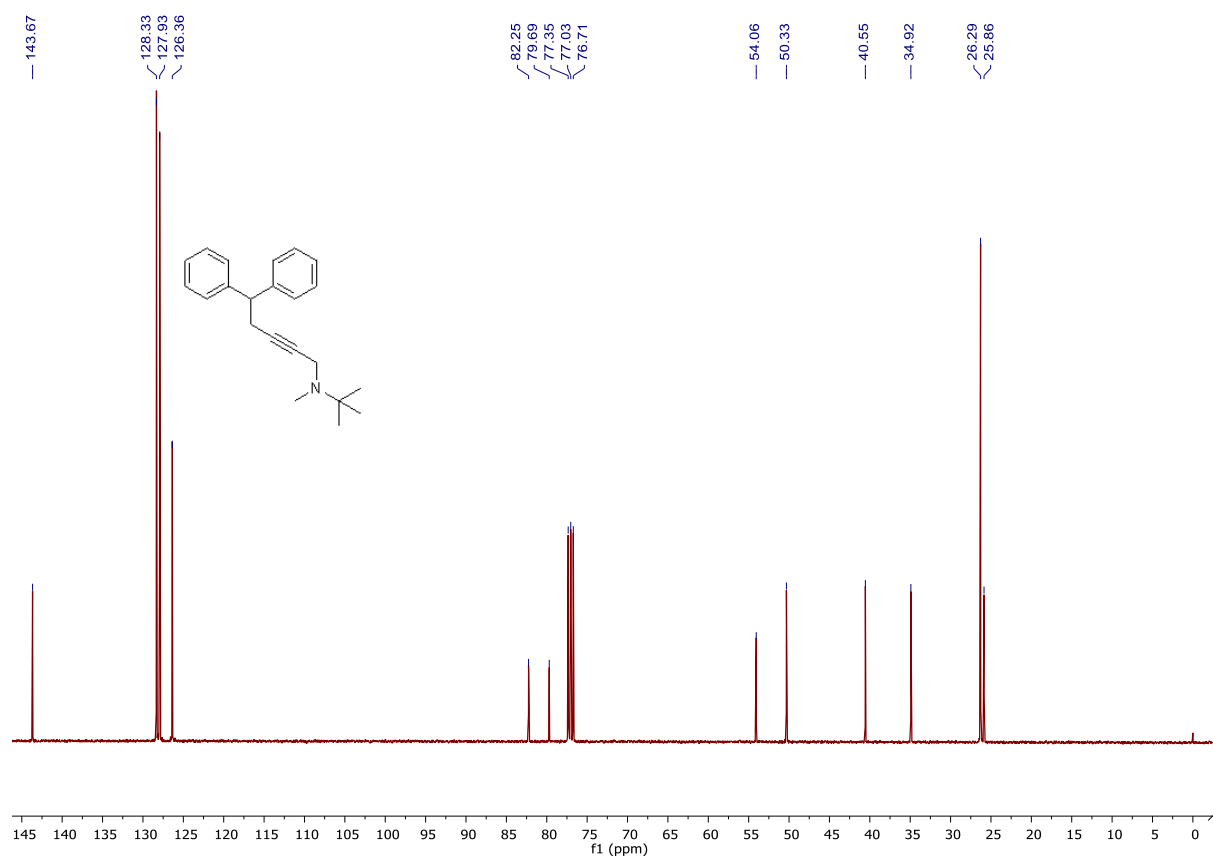


Figure S28: <sup>1</sup>H NMR *N,N*-diisopropyl-5,5-diphenylpent-2-yn-1-amine (29k)

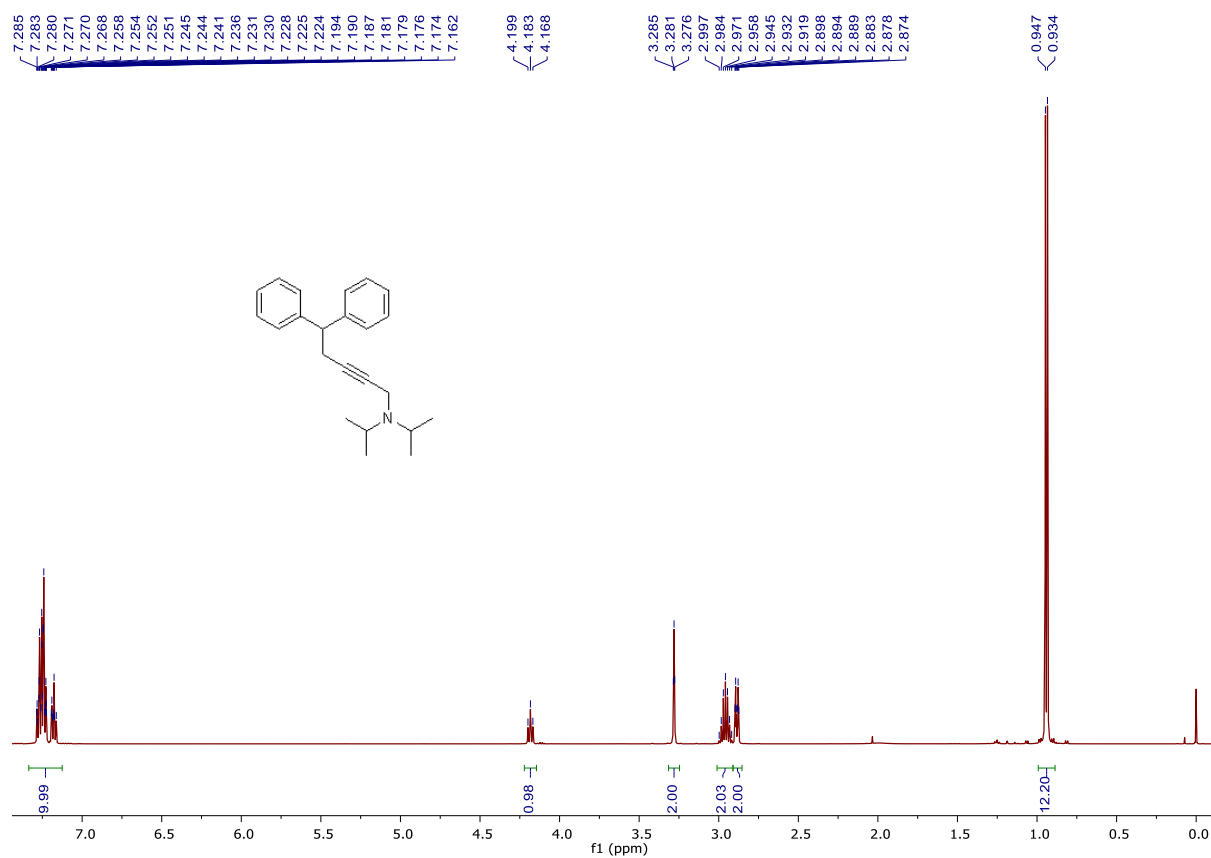


Figure S29: <sup>13</sup>C NMR *N,N*-diisopropyl-5,5-diphenylpent-2-yn-1-amine (29k)

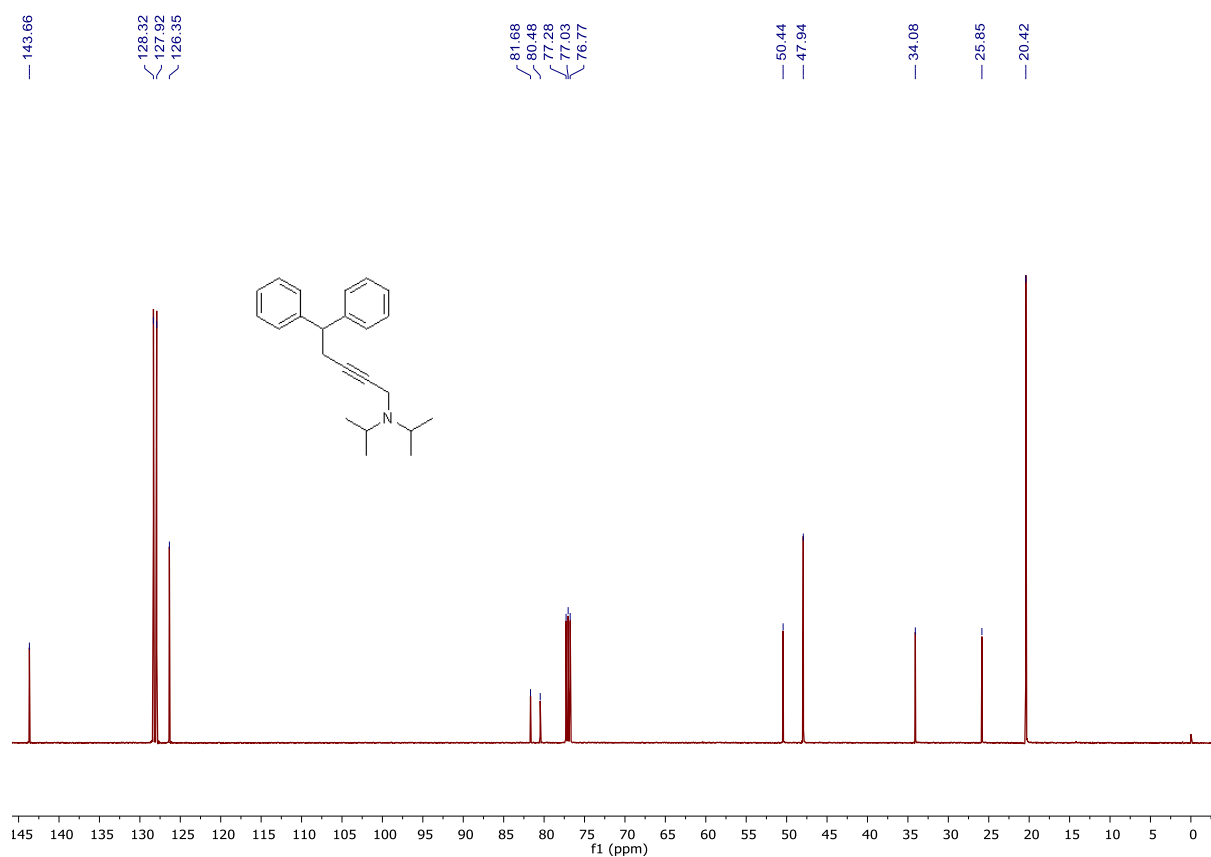


Figure S30: <sup>1</sup>H NMR *N*-allyl-*N*-(*tert*-butyl)undec-2-yn-1-amine (39)

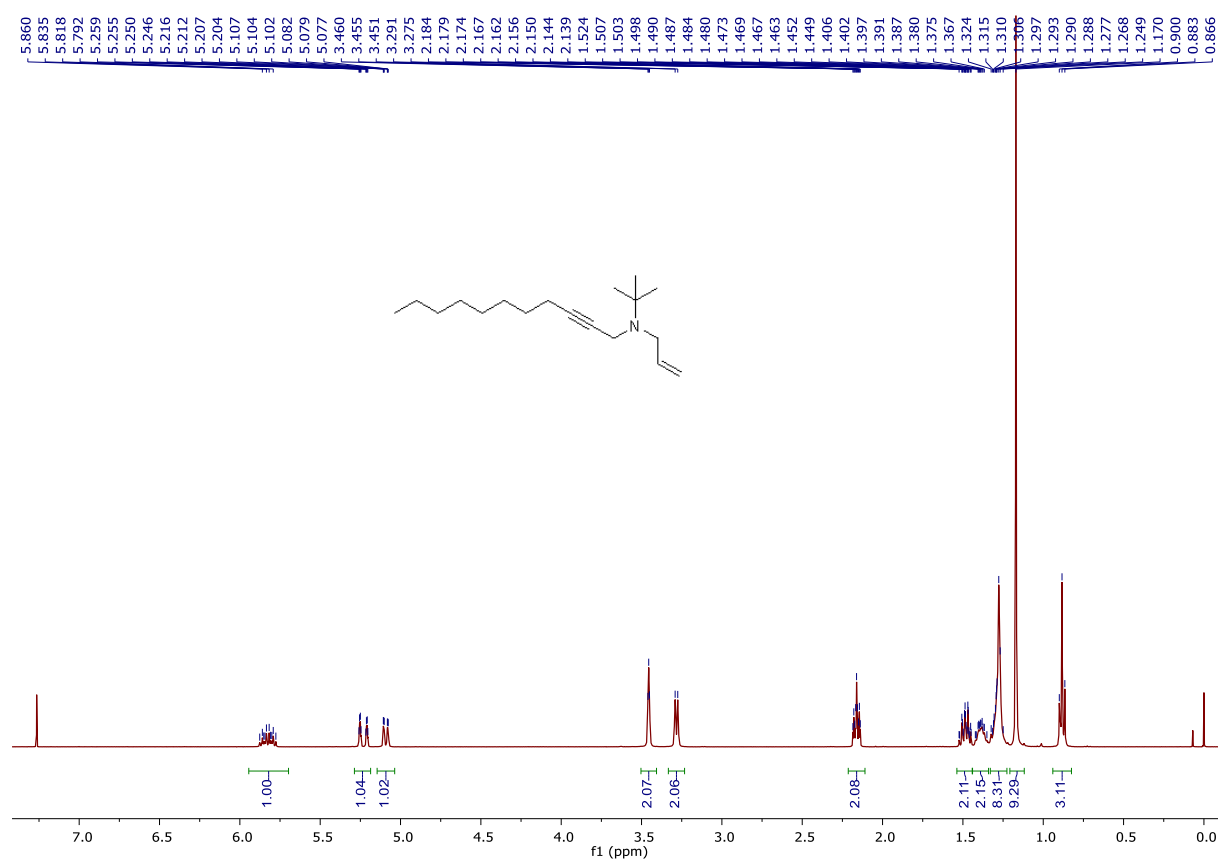


Figure S31: <sup>13</sup>C NMR *N*-allyl-*N*-(*tert*-butyl)undec-2-yn-1-amine (39)

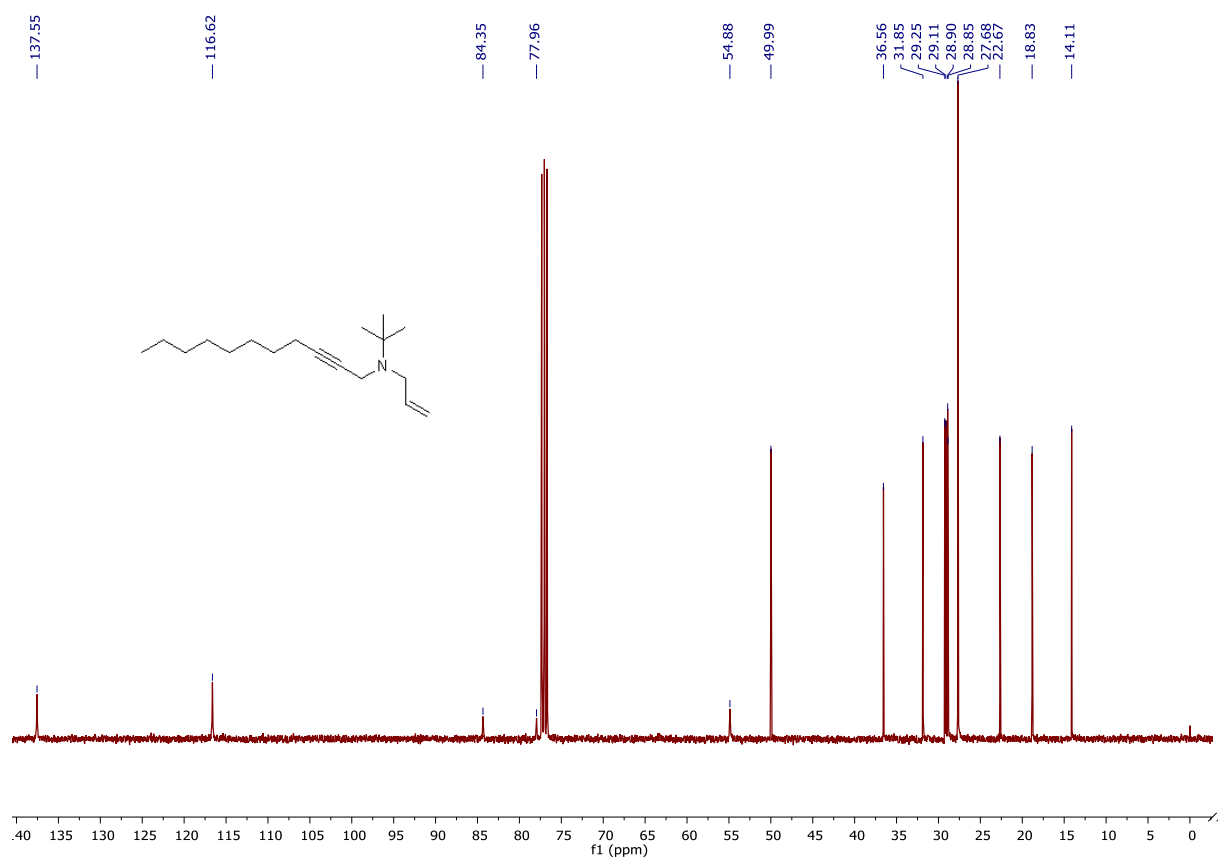




Figure S32: <sup>1</sup>H NMR *N*-allyl-*N*-(*tert*-butyl)-6-chlorohex-2-yn-1-amine (40)

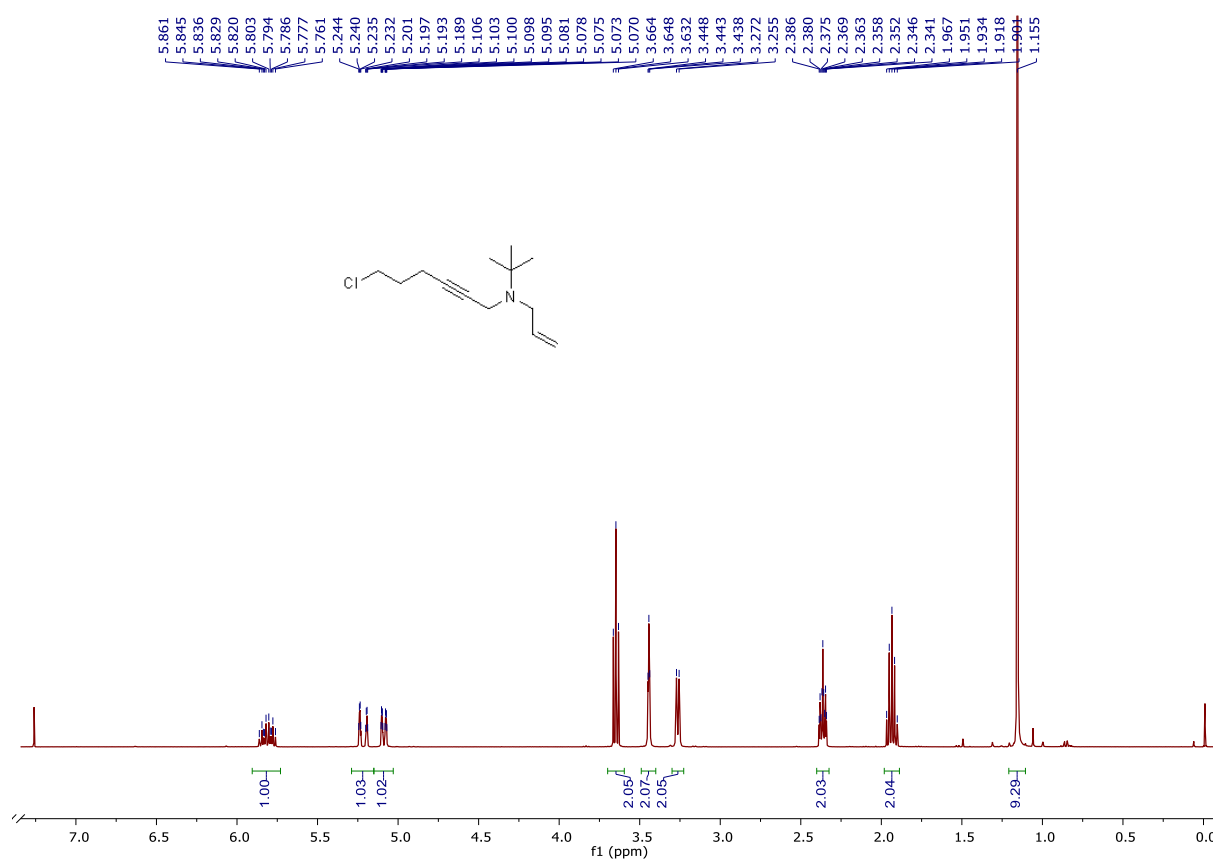


Figure S33: <sup>13</sup>C NMR *N*-allyl-*N*-(*tert*-butyl)-6-chlorohex-2-yn-1-amine (40)

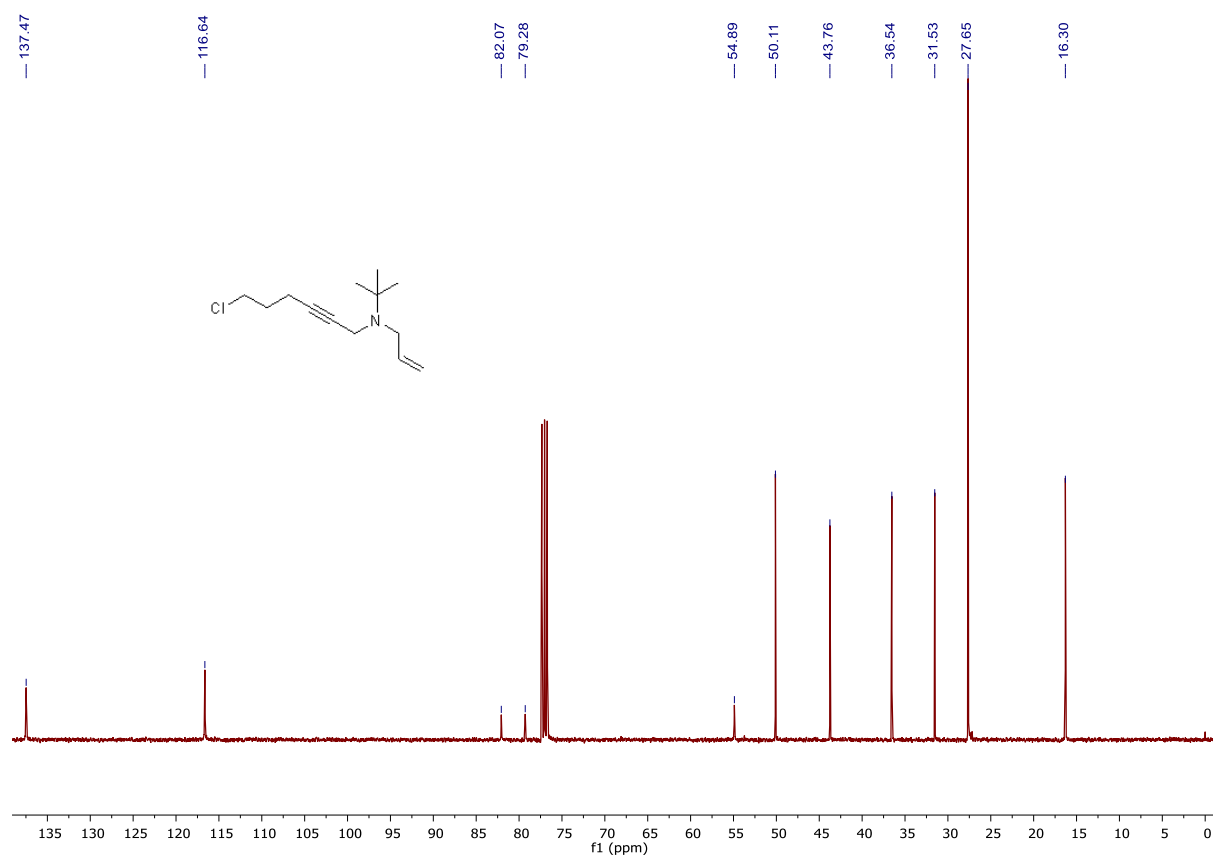


Figure S34: <sup>1</sup>H NMR 7-(allyl(*tert*-butyl)amino)hept-5-ynenitrile (41)

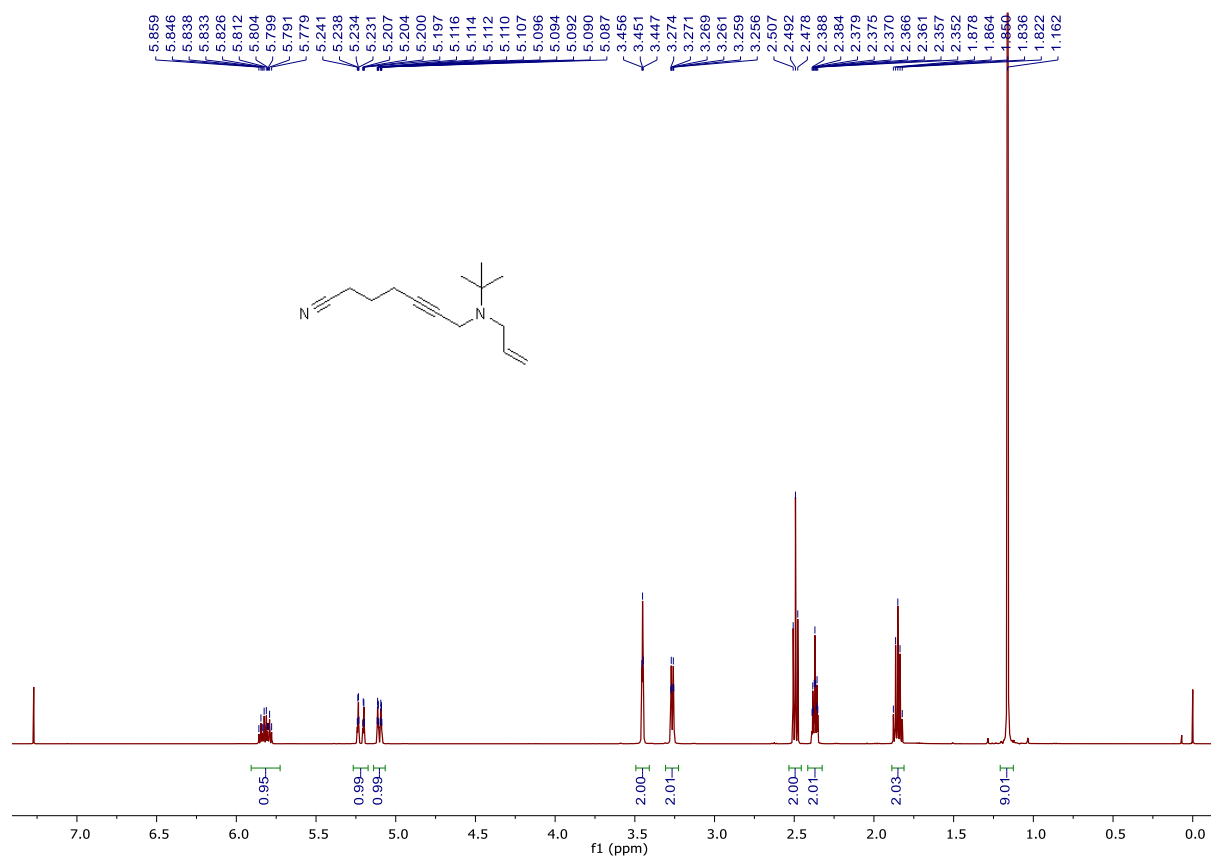


Figure S35: <sup>13</sup>C NMR 7-(allyl(*tert*-butyl)amino)hept-5-ynenitrile (41)

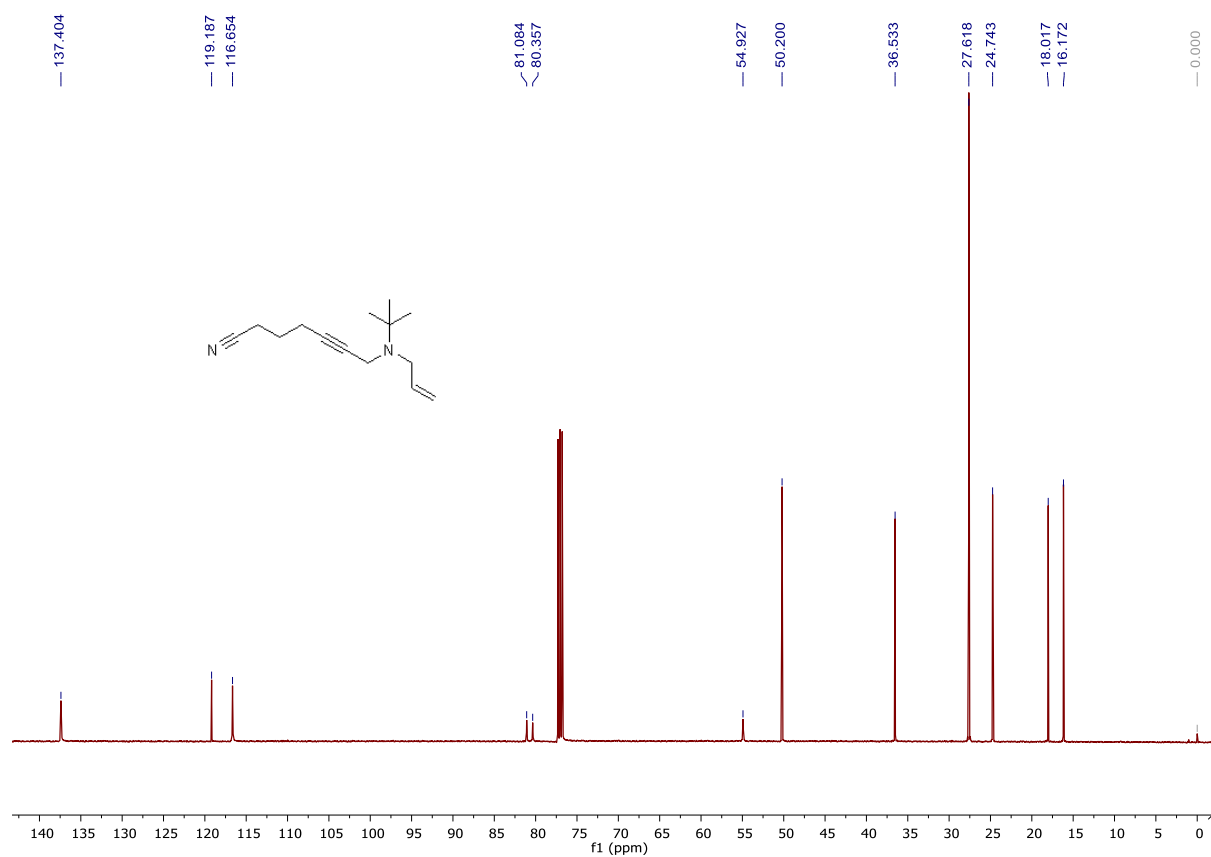


Figure S36: <sup>1</sup>H NMR *N*-allyl-4-(benzyloxy)-*N*-(*tert*-butyl)but-2-yn-1-amine (42)

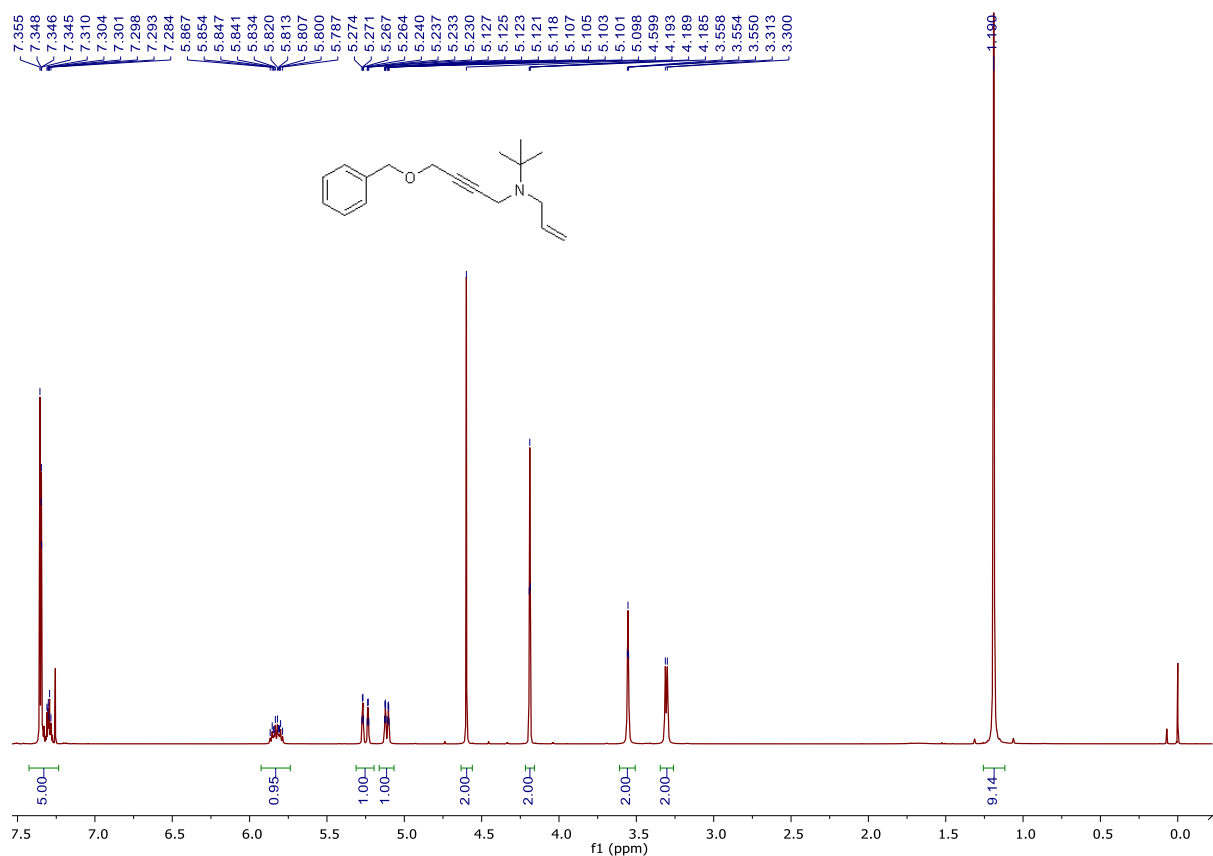


Figure S37: <sup>13</sup>C NMR *N*-allyl-4-(benzyloxy)-*N*-(*tert*-butyl)but-2-yn-1-amine (42)

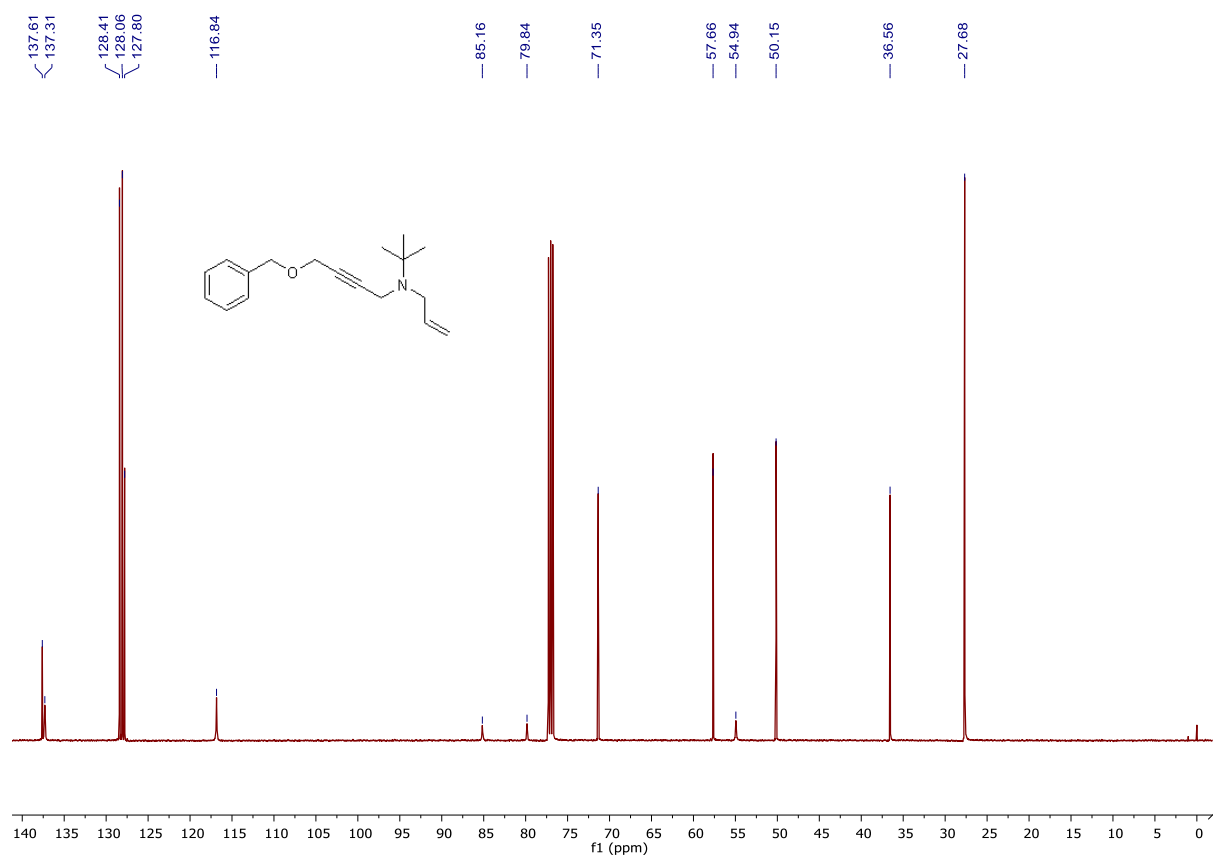


Figure S38: <sup>1</sup>H NMR ethyl 1-{4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (31a)

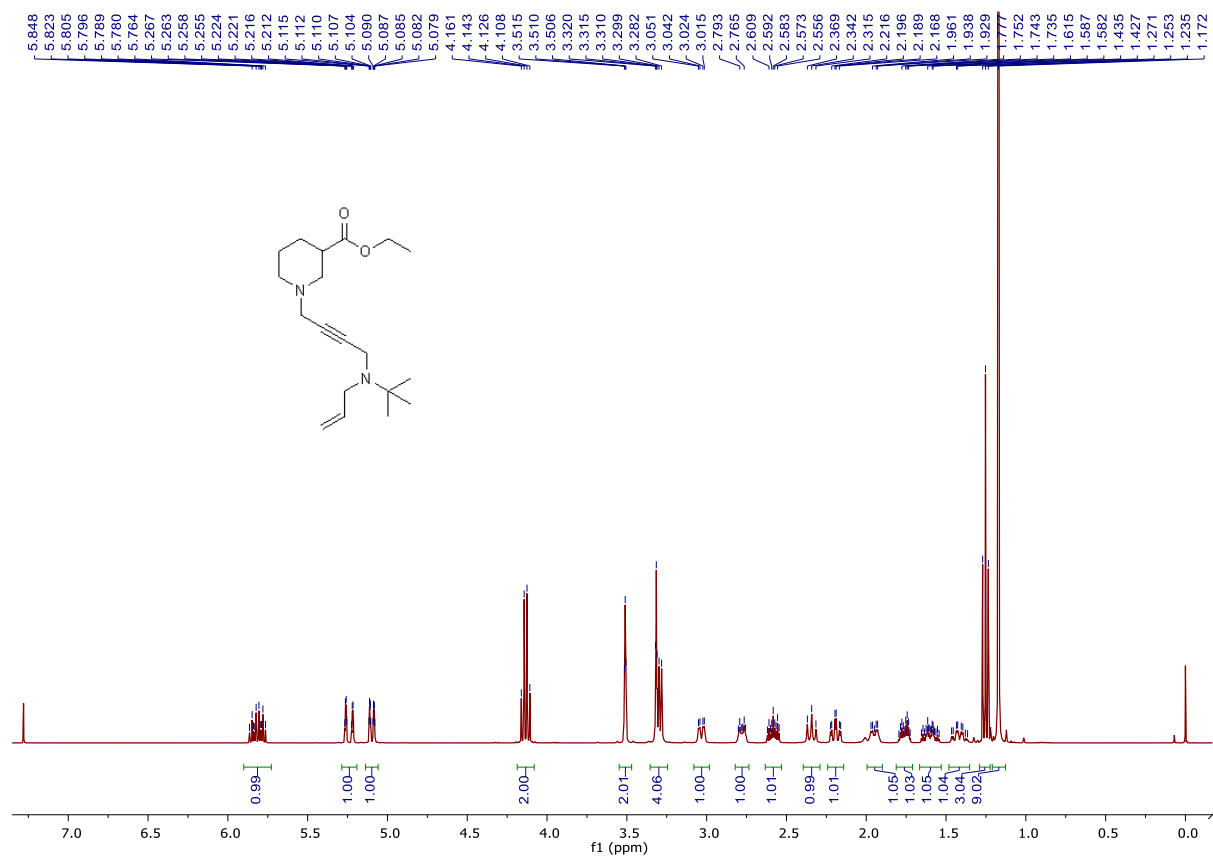


Figure S39:  $^{13}\text{C}$  NMR ethyl 1-{4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (31a)

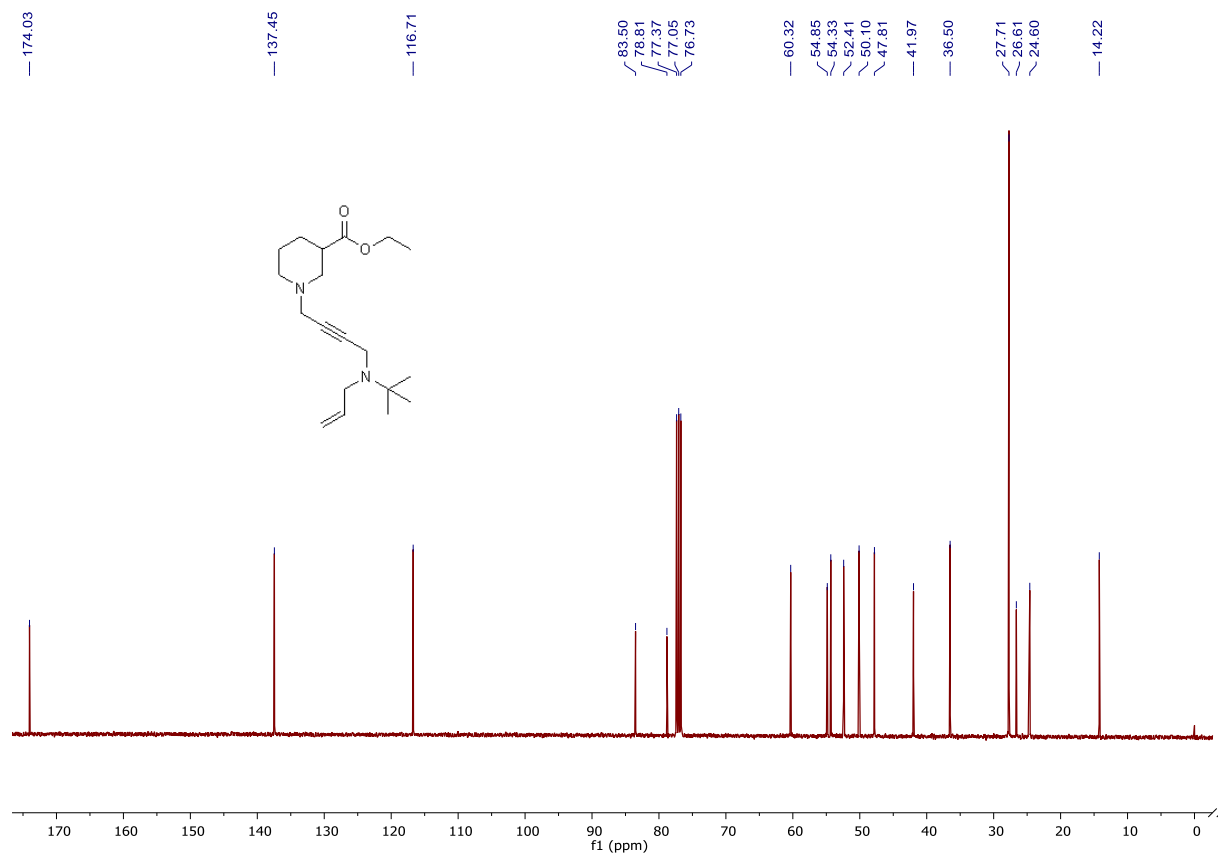
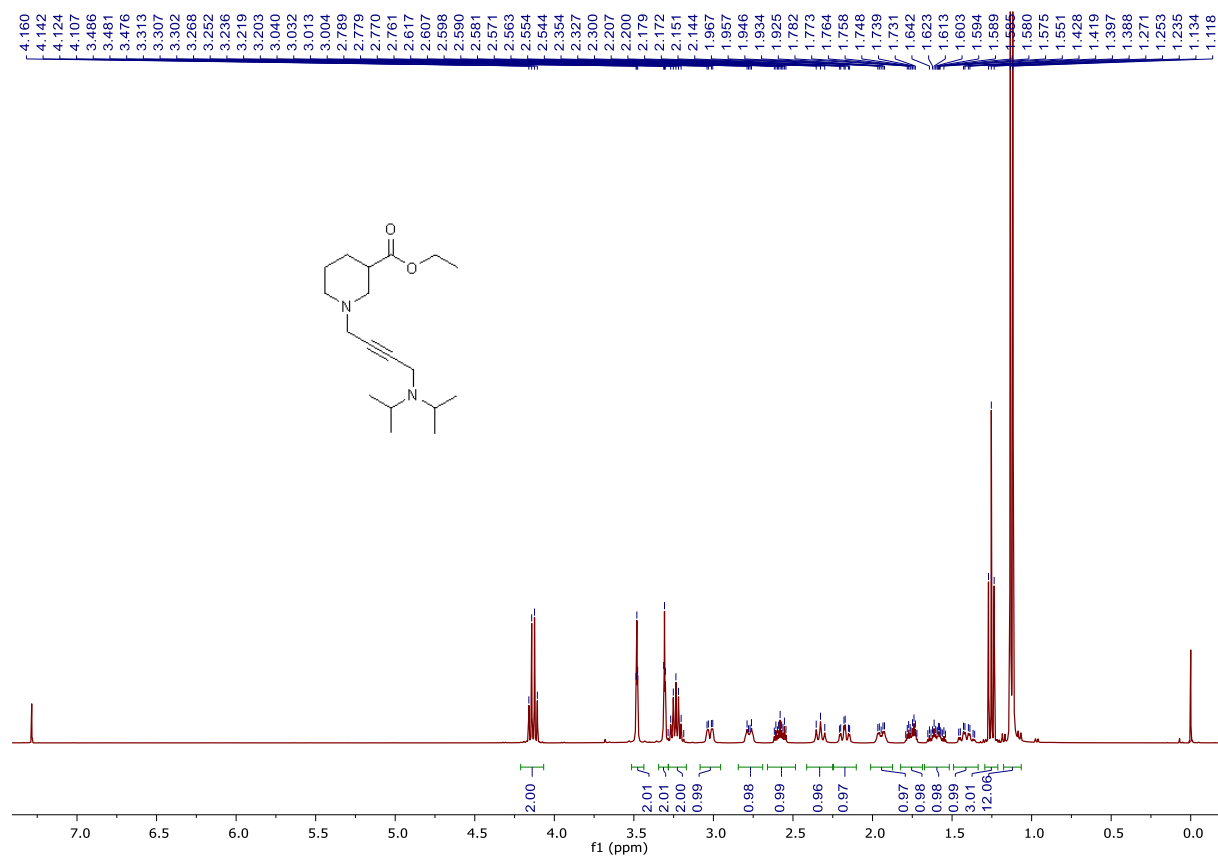
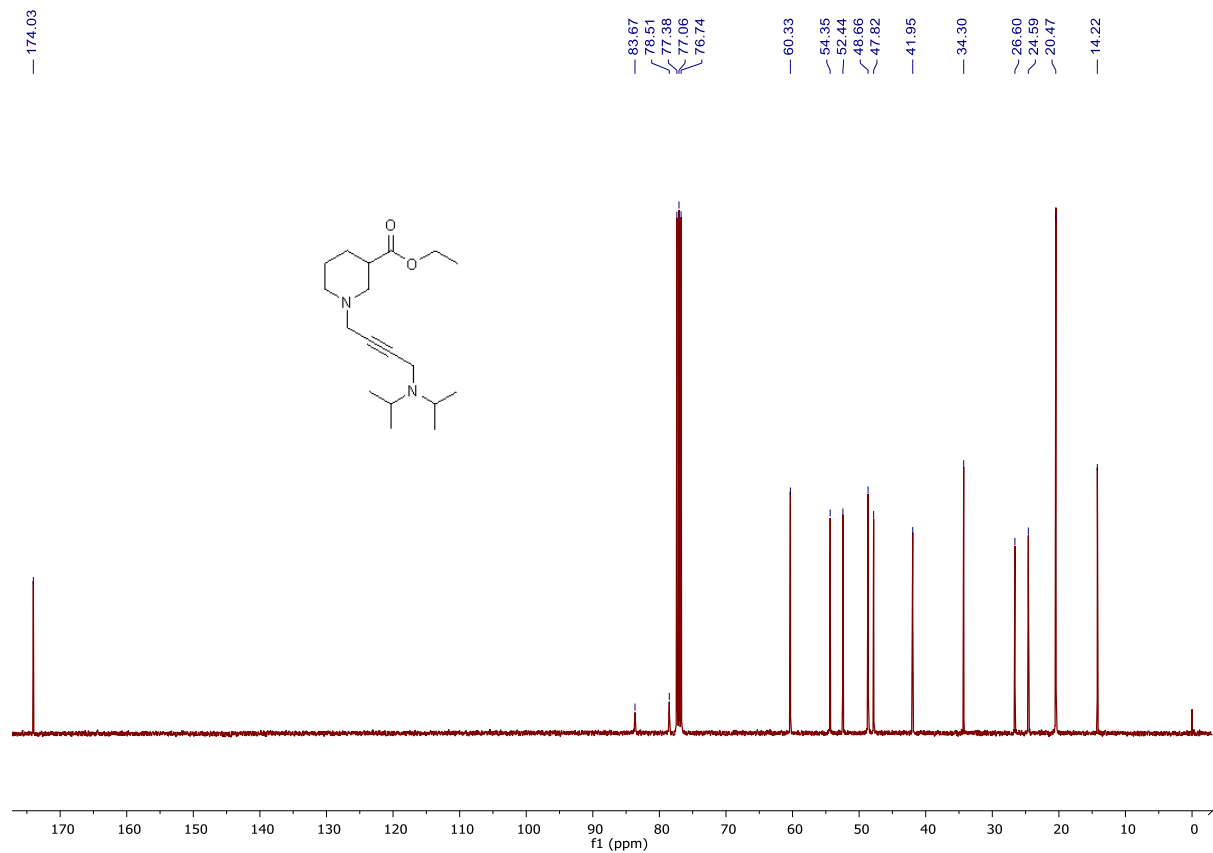


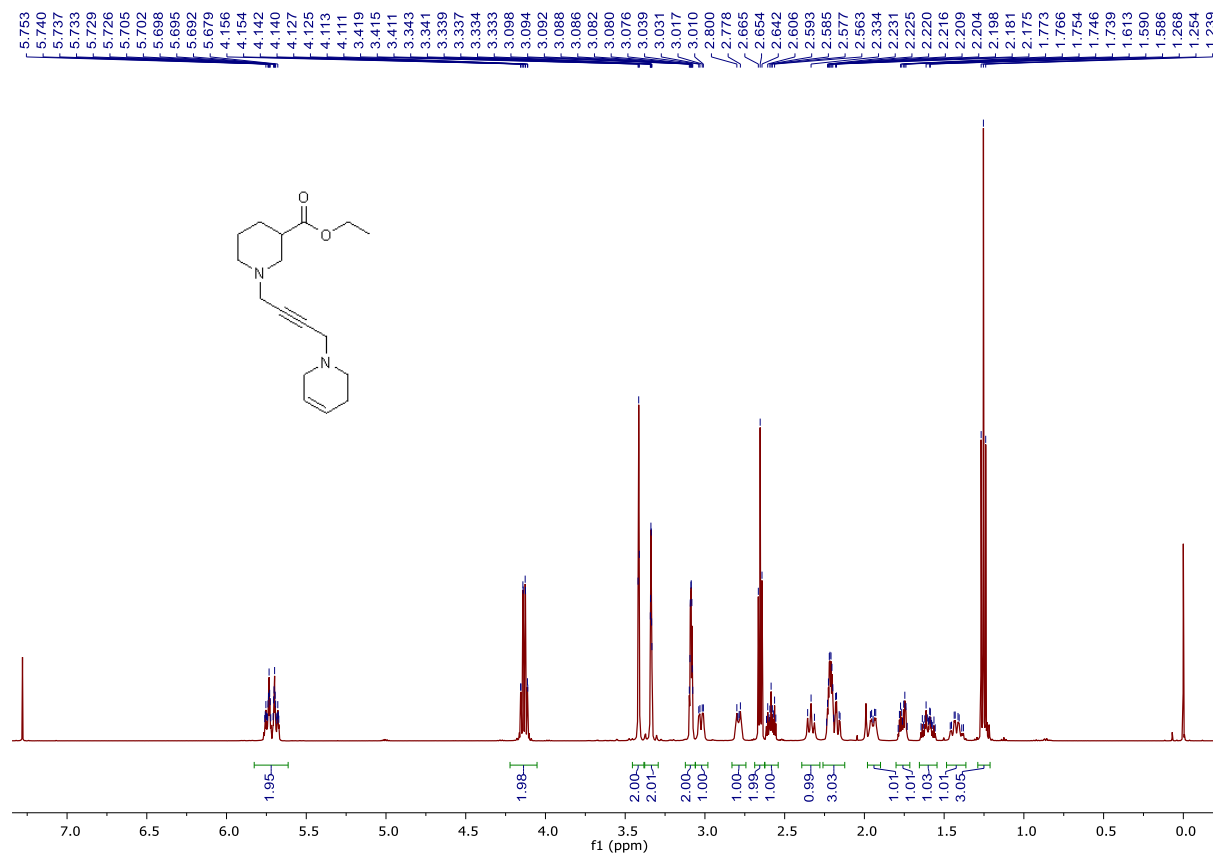
Figure S40: <sup>1</sup>H NMR ethyl 1-[4-(diisopropylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31b)



**Figure S41:  $^{13}\text{C}$  NMR ethyl 1-[4-(diisopropylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31b)**

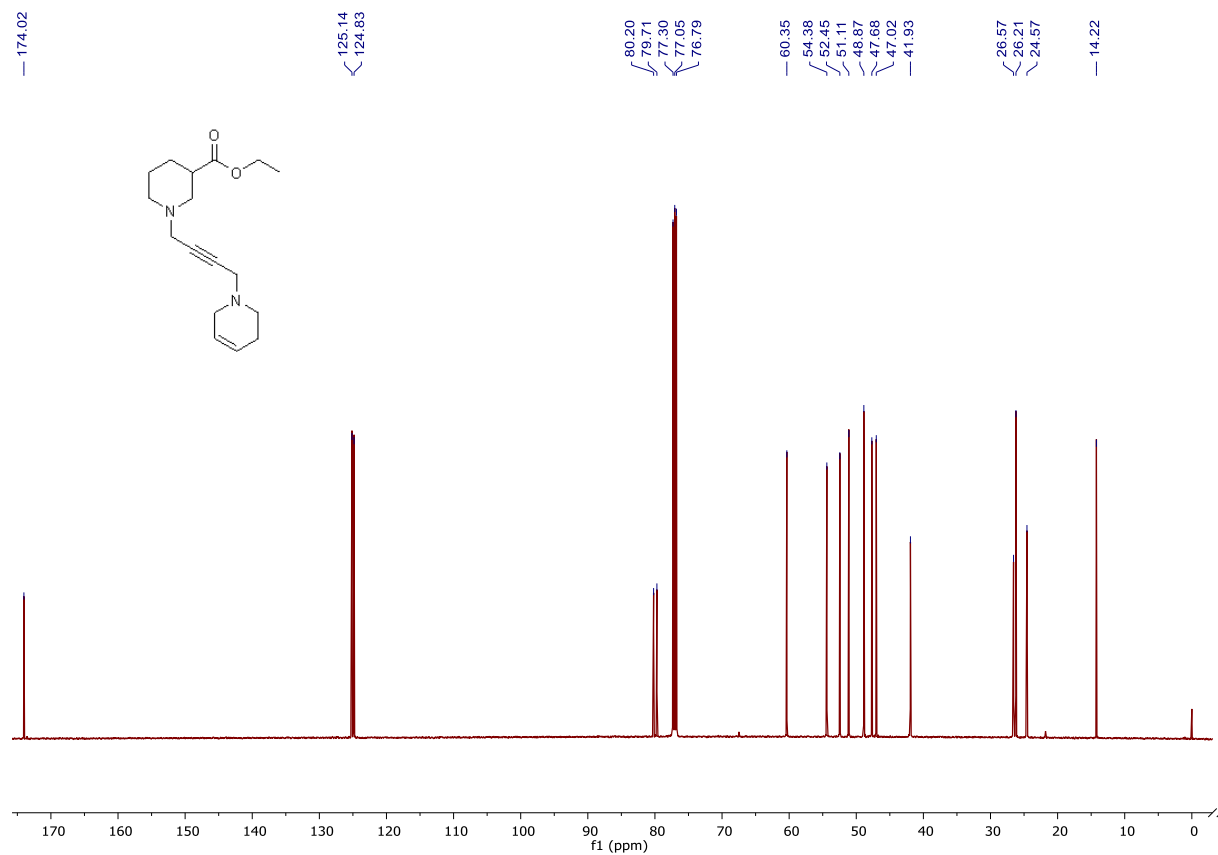


**Figure S42: <sup>1</sup>H NMR ethyl 1-{4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}piperidine-3-carboxylate (31c)**

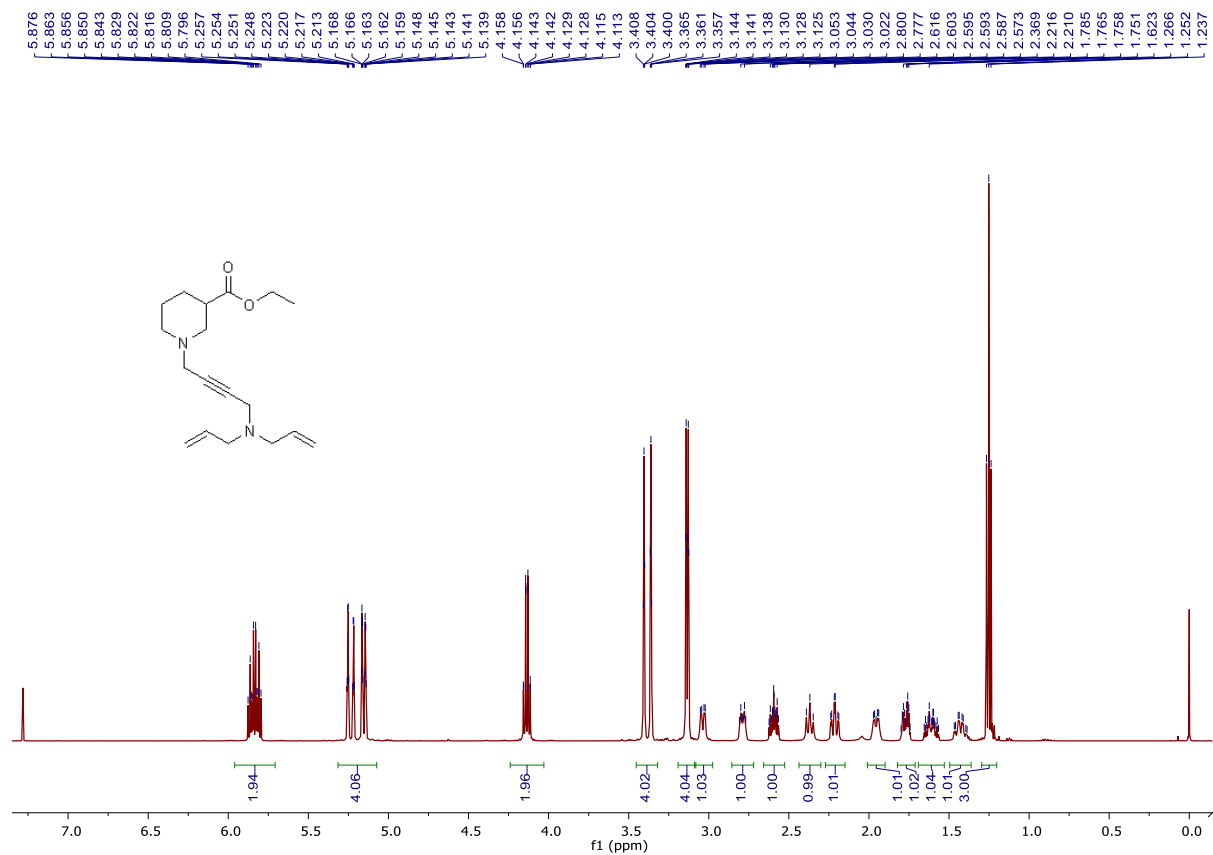




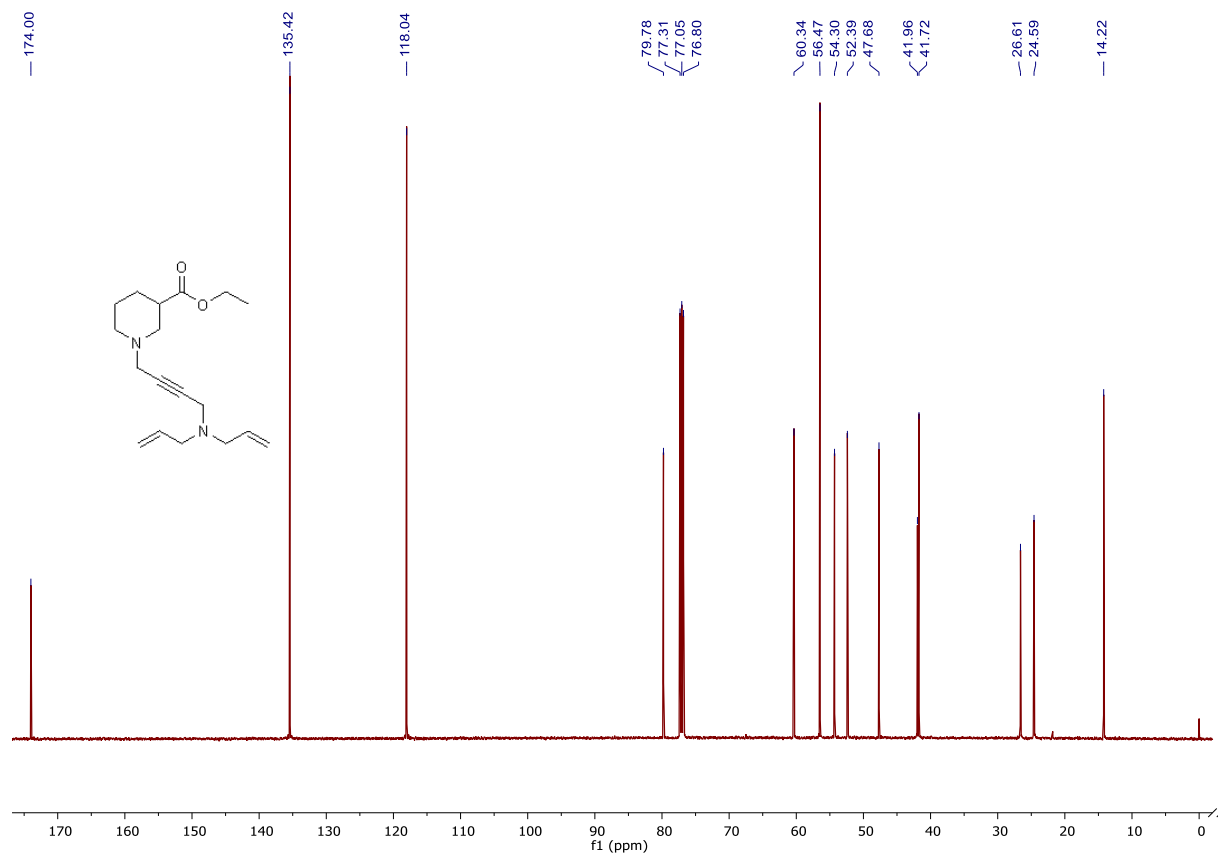
**Figure S43:**  $^{13}\text{C}$  NMR ethyl 1-{4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}piperidine-3-carboxylate (31c)



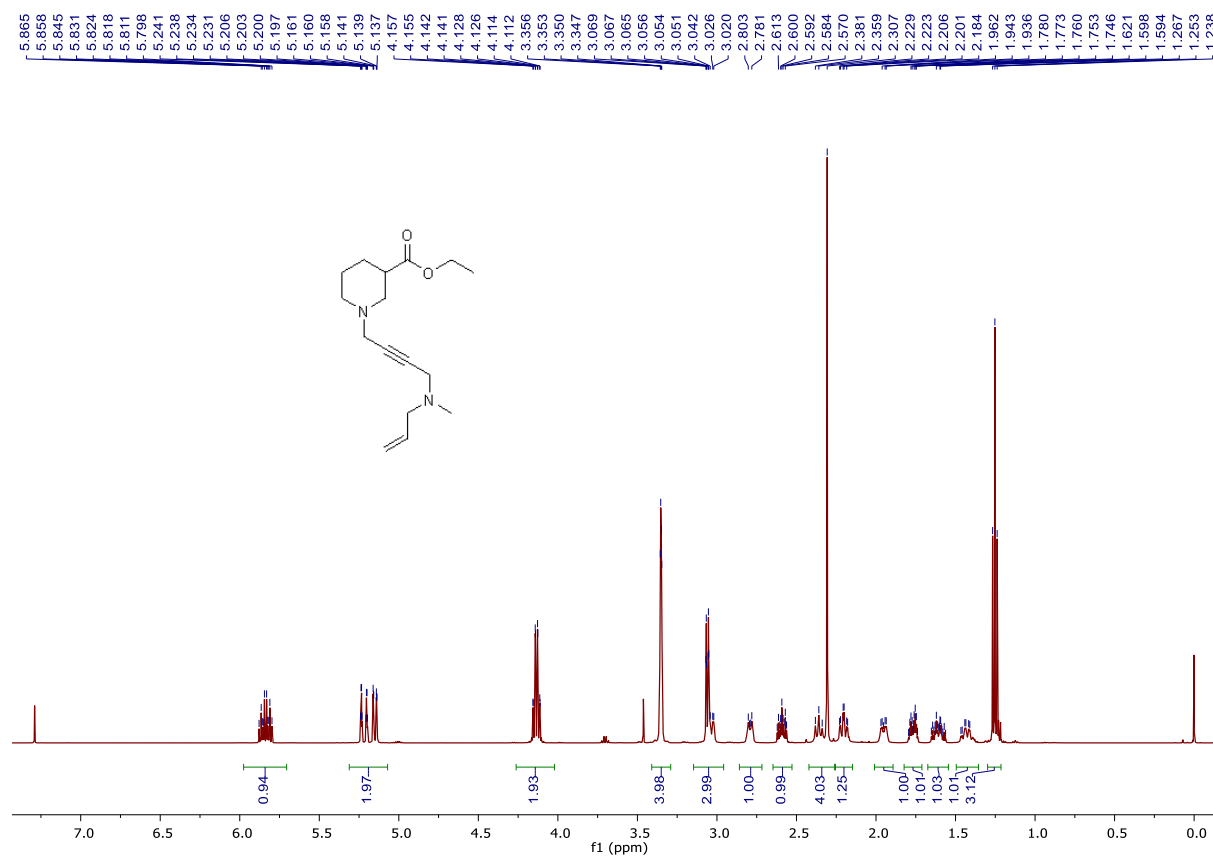
**Figure S44: <sup>1</sup>H NMR ethyl 1-[4-(diallylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31d)**



**Figure S45:**  $^{13}\text{C}$  NMR ethyl 1-[4-(diallylamino)but-2-yn-1-yl]piperidine-3-carboxylate (31d)



**Figure S46: <sup>1</sup>H NMR ethyl 1-(4-[allyl(methyl)amino]but-2-yn-1-yl)piperidine-3-carboxylate (31e)**



**Figure S47:  $^{13}\text{C}$  NMR ethyl 1-{4-[allyl(methyl)amino]but-2-yn-1-yl}piperidine-3-carboxylate (31e)**

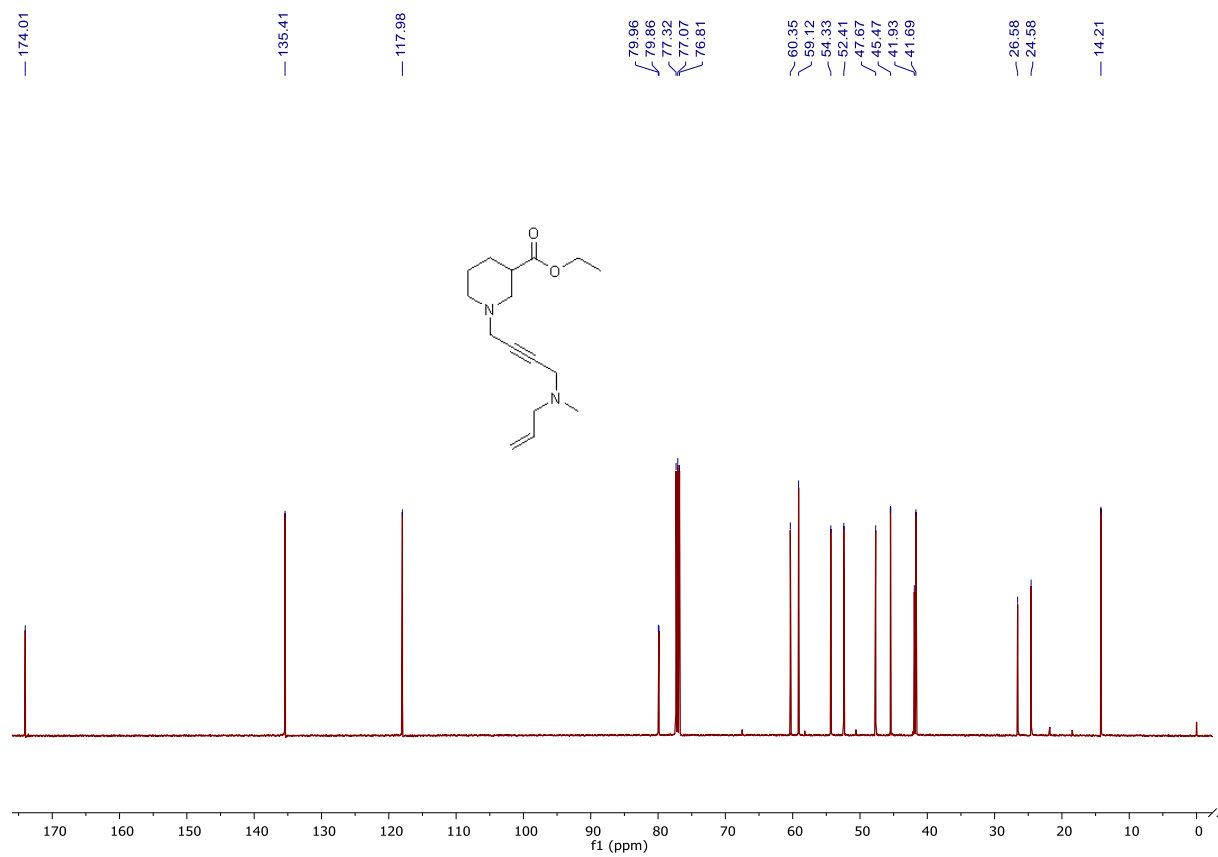


Figure S48: <sup>1</sup>H NMR ethyl 1-(4-[*tert*-butyl(isopropyl)amino]but-2-yn-1-yl)piperidine-3-carboxylate (31f)

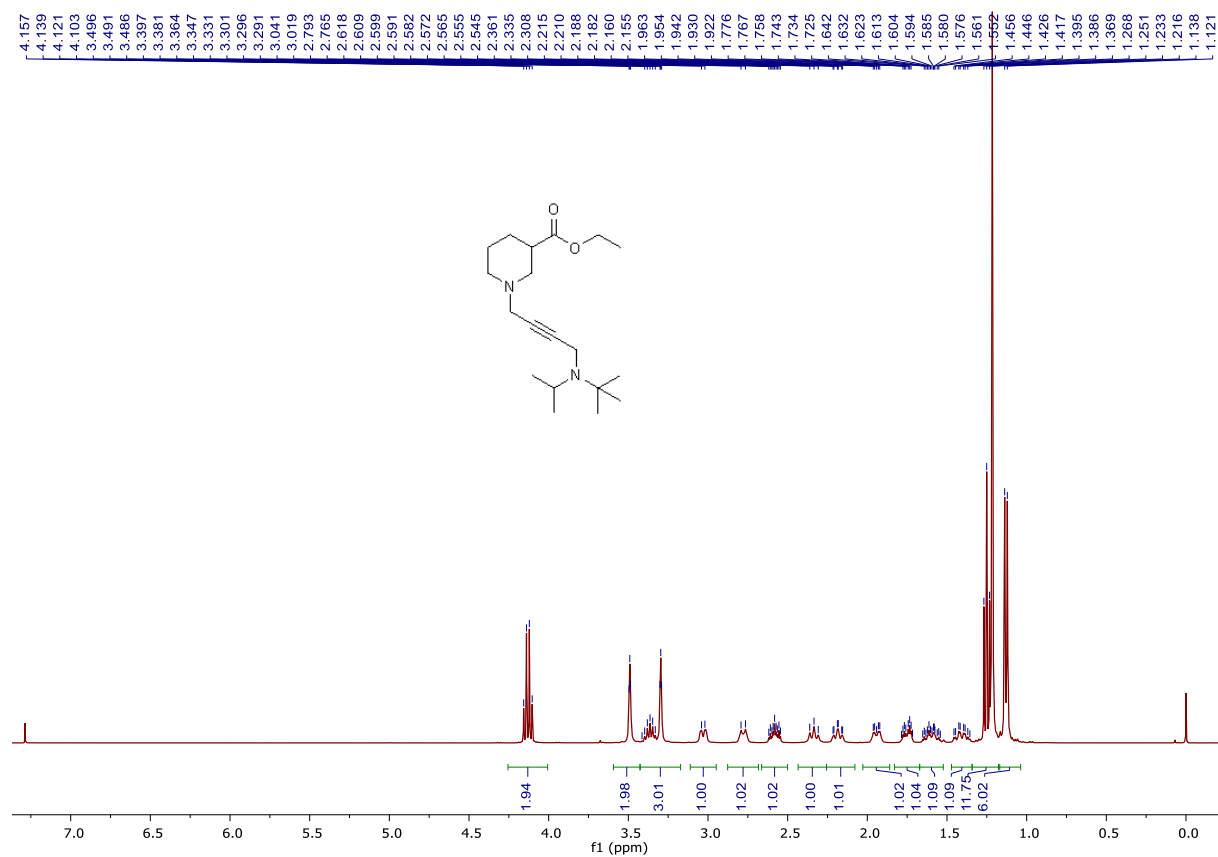


Figure S49:  $^{13}\text{C}$  NMR ethyl 1-(4-[*tert*-butyl(isopropyl)amino]but-2-yn-1-yl)piperidine-3-carboxylate (31f)

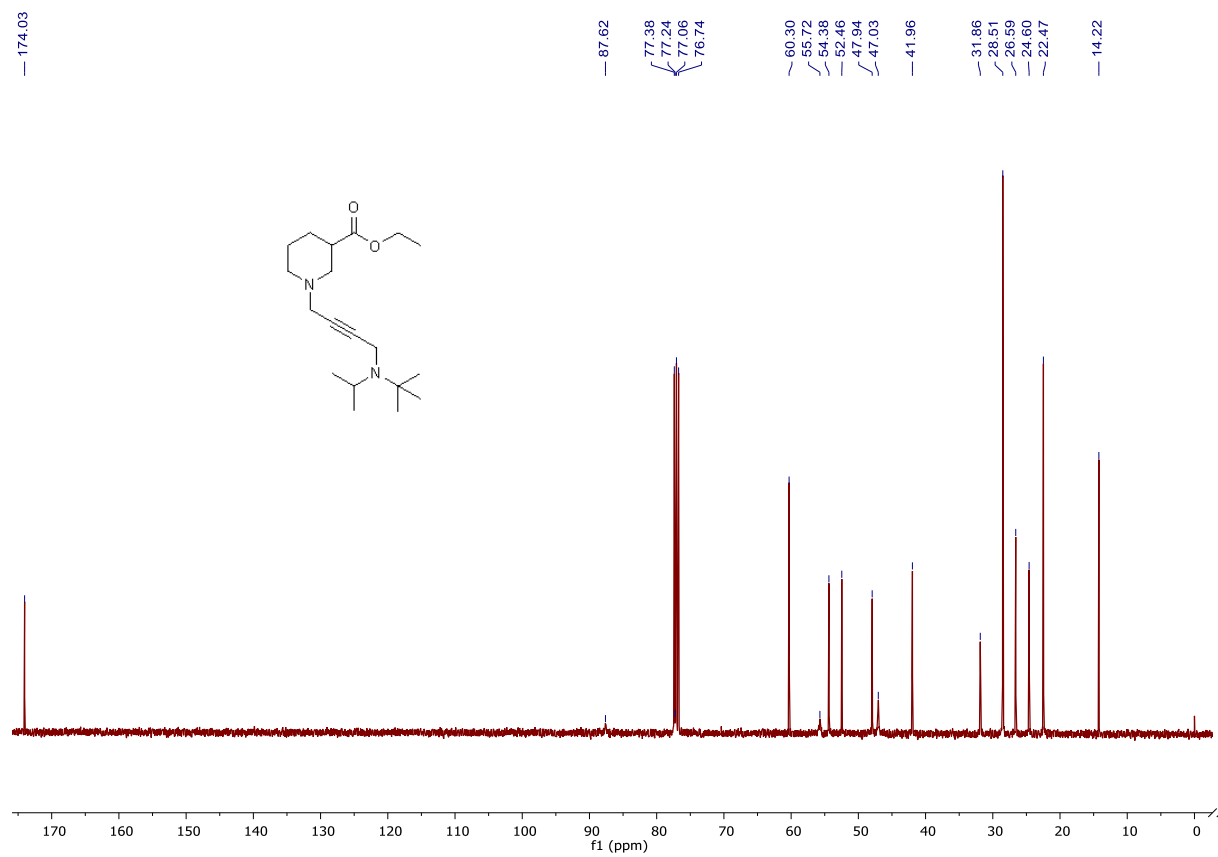


Figure S50: <sup>1</sup>H NMR *N,N*-diallyl-1,5,5-triphenylpent-2-yn-1-amine (29n)

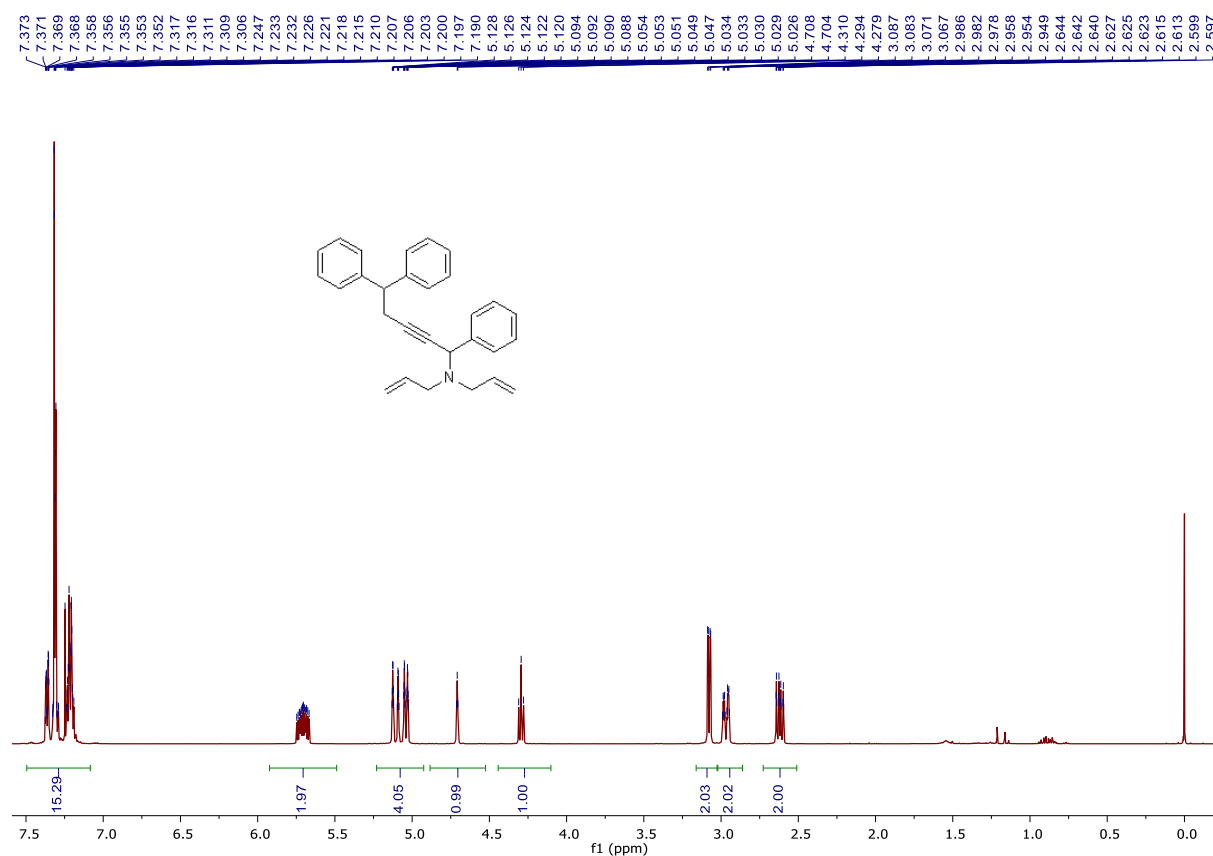


Figure S51: <sup>13</sup>C NMR *N,N*-diallyl-1,5,5-triphenylpent-2-yn-1-amine (29n)

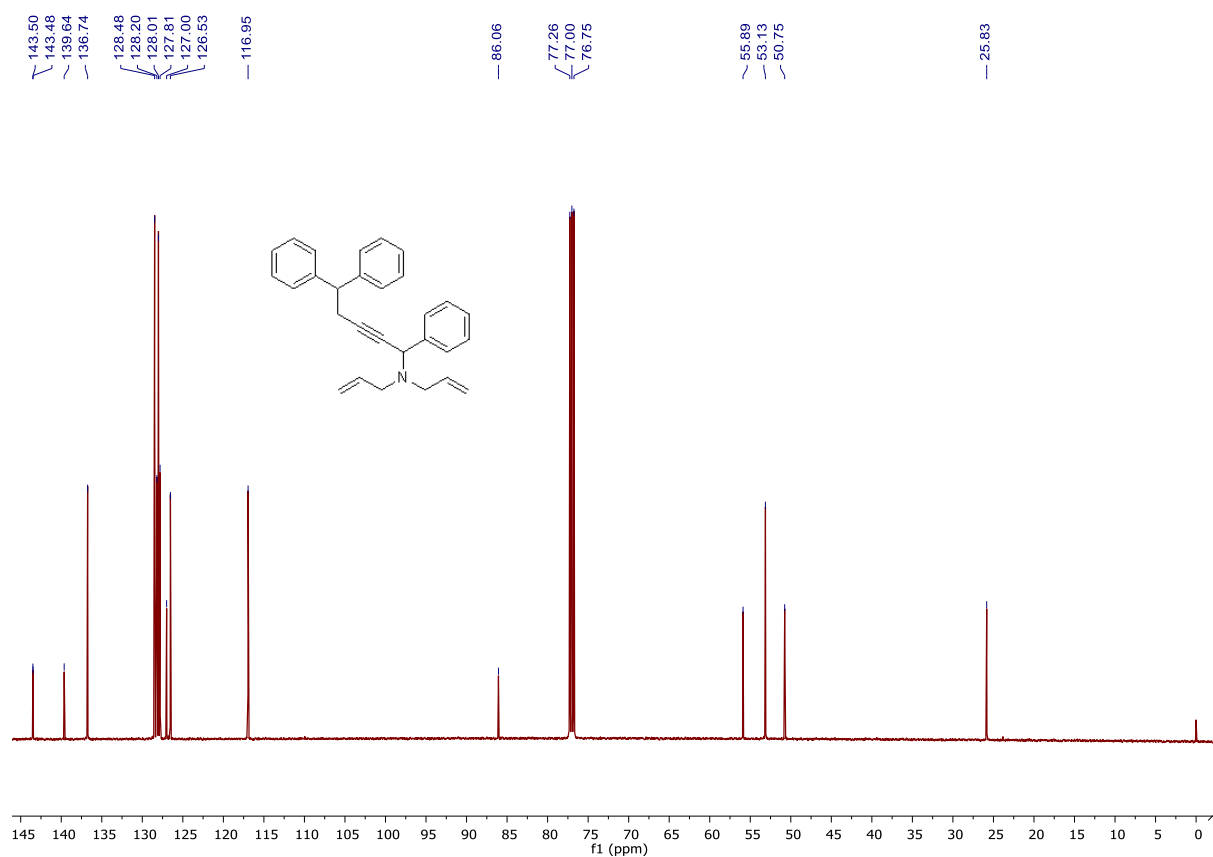




Figure S52: <sup>1</sup>H NMR *N*-allyl-*N*-methyl-1,5,5-triphenylpent-2-yn-1-amine (29o)

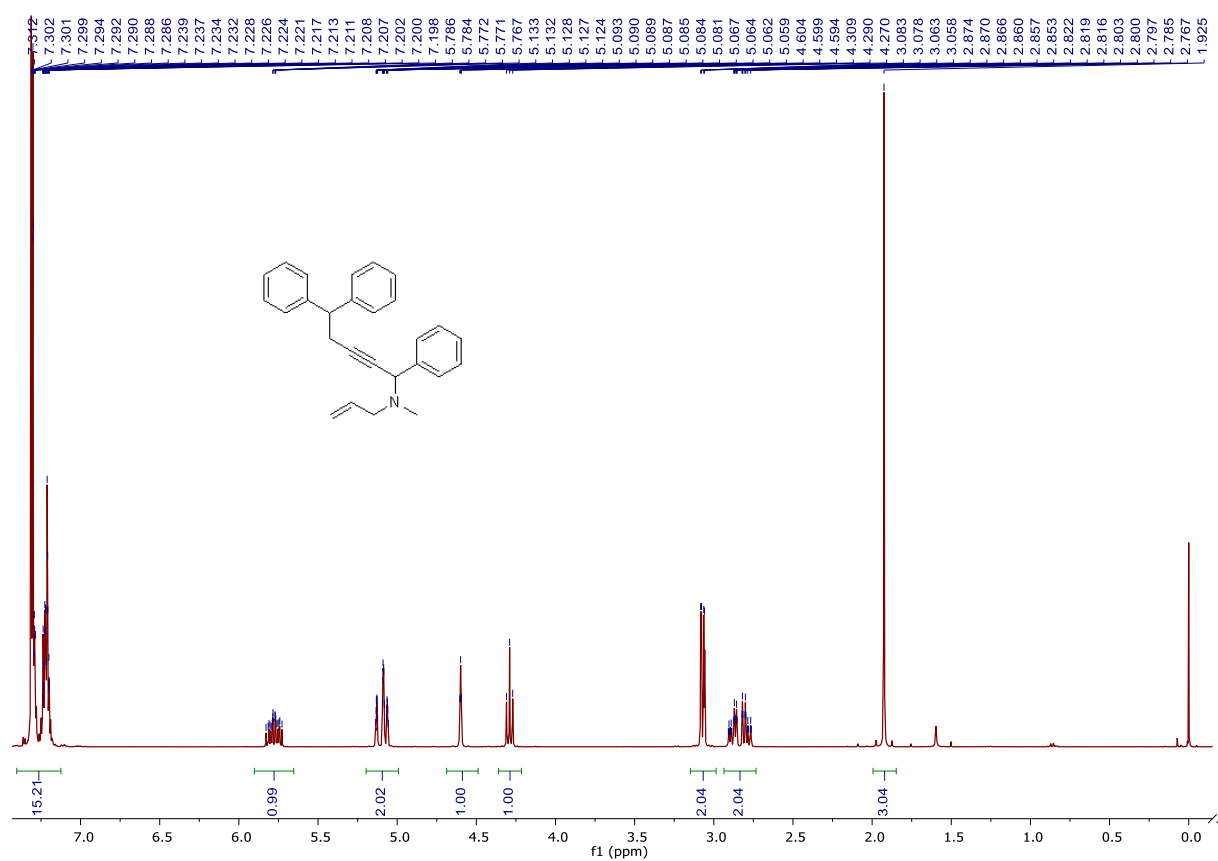
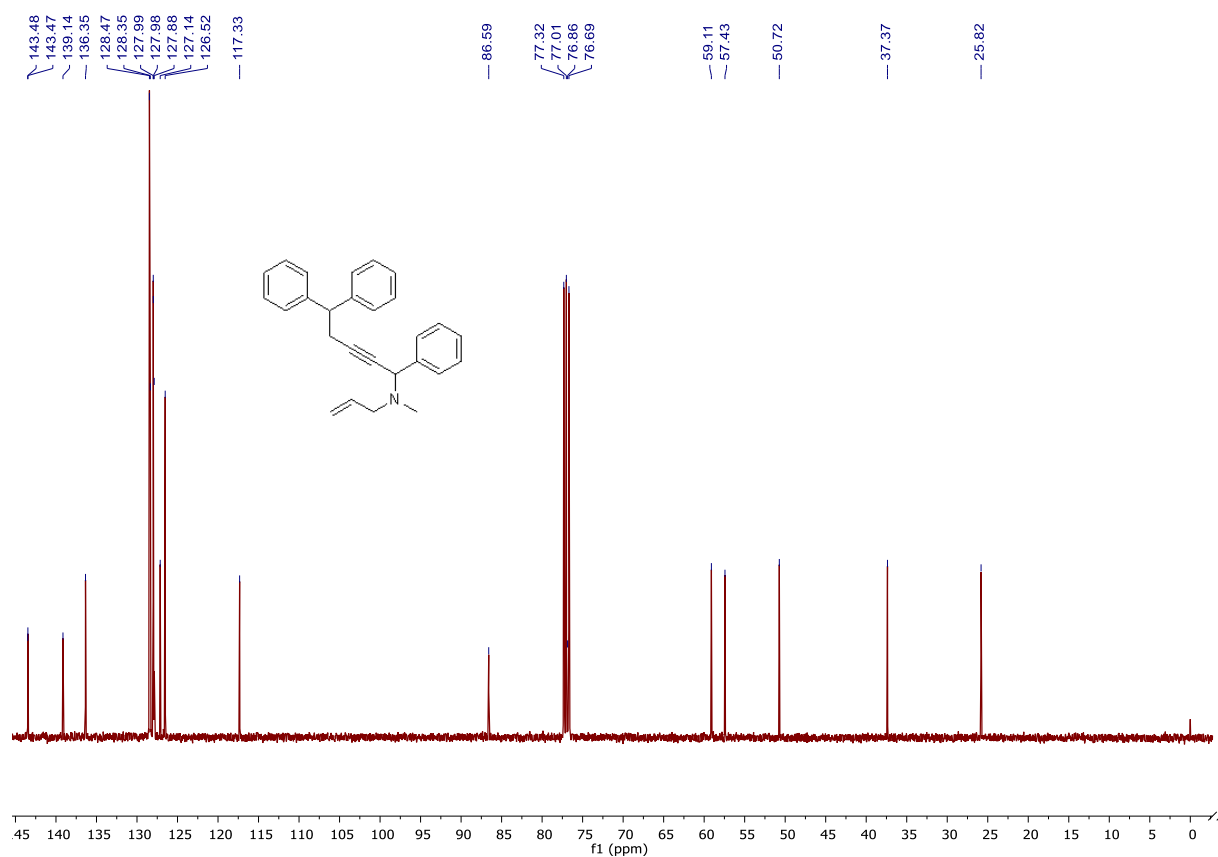


Figure S53: <sup>13</sup>C NMR *N*-allyl-*N*-methyl-1,5,5-triphenylpent-2-yn-1-amine (29o)



**Figure S54: <sup>1</sup>H NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-phenylbut-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31h); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-phenylbut-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31h)**

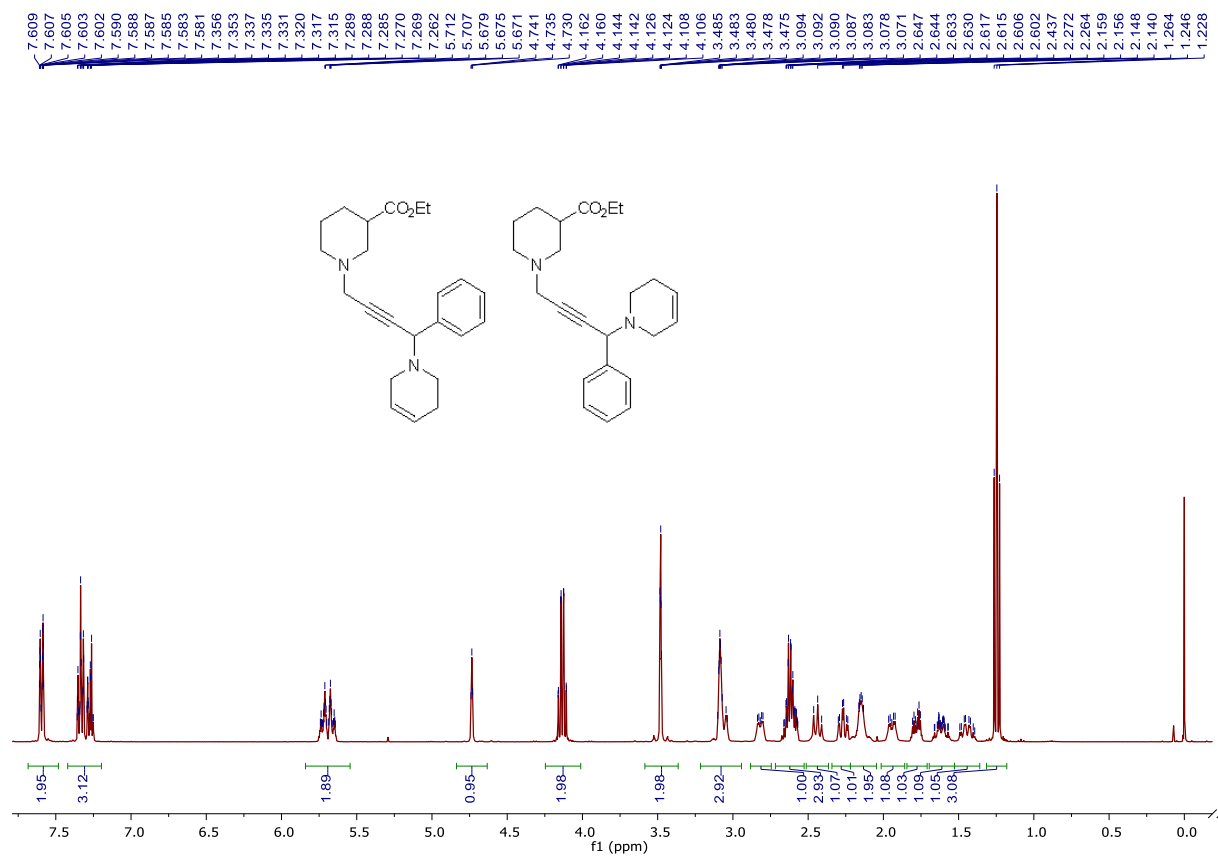


Figure S55:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-phenylbut-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31h); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-phenylbut-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31h)

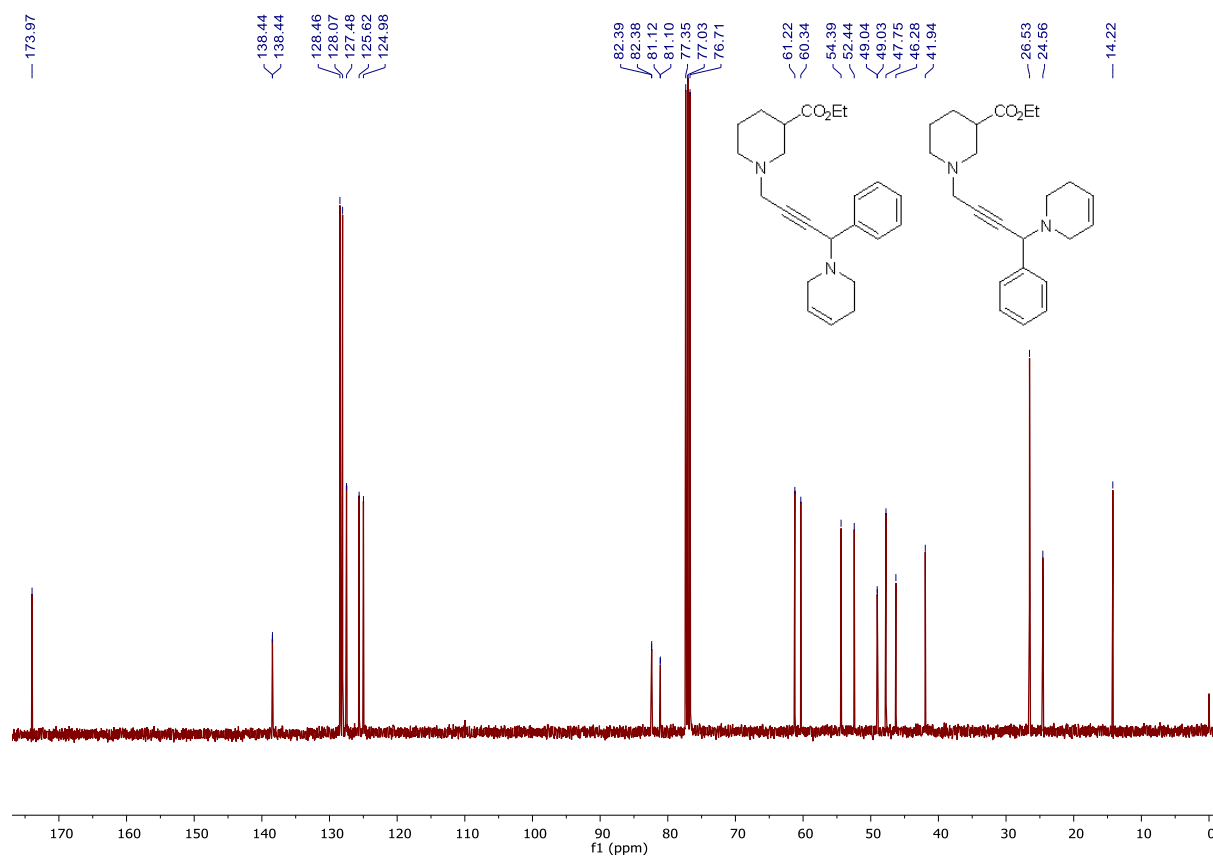


Figure S56: <sup>1</sup>H NMR 1-(1,5,5-triphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (29I)

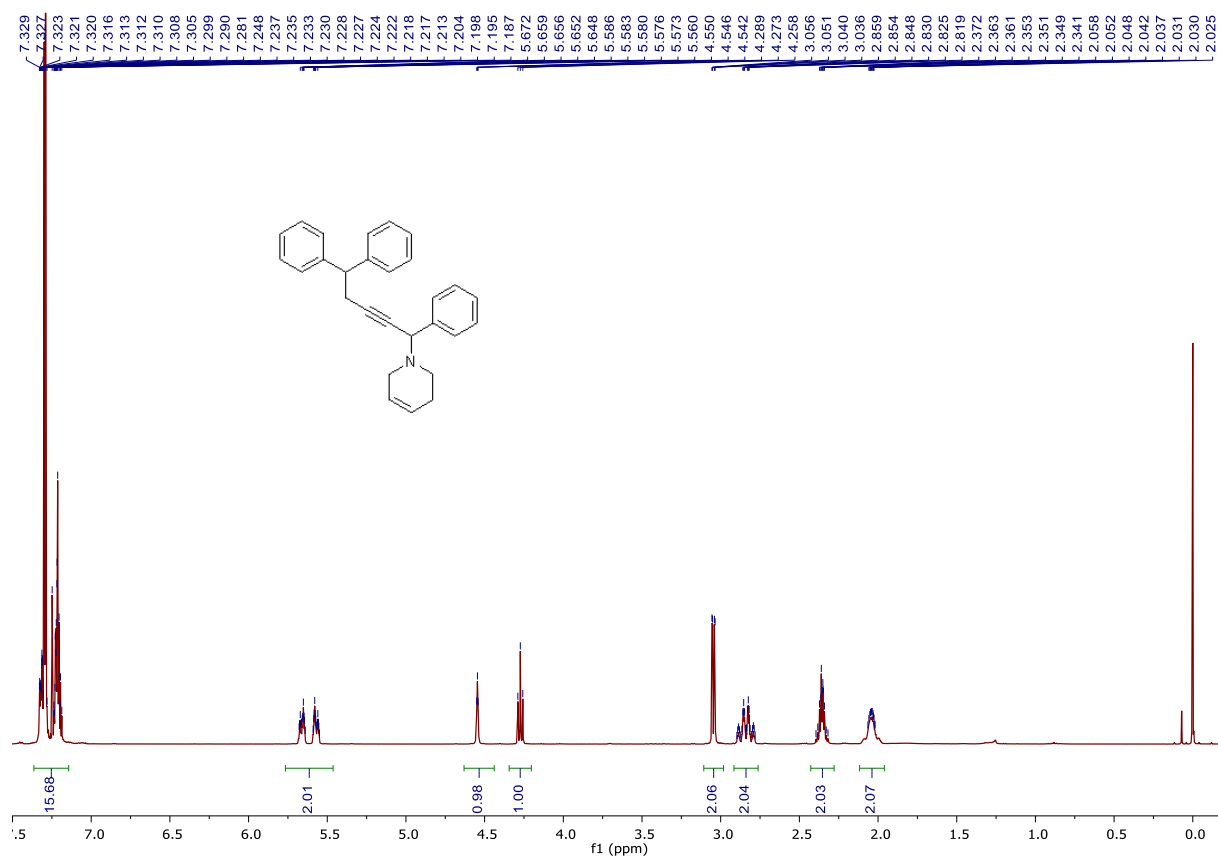


Figure S57: <sup>13</sup>C NMR 1-(1,5,5-triphenylpent-2-yn-1-yl)-1,2,3,6-tetrahydropyridine (29I)

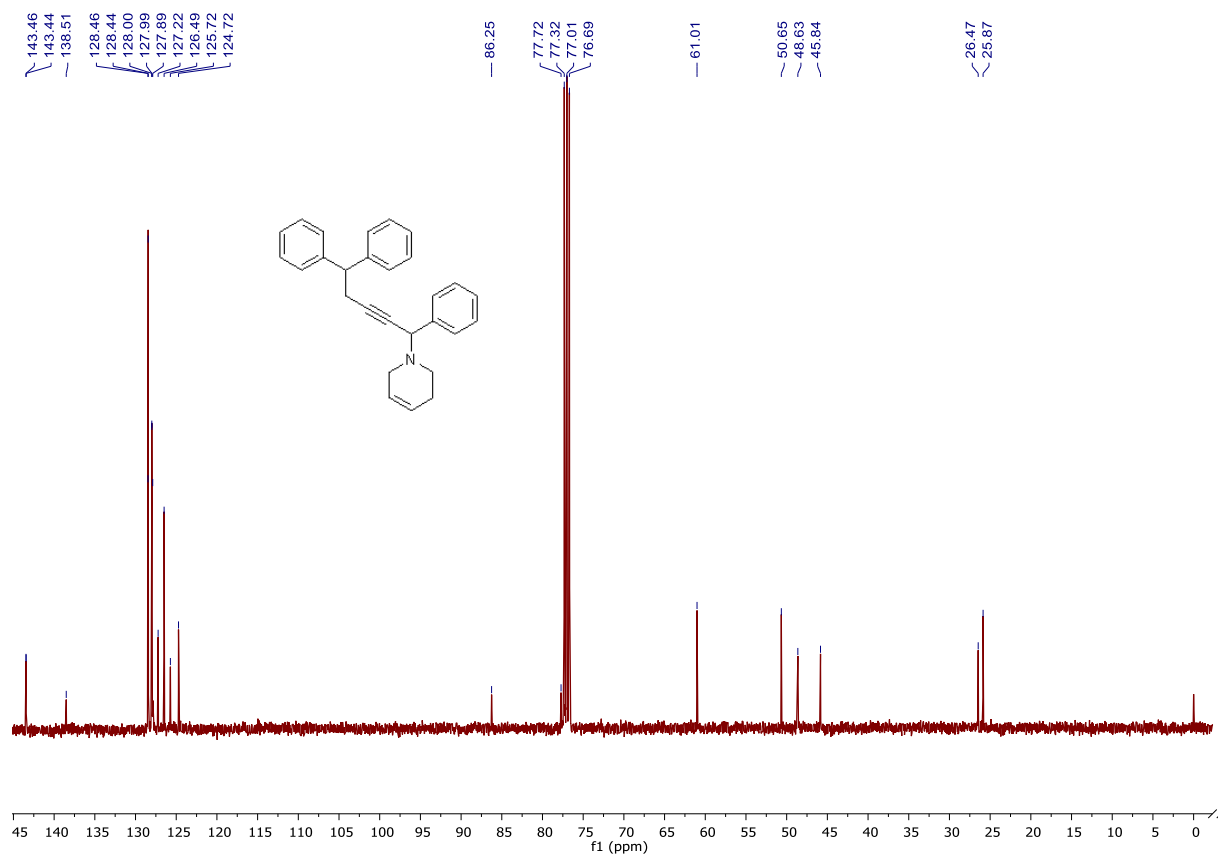


Figure S58: <sup>1</sup>H NMR *N*-allyl-*N*-(*tert*-butyl)-1,5,5-triphenylpent-2-yn-1-amine (29m)

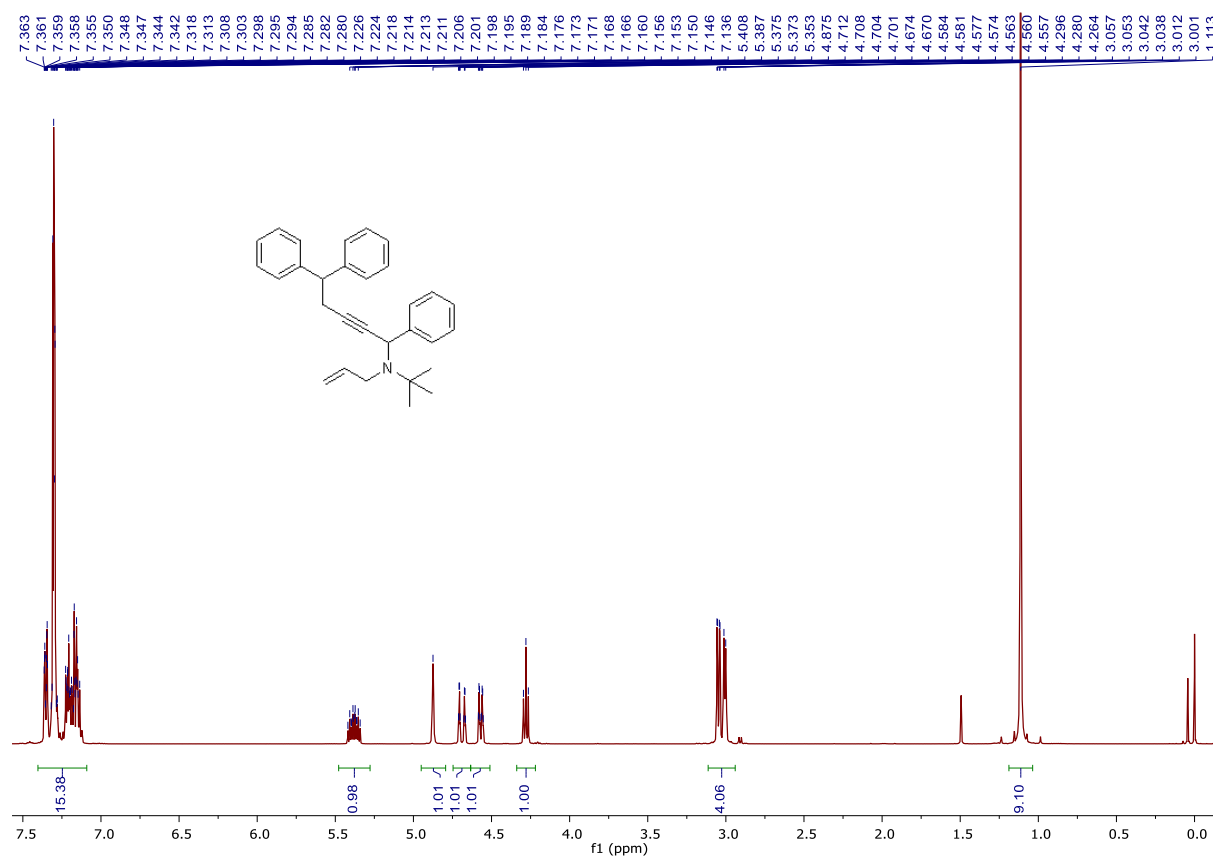
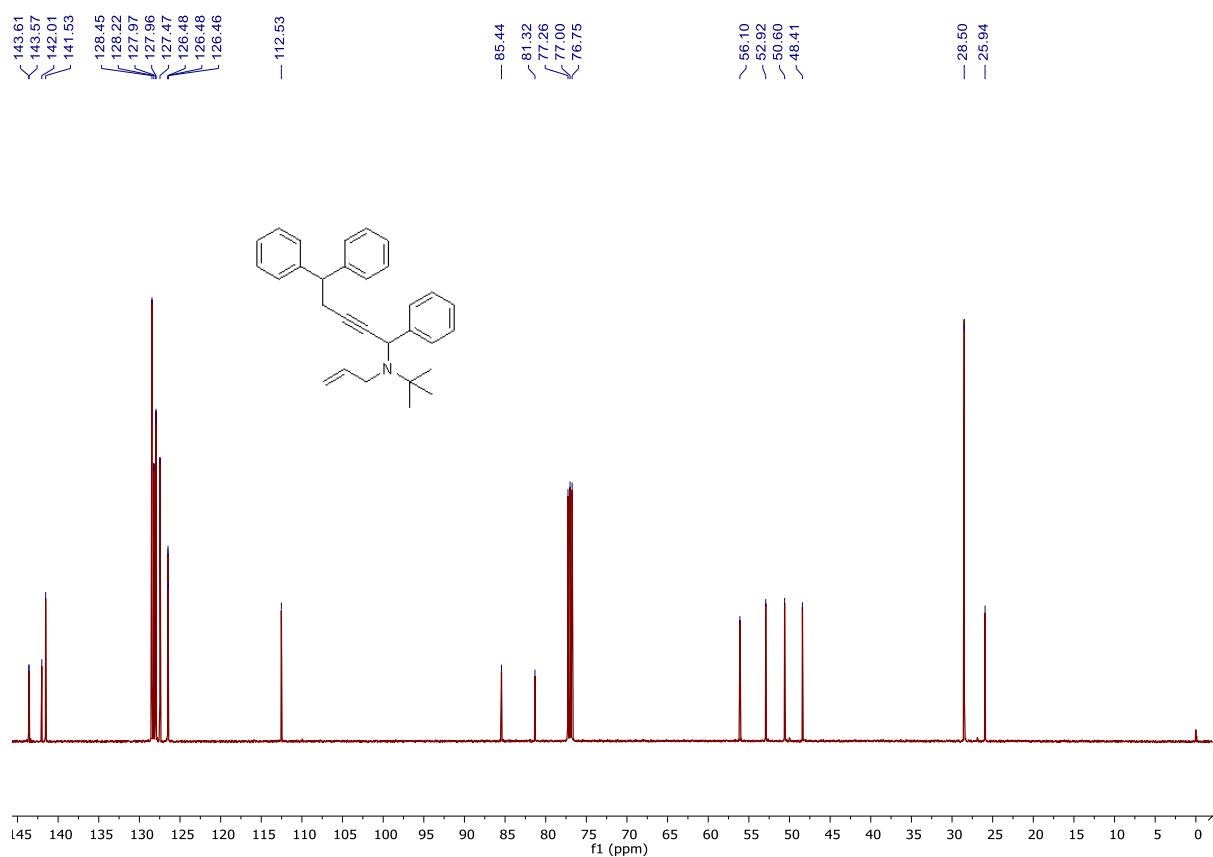
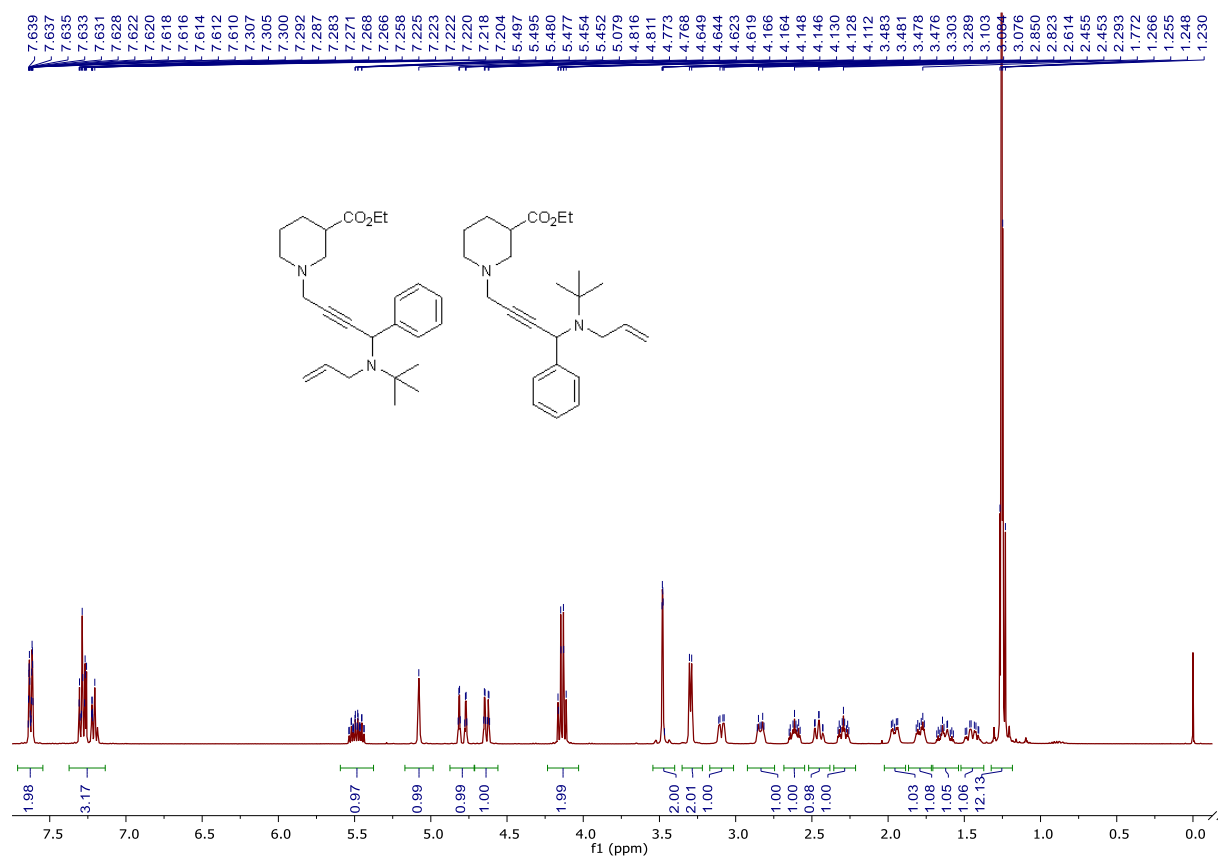


Figure S59: <sup>13</sup>C NMR *N*-allyl-*N*-(*tert*-butyl)-1,5,5-triphenylpent-2-yn-1-amine (29m)



**Figure S60: <sup>1</sup>H NMR *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-phenylbut-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31g); *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-phenylbut-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31g)**



**Figure S61:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-(4-[allyl(tert-butyl)amino]-4-phenylbut-2-yn-1-yl)(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31g); *rac*-[ethyl (*R*)-1-(4-[allyl(tert-butyl)amino]-4-phenylbut-2-yn-1-yl)(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31g)**

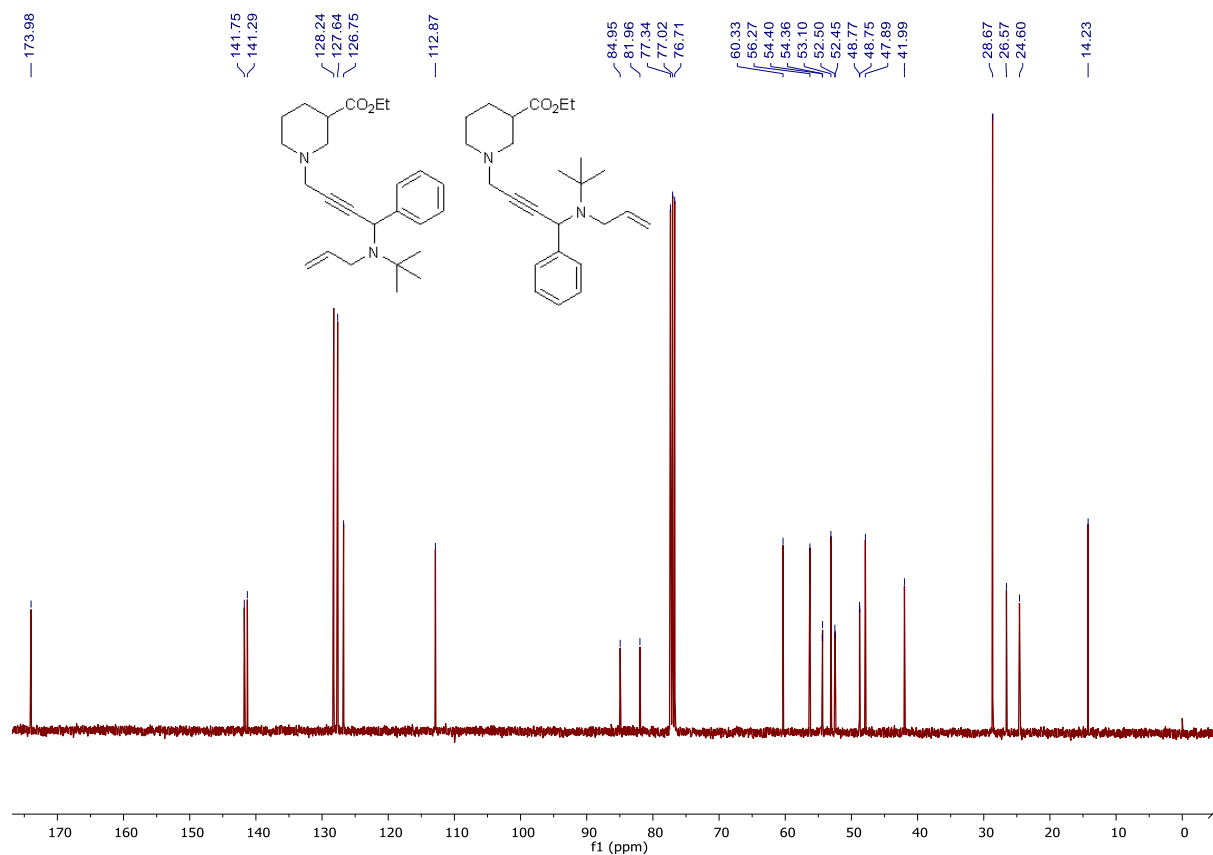
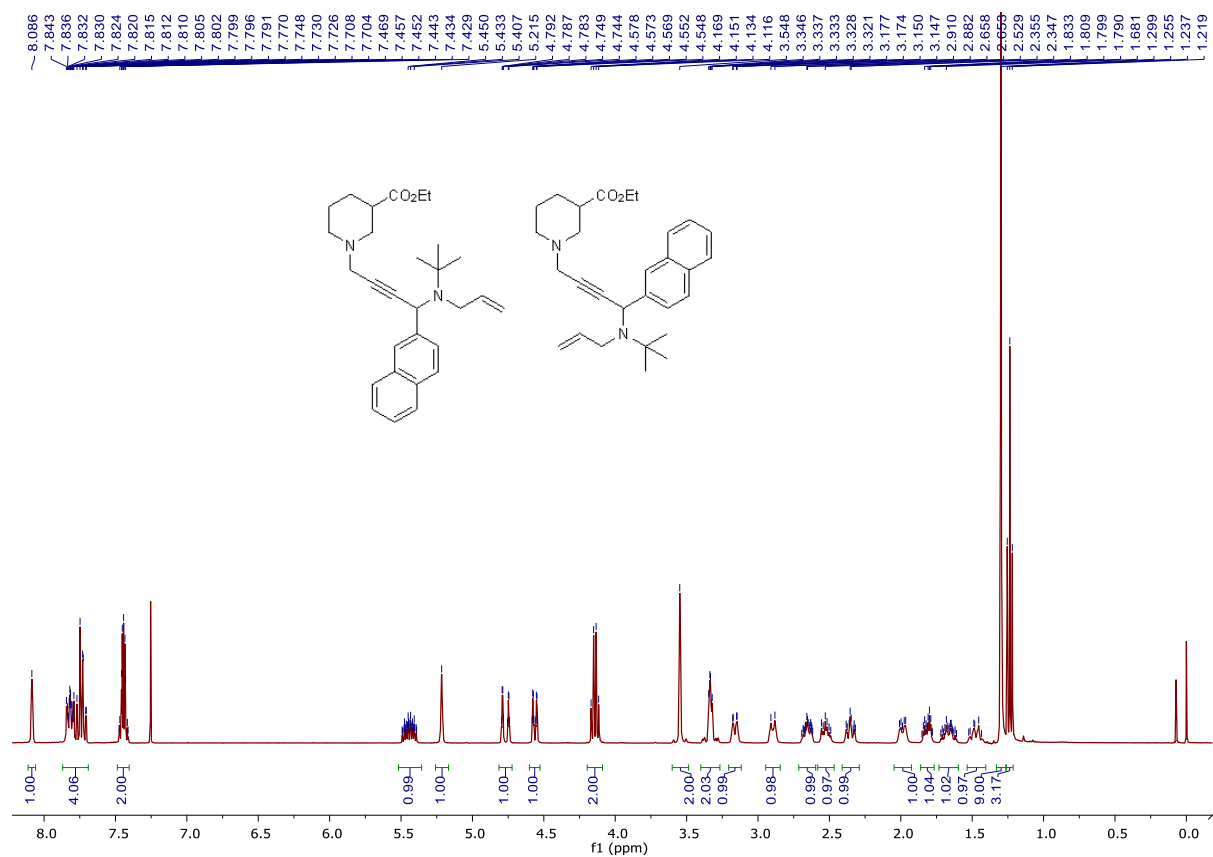
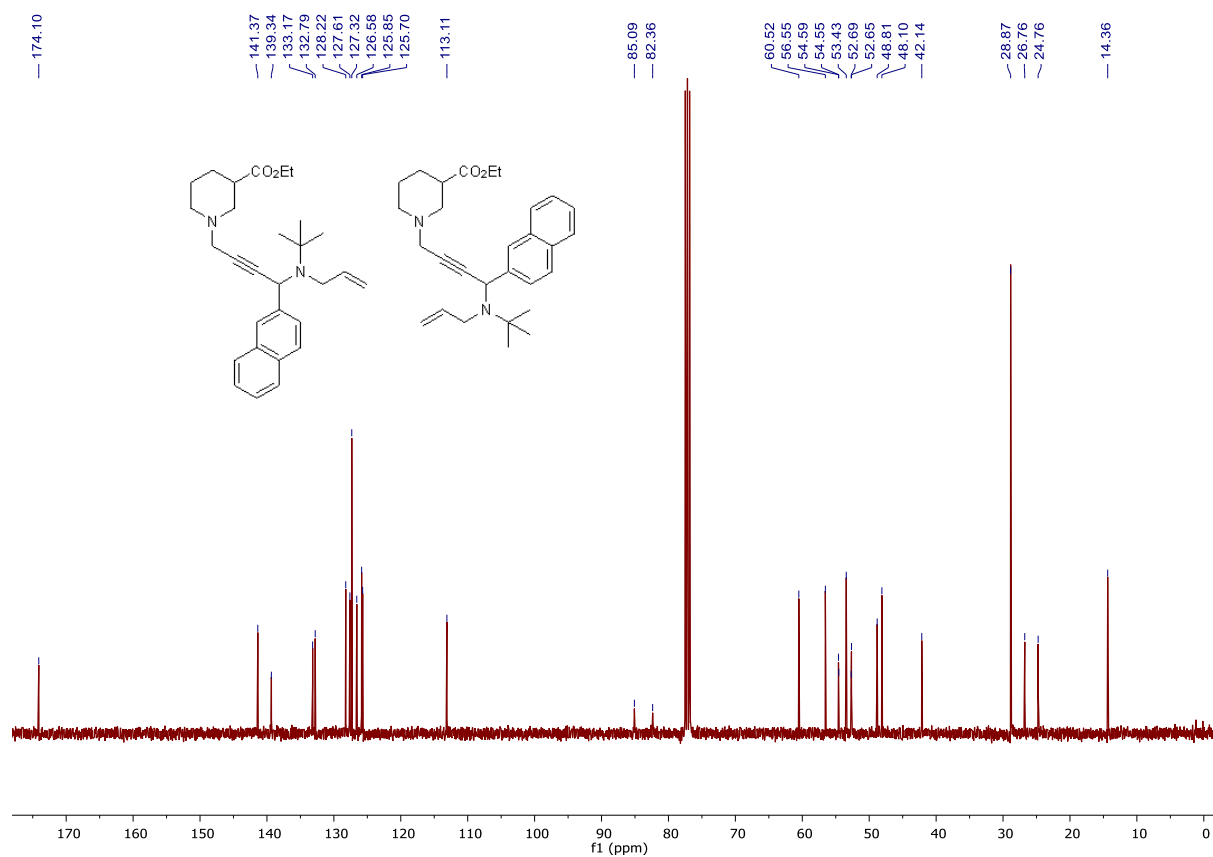


Figure S62:  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31i); *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31i)

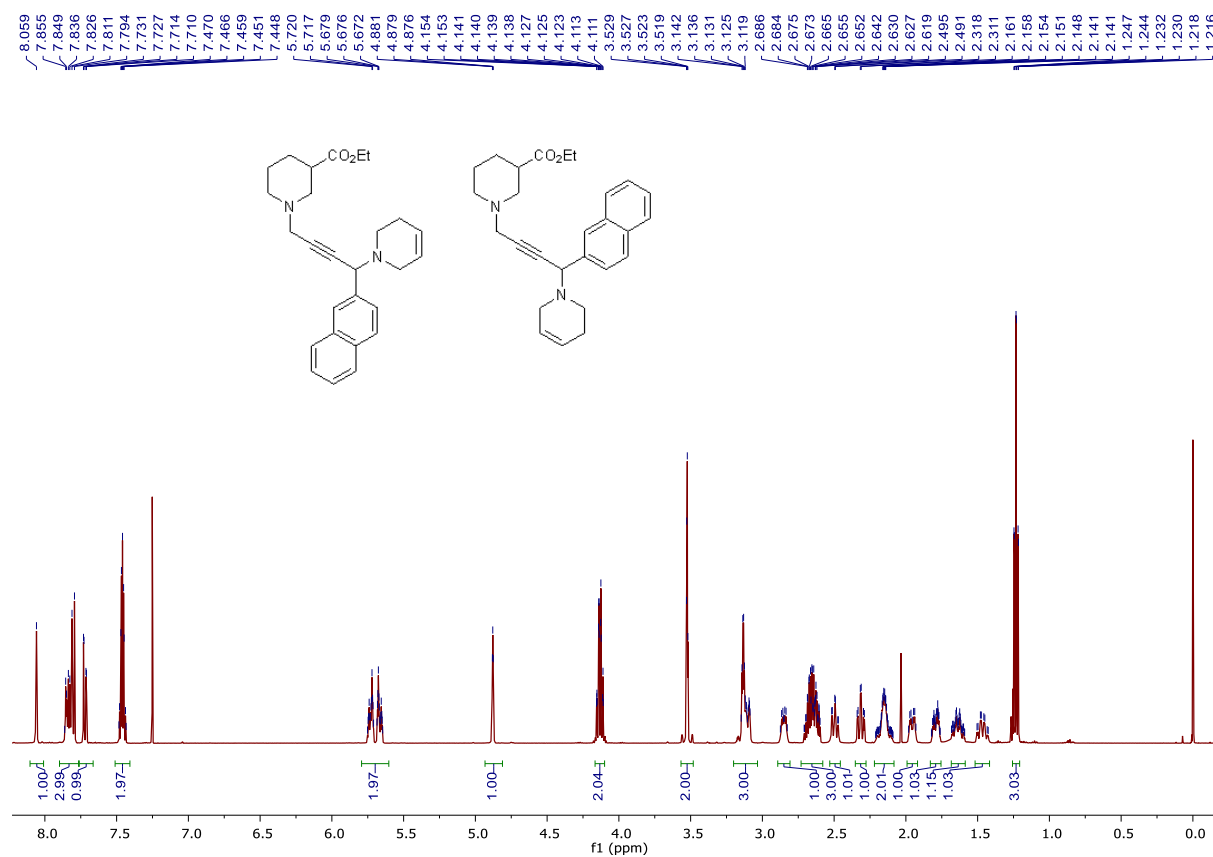




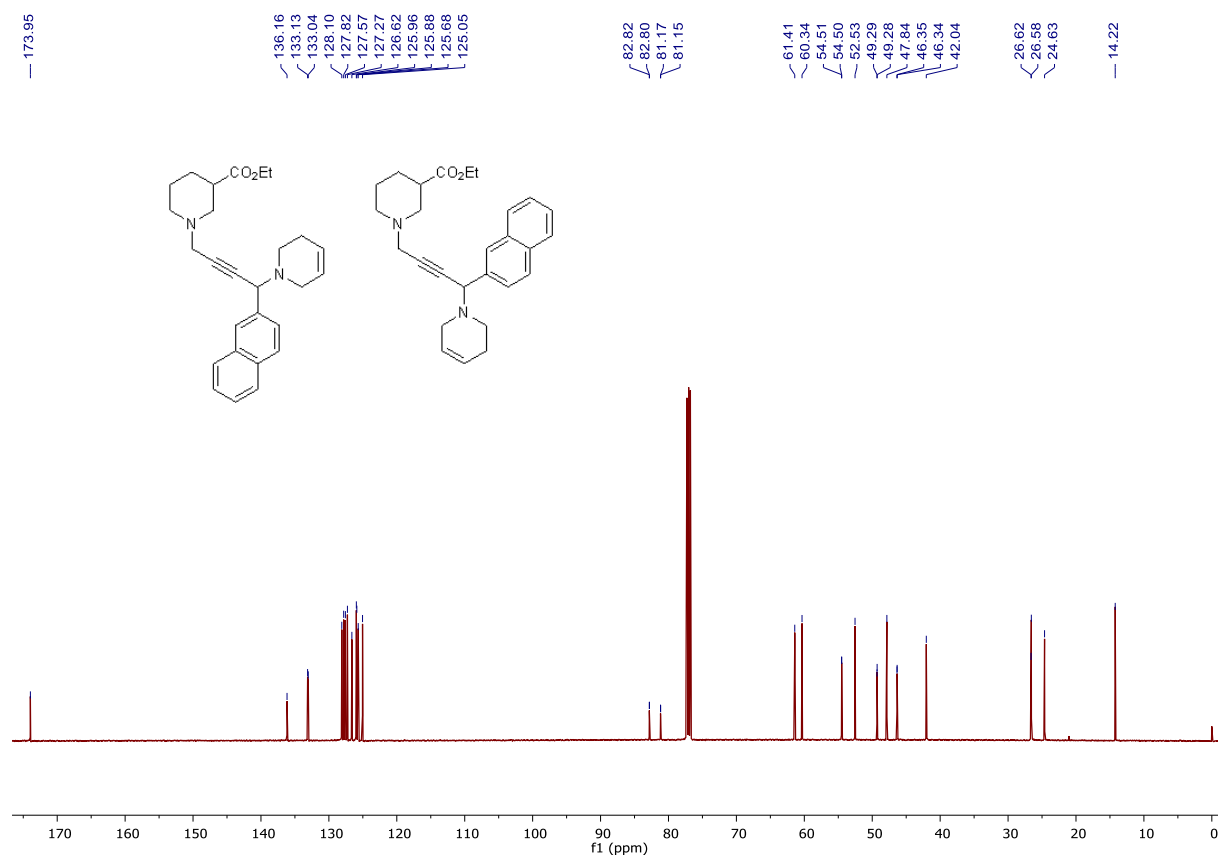
**Figure S63:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31i); *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31i)**



**Figure S64:**  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31j); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31j)



**Figure S65:**  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31j); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(naphthalen-2-yl)but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31j)



**Figure S66:  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31m); *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31m)**

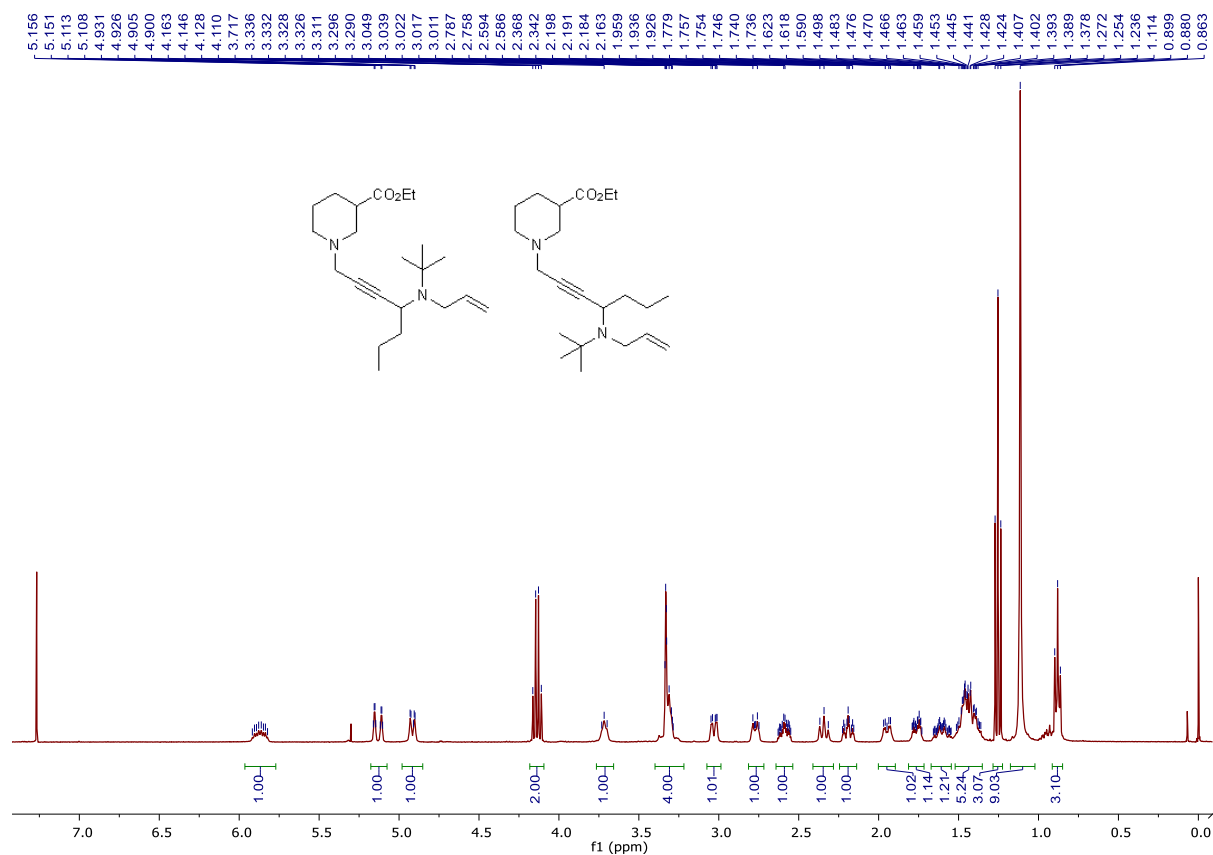


Figure S67:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31m); *rac*-[ethyl (*R*)-1-{4-[allyl(*tert*-butyl)amino]hept-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31m)

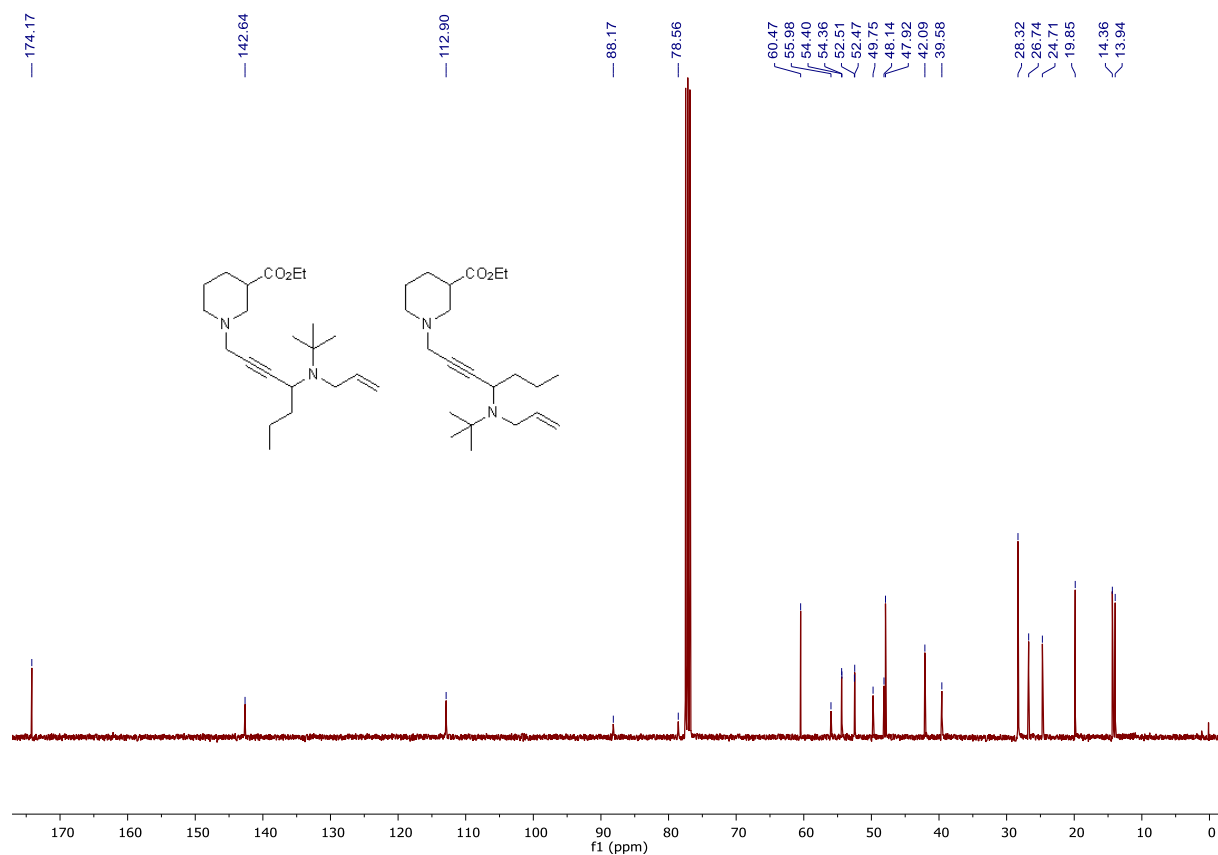


Figure S68:  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]hept-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31n); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]hept-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31n)

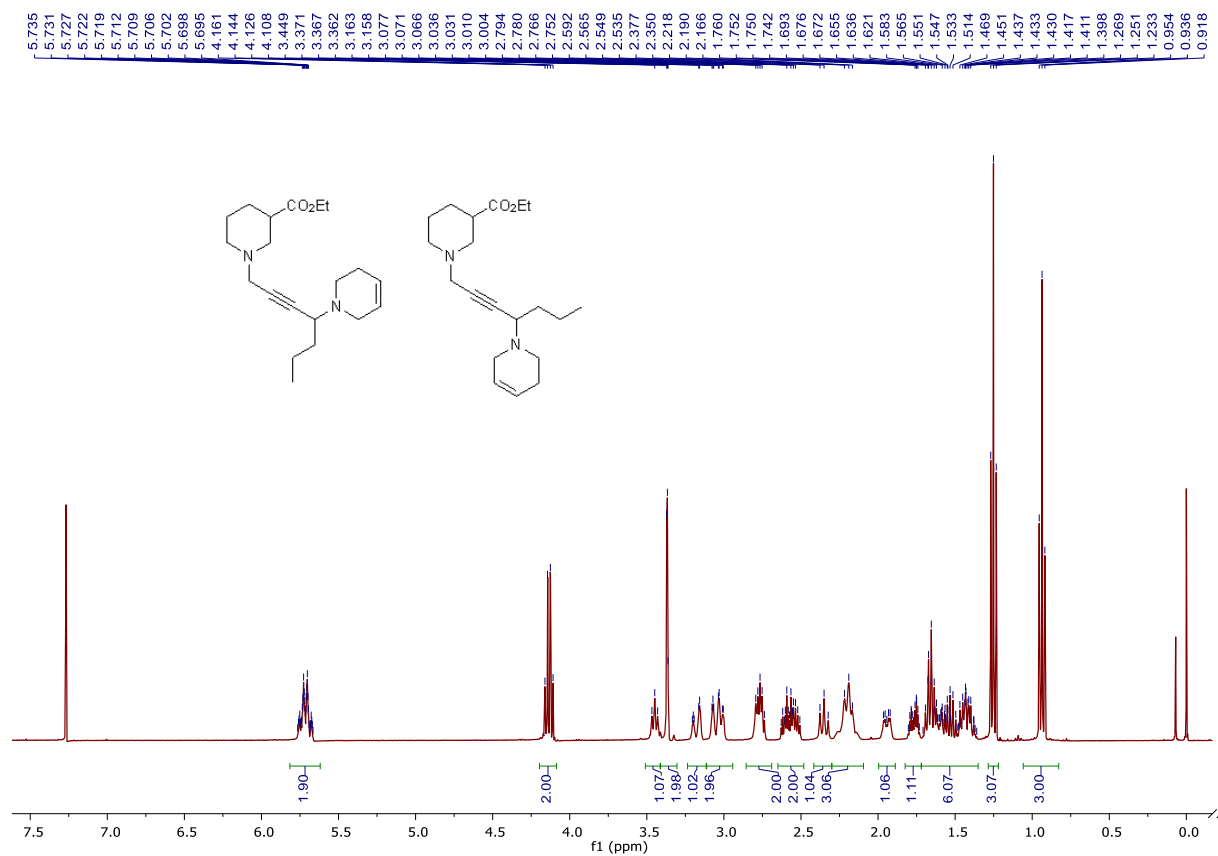
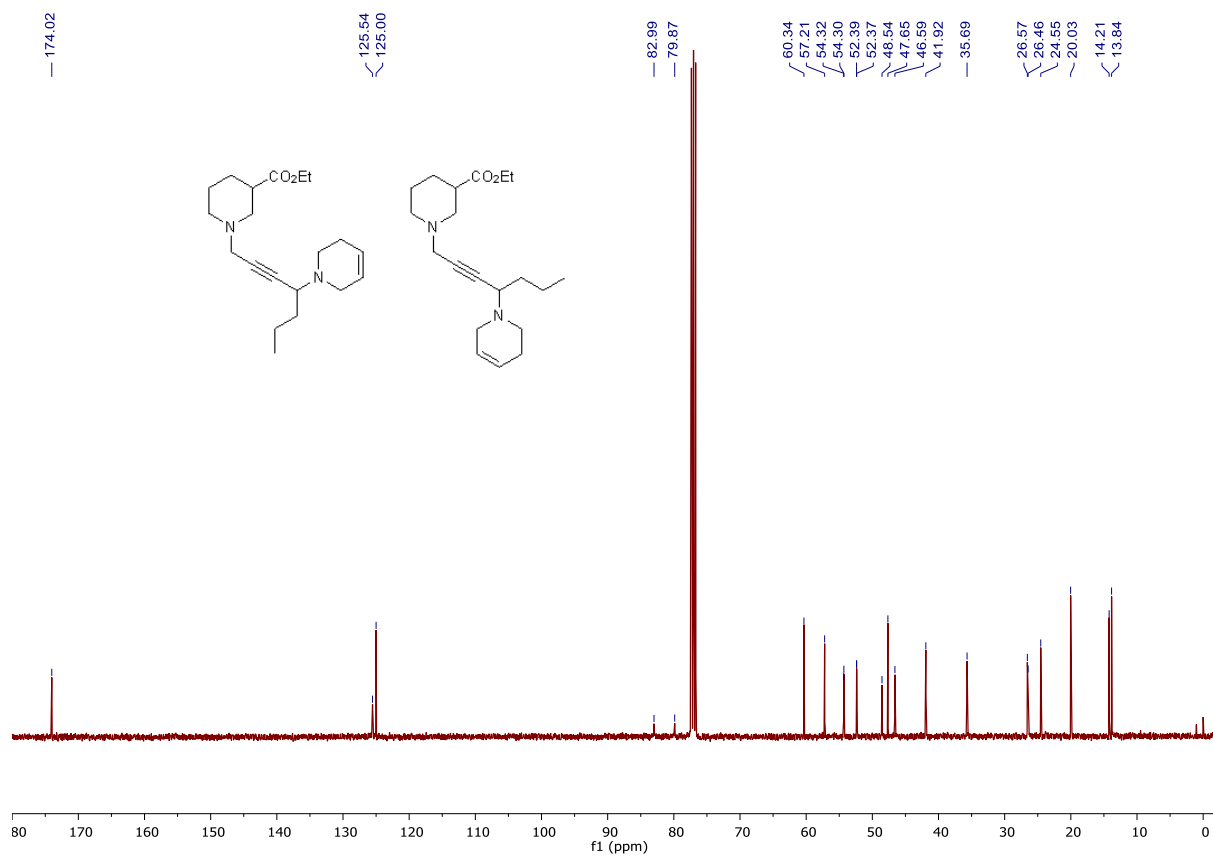
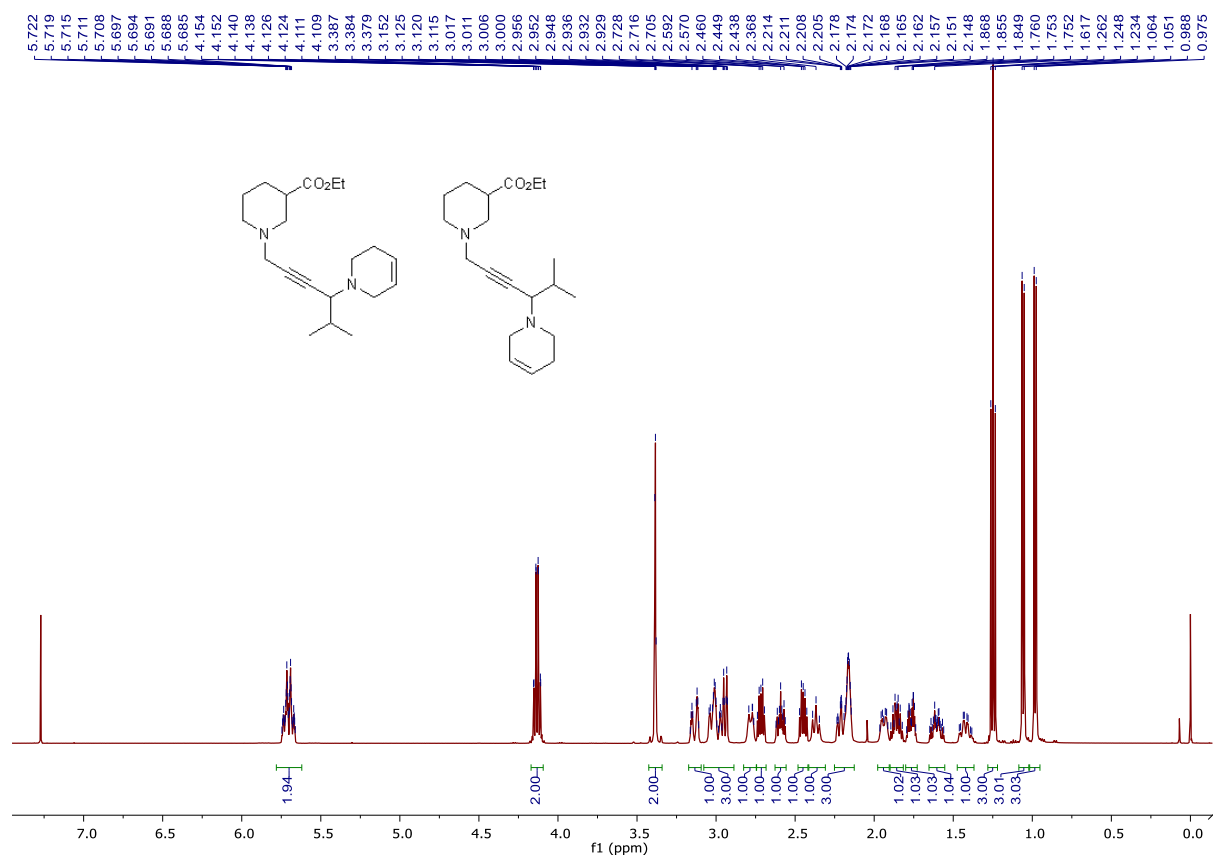


Figure S69:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]hept-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31n); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]hept-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31n)



**Figure S70:**  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-5-methylhex-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31o); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-5-methylhex-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31o)





**Figure S71:**  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-5-methylhex-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31o); *rac*-[ethyl (*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-5-methylhex-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31o)

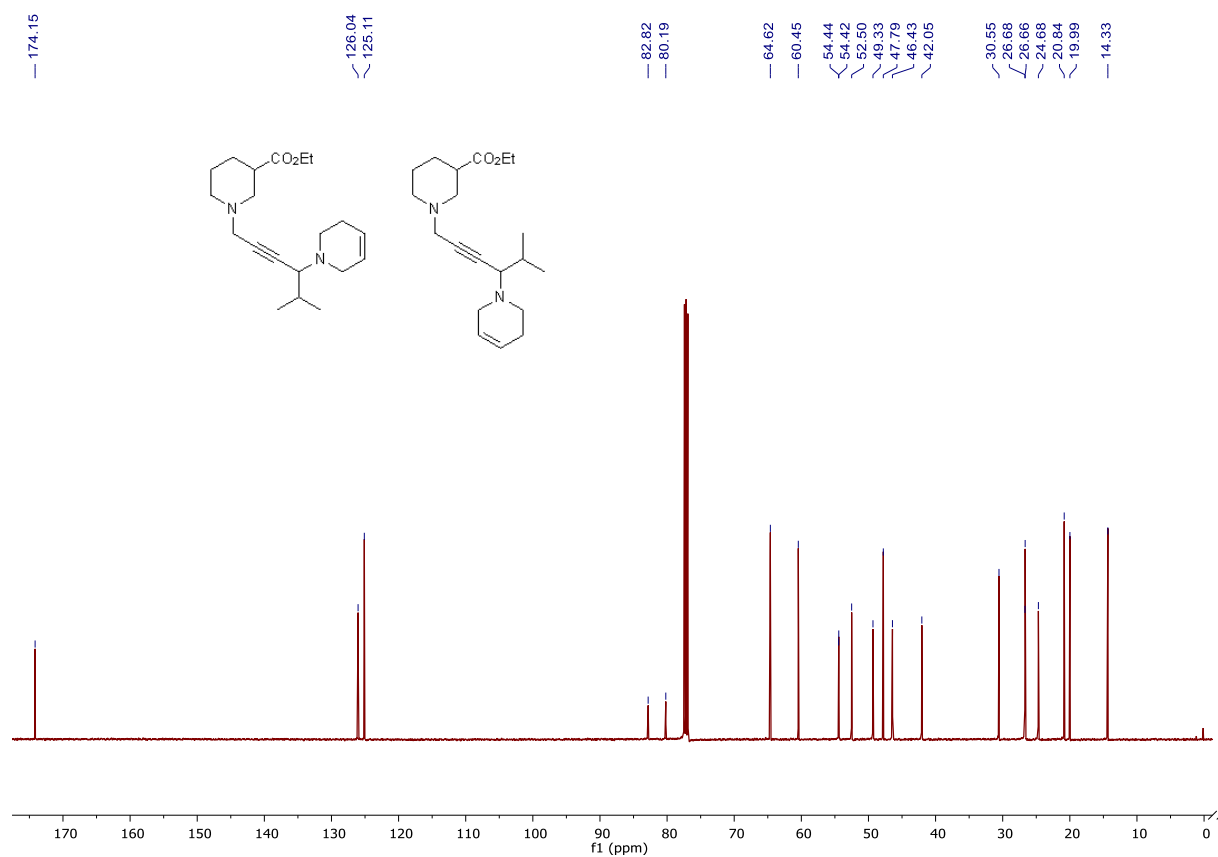


Figure S72:  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31k); *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31k)

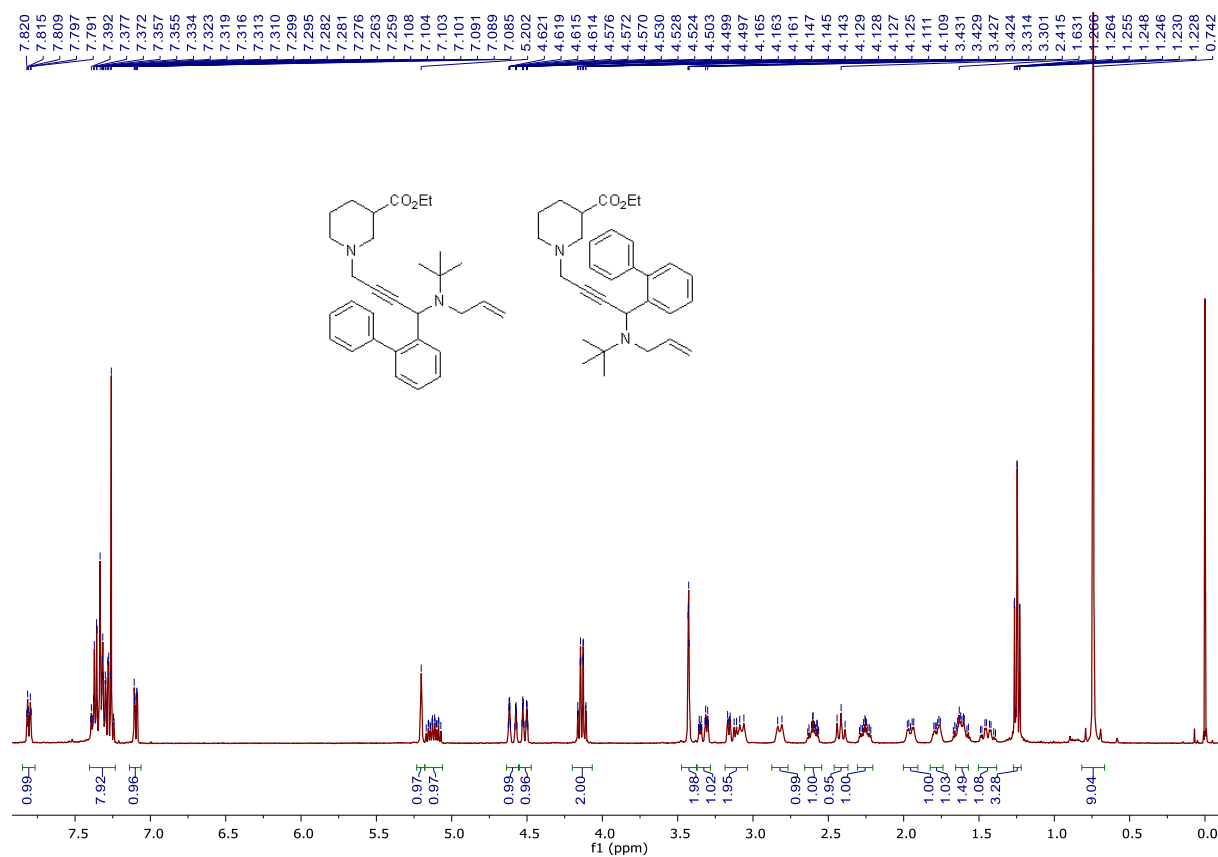
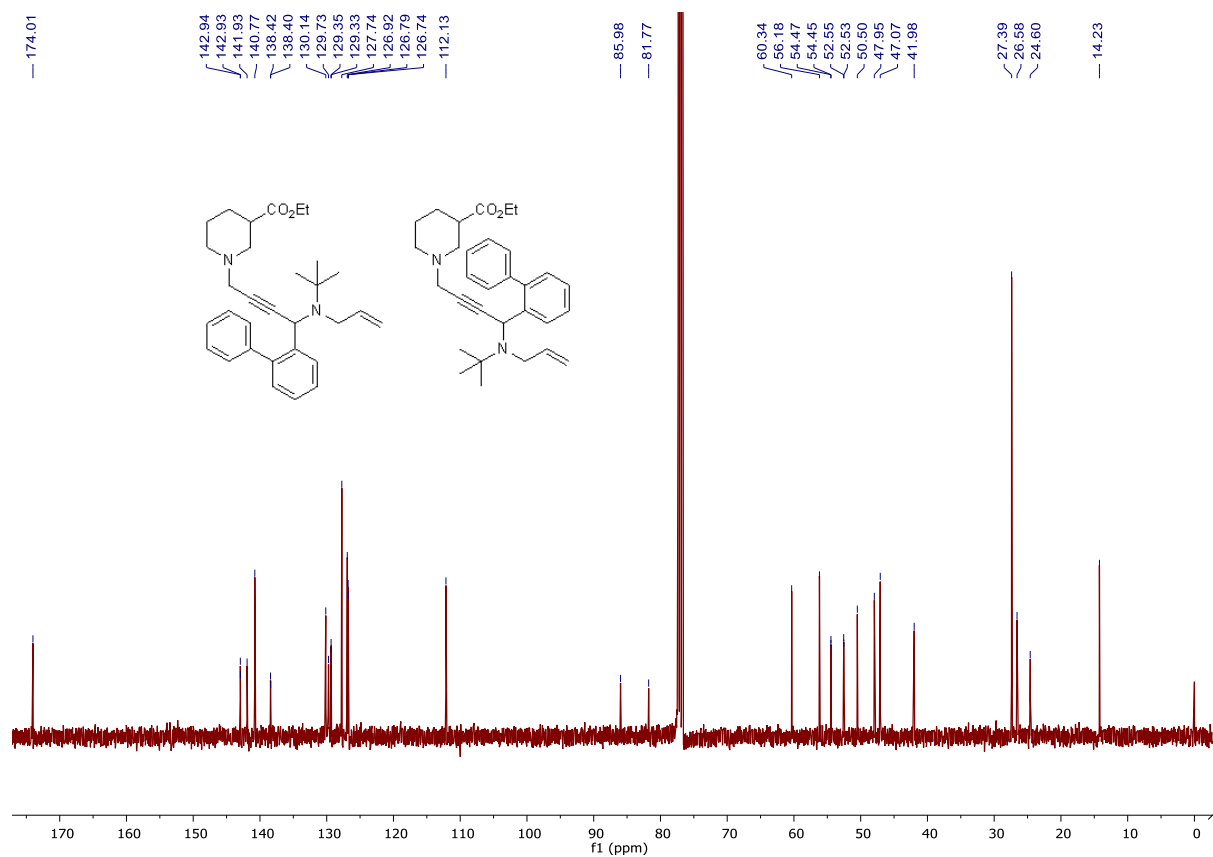
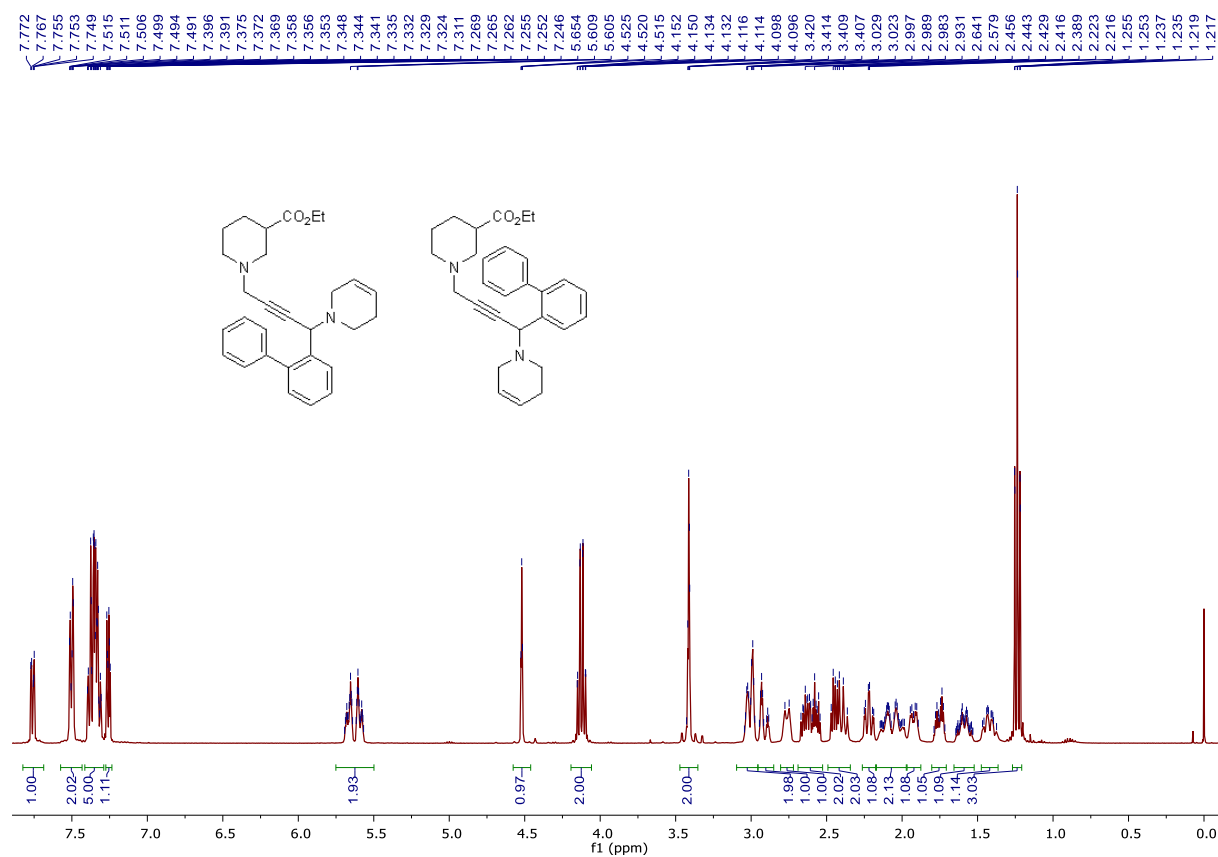


Figure S73:  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31k); *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[allyl(*tert*-butyl)amino]but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31k)



**Figure S74:  $^1\text{H}$  NMR *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31I); *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31I)**



**Figure S75:**  $^{13}\text{C}$  NMR *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R,R*)-31I); *rac*-[ethyl (*R*)-1-{4-[(1,1'-biphenyl)-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R,S*)-31I)

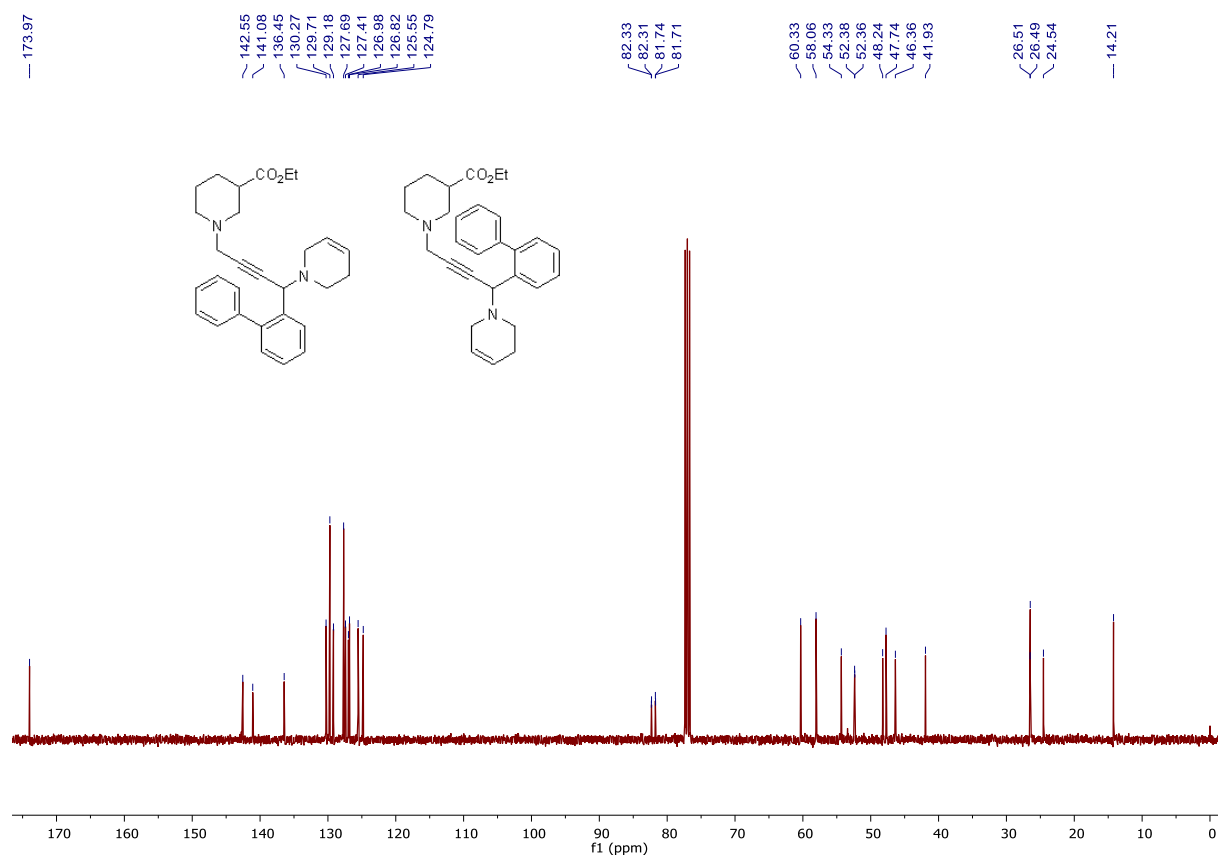


Figure S76: <sup>1</sup>H NMR penta-3,4-diene-1,1-diylidibenzene (32)

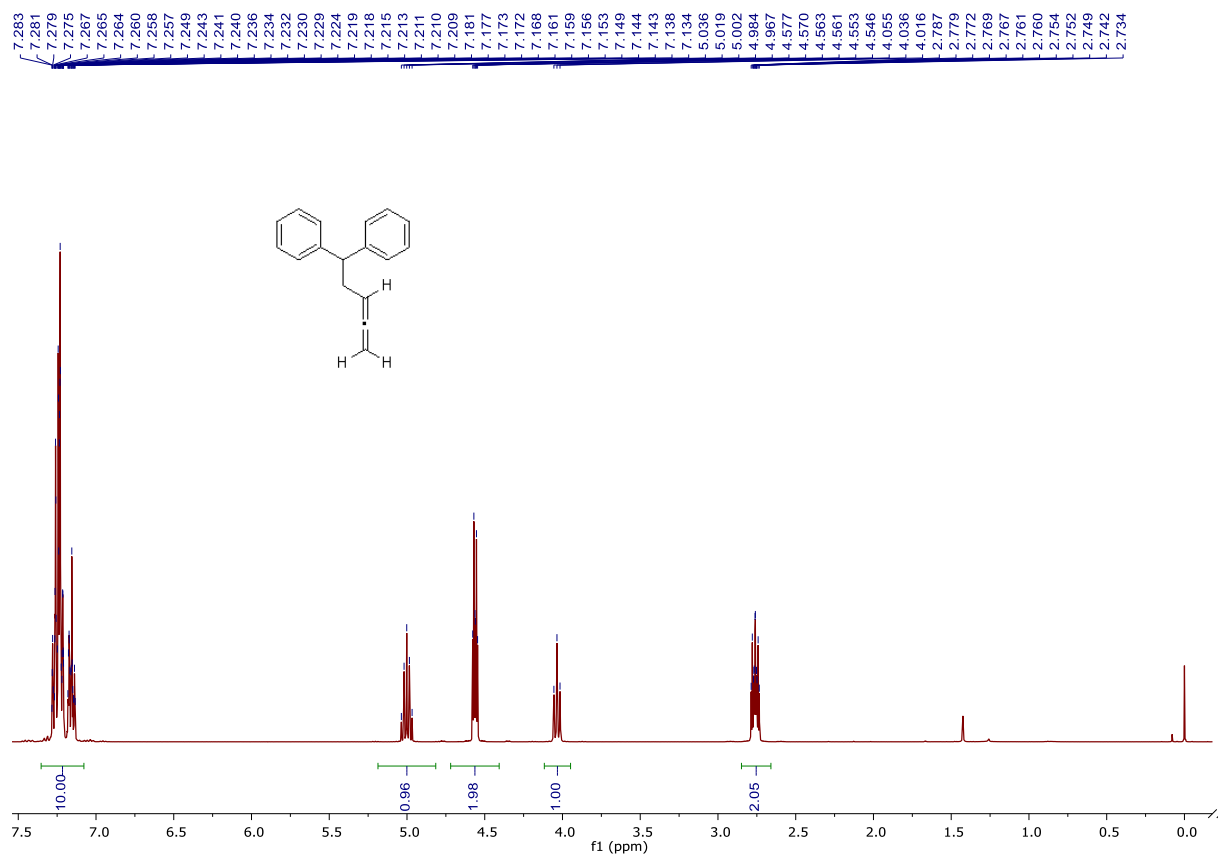


Figure S77: <sup>13</sup>C NMR penta-3,4-diene-1,1-diylidibenzene (32)

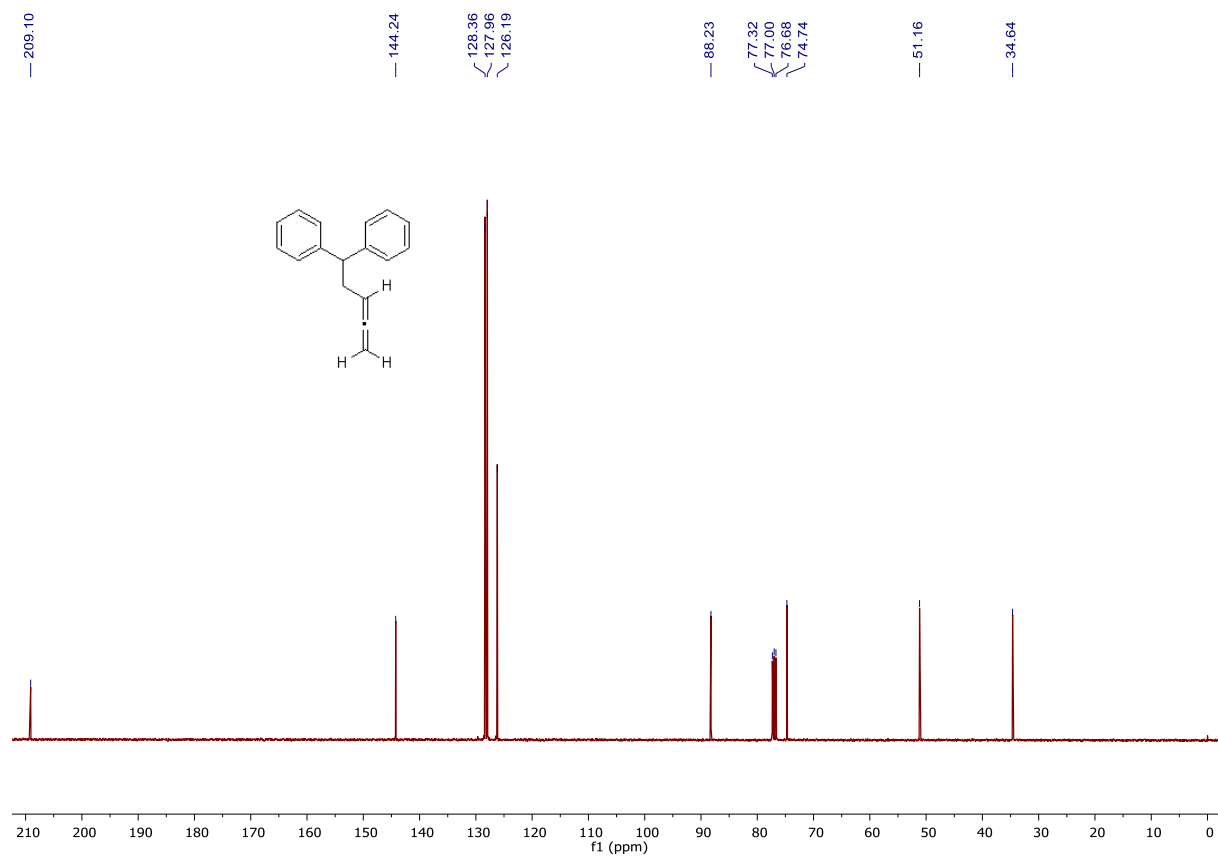


Figure S78: <sup>1</sup>H NMR undeca-1,2-diene (43)

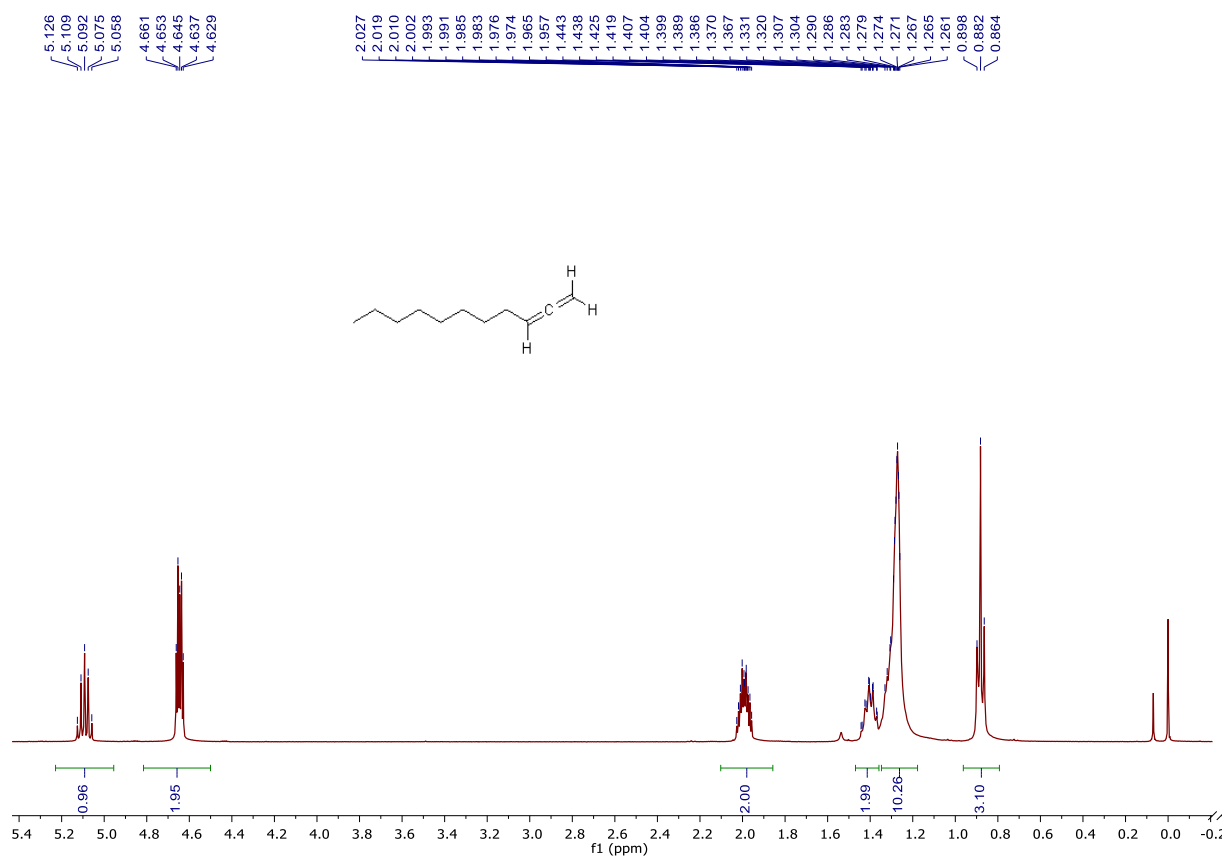


Figure S79: <sup>13</sup>C NMR undeca-1,2-diene (43)

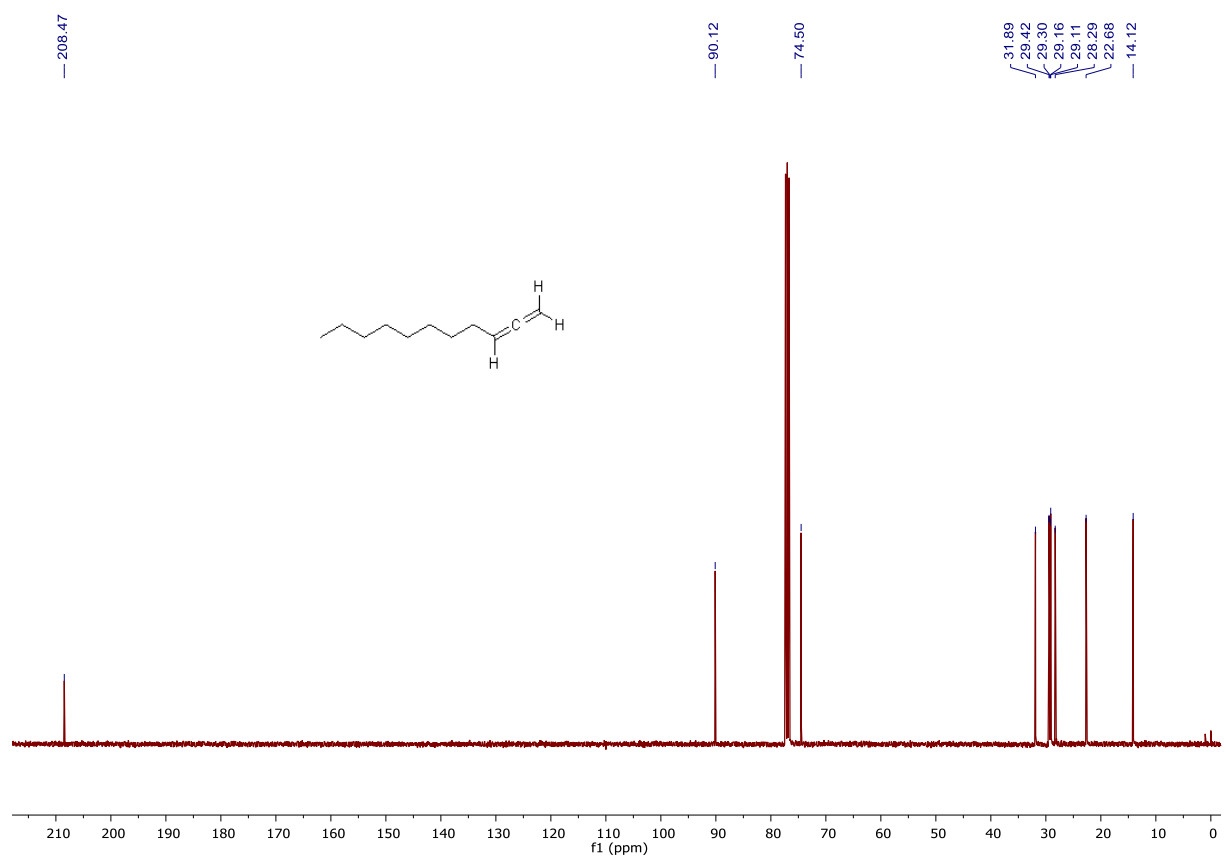


Figure S80: <sup>1</sup>H NMR 6-chlorohexa-1,2-diene (44)

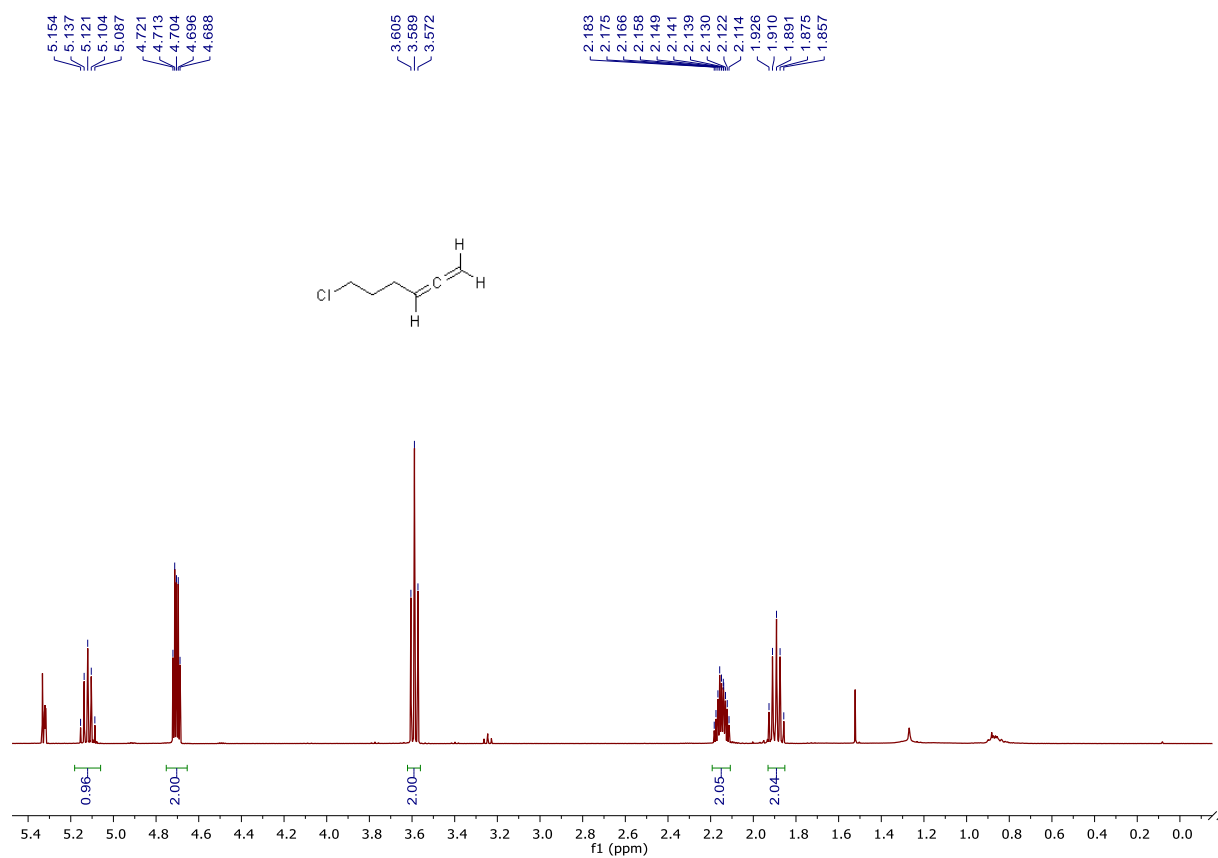


Figure S81: <sup>13</sup>C NMR 6-chlorohexa-1,2-diene (44)

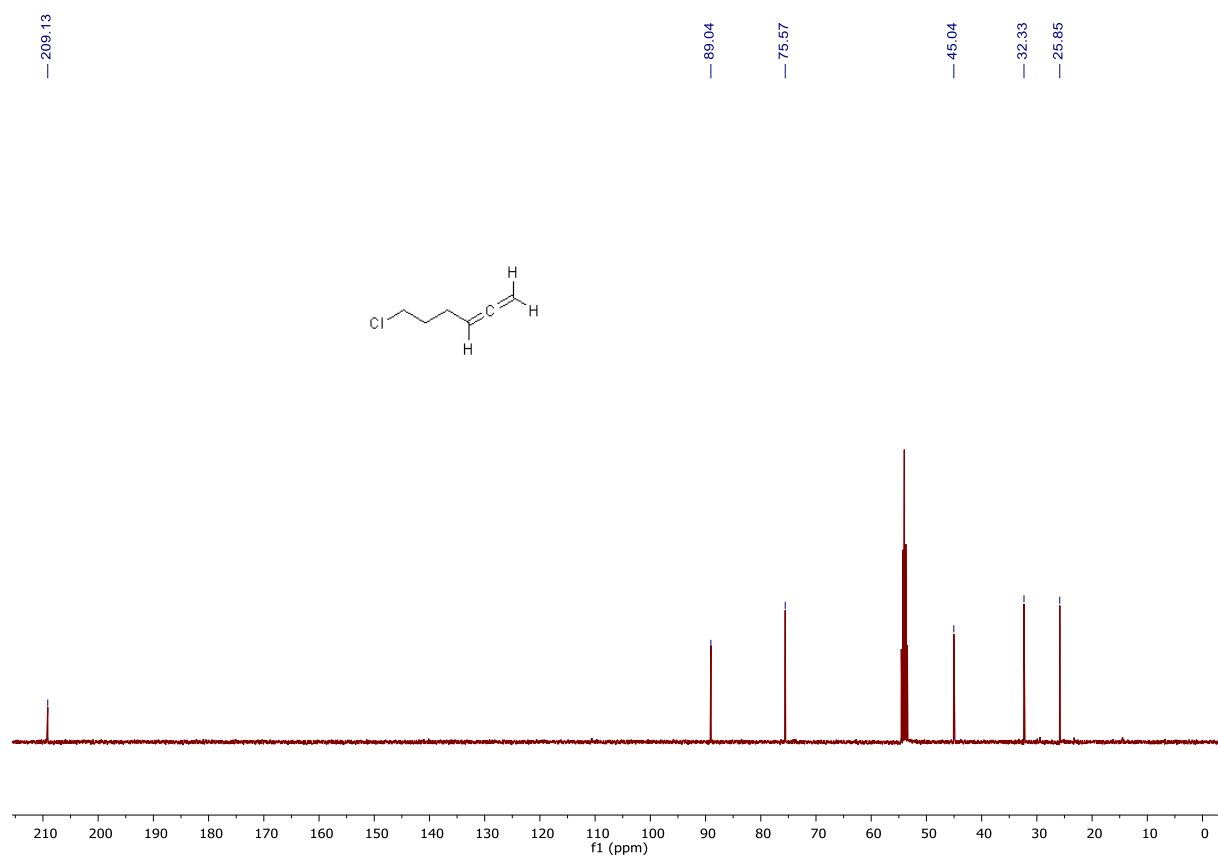




Figure S82: <sup>1</sup>H NMR hepta-5,6-dienitrile (45)

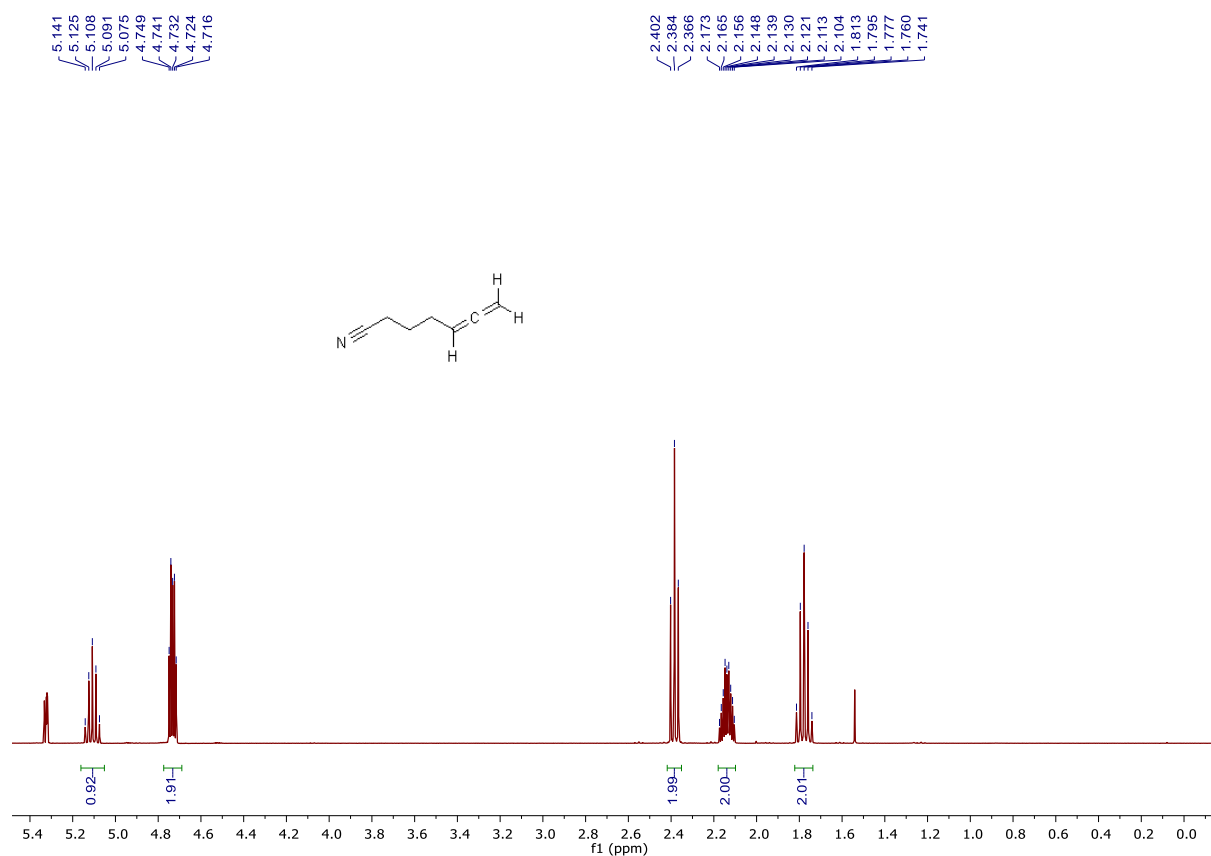


Figure S83: <sup>13</sup>C NMR hepta-5,6-dienitrile (45)

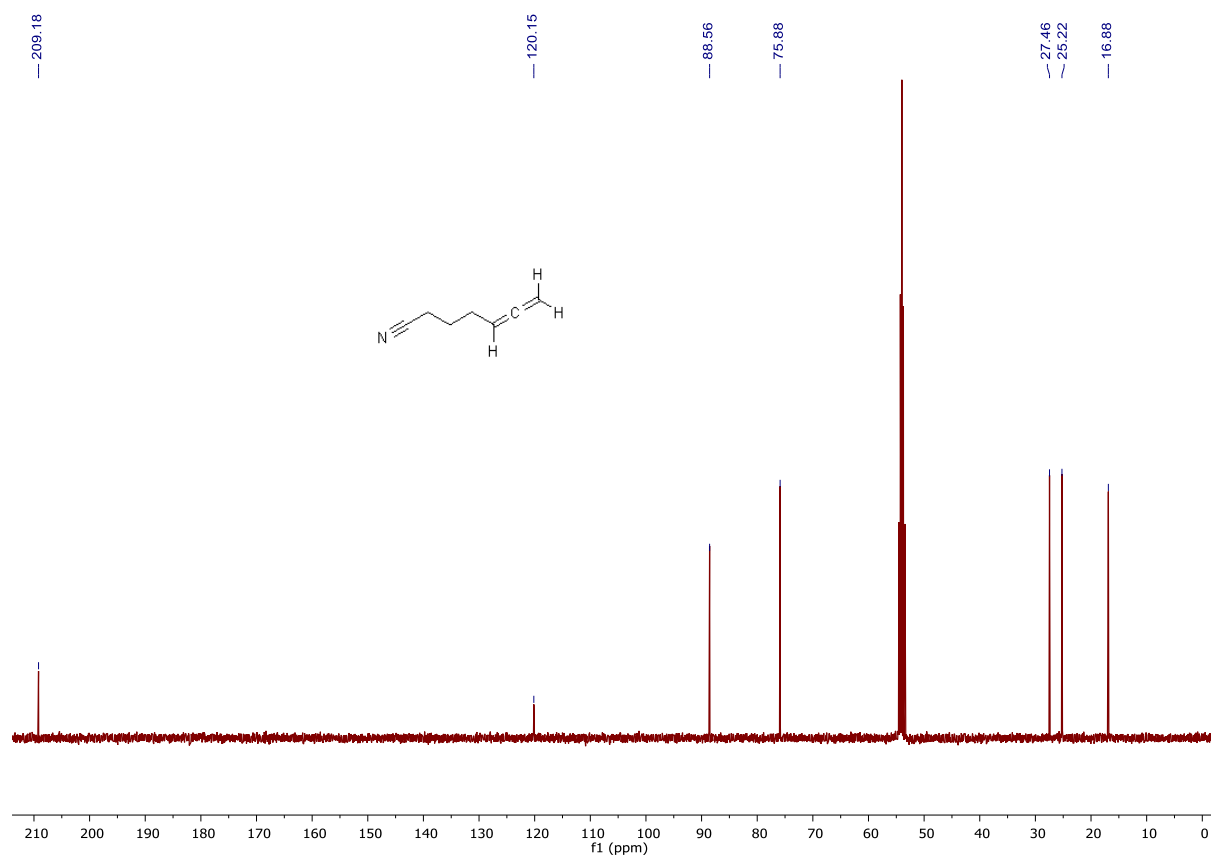


Figure S84: <sup>1</sup>H NMR [(buta-2,3-dien-1-yloxy)methyl]benzene (46)

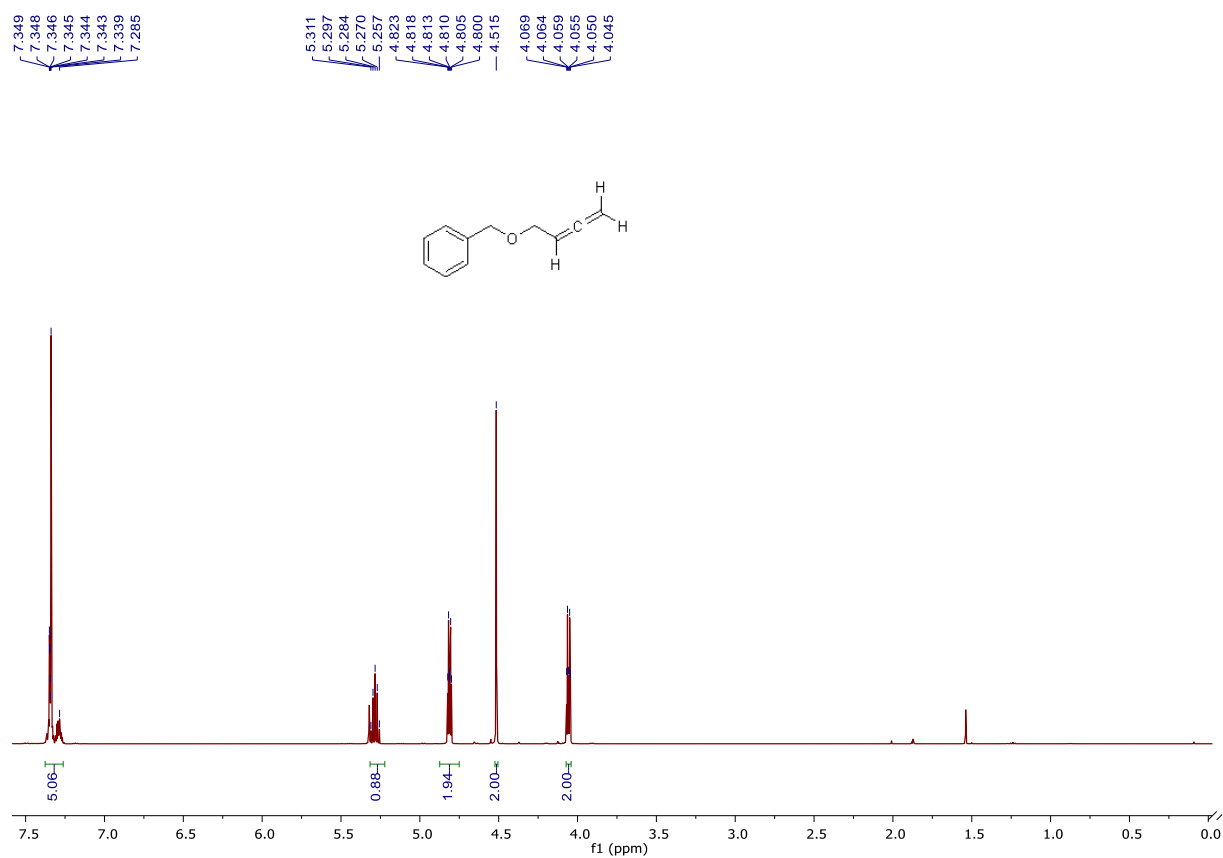


Figure S85: <sup>13</sup>C NMR [(buta-2,3-dien-1-yloxy)methyl]benzene (46)

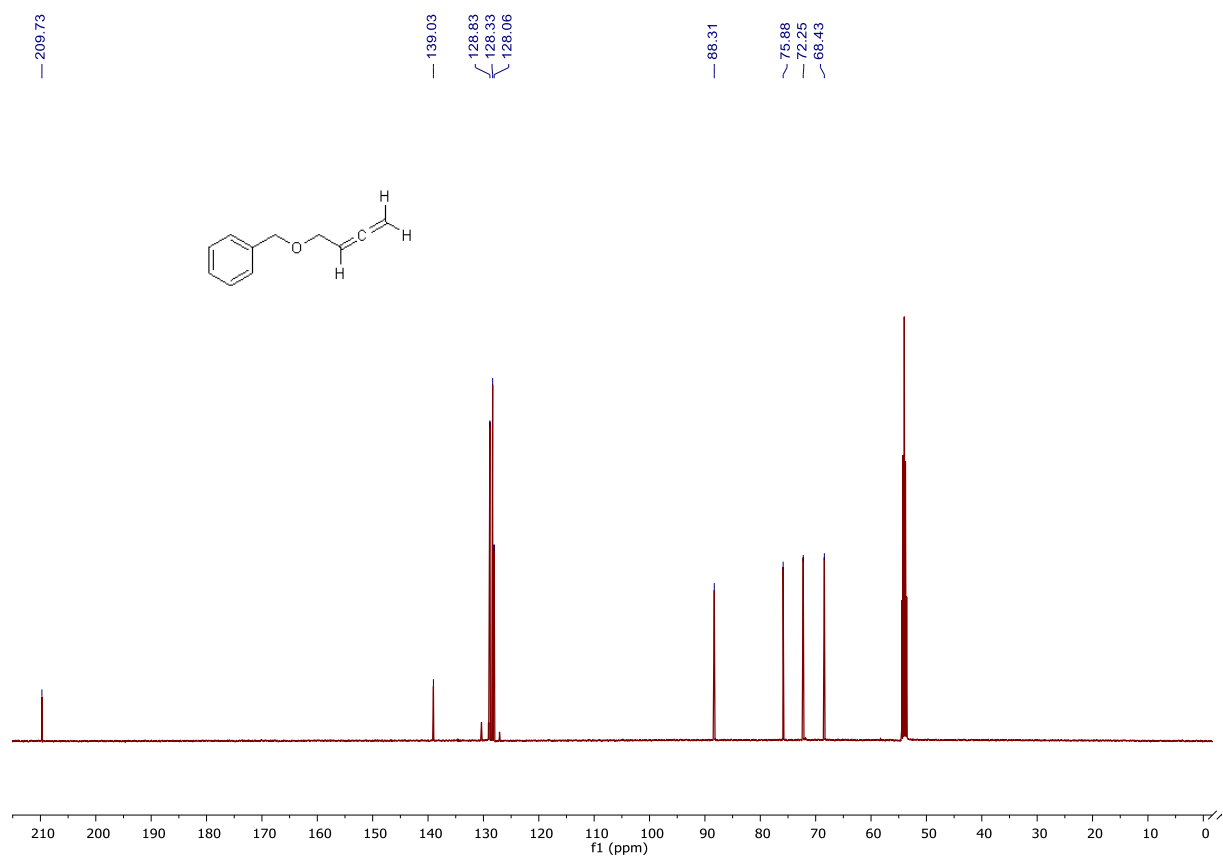


Figure S86: <sup>1</sup>H NMR penta-3,4-diene-1,1,5-triyltribenzene (47)

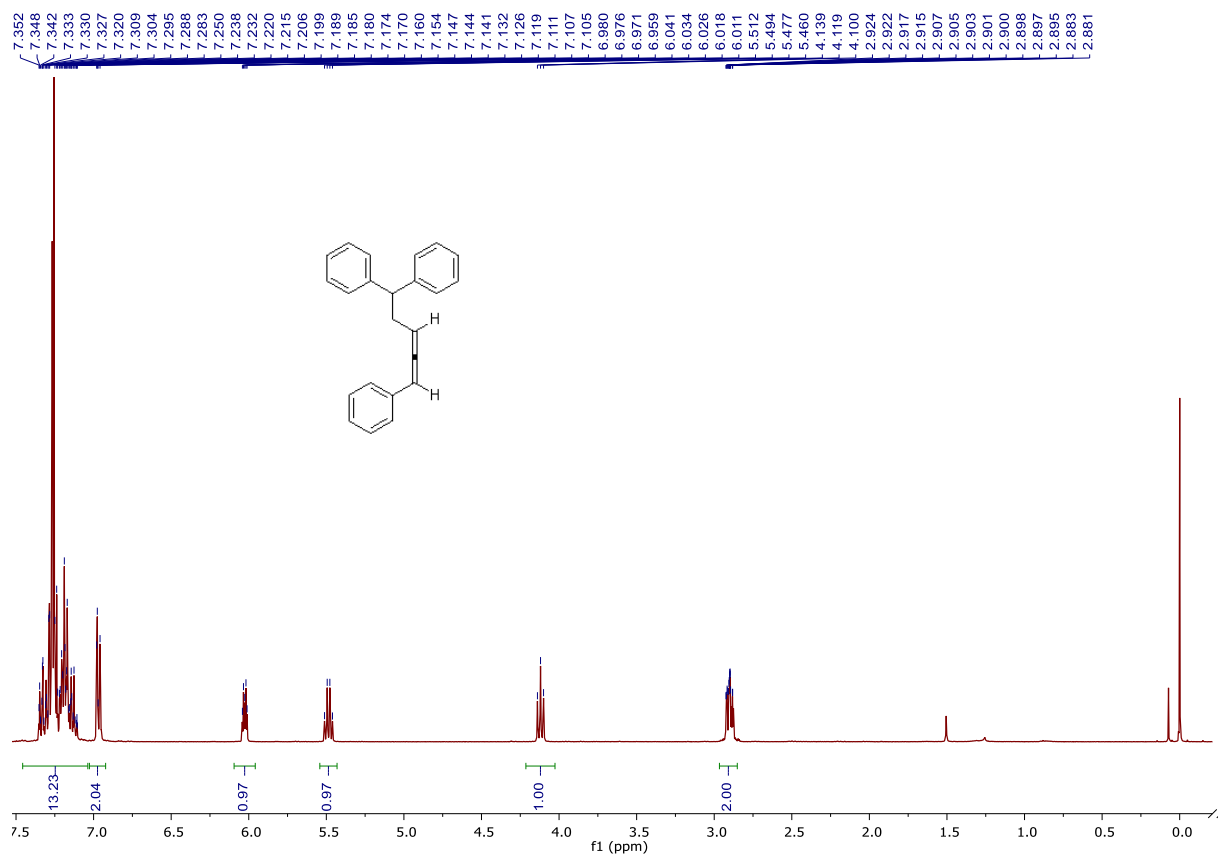


Figure S87: <sup>13</sup>C NMR penta-3,4-diene-1,1,5-triyltribenzene (47)

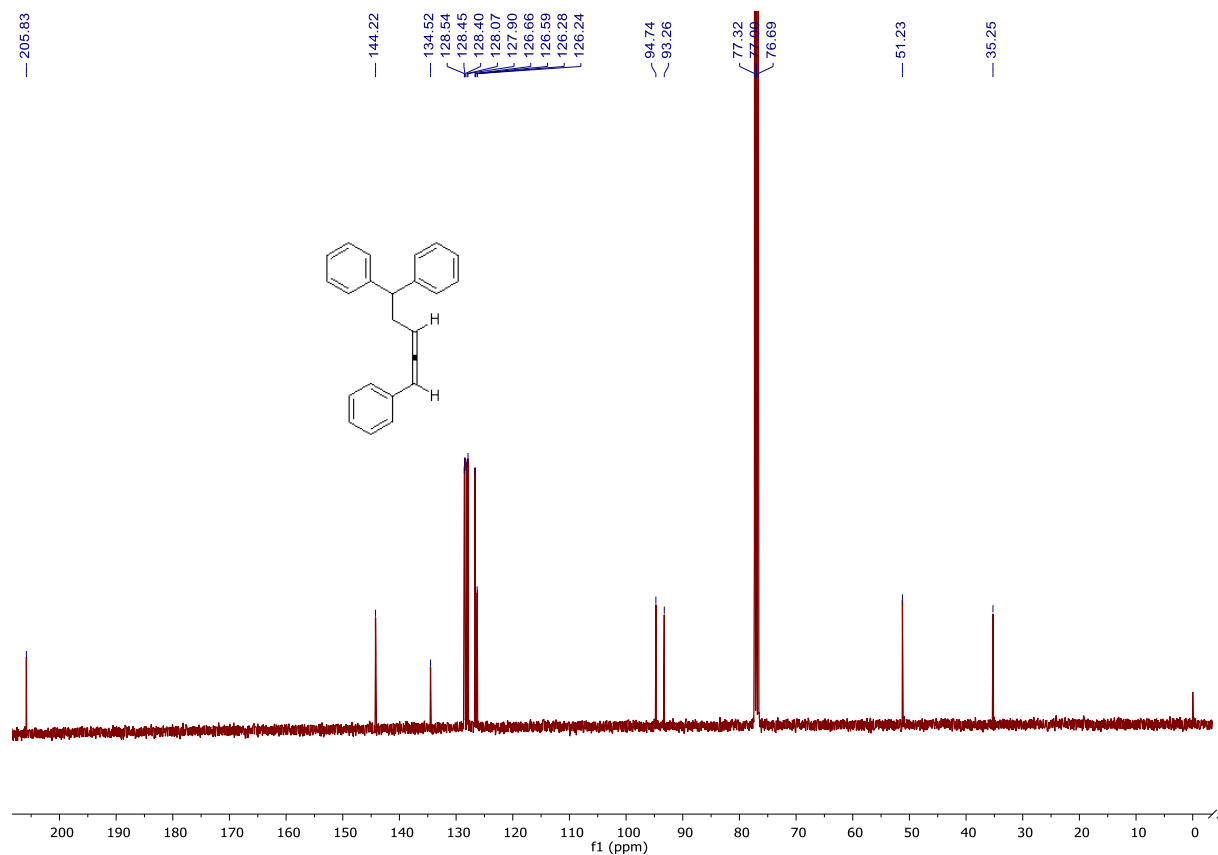


Figure S88: <sup>1</sup>H NMR ethyl 1-(buta-2,3-dien-1-yl)piperidine-3-carboxylate (24)

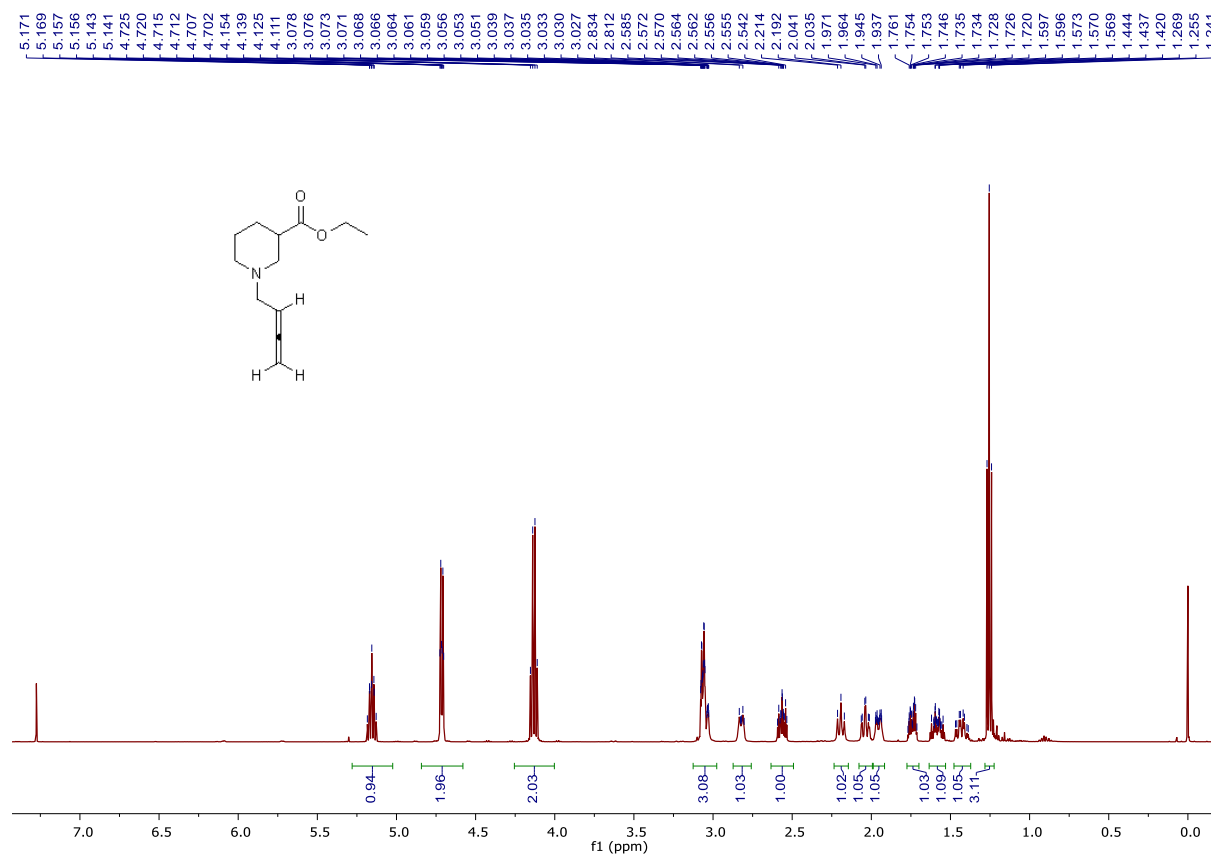
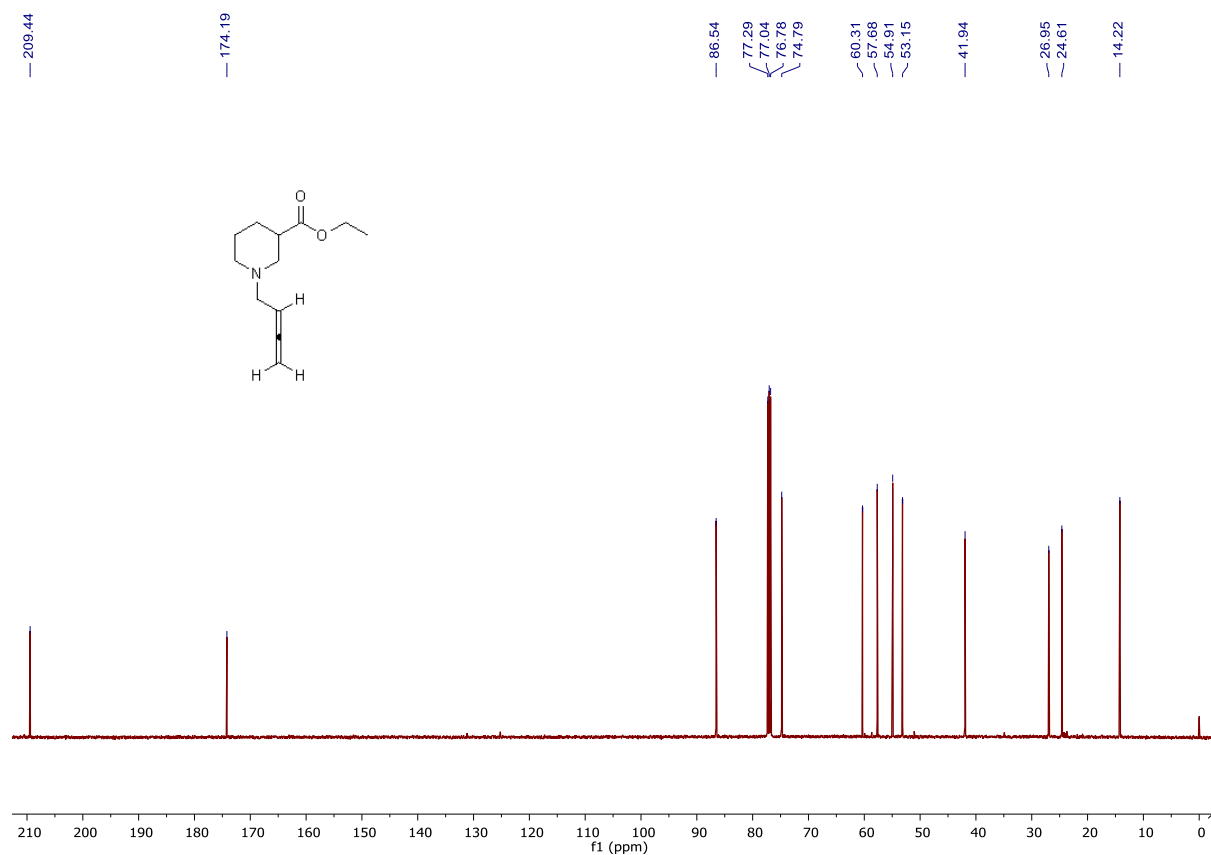
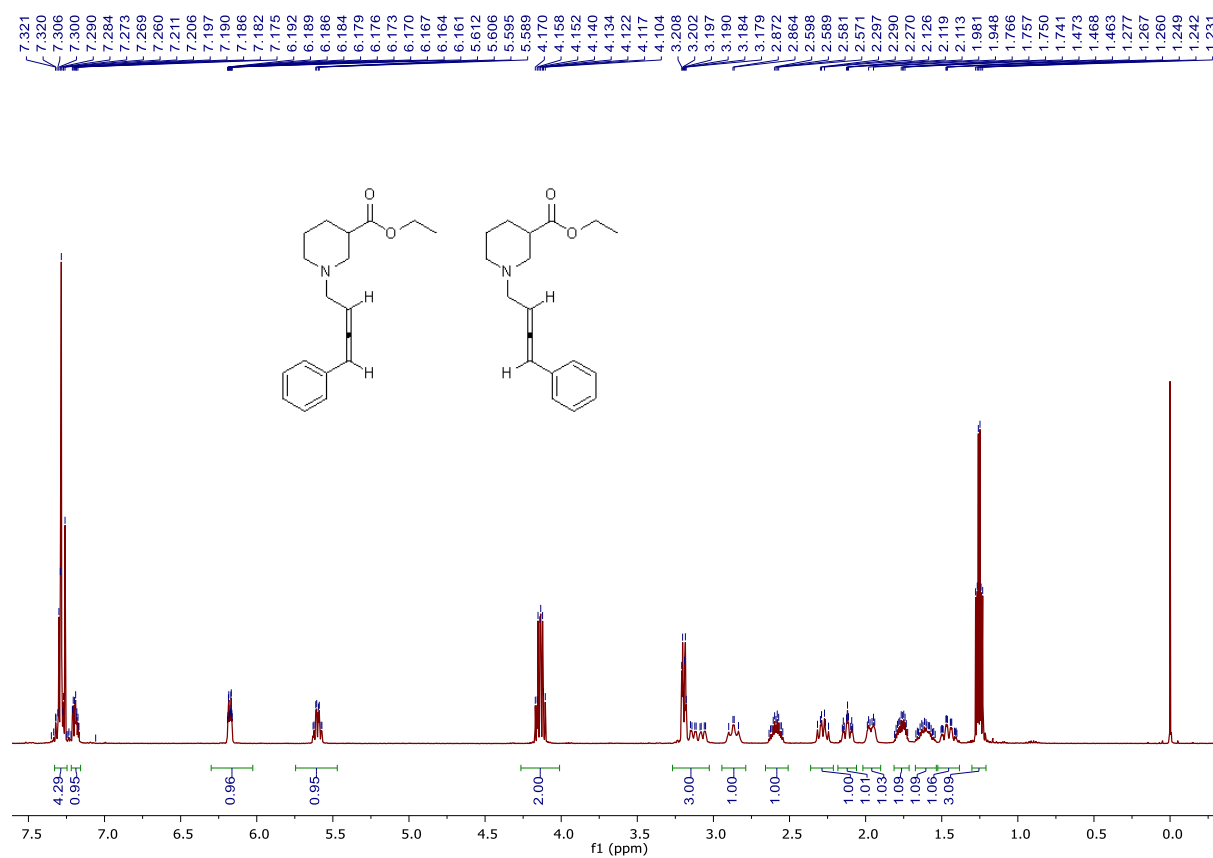


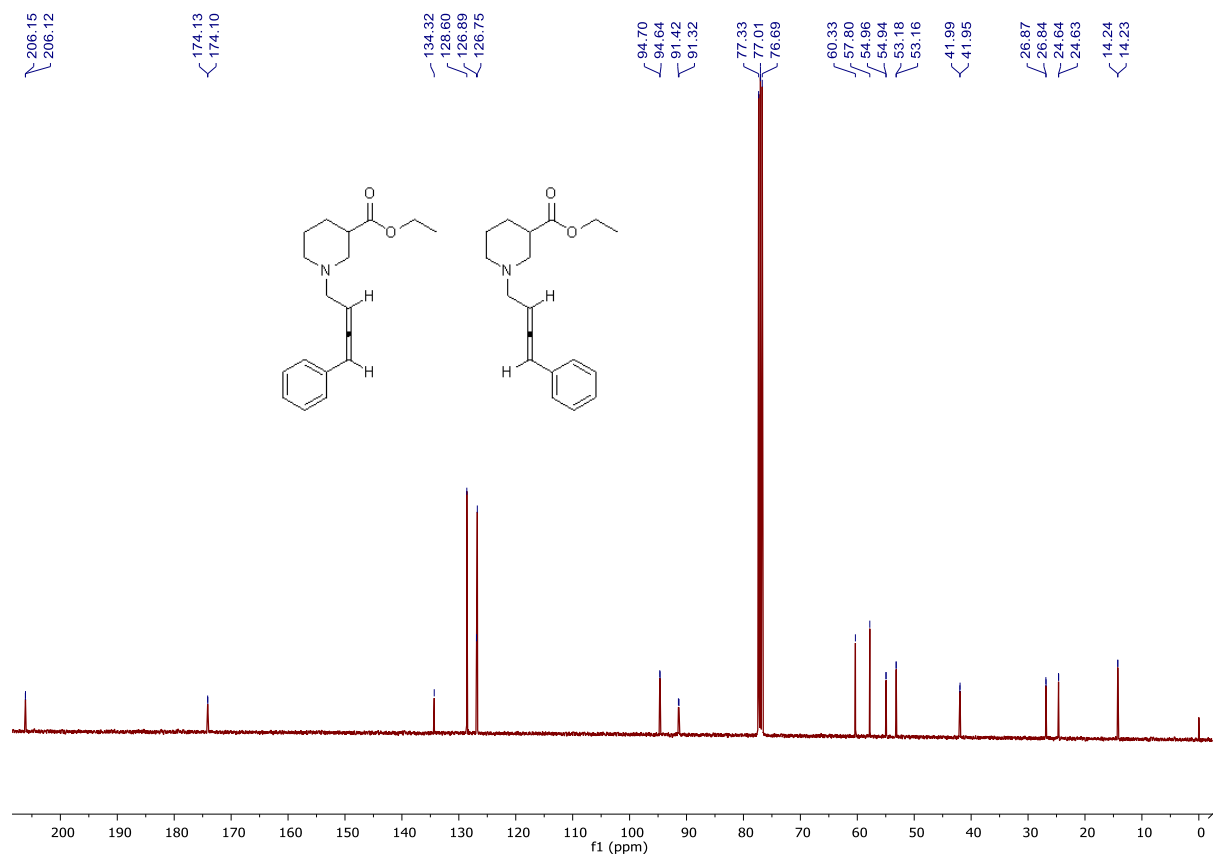
Figure S89: <sup>13</sup>C NMR ethyl 1-(buta-2,3-dien-1-yl)piperidine-3-carboxylate (24)



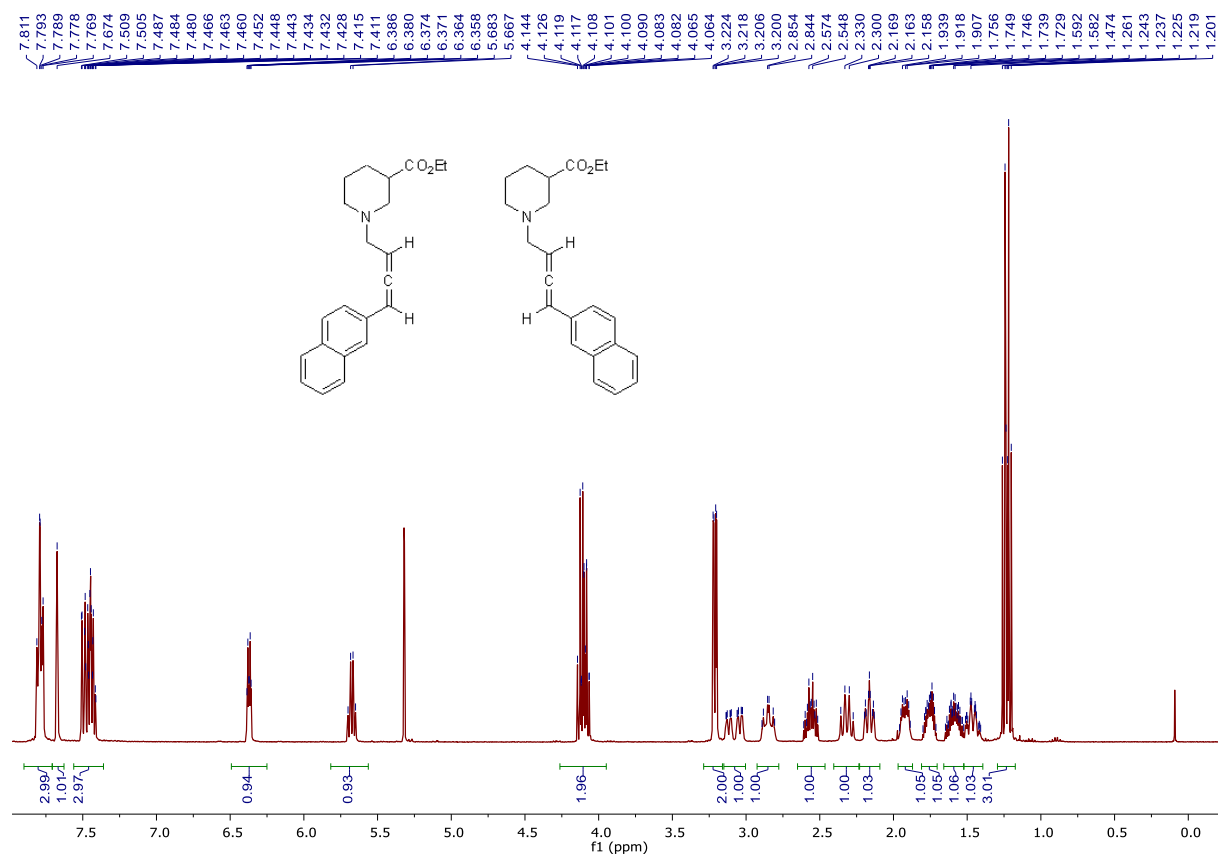
**Figure S90: <sup>1</sup>H NMR *rac*-[ethyl (*R<sub>a</sub>*)-1-(4-phenylbuta-2,3-dien-1-yl)(*S*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>,S*)-53a); *rac*-[ethyl (*R<sub>a</sub>*)-1-(4-phenylbuta-2,3-dien-1-yl)(*R*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>,R*)-53a)**



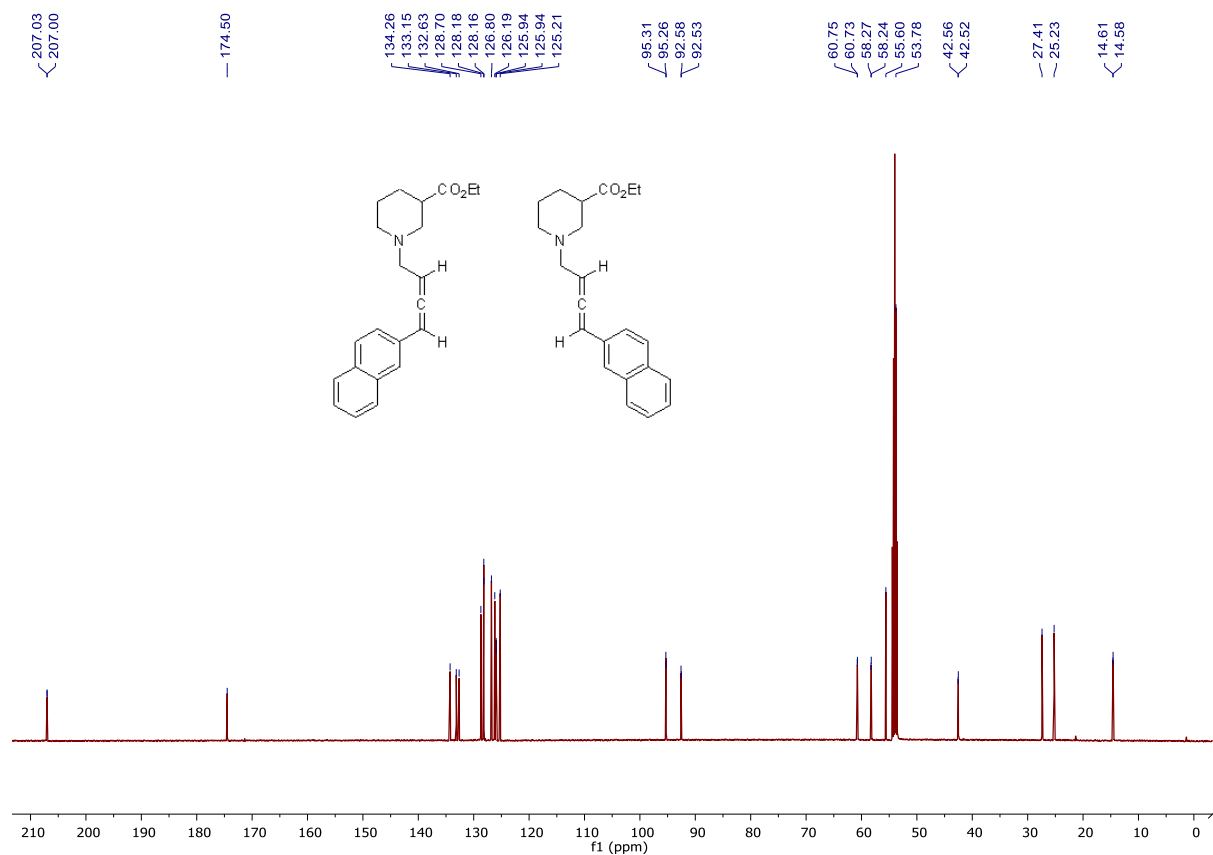
**Figure S91:  $^{13}\text{C}$  NMR *rac*-[ethyl ( $R_a$ )-1-(4-phenylbuta-2,3-dien-1-yl)( $S$ )-piperidine-3-carboxylate] (*rac*-( $R_a,S$ )-53a); *rac*-[ethyl ( $R_a$ )-1-(4-phenylbuta-2,3-dien-1-yl)( $R$ )-piperidine-3-carboxylate] (*rac*-( $R_a,R$ )-53a)**



**Figure S92: <sup>1</sup>H NMR *rac*-{ethyl (*R<sub>a</sub>*)1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl]}(*R*)-piperidine-3-carboxylate} (*rac*-(*R<sub>a</sub>*,*R*)-53b); *rac*-{ethyl (*R<sub>a</sub>*)1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl]}(*S*)-piperidine-3-carboxylate} (*rac*-(*R<sub>a</sub>*,*S*)-53b)**

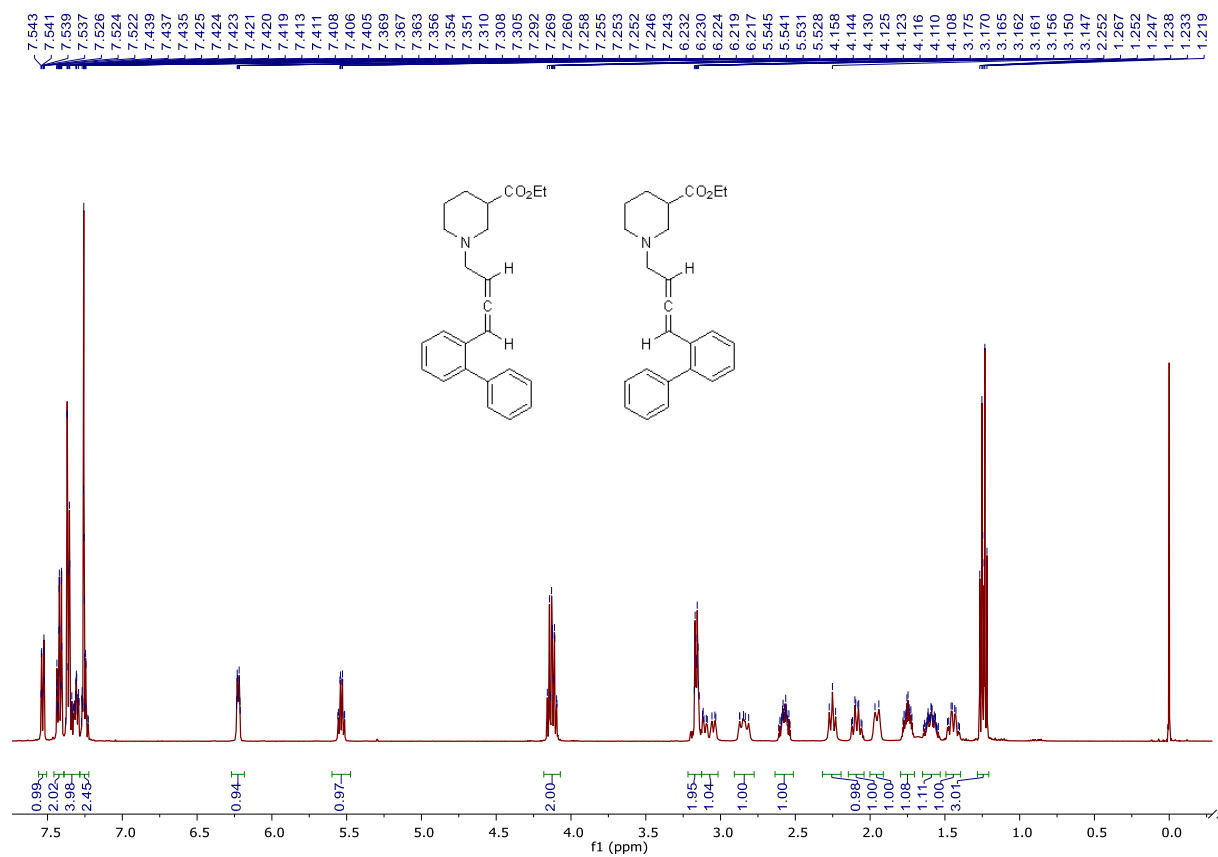


**Figure S93:  $^{13}\text{C}$  NMR *rac*-{ethyl (*R<sub>a</sub>*)1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl]}(*R*)-piperidine-3-carboxylate} (*rac*-(*R<sub>a</sub>*,*R*)-53b); *rac*-{ethyl (*R<sub>a</sub>*)1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl]}(*S*)-piperidine-3-carboxylate} (*rac*-(*R<sub>a</sub>*,*S*)-53b)**





**Figure S94: <sup>1</sup>H NMR *rac*-[ethyl (*R<sub>a</sub>*)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*R*)-53c); *rac*-[ethyl (*R<sub>a</sub>*)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*S*)-53c)**



**Figure S95:**  $^{13}\text{C}$  NMR *rac*-[ethyl (*R<sub>a</sub>*)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(*R*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*R*)-53c); *rac*-[ethyl (*R<sub>a</sub>*)-1-{4-[(1,1'-biphenyl)-2-yl]buta-2,3-dien-1-yl}(*S*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*S*)-53c)

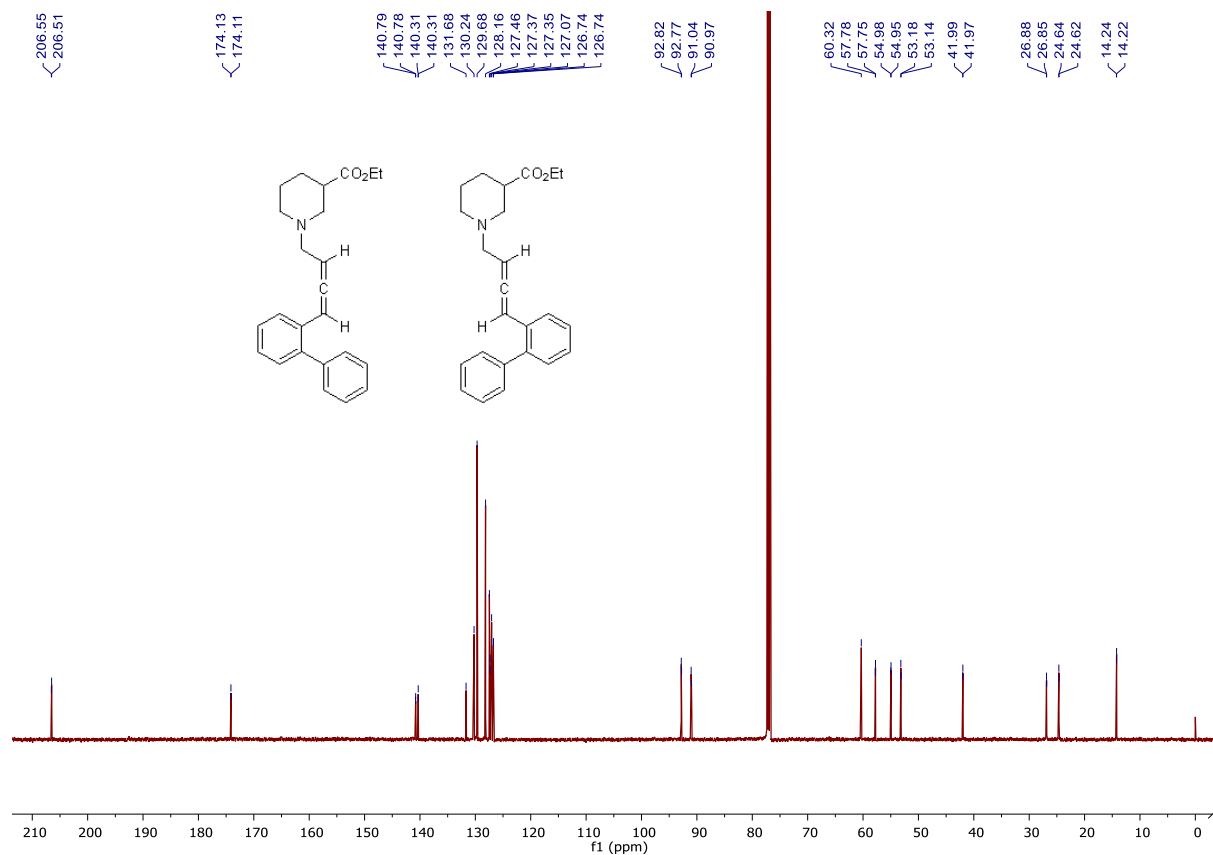
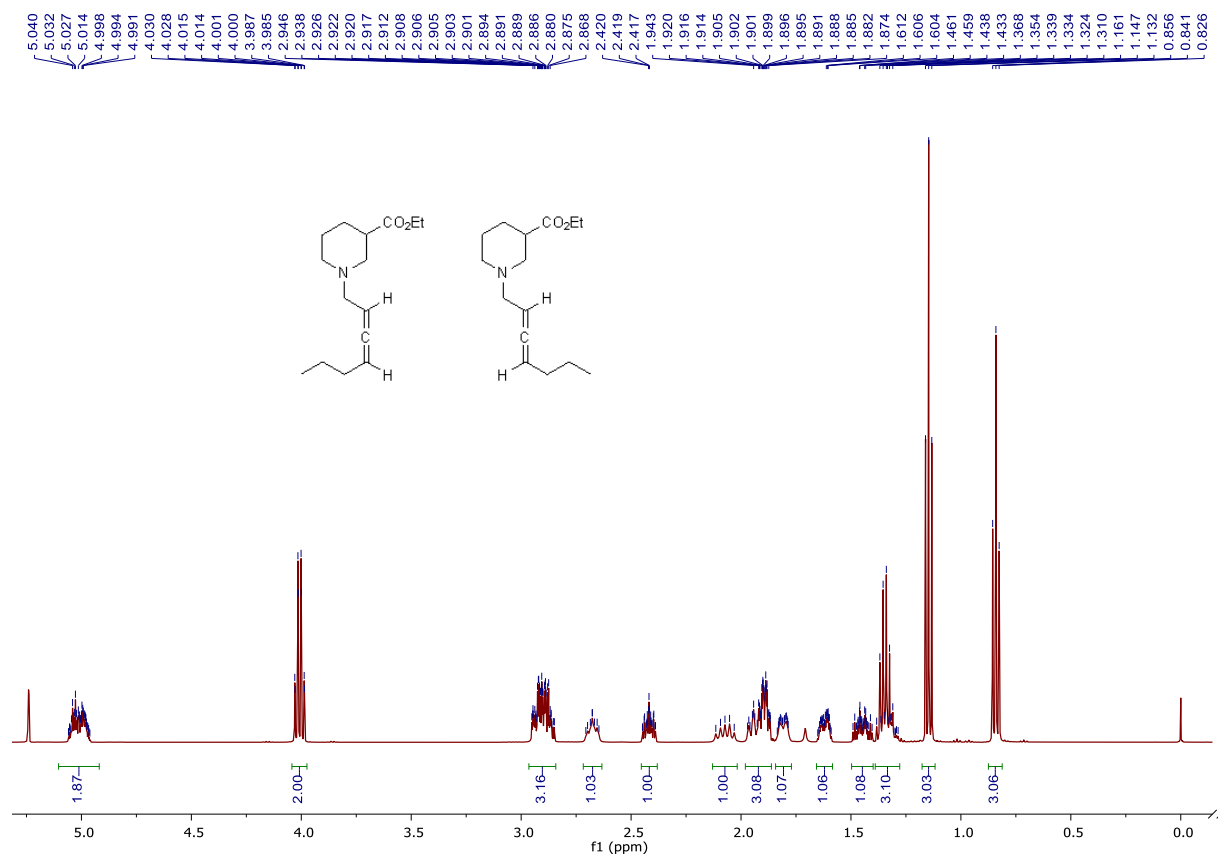
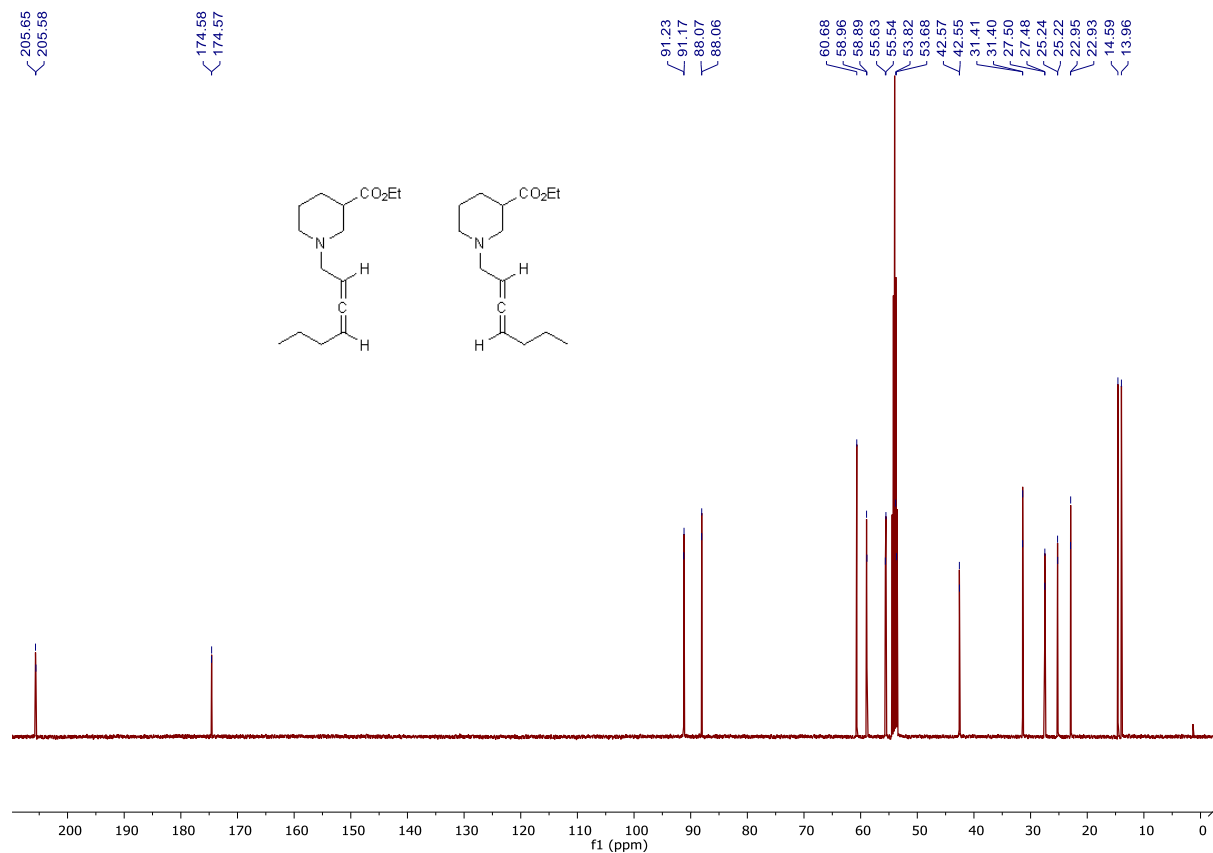


Figure S96:  $^1\text{H}$  NMR *rac*-[ethyl (*R<sub>a</sub>*)-1-(hepta-2,3-dien-1-yl)(*R*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*R*)-53d); *rac*-[ethyl (*R<sub>a</sub>*)-1-(hepta-2,3-dien-1-yl)(*S*)-piperidine-3-carboxylate] (*rac*-(*R<sub>a</sub>*,*S*)-53d)



**Figure S97:**  $^{13}\text{C}$  NMR *rac*-[ethyl ( $R_a$ )-1-(hepta-2,3-dien-1-yl)( $R$ )-piperidine-3-carboxylate] (*rac*-( $R_a,R$ )-53d); *rac*-[ethyl ( $R_a$ )-1-(hepta-2,3-dien-1-yl)( $S$ )-piperidine-3-carboxylate] (*rac*-( $R_a,S$ )-53d)



**Figure S98:  $^1\text{H}$  NMR *rac*-[ethyl ( $R_a$ )-1-(5-methylhexa-2,3-dien-1-yl)( $R$ )-piperidine-3-carboxylate] (*rac*-( $R_a,R$ )-53e); *rac*-[ethyl ( $R_a$ )-1-(5-methylhexa-2,3-dien-1-yl)( $S$ )-piperidine-3-carboxylate] (*rac*-( $R_a,S$ )-53e)**

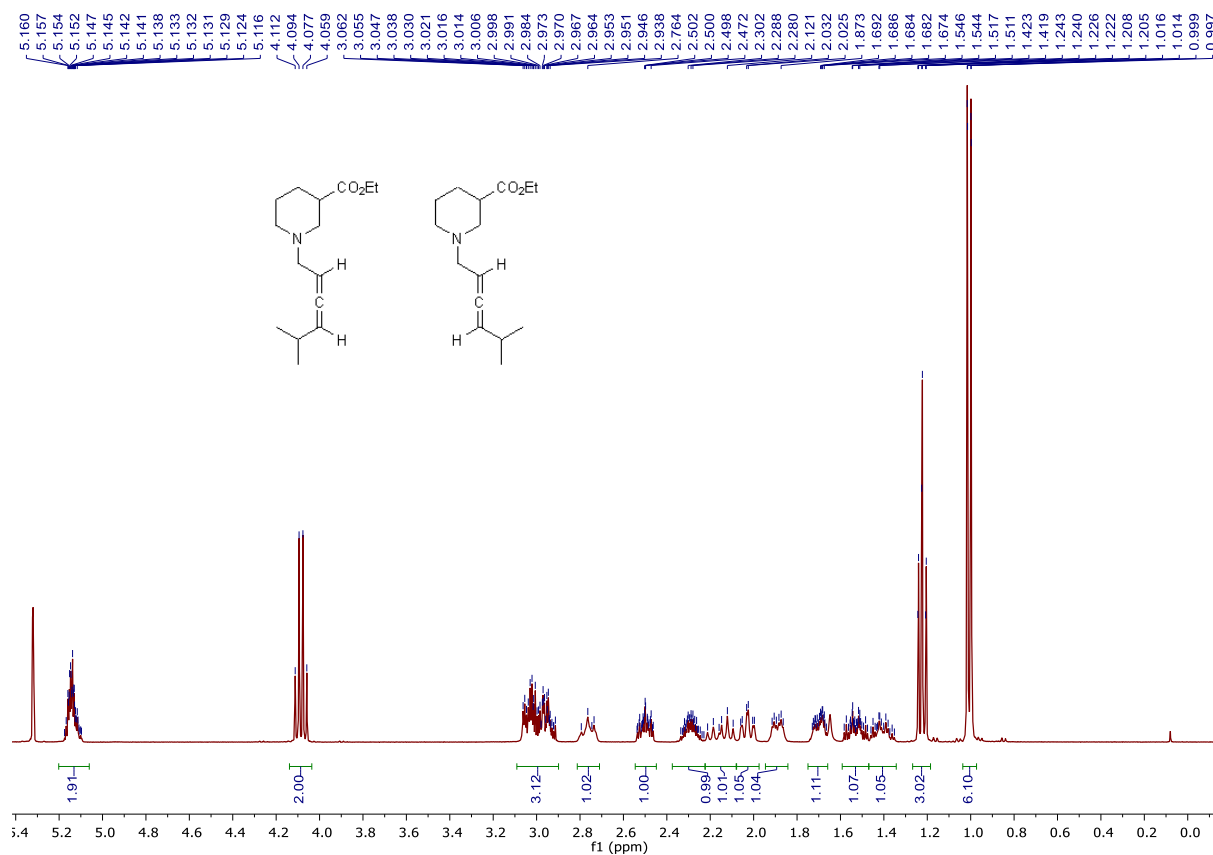
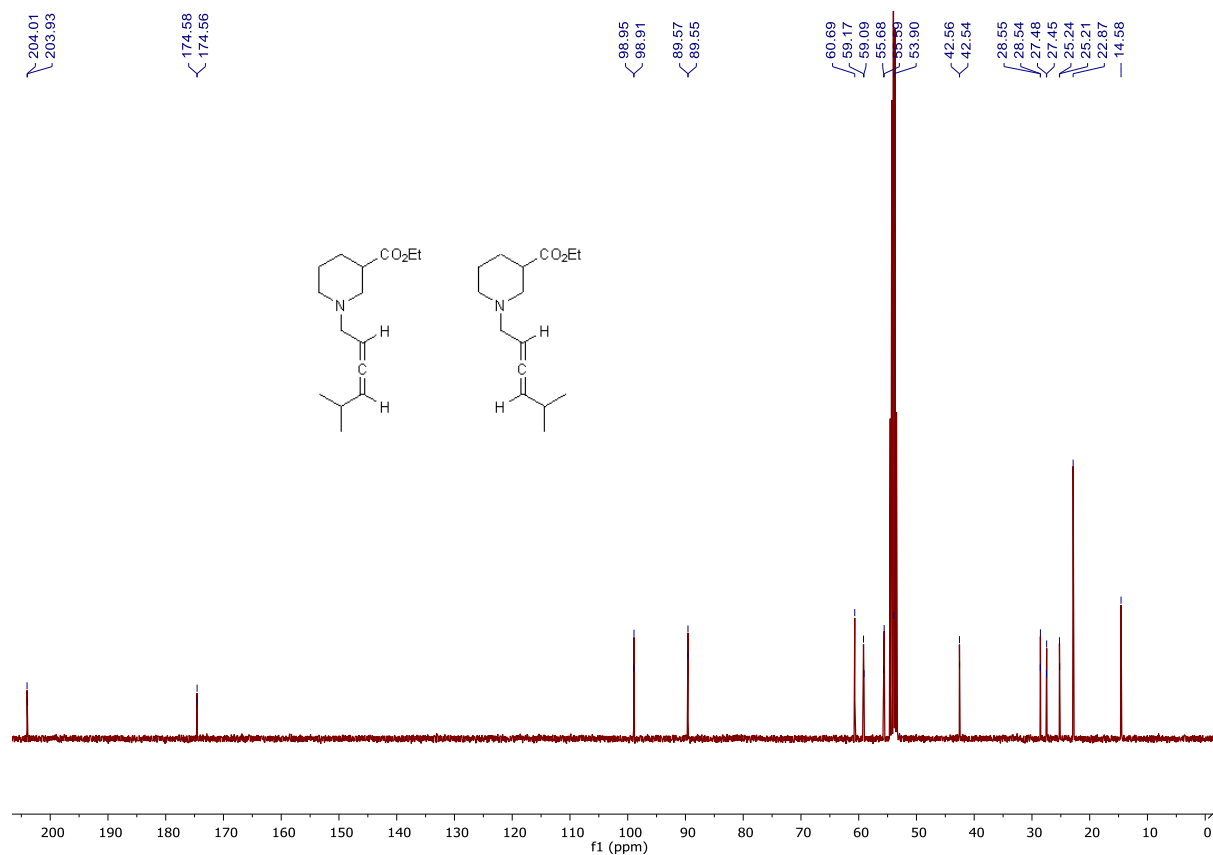


Figure S99:  $^{13}\text{C}$  NMR *rac*-[ethyl ( $R_a$ )-1-(5-methylhexa-2,3-dien-1-yl)( $R$ )-piperidine-3-carboxylate] (*rac*-( $R_a,R$ )-53e); *rac*-[ethyl ( $R_a$ )-1-(5-methylhexa-2,3-dien-1-yl)( $S$ )-piperidine-3-carboxylate] (*rac*-( $R_a,S$ )-53e)



## 3.2 Second Publication: “Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1” (*ChemMedChem* 2019, accepted article)

### 3.2.1 Summary of the Results

In this publication, a new series of nipecotic acid and guvacine derivatives has been synthesized and characterized regarding their inhibitory potency at mGAT1-4 and binding affinity for mGAT1. Compounds of the described class are defined by a four-carbon atom allenic spacer connecting the nitrogen of the polar nipecotic acid or guvacine subunit with a lipophilic aromatic residue. By applying the allyl(*tert*-butyl)amine and 1,2,5,6-tetrahydropyridine derived precursors established in the first publication, the two-step comprising ATA reaction delivered the desired compounds in good to excellent yields up to 95%. The applied synthesis method allowed to easily vary the terminal lipophilic monoaryl and biaryl residue of the desired 1,3-disubstituted allenes.

Among the compounds investigated, the nipecotic acid derivative **21p** (**Scheme 1**, *ChemMedChem* 2019), possessing an *o*-terphenyl residue, was identified as highly selective and most potent mGAT1 inhibitor in this study. For the (*R*)-nipecotic acid derived form of **21p**, the inhibitory potency in [<sup>3</sup>H]GABA-Uptake-Assays has been determined as  $pIC_{50} = 6.78 \pm 0.08$  and the binding affinity in MS Binding Assays as  $pK_i = 7.10 \pm 0.12$ , both being in the range of the known mGAT1 inhibitor tiagabine ( $pIC_{50} = 6.88 \pm 0.12$ ,  $pK_i = 7.43 \pm 0.11$ ). With guvacine instead of nipecotic acid as polar subunit in **21p**, a slightly lower inhibitory potency at mGAT1 and an equal high binding affinity for mGAT1 has been observed ( $pIC_{50} = 6.46 \pm 0.10$ ;  $pK_i = 7.07 \pm 0.11$ ).

A comparison showed that the nipecotic acid derivative with an allenic spacer bearing a 2-biphenyl residue possessed a higher inhibitory potency as compared to nipecotic acid derivatives equipped with 3- or 4-biphenyl residues, respectively. The introduction of halogen substituents in 2'- and 4'-position of the 2-biphenyl domain led to enhanced inhibitory potency and binding affinity for mGAT1. These observations were in good agreement with the results obtained in former studies,<sup>32,34</sup> in which four-carbon atom alkenyl and alkynyl spacer have been implemented instead of the herein described four-carbon atom allenic spacer.

Interestingly, also some of the nipecotic acid derived allenes bearing phenyl rings at the allene terminus that exhibit smaller substituents, such as halide or methoxy, showed reasonable inhibitory potencies at mGAT1, with pIC<sub>50</sub> values reaching up to 5.82 ± 0.04 (**21j**; pK<sub>i</sub> = 6.31 ± 0.08). Under consideration that the tested compounds still represent ~ 1:1 mixtures of racemic diastereomers, even more pronounced biological activity may be expected for the individual stereoisomers.

### *3.2.2 Declaration of contributions*

The synthesis of all described compounds as well as the evaluation of all corresponding analytical data were accomplished by myself. The practical performance of the biological testing and the determination of the pK<sub>i</sub> values and pIC<sub>50</sub> values were performed by the technical assistants Silke Duesing-Kropp, Miriam Sandner, and Tanja Franz under the supervision of Dr. Georg Höfner. I wrote the manuscript and generated all graphics and tables, supported by Prof. Dr. Klaus T. Wanner. The manuscript was corrected by Prof. Dr. Klaus T. Wanner.



# Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1

Maren Schaarschmidt, Georg Höfner, and Klaus T. Wanner\*<sup>[a]</sup>

A new class of nipecotic acid and guvacine derivatives has been synthesized and characterized for their inhibitory potency at mGAT1–4 and binding affinity for mGAT1. Compounds of the described class are defined by a four-carbon-atom allenyl spacer connecting the nitrogen atom of the nipecotic acid or guvacine head with an aromatic residue. Among the compounds investigated, the mixture of nipecotic acid derivatives *rac*-{(R<sub>s</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid and *rac*-{(S<sub>s</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid

(**21 p**), possessing an *o*-terphenyl residue, was identified as highly selective and the most potent mGAT1 inhibitor in this study. For the (*R*)-nipecotic acid derived form of **21 p**, the inhibitory potency in [<sup>3</sup>H]GABA uptake assays was determined as pIC<sub>50</sub> = 6.78 ± 0.08, and the binding affinity in MS Binding Assays as pK<sub>i</sub> = 7.10 ± 0.12. The synthesis of the designed compounds was carried out by a two-step procedure, generating the allene moiety via allenylation of terminal alkynes which allows broad variation of the terminal phenyl and biphenyl subunit.

## Introduction

γ-Aminobutyric acid (GABA, **1**, Figure 1) is a primary mediator of inhibitory transmission in the mammalian central nervous system (CNS). Epilepsy,<sup>[1]</sup> Alzheimer's disease,<sup>[2]</sup> depression,<sup>[3]</sup> neuropathic pain,<sup>[4]</sup> Huntington's disease, and Parkinson's disease<sup>[5]</sup> are neurological disorders that are assumed to be connected to an imbalance between excitatory neurotransmission mediated by glutamate and the inhibitory neurotransmission effected by GABA, due to decreased GABAergic signaling. Data from the World Health Organization (WHO) suggest that neurological disorders are represented with approximately 12% of all diseases in Europe.<sup>[6]</sup> Epilepsy, for example, affects 50 million people worldwide, but approved antiepileptic drugs available to date are still inadequate, as more than half of the treated patients either suffer from adverse side effects or continue to have seizures.<sup>[7]</sup> Hence, there is a great need for new antiepileptic drugs.

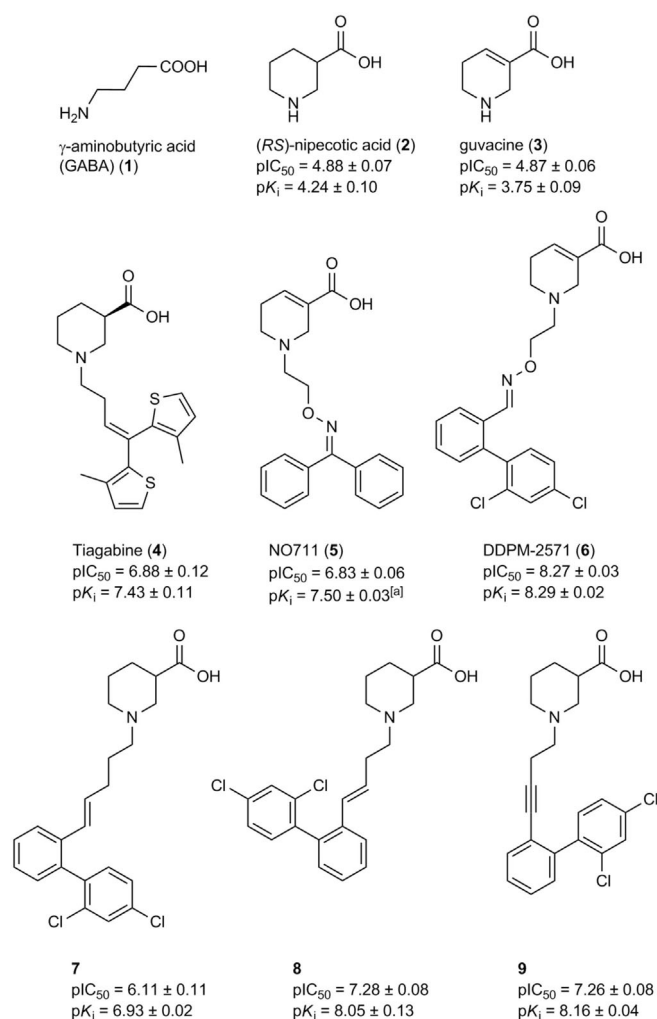
As GABAergic neurotransmission is terminated by specific GABA transport proteins responsible for the reuptake of GABA into the presynaptic neuron or its transport into glial cells,<sup>[8]</sup> one pharmacological approach is to enhance the concentration of GABA in the synaptic cleft by blocking the plasma-membrane-bound GABA transporters (GATs). GATs are Na<sup>+</sup>/Cl<sup>-</sup>-dependent neurotransmitter transporters of the solute carrier family 6 (SLC-6)<sup>[9]</sup> that are in charge of the removal of GABA from the synaptic cleft after a neuronal impulse. The known

four subtypes are termed as mGAT1, mGAT2, mGAT3, and mGAT4 when cloned from mice brain, whereas according to the International Union of Basic and Clinical Pharmacology (IUPHAR) for the GABA transporters the nomenclature GAT1, BGT1, GAT2, and GAT3 is used irrespective of the species.<sup>[10]</sup> mGAT1 is expressed in high density in the brain and closely along GABAergic pathways, in particular on presynaptic neurons. Hence, mGAT1 is considered to be the most important transporter subtype for neuronal GABA uptake, on the basis of which it is an interesting drug target.<sup>[8]</sup> Both mGAT1, the most abundant, and mGAT4, the second most abundant GABA transporter in the brain, are almost exclusively located in the CNS. In contrast, mGAT2 and mGAT3 are located with high density in liver and kidney, whereas they show a particularly low and regionally limited abundance in the brain. Thus, mGAT2 and mGAT3 appear to have a low level of influence on the control of seizure susceptibility.<sup>[11]</sup>

The first generation of in vitro inhibitors of GABA uptake includes cyclic analogues of GABA such as (*R,S*)-nipecotic acid (**2**, Figure 1) and the areca nut alkaloid guvacine (**3**, Figure 1). Although they exhibit reasonable inhibitory potency at mGAT1 (**2**: pIC<sub>50</sub> = 4.88 ± 0.07, **3**: pIC<sub>50</sub> = 4.87 ± 0.06, Figure 1), one drawback of these compounds is that their polar and zwitterionic character prevents them from passing the blood–brain barrier in significant amounts.<sup>[7]</sup> However, N-substitution of parent compounds **2** and **3** with lipophilic residues, in particular arylalkyl moieties, allows greater penetration of the blood–brain barrier and leads to a substantially improved potency at, and subtype selectivity for, GAT1. Two examples of such compounds are tiagabine (Gabitril®, **4**, Figure 1), which is used as add-on antiepileptic drug for the treatment of partial epileptic seizures,<sup>[7]</sup> and NO711 (**5**, Figure 1), representing an experimen-

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**Figure 1.** Structures of GABA and GAT1 inhibitors. Biological activity data refer to inhibitory potencies at mGAT1 (pIC<sub>50</sub>) and binding affinities for mGAT1 (pK<sub>i</sub>) determined on HEK293 cells. The quoted values were taken from Ref. [14] (2), Ref. [15] (3 and 4), Ref. [16] (5), Ref. [17] (6), Ref. [18] (7), Ref. [19] (8), and Ref. [20] (9). [a] From binding assays with [<sup>3</sup>H]NO711.

tal drug that has also been used as a native marker for mGAT1 in MS Binding Assays.<sup>[12]</sup> With the introduction of tiagabine as a drug, GAT1 has been validated as molecular target for the treatment of epilepsy. To improve the unfavorable pharmacokinetic properties of tiagabine (4) and to decrease the observed side effects such as dizziness, asthenia, nervousness, tremor, diarrhea, and depression,<sup>[13]</sup> several different structural elements of tiagabine and related compounds have been varied in order to identify compounds with higher selectivities and affinities and hence possibly fewer side effects. For example, through variation of the spacer between the amino acid moiety and the lipophilic aromatic residues with regard to length and functionalities, a new group of mGAT1 inhibitors was found, of which the guvacine derivative DDPM-2571 (6, Figure 1) and nipecotic acid derivatives 7–9 (Figure 1) are typical representatives. Among the tested bis-aromatic residues attached to the spacer, structure–activity relationship studies characterized a biphenyl moiety, carrying two chloro substituents at the 2'- and 4'-positions of the terminal phenyl ring, as most favorable

for the lipophilic part of these compounds with regard to inhibitory potency.<sup>[19]</sup> In addition, previous studies revealed that the shorter four-carbon-atom linker is more favorable than the longer five-carbon-atom linker for high binding affinity at mGAT1, illustrated by a direct comparison of the pK<sub>i</sub> values of compounds 7 and 8.<sup>[20]</sup>

Because of the unique chemical properties of allenes, such as their intrinsic three-carbon axial chirality, sterically less demanding linear structure, and high substituent-loading ability, the interest in this class of compounds is constantly growing. Although many natural products, molecular materials, and pharmaceuticals with an allene moiety are known,<sup>[21,22]</sup> allene derivatives are still thought to be highly reactive. However, many allenic compounds are fairly stable.<sup>[23]</sup> Hence, as an extension of the aforementioned studies regarding the structure–activity relationship of GAT1 inhibitors, we intended to explore the binding affinities of compounds that are closely related to 8 and 9 and its derivatives, but which bear an allenyl instead of an alkenyl or alkynyl spacer. For the efficient preparation of the desired compounds, a recently published two-step procedure<sup>[24]</sup> should be applied that preserves a high degree of flexibility regarding the substitution pattern of the aromatic residues attached to the allenyl spacer.

## Results and Discussion

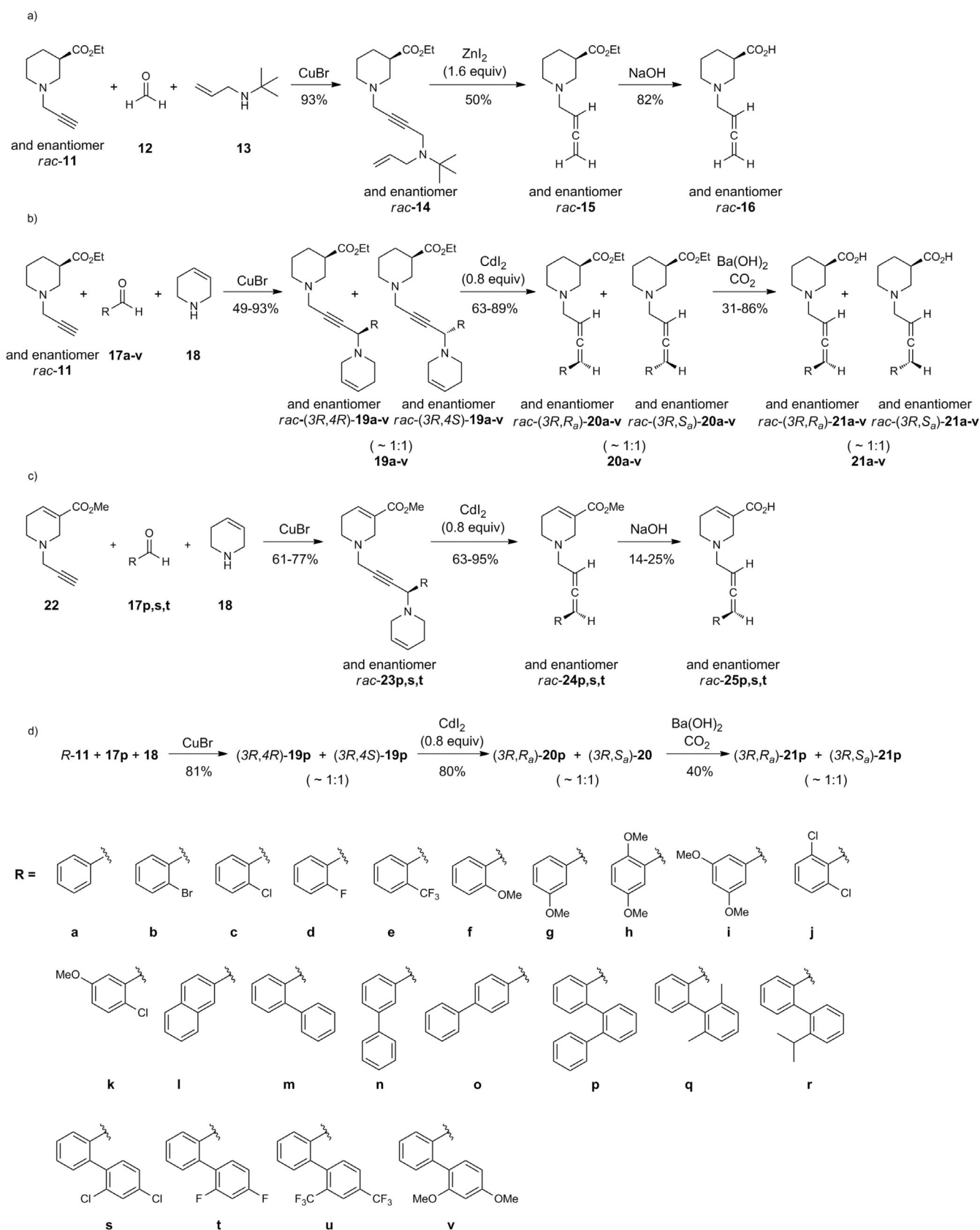
### Chemistry

#### Synthesis of nipecotic acid and guvacine derivatives containing a four-carbon-atom allenyl spacer

Synthesis of parent compound *rac*-16, nipecotic acid derived 1,3-disubstituted allenes 21 a–v<sup>1</sup> and guvacine derived 1,3-disubstituted allenes *rac*-25 p,s,t was realized following the synthetic route outlined in Scheme 1. N-Alkylation of ethyl nipecotate and methyl 1,2,5,6-tetrahydropyridine-3-carboxylate with propargyl bromide delivered terminal alkynes *rac*-11 and 22 (Scheme 1) that served as starting material for the allenylation reactions.<sup>[25]</sup>

Allenylation of terminal alkynes was then performed according to a recently developed two-step procedure.<sup>[24]</sup> This comprises the synthesis of an amino methylation product (e.g., *rac*-14) from the corresponding alkyne (e.g., *rac*-11) in a Cu<sup>I</sup>-catalyzed aldehyde–alkyne–amine reaction (A<sup>3</sup> coupling), the product of which is subsequently subjected to a Lewis acid catalyzed rearrangement reaction, a [1,5]-hydride transfer, yielding the desired allene (e.g., *rac*-15). In the case of constructing the terminal allene *rac*-15, the sterically demanding hydride donor allyl(*tert*-butyl)amine (13, Scheme 1 a) was used for the A<sup>3</sup> coupling. According to prior results,<sup>[24]</sup> amino methylation products derived from 13 are less prone to complexation of the hydride donor nitrogen atom (N-CH<sub>2</sub>CHCH<sub>2</sub>) by the Lewis acid required for the next step, the [1,5]-hydride transfer, and hence more suitable for the latter. Following the published

<sup>1</sup> For the sake of simplicity, compound numbers 19, 20, and 21 are used to denote the approximate 1:1 mixtures of the corresponding racemic diastereomers.



**Scheme 1.** Synthesis routes of a) nipecotic acid derived terminal allene *rac*-16, b) nipecotic acid derived 1,3-disubstituted allenes **21a–v**, c) guvacine derived 1,3-disubstituted allenes *rac*-**25p,s,t**, and d) (*R*)-nipecotic acid derived 1,3-disubstituted allenes (3*R*,*R*<sub>a</sub>)-**21p** and (3*R*,*S*<sub>a</sub>)-**21p**.

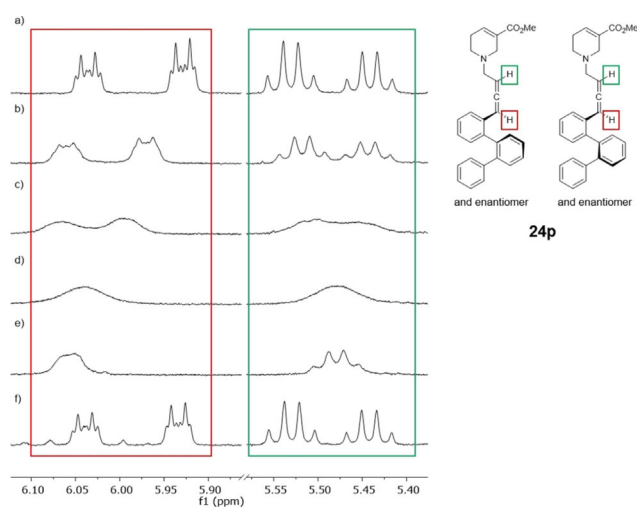
procedure upon reaction of *rac*-11 with formaldehyde (12) and allyl(*tert*-butyl)amine (13), the A<sup>3</sup> coupling product *rac*-14 was obtained in good yield (93%). Its subsequent transformation into terminal allene *rac*-15 was effected by ZnI<sub>2</sub> as catalyst, which provided higher yields than CdI<sub>2</sub> due to fewer side reactions. For the synthesis of the A<sup>3</sup> coupling products derived from aldehydes other than formaldehyde (12) instead of allyl(*tert*-butyl)amine (13), 1,2,5,6-tetrahydropyridine (18, Scheme 1 b–d) was used. This was more favorable, as the synthesis of the corresponding amino methylation products resulted in lower yields, and the subsequent [1,5]-hydride transfer reaction required extended reaction times when the sterically more demanding allyl(*tert*-butyl)amine (13) was used. It should be noted that in the case of the synthesis of 1,3-disubstituted allenes, large residues attached to the amino function serving as hydride donor such as the *tert*-butyl group present in 13 appear to be dispensable. This is due to the R group that is present in the amino methylation products when aldehydes (RCHO) are used in the A<sup>3</sup> coupling reaction. The steric shielding of the amino function by these R groups is sufficient to prevent the amino group from complexation by the Lewis acid that is required to induce the rearrangement reaction to the allenic compounds. Consequently, 1,2,5,6-tetrahydropyridine (18) represents the better choice over allyl(*tert*-butyl)amine (13) as hydride donor in such cases.<sup>[24]</sup> Aiming at target compounds covering a broad array of substituents R at the terminal position of the allene subunit, aldehydes 17 a–v, comprising halogen and methoxy substituted phenyls, naphthyl, and substituted biphenyl moieties, were selected as starting materials. Upon reaction of *rac*-11 and 22 with 18 as hydride donor, the A<sup>3</sup> coupling products 19 a–v and *rac*-23 p,s,t (Scheme 1) were obtained in reasonable to good yields (49–93%). Subsequent treatment of the latter compounds with CdI<sub>2</sub>, which appeared to be more suitable than ZnI<sub>2</sub> in this case, finally provided the desired 1,3-disubstituted allenes 20 a–v and *rac*-24 p,s,t in good to very good yields (63–95%). Hydrolysis of *rac*-15, 20 a–v, and *rac*-24 p,s,t to the free amino acids *rac*-16, 21 a–v, and *rac*-25 p,s,t (Scheme 1) could finally be accomplished under basic conditions applying NaOH or Ba(OH)<sub>2</sub>. The comparatively low yields of the ester hydrolysis are likely due to the instability of the allenyl moiety under the applied basic conditions used for ester cleavage and slightly acidic conditions, necessary for the isolation of the free amino acids. Fortunately, reversed-phase MPLC proved effective at removing decomposition products from the crude product obtained after workup, thus leading to the target compounds in pure form. The purified amino acids were finally stored at –25 °C, under which conditions no further decomposition was observed. For hydrolysis of the guvacine derivatives *rac*-24 p,s,t, higher yields were obtained if NaOH instead of Ba(OH)<sub>2</sub> was applied. Nevertheless, with only 14–25%, the yields for *rac*-25 p,s,t were still lower than the corresponding yields obtained for the hydrolysis of the nipecotic acid derivatives 20 a–v, leading to 21 a–v, indicating a higher instability of the guvacine-derived 1,3-disubstituted allenes toward acids and bases.

Finally, it should be noted that whereas propargylic amines *rac*-14 and *rac*-23 p,s,t, terminal allenes *rac*-15 and *rac*-16, and

guvacine-derived allenes *rac*-24 p,s,t and *rac*-25 p,s,t are single compounds (in racemic form), the propargylic amines 19 a–v and nipecotic acid derived 1,3-disubstituted allenes 20 a–v and 21 a–v were obtained as ≈ 1:1 mixtures of racemic diastereomers (ratio determined by <sup>1</sup>H NMR).

### Atropisomerism

For the nipecotic acid derivatives 19–21 p,r,s,u and guvacine derivatives *rac*-(23–25 p,s) bearing a 2-biphenyl moiety that carries a phenyl, isopropyl, chloro, or trifluoromethyl substituent at the 2'-position, atropisomeric forms could be observed in the NMR spectra. This behavior is exemplarily shown for compound *rac*-24 p in Figure 2. Due to the axis of chirality of the sterically hindered 2-biphenyl moiety present in addition to the axis of chirality of the allene moiety, *rac*-24 p is present as a mixture of racemic diastereomers. This becomes evident from the <sup>1</sup>H NMR spectra of *rac*-24 p (Figure 2 a), which shows, for example, two sets of signals for the two allenic protons that are to be assigned to the two atropisomeric forms present in a ratio of 45:55. When the temperature at which the <sup>1</sup>H NMR spectra were recorded was gradually raised to 393 K, the allenic signals of the two atropisomeric forms continuously merged to finally give a single signal for each of the two allenic protons (see Figure 2 a–e). Upon cooling the <sup>1</sup>H NMR sample down to 298 K, again a <sup>1</sup>H NMR spectrum (Figure 2 f) was obtained that was identical with the original one (Figure 2 a). Clearly, the exchange phenomena observed in the <sup>1</sup>H NMR spectra may be well explained by the presence of the aforementioned atropisomeric forms of 24 p. Regarding the analogous nipecotic acid derivatives 20 p, the situation is more complex due to the additional stereocenter present in the nipecotic acid moiety. A detailed discussion of the <sup>13</sup>C NMR spectra of *rac*-24 p in comparison with those of 20 p obtained at different temperatures that helped to interpret the observed <sup>1</sup>H and <sup>13</sup>C



**Figure 2.** <sup>1</sup>H NMR spectra of guvacine derivatives *rac*-24 p in [D<sub>5</sub>]nitrobenzene at a) 298 K, b) 333 K, c) 353 K, d) 373 K, e) 393 K, and f) 298 K.

signals of the diastereomeric compound mixtures is given in the Supporting Information (SI-Figure 1).

### Biological evaluations

For all synthesized nipecotic acid and guvacine derivatives bearing a four-carbon-atom allenyl spacer, including the esters *rac*-**15**, **20a–v** and *rac*-**24p,s,t** and the free amino acids *rac*-**16**, **21a–v** and *rac*-**25p,s,t**, binding affinities for mGAT1 were determined in MS Binding Assays with NO711 as native MS marker.<sup>[12]</sup> In addition, their functional activity was characterized in [<sup>3</sup>H]GABA uptake assays on HEK293 cells stably expressing the individual mouse GABA transporters mGAT1–mGAT4.<sup>[16]</sup> When NO711 binding or [<sup>3</sup>H]GABA uptake was decreased by at least 50% at a concentration of 100 μM, affinity in binding assays (given as p*K*<sub>i</sub> values) or inhibitory potencies in uptake assays (given as p*C*<sub>50</sub> values) were assessed, otherwise only the percentage of decrease in binding or the remaining specif-

ic [<sup>3</sup>H]GABA uptake at 100 μM is given. Compounds in Tables 1 and 2 were tested as ≈ 1:1 mixtures of racemic diastereomers. The biological results for each of the stereoisomers, that is, enantiomers and diastereomers, will most likely differ from the results obtained for the mixtures. Therefore, structure–activity relationships that are delineated from the obtained test data are to be considered as approximations only.

At first, parent compound *rac*-**16**, bearing solely a four-carbon-atom allenyl residue attached to the nitrogen atom of the nipecotic acid with no additional lipophilic substituent, was analyzed for its biological activity. Compared with (*R,S*)-nipecotic acid (**2**, Figure 1) and guvacine (**3**, Figure 1) the inhibitory potency of *rac*-**16** is one log unit lower at mGAT1 (*rac*-**16**: p*C*<sub>50</sub> = 3.89, Table 1, entry 1). Furthermore, compound *rac*-**16** exhibits low subtype selectivity for mGAT1. To increase the inhibitory potency at, and subtype selectivity for, mGAT1, lipophilic substituents had been introduced at the four-carbon-atom allenyl residue, resulting in nipecotic acid derived 1,3-dis-

**Table 1.** Nipecotic acid derivatives with a four-carbon-atom allenyl spacer and their inhibitory potencies at mGAT1–4 and binding affinities for mGAT1.

Entry	Compd <sup>[a]</sup>	R <sup>1</sup>	R <sup>2</sup>	p <i>K</i> <sub>i</sub> <sup>[b]</sup>		p <i>C</i> <sub>50</sub> <sup>[b]</sup>			
				mGAT1	mGAT1	mGAT2	mGAT3	mGAT4	
1	<i>rac</i> - <b>16</b>	H	–	3.58 ± 0.03	3.89	3.32	88%	94%	
2	<i>rac</i> - <b>15</b>	Et	–	81%	91%	85%	81%	87%	
3	<b>21a</b>	H		5.27 ± 0.05	4.73	87%	80%	83%	
4	<b>20a</b>	Et		67%	82%	52%	68%	64%	
5	<b>21b</b>	H		6.20 ± 0.05	5.45 ± 0.03	3.56	76%	79%	
6	<b>20b</b>	Et		71%	63%	4.58	4.56	4.36	
7	<b>21c</b>	H		6.48 ± 0.04	5.71 ± 0.07	52%	87%	3.05	
8	<b>20c</b>	Et		74%	4.17	4.43	4.58	4.20	
9	<b>21d</b>	H		5.41 ± 0.10	5.18 ± 0.07	83%	97%	3.02	
10	<b>20d</b>	Et		74%	58%	66%	4.26	4.05	
11	<b>21e</b>	H		5.98 ± 0.05	5.32 ± 0.05	86%	88%	3.14	
12	<b>20e</b>	Et		77%	4.22	4.30	4.42	4.59	
13	<b>21f</b>	H		5.51 ± 0.05	4.59	98%	50%	86%	
14	<b>20f</b>	Et		64%	73%	50%	50%	73%	
15	<b>21g</b>	H		5.41 ± 0.06	4.86 ± 0.10	77%	3.23	104%	
16	<b>20g</b>	Et		110%	69%	90%	59%	57%	
17	<b>21h</b>	H		6.34 ± 0.01	5.68 ± 0.08	3.07	3.34	3.30	
18	<b>20h</b>	Et		79%	4.03	70%	4.19	4.53	
19	<b>21i</b>	H		6.02 ± 0.04	5.37 ± 0.09	86%	3.04	107%	
20	<b>20i</b>	Et		107%	64%	85%	64%	79%	
21	<b>21j</b>	H		6.31 ± 0.08	5.82 ± 0.04	71%	75%	71%	
22	<b>20j</b>	Et		4.12	4.10	4.61	4.61	4.39	
23	<b>21k</b>	H		6.07 ± 0.10	5.33 ± 0.12	70%	81%	89%	
24	<b>20k</b>	Et		79%	4.31	4.51	4.55	4.60	
25	<b>21l</b>	H		5.95 ± 0.06	5.22 ± 0.12	92%	65%	67%	
26	<b>20l</b>	Et		65%	56%	4.40	4.60	4.22	

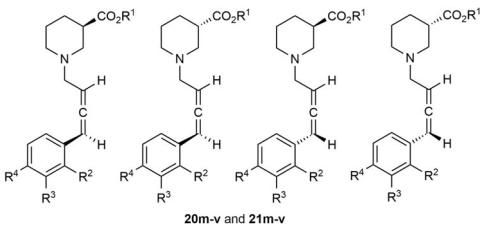
[a] Compounds **20a–l** and **21a–l** were tested as ≈ 1:1 mixture of racemic diastereomers. [b] Data are the mean ± SEM of three independent experiments, each performed in triplicate. Percentages represent the remaining [<sup>3</sup>H]GABA uptake in the presence of 100 μM inhibitor. At low p*C*<sub>50</sub> values, only one measurement was performed in triplicate, and therefore no SEM could be calculated.

substituted allenes **21 a–v**. At first, results of the biological characterization of the 1,3-disubstituted allenes bearing a monoaryl or naphthyl residue only (**21 a–l**, Table 1) will be discussed. By introducing a phenyl residue (**21 a**:  $pIC_{50}=4.73$ , Table 1, entry 3), the inhibitory potency could be increased by about one log unit relative to parent compound *rac*-**16**. Substitution of the phenyl moiety at the 2-position increased the inhibitory potency at mGAT1 except for a methoxy group. Thus, whereas a methoxy group as substituent at the 2-position (**21 f**:  $pIC_{50}=4.59$ , Table 1, entry 13) displayed a lower  $pIC_{50}$  value than that of unsubstituted **21 a**, the inhibitory potency increased from fluorine (**21 d**:  $pIC_{50}=5.18\pm 0.07$ , Table 1, entry 9) to trifluoromethyl (**21 e**:  $pIC_{50}=5.32\pm 0.05$ , Table 1, entry 11) to bromine (**21 b**:  $pIC_{50}=5.45\pm 0.03$ , Table 1, entry 5), ending up with a chlorine substituent (**21 c**:  $pIC_{50}=5.71\pm 0.07$ , Table 1, entry 7), for which the best inhibitory potency in this row was observed. A methoxy group at the 3-position of the terminal phenyl ring (**21 g**:  $pIC_{50}=4.86\pm 0.10$ , Table 1, entry 15) led to a slightly better  $pIC_{50}$  value than the analogous compound with a methoxy group at the 2-position (**21 f**:  $pIC_{50}=4.59$ , Table 1, entry 13). A further improvement could be achieved by introducing a second methoxy substituent, whereby substitution at the 2- and 5-positions of the phenyl ring (**21 h**:  $pIC_{50}=5.68\pm 0.08$ , Table 1, entry 17) is more favorable than substitution at the 3- and 5-positions (**21 i**:  $pIC_{50}=5.37\pm 0.09$ , Table 1, entry 19). As the chlorine substituent at the 2-position was well tolerated, an additional substituent was introduced in **21 c** in order to further improve biological activity, resulting in compound **21 j**, with a second chloro substituent at the 6-position, and compound **21 k**, with a methoxy group at the 5-position. The second chlorine slightly improved the inhibitory potency (**21 j**:  $pIC_{50}=5.82\pm 0.04$ , Table 1, entry 21), whereas the additional methoxy group caused a decrease in inhibition at mGAT1 (**21 k**:  $pIC_{50}=5.33\pm 0.12$ , Table 1, entry 23). The introduction of a naphthyl moiety (**21 l**:  $pIC_{50}=5.22\pm 0.12$ , Table 1, entry 25) led to a  $pIC_{50}$  value in the range of 2-fluoro-substituted phenyl derivative **21 d** ( $pIC_{50}=5.18\pm 0.07$ , Table 1, entry 9), hence possessing better inhibitory potency than **21 a**, exhibiting an unsubstituted phenyl residue. Regarding the subtype selectivity, all free amino acids **21 a–l** were distinctly more potent at mGAT1 than at mGAT2–4. As compared with the free amino acids **21 a–l**, the nipecotic acid esters **20 a–l** were distinctly weaker inhibitors at mGAT1 ( $pIC_{50}\leq 4.31$ , Table 1). Also at mGAT2–4, they showed only weak inhibitory potencies, which were largely in the range of that at mGAT1. However, the obtained  $pIC_{50}$  values of the esters **20 a–l** for the subtypes mGAT2–4 were mostly higher than those of the free amino acids **21 a–l** (for instance **20 d** and **21 d**, Table 1, entries 9 and 10).

From related nipecotic acid derived mGAT1 inhibitors, it is known that diaryl residues may effect a significant enhancement of inhibitory potencies when used as lipophilic domains.<sup>[26]</sup> Therefore, the influence of the presence of unsubstituted and substituted biphenyl moieties, attached to the *N*-allenyl spacer of the test compounds, on the biological activity was analyzed next. As can be seen from a comparison of data obtained for compounds **21 m** ( $pIC_{50}=5.42\pm 0.08$ , Table 2,

entry 1), **21 n** ( $pIC_{50}=4.85$ , Table 2, entry 3), and **21 o** ( $pIC_{50}=4.99\pm 0.06$ , Table 2, entry 5), possessing 2-, 3-, and 4-biphenyl moieties, respectively, the 2-biphenyl moiety gives rise to a distinctly higher  $pIC_{50}$  value of about half a log unit at mGAT1 as compared with the other two regioisomers. Hence, solely the substitution pattern of the 2-biphenyl residue as lipophilic domain had been varied and studied. Based on the results obtained in former studies, double substitution of the 2-biphenyl moiety is favorable for mGAT1 inhibitory potencies when performed at the 2'- and 4'-positions of the terminal phenyl residue. Substitution with chlorine (**21 s**:  $pIC_{50}=6.19\pm 0.10$ , Table 2, entry 13) and trifluoromethyl (**21 u**:  $pIC_{50}=5.78\pm 0.06$ , Table 2, entry 17) at the 2'- and 4'-positions of parent compound **21 m** ( $pIC_{50}=5.42\pm 0.08$ , Table 2, entry 1) enhances the inhibitory potency toward mGAT1, which is in good agreement with the results reported for the analogous systems with a four-carbon alkenyl and alkynyl spacer (e.g., **8** and **9**).<sup>[19,20]</sup> By replacing the 2'-H and 4'-H atoms of **21 m** with fluorine (**21 t**:  $pIC_{50}=5.55\pm 0.10$ , Table 2, entry 15) no significant increase in mGAT1 inhibition can be observed. A direct comparison of the functional activity of the structurally related compounds **8** and **9** (Figure 1) with that of **21 s** (Table 2, entry 13), however, reveals that the inhibitory potency ( $pIC_{50}$ ) of the compounds with an alkenyl (**8**) and an alkynyl (**9**) spacer at mGAT1 is about one log unit higher than that of the corresponding compound with an allenyl spacer (**21 s**).

Fortunately, a further increase in mGAT1 inhibitory potency relative to the dichloro derivative **21 s** is obtained with an additional phenyl ring at the 2'-position, leading to compound **21 p** possessing an *o*-terphenyl residue with a  $pIC_{50}$  value amounting to  $6.48\pm 0.11$  (Table 2, entry 7). Test compounds with alkyl substituents such as an isopropyl group at the 2'-position (**21 r**:  $pIC_{50}=6.28\pm 0.07$ , Table 2, entry 11) or methyl groups at the 2'- and 6'-positions (**21 q**:  $pIC_{50}=6.03\pm 0.08$ , Table 2, entry 9) deliver slightly lower but still reasonable  $pIC_{50}$  values, as well. The introduction of methoxy groups at the 2'- and 4'-positions, however, leads to a decrease in mGAT1 inhibition of the resulting derivative **21 v** ( $pIC_{50}=4.83$ , Table 2, entry 19) below the level of compound **21 m** with an unsubstituted 2-biphenyl subunit (**21 m**:  $pIC_{50}=5.42\pm 0.08$ , Table 2, entry 1). Compared with the free amino acids **21 m–v**, the corresponding ethyl esters **20 m–v** are significantly weaker inhibitors at mGAT1, except for **20 v** ( $pIC_{50}=4.56$ , Table 2, entry 20), for which the inhibitory potency is in the same range as that of the amino acid **21 v** ( $pIC_{50}=4.83$ , Table 2, entry 19). The free amino acids **21 m–v** (Table 2) possess distinct subtype selectivity in favor of mGAT1, being only weak inhibitors at mGAT2–4 with  $pIC_{50}$  values below 4.83 (**21 p**, Table 2, entry 7). In contrast, the corresponding ethyl esters **20 m–v** (Table 2) do not exhibit any distinct subtype selectivity. Thus, in the majority of cases the  $pIC_{50}$  values of esters **20 m–v** at mGAT1 and mGAT2–4 were in the same range or slightly higher for the latter. Interestingly, ester **20 v** exhibits its highest  $pIC_{50}$  value at mGAT4 which by amounting to  $pIC_{50}=5.11\pm 0.07$  (Table 2, entry 20) is more than one log unit higher than the  $pIC_{50}$  value of the free amino acid at that transporter subtype (**21 v**:  $pIC_{50}=3.80$  at mGAT4, Table 2, entry 19).

**Table 2.** Nipecotic acid derivatives possessing different biphenyl substituents at the 1,3-disubstituted allenyl spacer and their inhibitory potencies at mGAT1–4 and binding affinities for mGAT1.


Entry	Compd <sup>[a]</sup>	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	pK <sub>i</sub> <sup>[b]</sup>		pIC <sub>50</sub> <sup>[b]</sup>		
						mGAT1	mGAT1	mGAT2	mGAT3	mGAT4
1	<b>21 m</b>	H		H	H	5.97 ± 0.04	5.42 ± 0.08	3.61	3.77	4.12
2	<b>20 m</b>	Et		H	H	66 %	68 %	4.57	4.85 ± 0.08	4.90
3	<b>21 n</b>	H	H		H	5.88 ± 0.10	4.85	70 %	51 %	67 %
4	<b>20 n</b>	Et	H		H	76 %	52 %	4.23	4.40	4.39
5	<b>21 o</b>	H	H	H		5.10 ± 0.07	4.99 ± 0.06	4.03	3.96	3.75
6	<b>20 o</b>	Et	H	H		73 %	51 %	58 %	4.58	4.34
7	<b>21 p</b>	H		H	H	6.67 ± 0.08	6.48 ± 0.11	50 %	4.50	4.83
8	<b>20 p</b>	Et		H	H	64 %	4.23	54 %	4.39	51 %
9	<b>21 q</b>	H		H	H	6.17 ± 0.06	6.03 ± 0.08	57 %	61 %	4.16
10	<b>20 q</b>	Et		H	H	51 %	4.47	61 %	4.88 ± 0.06	4.81
11	<b>21 r</b>	H		H	H	6.51 ± 0.07	6.28 ± 0.07	4.10	58 %	4.67
12	<b>20 r</b>	Et		H	H	51 %	4.31	4.77	4.85	4.38
13	<b>21 s</b>	H		H	H	6.56 ± 0.06	6.19 ± 0.10	73 %	4.45	4.52
14	<b>20 s</b>	Et		H	H	5.69 ± 0.09	5.16 ± 0.10	4.84	4.21	4.85
15	<b>21 t</b>	H		H	H	6.32 ± 0.03	5.55 ± 0.10	103 %	60 %	4.07
16	<b>20 t</b>	Et		H	H	4.54	4.65	93 %	4.87 ± 0.05	4.97
17	<b>21 u</b>	H		H	H	6.19 ± 0.01	5.78 ± 0.06	62 %	4.67	4.47
18	<b>20 u</b>	Et		H	H	67 %	51 %	4.30	4.80	4.13
19	<b>21 v</b>	H		H	H	5.44 ± 0.02	4.83	3.32	3.98	3.80
20	<b>20 v</b>	Et		H	H	64 %	4.56	4.22	4.54	5.11 ± 0.07

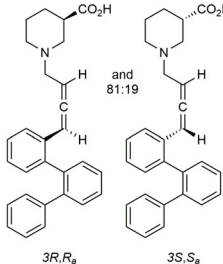
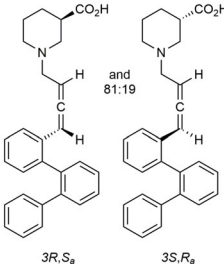
[a] Compounds **20m–v** and **21m–v** were tested as ≈1:1 mixture of racemic diastereomers. Atropisomers were observed for compounds **20/21 p** (ratio 45:55), **20/21 r** (ratio 49:51), **20/21 s** (ratio ≈50:50), and **20/21 u** (ratio ≈50:50). [b] Data are the mean ± SEM of three independent experiments, each performed in triplicate. Percentages represent the remaining [<sup>3</sup>H]GABA uptake in the presence of 100 μM inhibitor. At low pIC<sub>50</sub> values, only one measurement was performed in triplicate, and therefore no SEM could be calculated.

For mGAT1 inhibitors delineated from nipecotic acid, it is well known that the biological activity resides mainly in the *R* enantiomer. Thus, (*R*)-nipecotic acid (pIC<sub>50</sub> = 5.07 ± 0.02)<sup>[16]</sup> was found to be more potent than (*S*)-nipecotic acid (pIC<sub>50</sub> = 4.13 ± 0.05)<sup>[16]</sup> regarding their inhibitory potency at mGAT1 which is also true for derivatives such as tiagabine ((*R*)-**4**: IC<sub>50</sub> = 136 nM; (*S*)-**4**: IC<sub>50</sub> = 392 nM).<sup>[27]</sup> The mixture of enantiomeric and diastereomeric nipecotic acid derivatives **21 p** (Table 2, entry 7) exhibits a pIC<sub>50</sub> value of 6.48 ± 0.11 at mGAT1 which is the highest found in this study. Hence, also the (*R*)-nipecotic acid derived analogous mixture of compounds **21 p** was synthesized according to the standard procedure outlined above (Scheme 1), applying the enantiopure (*R*)-nipecotic acid ester as starting material for the preparation of alkyne (*R*)-**11** (Scheme 1d), to finally obtain a ≈1:1 mixture of the diastereomers (*3R,R<sub>a</sub>*)-**21 p** and (*3R,S<sub>a</sub>*)-**21 p** (and corresponding atropisomers as indicated before). Unfortunately, the obtained mixture of diastereomeric (*R*)-nipecotic acid derivatives (*3R,R<sub>a</sub>*)-**21 p**/*(3R,S<sub>a</sub>)*-**21 p** was contaminated with 19% of the enantiomeric (*S*)-nipecotic acid derivatives (*3S,R<sub>a</sub>*)-**21 p**/*(3S,S<sub>a</sub>)*-**21 p**

(Table 3), which is assumed to be due to insufficient enantiopurity of the commercial (*R*)-nipecotic acid ester used. Nevertheless, characterization of this mixture of compounds, which, despite extensive attempts, could not be separated into its enantiopure diastereomers, in mGAT1 binding and uptake assays showed, as expected, a clear increase in biological activity relative to the racemic mixture of diastereomeric compounds **21 p**. Whereas the latter, **21 p**, exhibited a pIC<sub>50</sub> of 6.48 ± 0.11 (Table 2, entry 7), the enantioenriched mixture (*3R,R<sub>a</sub>*)-**21 p**/*(3R,S<sub>a</sub>)*-**21 p** delivered a pIC<sub>50</sub> value of 6.78 ± 0.08 (Table 3), which is now in the same range as that of tiagabine (**4**: pIC<sub>50</sub> = 6.88 ± 0.12, Figure 1) and NO711 (**5**: pIC<sub>50</sub> = 6.83 ± 0.06, Figure 1).

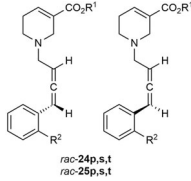






The biological investigation of analogues of **21 p**, **21 s** and **21 t**, exhibiting a guvacine instead of a nipecotic acid residue as polar subunit (Table 4), revealed that for all three guvacine derivatives *rac*-**25 p,s,t** the inhibitory potency at mGAT1 is very close, the pIC<sub>50</sub> values varying only from 6.39 to 6.46 (*rac*-**25 p**: pIC<sub>50</sub> = 6.46 ± 0.10, Table 4, entry 1; *rac*-**25 s**: pIC<sub>50</sub> = 6.39 ± 0.04, Table 4, entry 3; *rac*-**25 t**: pIC<sub>50</sub> = 6.43 ± 0.09, Table 4, entry 5).

**Table 3.** (*R*)-Nipecotic acid derived GAT inhibitor with a 1,3-disubstituted allene moiety exhibiting a terphenyl residue and its inhibitory potencies at mGAT1–4 and binding affinities for mGAT1.

Compd	 $pK_i^{[b]}$		 $pIC_{50}^{[b]}$			
	mGAT1	mGAT1	mGAT2	mGAT3	mGAT3	mGAT4
( <i>3R,R_a</i> )- <b>21 p</b> / <i>(3R,S_a)</i> - <b>21 p</b> <sup>[a]</sup> tiagabine ( <b>4</b> )	7.10 ± 0.12	6.78 ± 0.08	4.65	4.56	4.51	4.51
NO711 ( <b>5</b> )	7.50 ± 0.03	6.83 ± 0.06	3.20	3.62	3.62	3.07

[a] Contains 19% of the enantiomers (*3S,R\_a*)-**21 p** and (*3S,S\_a*)-**21 p**. Atropisomers are present in a ratio of 44:56. [b] Data are the mean ± SEM of three independent experiments, each performed in triplicate. Percentages represent the remaining [<sup>3</sup>H]GABA uptake in the presence of 100 μM inhibitor. At low pIC<sub>50</sub> values, only one measurement was performed in triplicate, and therefore no SEM could be calculated. Data for compounds **4** and **5** are from reference [16].

**Table 4.** Guvacine derived 1,3-disubstituted allenes and their inhibitory potencies at mGAT1–4 and binding affinities for mGAT1.

Entry	Compd <sup>[a]</sup>	R <sup>1</sup>	R <sup>2</sup>	 $pK_i^{[b]}$		$pIC_{50}^{[b]}$			
				mGAT1	mGAT1	mGAT2	mGAT3	mGAT3	mGAT4
1	<i>rac</i> - <b>25 p</b>	H		7.07 ± 0.11	6.46 ± 0.10	4.87	4.51	4.45	
2	<i>rac</i> - <b>24 p</b>	Me		54%	4.90	4.27	5.27 ± 0.11	4.70	
3	<i>rac</i> - <b>25 s</b>	H		7.09 ± 0.10	6.39 ± 0.04	4.74	4.60	4.61	
4	<i>rac</i> - <b>24 s</b>	Me		4.32	4.30	4.61	4.88	5.29 ± 0.12	
5	<i>rac</i> - <b>25 t</b>	H		6.63 ± 0.06	6.43 ± 0.09	56%	69%	64%	
6	<i>rac</i> - <b>24 t</b>	Me		54%	4.20	4.84	4.92	5.10 ± 0.03	

[a] Compounds were tested as racemates. Atropisomers were observed for *rac*-**24/25 p** (ratio 46:54) and *rac*-**24/25 s** (ratio ≈ 50:50). [b] Data are the mean ± SEM of three independent experiments, each performed in triplicate. Percentages represent the remaining [<sup>3</sup>H]GABA uptake in the presence of 100 μM inhibitor. At low pIC<sub>50</sub> values, only one measurement was performed in triplicate, and therefore no SEM could be calculated.

Indeed, the inhibitory potencies of the aforementioned compounds exhibiting either an *o*-terphenyl (*rac*-**25 p**) or a 2-biphenyl with chloro (*rac*-**25 s**) or fluoro (*rac*-**25 t**) substituents at the 2'- and 4'-positions as lipophilic residue are only nominally different. In addition, the inhibitory potency of these compounds, *rac*-**25 p**, *rac*-**25 s**, and *rac*-**25 t**, at mGAT1 equals that of the most potent nipecotic acid derivative of this study, **21 p**. Clearly, the nature of the lipophilic domain of the studied mGAT1 inhibitors has a larger influence in the case of the nipecotic acid derivatives, showing clear differences in the pIC<sub>50</sub> values (for **21 p**, **21 s**, and **21 t**) than for the analogous guvacine-derived compounds (*rac*-**25 p**, *rac*-**25 s**, and *rac*-**25 t**), for which they are equal considering SEM values. However, it should be kept in mind that the nipecotic acid derivatives **21 p,s,t** still represent mixtures of racemic diastereomers and

that the biological activity of the individual diastereomers may be quite different from that of the mixtures. In addition to their reasonable inhibitory potency at mGAT1, compounds *rac*-**25 p,s,t** also possess good subtype selectivity in favor of mGAT1, the pIC<sub>50</sub> values of mGAT1 as compared with mGAT2–4 differing by at least 1.5 log units. The methyl esters *rac*-**24 p**, *rac*-**24 s**, and *rac*-**24 t** (Table 4, entries 2, 4, and 6) were found to be weak mGAT1 inhibitors; the highest pIC<sub>50</sub> value reaches only 4.90. In contrast, methyl ester *rac*-**24 p** possesses good inhibitory potency at mGAT3 (*rac*-**24 p**: pIC<sub>50</sub> = 5.27 ± 0.11 at mGAT3, Table 4, entry 2) and methyl esters *rac*-**24 s** and *rac*-**24 t** at mGAT4, with pIC<sub>50</sub> values up to 5.29 (*rac*-**24 s**: pIC<sub>50</sub> = 5.29 ± 0.12 at mGAT4, Table 4, entry 4; *rac*-**24 t**: pIC<sub>50</sub> = 5.10 ± 0.03 at mGAT4, Table 4, entry 6), which are even better than those of the corresponding amino acids at the respective



transporter subtypes. However, the subtype selectivities the methyl esters *rac*-**24 p,s,t** display in favor of these individual GABA transporters (mGAT3 for *rac*-**24 p** and mGAT4 for *rac*-**24 s** and *rac*-**24 t**) are low.

The inhibitory potencies ( $pIC_{50}$ ) of all studied compounds at mGAT1 are about a half to one log unit lower than the corresponding  $pK_i$  values determined in MS Binding Assays for mGAT1 with NO711 as MS marker. Such a difference between  $pIC_{50}$  from GABA uptake assays at mGAT1 and  $pK_i$  values from MS Binding Assays for mGAT1 is a common phenomenon that is constantly observed for mGAT1 inhibitors when characterized in these test systems and likely to be at least partly due to the different buffer systems used in these assays.<sup>[15,17–20]</sup> With the  $pK_i$  values being in good accord with the  $pIC_{50}$  values, the conclusions drawn for the  $pIC_{50}$  values from the uptake assays are as well supported by the observed  $pK_i$  values.

## Conclusions

In summary, a new series of GABA uptake inhibitors with a four-carbon-atom allenyl spacer connecting nipecotic acid or guvacine via the amino nitrogen as polar subunit with a lipophilic aromatic residue, has been synthesized and characterized for their biological activity at mGAT1–4. By applying our recently published two-step procedure, comprising a Cu<sup>I</sup>-catalyzed aldehyde–alkyne–amine (A<sup>3</sup> coupling) and subsequent [1,5]-hydride transfer reaction, the allene-moiety-containing compounds could be established with good to excellent yields up to 95%. In addition, this procedure allowed us to easily vary the lipophilic residue attached to the allene termini of the desired compounds. Due to the presence of two stereogenic centers, a chiral center at the piperidine ring and the chiral axis arising from the allene moiety, the synthesis yielded the targeted nipecotic acid derivatives as a mixture of racemic diastereomers, the ratio of which amounted to approximately 1:1. With these mixtures being highly difficult to separate on the stage of the amino acid esters **20** as well as of the free amino acids **21**, the  $\approx$ 1:1 mixture of racemic diastereomers were used for biological testing. The *o*-terphenyl residue was found to be the most favorable lipophilic residue; compound **21 p** with nipecotic acid and compound *rac*-**25 p** with guvacine as polar subunit were found to be the most potent and selective mGAT1 inhibitors in this study. For the nipecotic acid derivative **21 p** the enantioenriched  $\approx$ 1:1 mixture of diastereomers (*3R,R*<sub>a</sub>)-**21 p**/*3R,S*<sub>a</sub>)-**21 p** ( $\approx$ 62% *ee*) was also synthesized and was found to exhibit a  $pIC_{50}$  value of  $6.78 \pm 0.08$  ( $pK_i = 7.10 \pm 0.12$ ). For the analogous guvacine derivative *rac*-**25 p**, the  $pIC_{50}$  amounted to  $6.46 \pm 0.10$  ( $pK_i = 7.07 \pm 0.11$ ). Interestingly, also some of the nipecotic acid derivatives with an allenic moiety equipped with phenyl rings possessing small substituents such as a halide or methoxy functions showed reasonable inhibitory potencies at mGAT1, with  $pIC_{50}$  values reaching up to  $5.82 \pm 0.04$  (**21 j**:  $pK_i = 6.31 \pm 0.08$ , Table 1, entry 21). Considering that the tested compounds still represent  $\approx$ 1:1 mixtures of racemic diastereomers, even more pronounced biological activities may be expected for individual stereoisomers.

## Experimental Section

### Chemistry

Unless otherwise noted, all reactions were performed in oven-dried glassware under moisture-free conditions and argon or nitrogen atmosphere. All commercially available reagents were used without further purification. Toluene and 1,4-dioxane were dried over sodium and distilled under nitrogen. Chlorobenzene was dried over CaCl<sub>2</sub>, distilled under nitrogen atmosphere, and stored over molecular sieves (4 Å) under nitrogen prior to use. For chromatographic purposes, only distilled solvents were used (EtOAc, PE 42–62 °C, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, *n*-pentane, Et<sub>2</sub>O, H<sub>2</sub>O). Flash column chromatography was performed using silica gel (grading 0.035–0.070 mm). Thin-layer chromatography (TLC) was carried out on precoated silica gel F<sub>254</sub> glass plates. Preparative MPLC was performed using a Büchi instrument (C-605 binary pump system, C-630 UV detector at 254 nm and C-660 fraction collector) and a Sepacore glass column B-685 (26 × 230 mm) equipped with Merck silica gel 60 (grading 0.015–0.040 mm) or YMC Gel SIL-HG (12 nm, 5–20 μm) for straight phase and YMC Gel Triart Prep C18-S (12 nm, 5–20 μm) for reversed phase. NMR spectra were measured at 298.1 K (unless otherwise noted) on 400 MHz (<sup>1</sup>H NMR: 400 MHz, <sup>13</sup>C NMR: 101 MHz) and 500 MHz (<sup>1</sup>H NMR: 500 MHz, <sup>13</sup>C NMR: 126 MHz) spectrometers. These NMR spectrometers were also used for DEPT, HMQC, HMBC, and COSY experiments. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts were referenced to the deuterated solvent signals, and coupling constants are stated with an accuracy of 0.5 Hz. MestreNova software was used for further analysis of the NMR data (*s*<sub>br</sub> = broad singlet, hept = septet, br = broad signal, dia = racemic diastereomers, atriso = atropisomer). IR spectra were recorded with an FT-IR spectrometer and Spectrum v2.00 software was used for analysis. High-resolution mass spectrometry was performed with a sector field mass spectrometer or an LTQ FT Ultra mass spectrometer. Optical rotations were determined with a 241 MC Polarimeter ADP440+ at  $\lambda = 589 \text{ cm}^{-1}$ . Purity testing of biologically tested compounds was done by Quantitative <sup>1</sup>H NMR (qH NMR).<sup>[28,29]</sup> qH NMR data based on peak area ratios are determined under conditions that assure complete relaxation. For qH NMR either benzyl benzoate (Lot #BCBN6347V: purity 99.43%; Lot #BCBS0231V: purity 99.84%) in CDCl<sub>3</sub>/CD<sub>2</sub>Cl<sub>2</sub>/C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub> or maleic acid (Lot #BCBM8127V: purity 99.94%) in D<sub>2</sub>O/MeOD was used as internal standard (Trace-CERT®, Sigma–Aldrich). The purity was calculated using the purity calculator of MestreNova NMR software (MestreLab Research S.L.). The purity of all tested compounds was > 95%. The ratio of the obtained diastereomeric compounds in racemic form after propargylic amine and allene synthesis is  $\approx$ 1:1 (determined by <sup>1</sup>H NMR). For analysis of the <sup>1</sup>H and <sup>13</sup>C NMR data of the allene-containing nipecotic acid derivatives **20 a–v** enrichment of each of the two racemic diastereomers was performed by MPLC. When a clear signal assignment was feasible, the signals were referred to as “dia1”, “dia2”, whereas not clearly assignable signals were labeled as “dia1 or dia2”. Signals belonging to the atropisomeric forms were identified by comparison of NMR spectra measured at RT and higher temperature. Analytical HPLC was performed on an Agilent 1100 instrument (G1329A ALS autosampler, G1316A column compartment, G1315B DAD detector, G1312A binary pump, G1322A degasser). See the Supporting Information for characterization data for the described compounds.

**General procedure for N-alkylation (GP1):** N-Alkylation was performed using a synthesis route similar to a procedure described previously.<sup>[25]</sup> Alkyne (1.00 equiv) and amine (1.20 equiv) were dissolved in acetone (2 mL mmol<sup>-1</sup>), and Na<sub>2</sub>CO<sub>3</sub> (2.50 equiv) and NaI (0.50 equiv) were added. The reaction mixture was held at reflux

for 72 h, and the reaction was monitored by TLC. For quenching,  $\text{CH}_2\text{Cl}_2$  (5 mL mmol<sup>-1</sup>) and water (5 mL mmol<sup>-1</sup>) were added, and the product was extracted five times with  $\text{CH}_2\text{Cl}_2$  (2.5 mL mmol<sup>-1</sup>). The combined organic phases were then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude product was purified by flash column chromatography to afford the desired alkyne as an oil.

**General procedure<sup>[30]</sup> for the preparation of biaryl aldehydes (GP2):** A mixture of toluene, ethanol and 2 M aqueous  $\text{Na}_2\text{CO}_3$  (1:1:1, v/v/v, 15 mL) was flushed for 10 min with argon. The bromine compound (1.0 mmol, 1 equiv), the boronic acid (1.0 mmol, 1 equiv) and  $\text{Pd}(\text{PPh}_3)_4$  (5 mol%) were added, and the mixture was heated at 80 °C. The progress of the reaction was monitored by TLC. After complete conversion, the reaction mixture was cooled to RT and extracted three times with toluene (10 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated in vacuum. The crude product was then purified by column chromatography (gradient elution *n*-pentane/ $\text{Et}_2\text{O}$  = 99:1, *n*-pentane/ $\text{Et}_2\text{O}$  = 9:1).

**General procedure for the A<sup>3</sup> coupling reaction (GP3):** To a Schlenk flask was added CuBr (0.15 equiv) and molecular sieves (4 Å). Toluene (5.00 mL mmol<sup>-1</sup>) was then added, followed by the addition of the corresponding aldehyde (1.80 equiv), amine (1.40 equiv) and alkyne (1.00 equiv). The reaction mixture was stirred at RT overnight. The completion of the reaction was monitored by TLC. The reaction mixture was then filtered, washed with EtOAc and concentrated under vacuum. The crude product was purified by flash column chromatography to afford the corresponding propargylic amine. This procedure was performed according to a procedure described by Yu et al.<sup>[31]</sup>

**General procedure<sup>[32,24]</sup> for the conversion of propargylic amines to allenes (GP4):** To a Schlenk tube  $\text{CdI}_2$  (0.8 equiv) was added under argon. The  $\text{CdI}_2$  was then heated with a heat gun under vacuum until the pale-yellow solid turned to darker yellow. Chlorobenzene (8.0 mL mmol<sup>-1</sup>) was added, followed by the propargylic amine (1.0 equiv). The reaction mixture was stirred at 100 °C until all starting material was consumed (detection by TLC). After cooling to RT the crude product was purified by flash column chromatography to afford the corresponding allene.

**General procedure<sup>[33]</sup> for ester hydrolysis with NaOH (GP5):** The ester was dissolved in EtOH (5.0 mL mmol<sup>-1</sup>), and 2 N NaOH (1.5 mL mmol<sup>-1</sup>, 3 equiv) was added. The mixture was stirred at RT until TLC (EtOAc) showed completion of the reaction. The solvent was then completely removed under reduced pressure. The solid residue was dissolved in (25 mL mmol<sup>-1</sup>) of water, and the solution was adjusted to pH 6–7 (indicator paper). The amino acid was then extracted several times with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was removed under reduced pressure. The residue was dissolved in MeOH (5.0 mL mmol<sup>-1</sup>) followed by the addition of water (50 mL mmol<sup>-1</sup>) and was then freeze dried to give the corresponding amino acid as an amorphous solid.

**General procedure<sup>[14]</sup> for ester hydrolysis with Ba(OH)<sub>2</sub> (GP6):** The ester (1 equiv) was dissolved in EtOH/H<sub>2</sub>O (2:1) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (2 equiv) was added. The suspension was then stirred at RT. After completion of the reaction, CO<sub>2</sub> was bubbled through the suspension until no further BaCO<sub>3</sub> precipitated. The suspension was then filtered through a syringe filter (25 mm) and purified by RP-MPLC. After freeze drying the corresponding free amino acid could be obtained as white to yellow amorphous solid.

**Ethyl 1-(prop-2-yn-1-yl)(R)-piperidine-3-carboxylate ((R)-11):** GP1 was followed applying propargyl bromide solution (80 wt% in xylene, 0.56 mL, 5.0 mmol), ethyl (R)-piperidine-3-carboxylate (0.86 mL, 6.0 mmol, the commercially available 97% (R)-piperidine-3-carboxylate contained 19% of the S enantiomer), acetone (10 mL),  $\text{Na}_2\text{CO}_3$  (1.33 g, 12.5 mmol) and NaI (375 mg, 2.50 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired alkyne (R)-11 as pale-yellow oil (651 mg, 67%).

**rac-[1-(Buta-2,3-dien-1-yl)piperidine-3-carboxylic acid] (rac-16):** GP5 was followed using nipecotic acid ester *rac*-15 (0.10 mmol, 21 mg), EtOH (0.5 mL) and 2 M NaOH (0.15 mL) for 4 h. Instead of extracting the product with  $\text{CH}_2\text{Cl}_2$ , the neutral water phase was directly freeze dried. The resulting white powder was then partly dissolved in  $\text{Et}_2\text{O}$  and filtered. After removing the solvent under reduced pressure the residue was freeze dried to obtain the desired amino acid *rac*-16 as colorless oil (15 mg, 82%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 96%.

**2',6'-Dimethyl-[1,1'-biphenyl]-2-carbaldehyde (17 q):** GP2 was followed using 2-bromobenzaldehyde (0.24 mL, 2.0 mmol), (2,6-dimethylphenyl)boronic acid (300 mg, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (116 mg, 0.100 mmol) in 30 mL of the solvent mixture for 4 h. Purification afforded the desired aldehyde 17 q as colorless crystals (303 mg, 72%). Analytical and spectroscopic data are consistent with those reported earlier.<sup>[34]</sup>

**2'-Isopropyl-[1,1'-biphenyl]-2-carbaldehyde (17 r):** GP2 was followed using 2-bromobenzaldehyde (0.24 mL, 2.0 mmol), (2-isopropylphenyl)boronic acid (328 mg, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (116 mg, 0.100 mmol) in 30 mL of the solvent mixture for 2.25 h. Purification afforded the desired aldehyde 17 r as colorless viscous oil (384 mg, 86%). Analytical and spectroscopic data are consistent with those reported earlier.<sup>[35]</sup>

**2',4'-Dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (17 v):** GP2 was followed using 2-bromobenzaldehyde (0.24 mL, 2.0 mmol), 2,4-dimethoxyphenylboronic acid (364 mg, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (116 mg, 0.100 mmol) in 30 mL of the solvent mixture for 6.5 h. Purification via column chromatography (*n*-pentane/ $\text{Et}_2\text{O}$  8:2) afforded the desired aldehyde 17 v as pale-yellow viscous oil (318 mg, 66%).

**rac-[Ethyl (4R)-1-{4-(2-bromophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4R)-19 b) and rac-[ethyl (4S)-1-{4-(2-bromophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4S)-19 b):** GP3 was followed using CuBr (32 mg, 0.23 mmol), toluene (7.5 mL), 2-bromobenzaldehyde (0.33 mL, 2.7 mmol), 1,2,3,4-tetrahydropyridine (0.20 mL, 2.1 mmol) and alkyne *rac*-11 (293 mg, 1.50 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3R,4R)-19 b and *rac*-(3R,4S)-19 b as colorless viscous oil (460 mg, 69%).

**rac-[Ethyl (4R)-1-{4-(2-chlorophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4R)-19 c) and rac-[ethyl (4S)-1-{4-(2-chlorophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4S)-19 c):** GP3 was followed using CuBr (86 mg, 0.60 mmol), toluene (20 mL), 2-chlorobenzaldehyde (0.81 mL, 7.2 mmol), 1,2,3,4-tetrahydropyridine (0.52 mL, 5.6 mmol) and alkyne *rac*-11 (781 mg, 4.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3R,4R)-19 c and *rac*-(3R,4S)-19 c as yellow viscous oil (1,34 g, 83%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-fluorophenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*d*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-fluorophenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*d*): GP3 was followed using CuBr (65 mg, 0.45 mmol), toluene (15 mL), 2-fluorobenzaldehyde (0.59 mL, 5.4 mmol), 1,2,3,4-tetrahydropyridine (0.39 mL, 4.2 mmol) and alkyne *rac*-11 (586 mg, 3.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*d* and *rac*-(3*R*,4*S*)-19*d* as yellow viscous oil (560 mg, 49%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-[2-(trifluoromethyl)phenyl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*e*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-[2-(trifluoromethyl)phenyl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*e*): GP3 was followed using CuBr (86 mg, 0.60 mmol), toluene (20 mL), 2-(trifluoromethyl)benzaldehyde (0.97 mL, 7.2 mmol), 1,2,3,4-tetrahydropyridine (0.52 mL, 5.6 mmol) and alkyne *rac*-11 (781 mg, 4.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*e* and *rac*-(3*R*,4*S*)-19*e* as yellow viscous oil (994 mg, 57%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-methoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*f*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-methoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*f*): GP3 was followed using CuBr (65 mg, 0.45 mmol), toluene (15 mL), *o*-anisaldehyde (0.67 mL, 5.4 mmol), 1,2,3,4-tetrahydropyridine (0.39 mL, 4.2 mmol) and alkyne *rac*-11 (586 mg, 3.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 6:4) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*f* and *rac*-(3*R*,4*S*)-19*f* as yellow viscous oil (991 mg, 83%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3-methoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*g*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3-methoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*g*): GP3 was followed using CuBr (43 mg, 0.30 mmol), toluene (10 mL), *m*-anisaldehyde (0.44 mL, 3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and alkyne *rac*-11 (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 6:4) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*g* and *rac*-(3*R*,4*S*)-19*g* as yellow viscous oil (656 mg, 83%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*h*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*h*): GP3 was followed using CuBr (43 mg, 0.30 mmol), toluene (10 mL), 2,5-dimethoxybenzaldehyde (598 mg, 3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and alkyne *rac*-11 (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 1:1) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*h* and *rac*-(3*R*,4*S*)-19*h* as yellow viscous oil (591 mg, 69%).

*rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*i*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*i*): GP3 was followed using CuBr (43 mg, 0.30 mmol), toluene (10 mL), 3,5-dimethoxybenzaldehyde (598 mg,

3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and alkyne *rac*-11 (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 1:1) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*i* and *rac*-(3*R*,4*S*)-19*i* as yellow viscous oil (527 mg, 62%).

*rac*-[Ethyl (4*R*)-1-{4-(2-chloro-5-methoxyphenyl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*k*) and *rac*-[ethyl (4*S*)-1-{4-(2-chloro-5-methoxyphenyl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*k*): GP3 was followed using CuBr (32.3 mg, 0.225 mmol), toluene (9.0 mL), 2-chloro-5-methoxybenzaldehyde (461 mg, 2.70 mmol), 1,2,3,4-tetrahydropyridine (0.20 mL, 2.1 mmol) and alkyne *rac*-11 (293 mg, 1.50 mmol). The crude product was purified by column chromatography (gradient elution PE/EtOAc 8:2 to PE/EtOAc 6:4) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*k* and *rac*-(3*R*,4*S*)-19*k* as yellow viscous oil (411 mg, 64%).

*rac*-[Ethyl (4*R*)-1-{4-([1,1'-biphenyl]-3-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*n*) and *rac*-[ethyl (4*S*)-1-{4-([1,1'-biphenyl]-3-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*n*): GP3 was followed using CuBr (47 mg, 0.33 mmol), toluene (11 mL), 3-biphenylcarboxaldehyde (0.65 mL, 4.0 mmol), 1,2,3,4-tetrahydropyridine (0.29 mL, 3.1 mmol) and alkyne *rac*-11 (430 mg, 2.20 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*n* and *rac*-(3*R*,4*S*)-19*n* as yellow viscous oil (860 mg, 88%).

*rac*-[Ethyl (4*R*)-1-{4-([1,1'-biphenyl]-4-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*o*) and *rac*-[ethyl (4*S*)-1-{4-([1,1'-biphenyl]-4-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*o*): GP3 was followed using CuBr (43 mg, 0.30 mmol), toluene (10 mL), 4-biphenylcarboxaldehyde (656 mg, 3.6 mmol), 1,2,3,4-tetrahydropyridine (0.26 mL, 2.8 mmol) and alkyne *rac*-11 (391 mg, 2.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*o* and *rac*-(3*R*,4*S*)-19*o* as yellow viscous oil (726 mg, 82%).

*rac*-[Ethyl (4*R*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*p*) and *rac*-[ethyl (4*S*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*p*): GP3 was followed using CuBr (10.8 mg, 0.075 mmol), toluene (2.5 mL), [1,1':2',1'']terphenyl-2-carbaldehyde (17*p*) (207 mg, 0.800 mmol), 1,2,3,4-tetrahydropyridine (0.07 mL, 0.70 mmol) and alkyne *rac*-11 (97.6 mg, 0.500 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*p* and *rac*-(3*R*,4*S*)-19*p* as colorless viscous oil (204 mg, 79%).

Ethyl (4*R*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate ((3*R*,4*R*)-19*p*) and ethyl (4*S*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate ((3*R*,4*S*)-19*p*): GP3 was followed using CuBr (25.1 mg, 0.175 mmol), toluene (6.0 mL), [1,1':2',1'']terphenyl-2-carbaldehyde (482 mg, 1.86 mmol), 1,2,3,4-tetrahydropyridine (0.15 mL, 1.6 mmol) and alkyne (*R*)-11 (227 mg, 1.17 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines (3*R*,4*R*)-19*p* and (3*R*,4*S*)-19*p* as colorless viscous oil (487 mg, 81%).

*rac*-[Ethyl (4*R*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*q*) and *rac*-[ethyl (4*S*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*q*): GP3 was followed using CuBr (12 mg, 0.08 mmol), toluene (2.0 mL), 2',6'-dimethyl-[1,1'-biphenyl]-2-carbaldehyde (**17** *q*) (185 mg, 0.880 mmol), 1,2,3,4-tetrahydropyridine (0.07 mL, 0.77 mmol) and alkyne *rac*-11 (107 mg, 0.550 mmol). The crude product was purified by column chromatography (PE/EtOAc 8:2) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*q* and *rac*-(3*R*,4*S*)-19*q* as colorless viscous oil (198 mg, 76%).

*rac*-[Ethyl (4*R*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*r*) and *rac*-[ethyl (4*S*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*r*): GP3 was followed using CuBr (22 mg, 0.15 mmol), toluene (6.0 mL), 2'-isopropyl-[1,1'-biphenyl]-2-carbaldehyde (**17** *r*) (359 mg, 1.60 mmol), 1,2,3,4-tetrahydropyridine (0.13 mL, 1.4 mmol) and alkyne *rac*-11 (195 mg, 1.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 8:2) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*r* and *rac*-(3*R*,4*S*)-19*r* as yellow viscous oil (335 mg, 69%).

*rac*-[Ethyl (4*R*)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*s*) and *rac*-[ethyl (4*S*)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*s*): GP3 was followed using CuBr (21.5 mg, 0.150 mmol), toluene (5.0 mL), 2',4'-dichloro-[1,1'-biphenyl]-2-carbaldehyde (**17** *s*) (452 mg, 1.80 mmol), 1,2,3,4-tetrahydropyridine (0.13 mL, 1.4 mmol) and alkyne *rac*-11 (195 mg, 1.00 mmol). The crude product was purified by column chromatography (PE/EtOAc 8:2) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*s* and *rac*-(3*R*,4*S*)-19*s* as colorless viscous oil (346 mg, 68%).

*rac*-[Ethyl (4*R*)-1-[4-(2',4'-difluoro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*t*) and *rac*-[ethyl (4*S*)-1-[4-(2',4'-difluoro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*t*): GP3 was followed using CuBr (10.8 mg, 0.075 mmol), toluene (2.5 mL), 2',4'-difluoro-[1,1'-biphenyl]-2-carbaldehyde (**17** *t*) (175 mg, 0.800 mmol), 1,2,3,4-tetrahydropyridine (0.07 mL, 0.70 mmol) and alkyne *rac*-11 (97.6 mg, 0.500 mmol). The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*t* and *rac*-(3*R*,4*S*)-19*t* as yellow viscous oil (212 mg, 89%).

*rac*-[Ethyl (4*R*)-1-[4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*u*) and *rac*-[ethyl (4*S*)-1-[4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*u*): GP3 was followed using CuBr (17 mg, 0.12 mmol), toluene (4.0 mL), 2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-carbaldehyde (**17** *u*) (455 mg, 1.43 mmol), 1,2,3,4-tetrahydropyridine (0.10 mL, 1.1 mmol) and alkyne *rac*-11 (155 mg, 0.795 mmol). The crude product was purified by column chromatography (gradient elution PE/EtOAc 9:1 to PE/EtOAc 7:3) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*u* and *rac*-(3*R*,4*S*)-19*u* as yellow viscous oil (326 mg, 71%).

*rac*-[Ethyl (4*R*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*v*) and *rac*-[ethyl (4*S*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*v*): GP3 was followed using CuBr (14 mg, 0.10 mmol), toluene (3.3 mL), 2',4'-dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (**17** *v*) (291 mg, 1.20 mmol), 1,2,3,4-tetrahydropyridine (0.09 mL, 0.93 mmol) and alkyne *rac*-11 (130 mg, 0.667 mmol). The crude product was purified by column chromatography (gradient elution PE/EtOAc 6:4, EtOAc) to afford the desired propargylic amines *rac*-(3*R*,4*R*)-19*v* and *rac*-(3*R*,4*S*)-19*v* as yellow viscous oil (313 mg, 93%).

*rac*-[Ethyl (*R<sub>a</sub>*)-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R<sub>a</sub>*)-20*b*) and *rac*-[ethyl (*S<sub>a</sub>*)-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S<sub>a</sub>*)-20*b*): GP4 was followed applying Cdl<sub>2</sub> (293 mg, 0.800 mmol), chlorobenzene (8.0 mL) and propargylic amines *rac*-(3*R*,4*R*)-19*b* and *rac*-(3*R*,4*S*)-19*b* (445 mg, 1.00 mmol). The reaction mixture was stirred at 100 °C for 1.25 h and was purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R<sub>a</sub>*)-20*b* and *rac*-(3*R*,*S<sub>a</sub>*)-20*b* as yellow viscous oil (296 mg, 81%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 98%.

*rac*-[Ethyl (*R<sub>a</sub>*)-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R<sub>a</sub>*)-20*c*) and *rac*-[ethyl (*S<sub>a</sub>*)-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S<sub>a</sub>*)-20*c*): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-19*c* and *rac*-(3*R*,4*S*)-19*c* (200 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R<sub>a</sub>*)-20*c* and *rac*-(3*R*,*S<sub>a</sub>*)-20*c* as yellow viscous oil (129 mg, 81%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 98%.

*rac*-[Ethyl (*R<sub>a</sub>*)-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R<sub>a</sub>*)-20*d*) and *rac*-[ethyl (*S<sub>a</sub>*)-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S<sub>a</sub>*)-20*d*): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-19*d* and *rac*-(3*R*,4*S*)-19*d* (192 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.75 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R<sub>a</sub>*)-20*d* and *rac*-(3*R*,*S<sub>a</sub>*)-20*d* as yellow viscous oil (121 mg, 80%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 96%.

*rac*-[Ethyl (*R<sub>a</sub>*)-1-[4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R<sub>a</sub>*)-20*e*) and *rac*-[ethyl (*S<sub>a</sub>*)-1-[4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S<sub>a</sub>*)-20*e*): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4.0 mL) and propargylic amines *rac*-(3*R*,4*R*)-19*e* and *rac*-(3*R*,4*S*)-19*e* (217 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.75 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R<sub>a</sub>*)-20*e* and *rac*-(3*R*,*S<sub>a</sub>*)-20*e* as yellow viscous oil (153 mg, 86%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 98%.

*rac*-[Ethyl (*R<sub>a</sub>*)-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R<sub>a</sub>*)-20*f*) and *rac*-[ethyl (*S<sub>a</sub>*)-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S<sub>a</sub>*)-20*f*): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-

(3*R*,4*R*)-**19 f** and *rac*-(3*R*,4*S*)-**19 f** (198 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.75 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 f** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 f** as yellow viscous oil (94.2 mg, 63%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 98%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 g**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 g**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 g** and *rac*-(3*R*,4*S*)-**19 g** (198 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 2 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 g** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 g** as yellow viscous oil (119 mg, 76%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 98%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 h**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 h**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 h** and *rac*-(3*R*,4*S*)-**19 h** (213 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 2 h and purified by column chromatography (PE/EtOAc 6:4) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 h** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 h** as yellow viscous oil (120 mg, 70%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): ≥ 99%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 i**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 i**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 i** and *rac*-(3*R*,4*R*)-**19 i** (213 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 2 h and purified by column chromatography (PE/EtOAc 6:4) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 i** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 i** as yellow viscous oil (118 mg, 68%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 99%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 j**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 j**): GP4 was followed applying Cdl<sub>2</sub> (107 mg, 0.292 mmol), chlorobenzene (3.0 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 j** and *rac*-(3*R*,4*S*)-**19 j** (159 mg, due to purification problems a crude mixture was applied). The reaction mixture was stirred at 100 °C for 2 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 j** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 j** as yellow viscous oil (42 mg, 8% over two steps). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 k**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 k**): GP4 was followed applying Cdl<sub>2</sub> (260 mg, 0.710 mmol), chlorobenzene (7.0 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 k** and *rac*-(3*R*,4*S*)-**19 k** (383 mg, 0.888 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 k** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 k** as yellow

viscous oil (228 mg, 73%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 n**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 n**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 n** and *rac*-(3*R*,4*S*)-**19 n** (221 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 2.00 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 n** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 n** as yellow viscous oil (143 mg, 79%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 97%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 o**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 o**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 o** and *rac*-(3*R*,4*S*)-**19 o** (221 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.75 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 o** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 o** as yellow viscous oil (142 mg, 79%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 97%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 p**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 p**): GP4 was followed applying Cdl<sub>2</sub> (121 mg, 0.331 mmol), chlorobenzene (3.3 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 p** and *rac*-(3*R*,4*S*)-**19 p** (215 mg, 0.414 mmol). The reaction mixture was stirred at 100 °C for 1.25 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 p** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 p** as yellow viscous oil (156 mg, 86%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 99%.

Ethyl (*R*<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate ((3*R*,*R*<sub>a</sub>)-**20 p**) and ethyl (*S*<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate ((3*R*,*S*<sub>a</sub>)-**20 p**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4.0 mL) and propargylic amines (3*R*,4*R*)-**19 p** and (3*R*,4*S*)-**19 p** (259 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes (3*R*,*R*<sub>a</sub>)-**20 p** and (3*R*,*S*<sub>a</sub>)-**20 p** as yellow viscous oil (174 mg, 80%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 q**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*S*<sub>a</sub>)-**20 q**): GP4 was followed applying Cdl<sub>2</sub> (116 mg, 0.316 mmol), chlorobenzene (3.2 mL) and propargylic amines *rac*-(3*R*,4*R*)-**19 q** and *rac*-(3*R*,4*S*)-**19 q** (186 mg, 0.395 mmol). The reaction mixture was stirred at 100 °C for 1.50 h and purified by column chromatography (PE/EtOAc 8:2) to afford the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-**20 q** and *rac*-(3*R*,*S*<sub>a</sub>)-**20 q** as yellow viscous oil (123 mg, 80%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 99%.

*rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate (*rac*-(3*R*,*R*<sub>a</sub>)-**20 r**) and *rac*-

{ethyl ( $S_a$ )-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $S_a$ )-20r): GP4 was followed applying  $CdI_2$  (186 mg, 0.508 mmol), chlorobenzene (5.0 mL) and propargylic amines *rac*-(3R,4R)-19r and *rac*-(3R,4S)-19r (308 mg, 0.635 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3R, $R_a$ )-20r and *rac*-(3R, $S_a$ )-20r as yellow viscous oil (203 mg, 79%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 97%.

*rac*-{Ethyl ( $R_a$ )-1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $R_a$ )-20s) and *rac*-{ethyl ( $S_a$ )-1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $S_a$ )-20s): GP4 was followed applying  $CdI_2$  (88.0 mg, 0.240 mmol), chlorobenzene (2.5 mL) and propargylic amines *rac*-(3R,4R)-19s and *rac*-(3R,4S)-19s (153 mg, 0.300 mmol). The reaction mixture was stirred at 100 °C for 1.25 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3R, $R_a$ )-20s and *rac*-(3R, $S_a$ )-20s as yellow viscous oil (111 mg, 86%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 99%.

*rac*-{Ethyl ( $R_a$ )-1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $R_a$ )-20t) and *rac*-{ethyl ( $S_a$ )-1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $S_a$ )-20t): GP4 was followed applying  $CdI_2$  (103 mg, 0.280 mmol), chlorobenzene (2.8 mL) and propargylic amines *rac*-(3R,4R)-19t and *rac*-(3R,4S)-19t (168 mg, 0.350 mmol). The reaction mixture was stirred at 100 °C for 1.25 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3R, $R_a$ )-20t and *rac*-(3R, $S_a$ )-20t as yellow viscous oil (123 mg, 89%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 96%.

*rac*-{Ethyl ( $R_a$ )-1-[4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $R_a$ )-20u) and *rac*-{ethyl ( $S_a$ )-1-[4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $S_a$ )-20u): GP4 was followed applying  $CdI_2$  (138 mg, 0.375 mmol), chlorobenzene (4.0 mL) and propargylic amines *rac*-(3R,4R)-19u and *rac*-(3R,4S)-19u (271 mg, 0.469 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 7:3) to afford the desired allenes *rac*-(3R, $R_a$ )-20u and *rac*-(3R, $S_a$ )-20u as yellow viscous oil (198 mg, 85%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 97%.

*rac*-{Ethyl ( $R_a$ )-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $R_a$ )-20v) and *rac*-{ethyl ( $S_a$ )-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R, $S_a$ )-20v): GP4 was followed applying  $CdI_2$  (173 mg, 0.472 mmol), chlorobenzene (5.0 mL) and propargylic amines *rac*-(3R,4R)-19v and *rac*-(3R,4S)-19v (297 mg, 0.590 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 1:1) to afford the desired allenes *rac*-(3R, $R_a$ )-20v and *rac*-(3R, $S_a$ )-20v as yellow viscous oil (184 mg, 74%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBN6347V): 96%.

*rac*-[( $R_a$ )-1-(4-Phenylbuta-2,3-dien-1-yl)(3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21a) and *rac*-[( $S_a$ )-1-(4-phenylbuta-2,3-dien-1-yl)(3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21a): GP5 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20a and *rac*-(3R, $S_a$ )-20a (0.11 mmol, 30 mg) for 1.5 h to afford the desired amino acids

*rac*-(3R, $R_a$ )-21a and *rac*-(3R, $S_a$ )-21a as amorphous white solid (21.1 mg, 78%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 97%.

*rac*-[( $R_a$ )-1-[4-(2-Bromophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21b) and *rac*-[( $S_a$ )-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21b): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20b and *rac*-(3R, $S_a$ )-20b (91 mg, 0.25 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (158 mg, 0.500 mmol) in 1.8 mL EtOH/H<sub>2</sub>O (2:1) for 24 h to afford the desired amino acids *rac*-(3R, $R_a$ )-21b and *rac*-(3R, $S_a$ )-21b as pale-yellow amorphous solid (72.2 mg, 86%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-[( $R_a$ )-1-[4-(2-Chlorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21c) and *rac*-[( $S_a$ )-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21c): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20c and *rac*-(3R, $S_a$ )-20c (128 mg, 0.400 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (252 mg, 0.800 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3R, $R_a$ )-21c and *rac*-(3R, $S_a$ )-21c were obtained as pale-yellow amorphous solid (91.8 mg, 79%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 96%.

*rac*-[( $R_a$ )-1-[4-(2-Fluorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21d) and *rac*-[( $S_a$ )-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21d): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20d and *rac*-(3R, $S_a$ )-20d (130 mg, 0.430 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (271 mg, 0.860 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3R, $R_a$ )-21d and *rac*-(3R, $S_a$ )-21d were obtained as white amorphous solid (36.8 mg, 31%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V):  $\geq 99\%$ .

*rac*-[( $R_a$ )-1-[4-[2-(Trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21e) and *rac*-[( $S_a$ )-1-[4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21e): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20e and *rac*-(3R, $S_a$ )-20e (192 mg, 0.544 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (343 mg, 1.09 mmol) in 4.2 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3R, $R_a$ )-21e and *rac*-(3R, $S_a$ )-21e were obtained as white amorphous solid (136 mg, 77%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-[( $R_a$ )-1-[4-(2-Methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21f) and *rac*-[( $S_a$ )-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21f): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20f and *rac*-(3R, $S_a$ )-20f (128 mg, 0.405 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (256 mg, 0.810 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3R, $R_a$ )-21f and *rac*-(3R, $S_a$ )-21f were obtained as white amorphous solid (85.0 mg, 73%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 99%.

*rac*-[( $R_a$ )-1-[4-(3-Methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $R_a$ )-21g) and *rac*-[( $S_a$ )-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid] (*rac*-(3R, $S_a$ )-21g): GP6 was followed using nipecotic acid esters *rac*-(3R, $R_a$ )-20g and *rac*-(3R, $S_a$ )-20g (106 mg, 0.335 mmol) and  $Ba(OH)_2 \cdot 8H_2O$  (211 mg, 0.670 mmol) in 2.5 mL EtOH/H<sub>2</sub>O (2:1) over-

night. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **g** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **g** were obtained as white amorphous solid (58.4 mg, 61%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 96%.

*rac*-{(R<sub>a</sub>)-1-[4-(2,5-Dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **h**) and *rac*-{(S<sub>a</sub>)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **h**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **h** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **h** (121 mg, 0.350 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (221 mg, 0.700 mmol) in 2.7 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **h** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **h** were obtained as yellow amorphous solid (87.0 mg, 78%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 97%.

*rac*-{(R<sub>a</sub>)-1-[4-(3,5-Dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **i**) and *rac*-{(S<sub>a</sub>)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **i**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **i** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **i** (114 mg, 0.330 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (208 mg, 0.660 mmol) in 2.5 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **i** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **i** were obtained as pale-yellow amorphous solid (72.3 mg, 69%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 97%.

*rac*-{(R<sub>a</sub>)-1-[4-(2,6-Dichlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **j**) and *rac*-{(S<sub>a</sub>)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **j**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **j** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **j** (44.0 mg, 0.124 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (78.2 mg, 0.248 mmol) in 0.9 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **j** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **j** were obtained as white amorphous solid (31.2 mg, 77%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 97%.

*rac*-{(R<sub>a</sub>)-1-[4-(2-Chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **k**) and *rac*-{(S<sub>a</sub>)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **k**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **k** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **k** (165 mg, 0.473 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (298 mg, 0.946 mmol) in 3.3 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **k** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **k** were obtained as pale-yellow amorphous solid (99.0 mg, 65%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 95%.

*rac*-{(R<sub>a</sub>)-1-[4-(Naphthalen-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **l**) and *rac*-{(S<sub>a</sub>)-1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **l**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **l** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **l** (97 mg, 0.29 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (183 mg, 0.580 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **l** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **l** were obtained as white amorphous solid (69.2 mg, 78%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 95%.

*rac*-{(R<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **m**) and *rac*-{(S<sub>a</sub>)-1-[4-([1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **m**): GP5 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **m** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **m** (102 mg, 0.230 mmol)

for 2 h to afford the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **m** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **m** as pale-yellow amorphous solid (40.9 mg, 53%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 97%.

*rac*-{(R<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **n**) and *rac*-{(S<sub>a</sub>)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **n**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **n** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **n** (143 mg, 0.395 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (249 mg, 0.790 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **n** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **n** were obtained as white amorphous solid (77.4 mg, 59%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 96%.

*rac*-{(R<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **o**) and *rac*-{(S<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **o**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **o** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **o** (138 mg, 0.382 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (241 mg, 0.764 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **o** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **o** were obtained as white amorphous solid (68.4 mg, 54%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-{(R<sub>a</sub>)-1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **p**) and *rac*-{(S<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **p**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **p** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **p** (127 mg, 0.290 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (183 mg, 0.580 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) for 24 h. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **p** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **p** were obtained as white amorphous solid (70.0 mg, 59%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 99%.

(R<sub>a</sub>)-1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid ((3*R*,*R*<sub>a</sub>)-21 **p**) and (S<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid ((3*R*,*S*<sub>a</sub>)-21 **p**): GP6 was followed using nipecotic acid esters (3*R*,*R*<sub>a</sub>)-20 **p** and (3*R*,*S*<sub>a</sub>)-20 **p** (85.0 mg, 0.194 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (122 mg, 0.388 mmol) in 1.4 mL EtOH/H<sub>2</sub>O (2:1) at RT overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids (3*R*,*R*<sub>a</sub>)-21 **p** and (3*R*,*S*<sub>a</sub>)-21 **p** were obtained as white amorphous solid (32 mg, 40%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-{(R<sub>a</sub>)-1-[4-(2',6'-Dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **q**) and *rac*-{(S<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **q**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-20 **q** and *rac*-(3*R*,*S*<sub>a</sub>)-20 **q** (104 mg, 0.266 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (168 mg, 0.532 mmol) in 2.0 mL EtOH/H<sub>2</sub>O (2:1) for 7.5 h. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-21 **q** and *rac*-(3*R*,*S*<sub>a</sub>)-21 **q** were obtained as white amorphous solid (63.8 mg, 66%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-{(R<sub>a</sub>)-1-[4-(2'-Isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*R*<sub>a</sub>)-21 **r**) and *rac*-{(S<sub>a</sub>)-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid (*rac*-(3*R*,*S*<sub>a</sub>)-21 **r**): GP6 was followed

using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-**20r** and *rac*-(3*R*,*S*<sub>a</sub>)-**20r** (127 mg, 0.315 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (199 mg, 0.630 mmol) in 2.4 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**21r** and *rac*-(3*R*,*S*<sub>a</sub>)-**21r** were obtained as white amorphous solid (54.6 mg, 46%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 99%.

*rac*-{(3*R*,*S*<sub>a</sub>)-1-[4-(2',4'-Dichloro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-**21s**) and *rac*-{(3*S*<sub>a</sub>)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-**21s**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-**20s** and *rac*-(3*R*,*S*<sub>a</sub>)-**20s** (125 mg, 0.290 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (183 mg, 0.580 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) for 48 h. After purification by RP-MPLC (gradient elution with MeOH/H<sub>2</sub>O 6:4, MeOH) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**21s** and *rac*-(3*R*,*S*<sub>a</sub>)-**21s** were obtained as white amorphous solid (62.1 mg, 53%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): ≥ 99%.

*rac*-{(3*R*,*S*<sub>a</sub>)-1-[4-(2',4'-Difluoro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-**21t**) and *rac*-{(3*S*<sub>a</sub>)-1-[4-(2',4'-difluoro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-**21t**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-**20t** and *rac*-(3*R*,*S*<sub>a</sub>)-**20t** (109 mg, 0.275 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (174 mg, 0.550 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) for 8.5 h. After purification by RP-MPLC (gradient elution with MeOH/H<sub>2</sub>O 6:4—MeOH/H<sub>2</sub>O 7:3) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**21t** and *rac*-(3*R*,*S*<sub>a</sub>)-**21t** were obtained as white amorphous solid (53.6 mg, 53%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 99%.

*rac*-{(3*R*,*S*<sub>a</sub>)-1-[4-(2',4'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-**21u**) and *rac*-{(3*S*<sub>a</sub>)-1-[4-(2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-**21u**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-**20u** and *rac*-(3*R*,*S*<sub>a</sub>)-**20u** (116 mg, 0.234 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (148 mg, 0.468 mmol) in 2.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (gradient elution MeOH/H<sub>2</sub>O 6:4 to MeOH/H<sub>2</sub>O 8:2) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**21u** and *rac*-(3*R*,*S*<sub>a</sub>)-**21u** were obtained as white amorphous solid (49.6 mg, 45%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

*rac*-{(3*R*,*S*<sub>a</sub>)-1-[4-(2',4'-Dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-**21v**) and *rac*-{(3*S*<sub>a</sub>)-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-**21v**): GP6 was followed using nipecotic acid esters *rac*-(3*R*,*R*<sub>a</sub>)-**20v** and *rac*-(3*R*,*S*<sub>a</sub>)-**20v** (103 mg, 0.245 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (155 mg, 0.490 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**21v** and *rac*-(3*R*,*S*<sub>a</sub>)-**21v** were obtained as white amorphous solid (49.1 mg, 51%). Average purity by qH NMR (internal calibrant: maleic acid Lot #BCBM8127V): 98%.

**Methyl 1-(prop-2-yn-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (22)**: GP1 was followed applying propargyl bromide solution (80 wt% in xylene, 1.11 mL, 10.0 mmol), methyl 1,2,5,6-tetrahydropyridine-3-carboxylate (1.69 g, 12.0 mmol), acetonitrile (20 mL), Na<sub>2</sub>CO<sub>3</sub> (2.65 g, 25.0 mmol) and NaI (749 mg, 5.00 mmol). The reaction mixture was heated to 90 °C for 5 h and stirred at RT overnight. The crude product was purified by column chromatography (PE/EtOAc 7:3) to afford the desired alkyne **22** as yellow oil (1.10 g, 61%).

*rac*-[Methyl 1-[4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**23p**): GP3 was followed using CuBr (11 mg, 0.08 mmol), toluene (3.0 mL), [1,1':2',1''-terphenyl]-2-carbaldehyde (**17p**) (207 mg, 0.800 mmol), 1,2,3,4-tetrahydropyridine (0.07 mL, 0.70 mmol) and alkyne **22** (90 mg, 0.50 mmol). The crude product was purified by column chromatography (PE/EtOAc 1:1) to afford the desired propargylic amine *rac*-**23p** as yellow viscous oil (192 mg, 77%).

*rac*-[Methyl 1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**23s**): GP3 was followed using CuBr (21.3 mg, 0.148 mmol), toluene (6.0 mL), 2',4'-dichloro-[1,1'-biphenyl]-2-carbaldehyde (**17s**) (398 mg, 1.58 mmol), 1,2,3,4-tetrahydropyridine (0.13 mL, 1.4 mmol) and alkyne **22** (177 mg, 0.990 mmol). The crude product was purified by column chromatography (PE/EtOAc 6:4) to afford the desired propargylic amine *rac*-**23s** as yellow viscous oil (319 mg, 65%).

*rac*-[Methyl 1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**23t**): GP3 was followed using CuBr (23.7 mg, 0.165 mmol), toluene (6.0 mL), 2',4'-difluoro-[1,1'-biphenyl]-2-carbaldehyde (**17t**) (384 mg, 1.76 mmol), 1,2,3,4-tetrahydropyridine (0.14 mL, 1.5 mmol) and alkyne **22** (197 mg, 1.10 mmol). The crude product was purified by column chromatography (PE/EtOAc 6:4) to afford the desired propargylic amine *rac*-**23t** as yellow viscous oil (311 mg, 61%).

*rac*-[Methyl 1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**24p**): GP4 was followed applying Cdl<sub>2</sub> (82.1 mg, 0.224 mmol), chlorobenzene (3.0 mL) and propargylic amine *rac*-**23p** (141 mg, 0.280 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 1:1) to afford the desired allene *rac*-**24p** as yellow viscous oil (112 mg, 95%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 97%.

*rac*-[Methyl 1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**24s**): GP4 was followed applying Cdl<sub>2</sub> (135 mg, 0.368 mmol), chlorobenzene (4.0 mL) and propargylic amine *rac*-**23s** (228 mg, 0.460 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (PE/EtOAc 6:4) to afford the desired allene *rac*-**24s** as yellow viscous oil (157 mg, 83%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

*rac*-[Methyl 1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (*rac*-**24t**): GP4 was followed applying Cdl<sub>2</sub> (147 mg, 0.400 mmol), chlorobenzene (4.0 mL) and propargylic amine *rac*-**23t** (231 mg, 0.500 mmol). The reaction mixture was stirred at 100 °C for 1.5 h and purified by column chromatography (*n*-pentane/Et<sub>2</sub>O 1:1) to afford the desired allene *rac*-**24t** as yellow viscous oil (121 mg, 63%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

*rac*-{1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-**25p**): GP5 was followed using methyl ester *rac*-**24p** (271 mg, 0.643 mmol) and 2*N* NaOH (0.96 mL) in MeOH (3.2 mL) overnight. After neutralization with phosphate buffer (pH 7) the water phase was freeze dried. The resulting white powder was then partly dissolved in Et<sub>2</sub>O and



filtered. After removing the solvent under reduced pressure the residue was purified via RP-MPLC (MeOH/H<sub>2</sub>O 7:3) to afford the desired amino acid *rac*-25p as white amorphous solid (55.8 mg, 21%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 97%.

***rac*-{1-[4-(2',4'-Difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-25t):** GP5 was followed using methyl ester *rac*-24t (103 mg, 0.270 mmol) and 2 N NaOH (0.41 mL) in MeOH (1.35 mL) for 7 h. After neutralization with phosphate buffer (pH 7) the water phase was freeze dried. The resulting white powder was then partly dissolved in Et<sub>2</sub>O and filtered. After removing the solvent under reduced pressure the residue was purified via RP-MPLC (MeOH/H<sub>2</sub>O 6:4) to afford the desired amino acid *rac*-25t as white amorphous solid (25 mg, 25%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 98%.

***rac*-{1-[4-(2',4'-Dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-25s):** GP5 was followed using methyl ester *rac*-24s (119 mg, 0.287 mmol) and 2 N NaOH (0.63 mL) in MeOH (1.5 mL) for 8 h. After neutralization with phosphate buffer (pH 7) the water phase was freeze dried. The resulting white powder was then partly dissolved in Et<sub>2</sub>O and filtered. After removing the solvent under reduced pressure the residue was purified via RP-MPLC (gradient elution MeOH/H<sub>2</sub>O 6:4 to MeOH/H<sub>2</sub>O 7:3) to afford the desired amino acid *rac*-25s as pale-yellow amorphous solid (15.5 mg, 14%). Average purity by qH NMR (internal calibrant: benzyl benzoate Lot #BCBS0231V): 96%.

### Biological evaluation

**MS Binding Assays:** The MS Binding Assays were performed with mGAT1 membrane preparations obtained from a stable HEK293 cell line and NO711 as unlabeled marker in competitive binding experiments as described previously.<sup>[12]</sup>

**[<sup>3</sup>H]GABA uptake assays:** The [<sup>3</sup>H]GABA uptake assays were performed in a 96-well plate format with intact HEK293 cells stably expressing mGAT1, mGAT2, mGAT3, mGAT4 as described earlier.<sup>[16]</sup>

### Conflict of interest

The authors declare no conflict of interest.

**Keywords:** allenyl spacer · GABA uptake inhibitors · guvacine · mGAT1 · nipecotic acid

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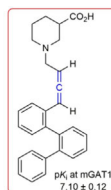
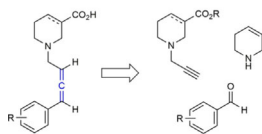
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## FULL PAPERS

M. Schaarschmidt, G. Höfner,  
K. T. Wanner\*



### Synthesis and Biological Evaluation of Nipepicotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1



**Allenens as pharmacological moiety:** A series of N-substituted nipecotic acid and guvacine derivatives with various aromatic moieties attached via a four-carbon *N*-allenyl spacer were synthesized through 1,2,5,6-tetrahydropyridine-mediated allenylation of terminal alkynes. Some nipecotic acid derivatives were identified as potent and subtype-selective mGAT1 inhibitors in binding and uptake assays.

## Supporting Information

### **Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1**

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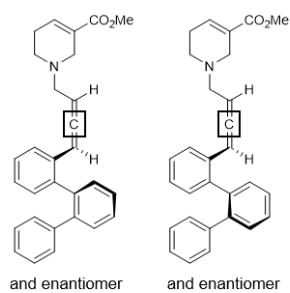
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## Content

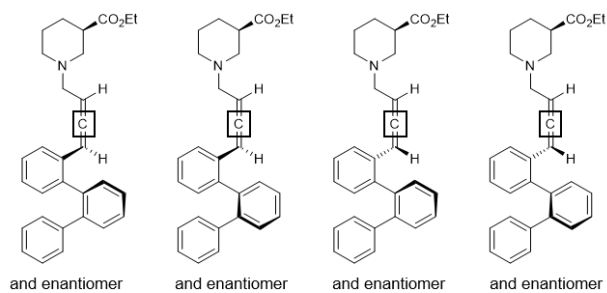
1. Atropisomerism: Comparison of  $^{13}\text{C}$  NMR spectra of **24p** with **20p**
2. Spectral and physical data (including analytical data for compound **21p**)

### 1. Atropisomerism: Comparison of $^{13}\text{C}$ NMR spectra of **24p** with **20p**

A comparison of the  $^{13}\text{C}$  NMR spectra of guvacine derivatives **24p** (SI-Figure 1), exhibiting a stereocenter and an axis of chirality at room temperature, with the  $^{13}\text{C}$  NMR spectra of the racemic diastereomer mixture of nipecotic acid derivatives **20p** (SI-Figure 1), exhibiting a stereocenter at the nipecotic acid and two axes of chirality, i.e. the axial chirality of the allene and the atropisomers, at room temperature, helps to interpret the measured NMR spectra of related nipecotic acid derivatives correctly. The  $^{13}\text{C}$  signal of the inner allene carbon of **24p** was measured as two signals at 298 K, one for each of the atropisomeric forms (SI-Figure 1a). When the temperature, at which the  $^{13}\text{C}$  NMR spectrum was recorded, was raised to 393 K the allenic carbon signals of the two atropisomeric forms continuously merged to give finally a single signal (SI-Figure 1b). The nipecotic acid derivative mixture **20p**, consisting of four diastereomeric compounds in racemic form, exhibits four  $^{13}\text{C}$  signals for the inner allene carbon at 298 K (SI-Figure 1c). Heating to 393 K succeeded in overcoming the rotational barrier of the atropisomeric forms fast enough to measure two  $^{13}\text{C}$  signals instead of four (SI-Figure 1d), which are assigned to the signals of the two remaining racemic diastereomers.

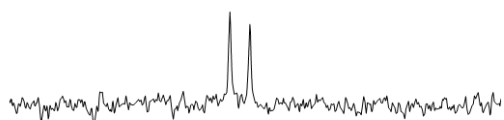


**24p**

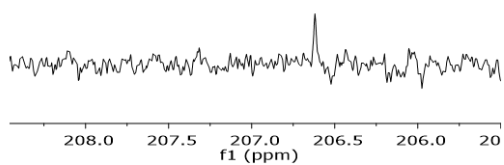


**20p**

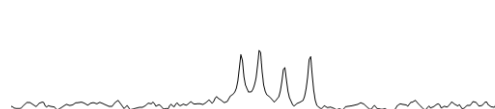
a) 298 K



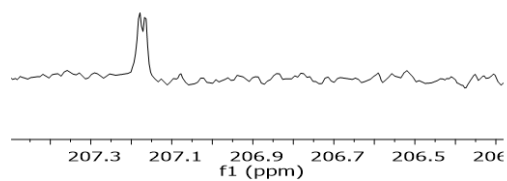
b) 393 K



c) 298 K



d) 393 K



**SI-Figure 1.** Cutout of  $^{13}\text{C}$  NMR spectra of guvacine derivatives **24p** and nipecotic acid derivatives **20p** in nitrobenzene- $d_5$  measured at 298 K (upper spectra a and c) and at 393 K (lower spectra b and d).

## 2. Spectral and physical data for compounds *R*-11, *rac*-16, 17q,r,v, 19b-i, 19k, 19n-v, 20b-k, 20n-v, 21a-v, 22, *rac*-23p,s,t, *rac*-24p,s,t and *rac*-25p,s,t

### Ethyl 1-(prop-2-yn-1-yl)(*R*)-piperidine-3-carboxylate (*R*-11):

$R_f=0.21$  (PE/EtOAc 7:3);  $[\alpha]_D^{22}=+4.58$  ( $c=2.76$  g/100 mL in chloroform);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta=1.25$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J=11.7/3.9$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.52–1.66 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.69–1.81 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.86–1.99 (m, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 2.19 (td,  $J=11.1/3.1$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.24 (t,  $J=2.4$  Hz, 1H,  $\text{NCH}_2\text{C}\equiv\text{CH}$ ), 2.37 (t,  $J=10.7$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 2.58 (tt,  $J=10.7/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$ ), 2.68–2.83 (m, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.00 (ddt,  $J=10.9/3.4/1.5$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 3.32 (d,  $J=2.4$  Hz, 2H,  $\text{NCH}_2\text{C}\equiv\text{CH}$ ), 4.13 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta=14.3$  ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_2$ ), 26.6 ( $\text{CH}_2$ ), 42.0 ( $\text{CH}$ ), 47.4 ( $\text{CH}_2$ ), 52.4 ( $\text{CH}_2$ ), 54.3 ( $\text{CH}_2$ ), 60.5 ( $\text{CH}_2$ ), 73.3 ( $\text{CH}$ ), 78.9 ( $\text{C}$ ), 174.1 ( $\text{C}$ ); IR (film):  $\tilde{\nu}=3297, 2941, 2806, 1731, 1468, 1451, 1368, 1311, 1223, 1182, 1153, 1133, 1095, 1031, 900, 864, 793$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{11}\text{H}_{17}\text{NO}_2$ : 196.1338, found: 196.1331.

### *rac*-[1-(Buta-2,3-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-16):

$^1\text{H NMR}$  (400 MHz,  $\text{D}_2\text{O}$ , 1M NaOD):  $\delta=1.18$  (qd,  $J=12.7/4.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.39 (qt,  $J=12.4/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.58–1.68 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.75–1.85 (m, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.88 (td,  $J=12.0/2.9$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 1.93 (t,  $J=11.4$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 2.23 (tt,  $J=12.1/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$ ), 2.81 (d,  $J=11.6$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.89–3.00 (m, 3H,  $\text{NCH}_2\text{CHCCH}_2$  and  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 4.70 (dt,  $J=6.6/2.4$  Hz, 2H,  $\text{NCH}_2\text{CHCCH}_2$ ), 5.09 (p,  $J=7.1$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}_2$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{D}_2\text{O}$ , 1M NaOD):  $\delta=24.0$  ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 44.8 ( $\text{CH}$ ), 52.3 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}_2$ ), 56.5 ( $\text{CH}_2$ ), 74.8 ( $\text{CH}_2$ ), 85.2 ( $\text{CH}$ ), 183.4 ( $\text{C}$ ), 209.5 ( $\text{C}$ ); IR (film):  $\tilde{\nu}=3409, 3062, 2949, 2864, 2807, 2502, 2364, 1956, 1708, 1588, 1468, 1451, 1390, 1280, 1150, 1092, 1067, 1045, 955, 857, 768$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{10}\text{H}_{15}\text{NO}_2$ : 182.1181, found: 182.1176.

### 2',6'-Dimethyl-[1,1'-biphenyl]-2-carbaldehyde (17q):

$R_f=0.53$  (PE, 5% EtOAc), mp: 42 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.96$  (s, 6H,  $\text{CH}_3$ ), 7.11–7.17 (m, 2H,  $\text{H}_3\text{CCCHCHCHCCH}_3$ ), 7.19–7.26 (m, 2H,  $\text{H}_3\text{CCCHCHCHCCH}_3$  and  $\text{CHOCCHCHCHCHC}$ ), 7.49–7.56 (m, 1H,  $\text{CHOCCHCHCHCHC}$ ), 7.69 (td,  $J=7.5/1.5$  Hz, 1H,  $\text{CHOCCHCHCHCHC}$ ), 8.01 (ddd,  $J=7.8/1.5/0.6$  Hz, 1H,  $\text{CHOCCHCHCHCHC}$ ), 9.63 (d,  $J=0.8$  Hz, 1H,  $\text{CHO}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=21.2$  ( $\text{CH}_3$ ), 127.8 ( $\text{CH}$ ), 127.9 ( $\text{CH}$ ), 128.3 ( $\text{CH}$ ), 128.4 ( $\text{CH}$ ), 131.2 ( $\text{CH}$ ), 134.3 ( $\text{C}$ ), 134.9 ( $\text{CH}$ ), 136.9 ( $\text{C}$ ), 137.9 ( $\text{C}$ ), 145.5 ( $\text{C}$ ), 192.5 ( $\text{CH}$ ); IR (KBr):  $\tilde{\nu}=3062, 3021, 2965, 2921, 2835, 2744, 1694, 1651, 1596, 1463, 1446, 1389, 1293, 1257, 1240, 1194, 1159, 1107, 1030, 1004, 826, 767, 748, 687, 638$   $\text{cm}^{-1}$ ; HRMS-EI  $m/z$  calcd for  $\text{C}_{15}\text{H}_{14}\text{O}$ : 210.1045, found: 210.1037.

### 2'-Isopropyl-[1,1'-biphenyl]-2-carbaldehyde (17r):

$R_f=0.60$  (PE, 5% EtOAc),  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.08$  (d,  $J=6.8$  Hz, 3H,  $\text{CHCH}_3$ ), 1.12 (d,  $J=6.8$  Hz, 3H,  $\text{CHCH}_3$ ), 2.74 (hept,  $J=6.9$  Hz, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 7.14 (ddd,  $J=7.6/1.3/0.7$  Hz, 1H, ArH), 7.24 (ddd,  $J=7.6/6.3/2.4$  Hz, 1H, ArH), 7.33 (ddd,  $J=7.6/1.3/0.6$  Hz, 1H,  $\text{CHOCCHCHCHCH}$ ), 7.38–7.47 (m, 2H, ArH), 7.49–7.55 (m, 1H,  $\text{CHOCCHCHCHCH}$ ), 7.64 (td,  $J=7.5/1.5$  Hz, 1H,  $\text{CHOCCHCHCHCH}$ ), 7.99 (ddd,  $J=7.8/1.5/0.6$  Hz, 1H,  $\text{CHOCCHCHCHCH}$ ), 9.75 (d,  $J=0.8$  Hz, 1H,  $\text{CHO}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=23.7$  ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_3$ ), 30.6 ( $\text{CH}$ ), 125.8 ( $\text{CH}$ ), 126.1 ( $\text{CH}$ ), 127.4 ( $\text{CH}$ ), 128.3 ( $\text{CH}$ ), 129.2 ( $\text{CH}$ ), 130.8 ( $\text{CH}$ ), 131.7 ( $\text{CH}$ ), 134.0 ( $\text{CH}$ ), 134.8 ( $\text{C}$ ), 137.0 ( $\text{C}$ ), 146.1 ( $\text{C}$ ), 147.7 ( $\text{C}$ ), 192.5 ( $\text{CH}$ ); IR (film):  $\tilde{\nu}=3061, 3021, 2962, 2926, 2868, 2746, 1694, 1651, 1597, 1472, 1443, 1390, 1364, 1252, 1194, 1159, 1102, 1034, 825, 797, 756$   $\text{cm}^{-1}$ ; HRMS-EI  $m/z$  calcd for  $\text{C}_{16}\text{H}_{16}\text{O}$ : 224.1201, found: 224.1196.

### 2',4'-Dimethoxy-[1,1'-biphenyl]-2-carbaldehyde (17v):

$R_f=0.37$  (*n*-pentane/ $\text{Et}_2\text{O}$  8:2),  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=3.72$  (s, 3H,  $\text{OCH}_3$ ), 3.86 (s, 3H,  $\text{OCH}_3$ ), 6.56 (d,  $J=2.4$  Hz, 1H,  $\text{CHOCCHCHCOMeCHCOMe}$ ), 6.63 (dd,  $J=8.3/2.4$  Hz, 1H,  $\text{CHOCCHCHCOMeCHCOMe}$ ), 7.20 (d,  $J=8.3$  Hz, 1H,  $\text{CHOCCHCHCOMeCHCOMe}$ ), 7.34 (dd,

$J=7.7/1.2$  Hz, 1H, CHOCCHCHCHCHC), 7.45 (tt,  $J=7.6/1.1$  Hz, 1H, CHOCCHCHCHCHC), 7.63 (td,  $J=7.5/1.5$  Hz, 1H, CHOCCHCHCHCHC), 7.92 (dd,  $J=7.8/1.4$  Hz, 1H, CHOCCHCHCHCHC), 9.76 (d,  $J=0.8$  Hz, 1H, CHO);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=55.9$  ( $\text{CH}_3$ ), 56.0 ( $\text{CH}_3$ ), 98.8 (CH), 105.6 (CH), 119.9 (C), 126.9 (CH), 127.9 (CH), 132.0 (CH), 132.4 (CH), 134.1 (CH), 134.8 (C), 142.3 (C), 158.2 (C), 162.0 (C), 192.9 (CH); IR (film):  $\tilde{\nu}=3002, 2938, 2837, 2751, 1694, 1655, 1611, 1597, 1582, 1509, 1464, 1438, 1414, 1392, 1308, 1285, 1263, 1240, 1208, 1159, 1136, 1096, 1052, 1030, 1002, 933, 917, 829, 767$   $\text{cm}^{-1}$ ; HRMS-EI  $m/z$  calcd for  $\text{C}_{15}\text{H}_{14}\text{O}_3$ : 242.0943, found: 242.0937.

**rac-[Ethyl (4R)-1-{4-(2-bromophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4R)-19b) and rac-[ethyl (4S)-1-{4-(2-bromophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4S)-19b):**

$R_f=0.43$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta=1.25$  (t,  $J=7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.38–1.49 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.67 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.73–1.81 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.89–1.99 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.02–2.12 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.13–2.29 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.41 (t,  $J=10.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.55–2.63 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.68 (t,  $J=5.4$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.75–2.83 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 3.00–3.10 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 3.12–3.20 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 3.45 (t,  $J=2.1$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 4.13 (q,  $J=7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.98 (t,  $J=2.1$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 5.60–5.74 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 7.14 (td,  $J=7.6/1.7$  Hz, 1 H, BrCCHCHCHCH), 7.30 (td,  $J=7.5/1.3$  Hz, 1 H, BrCCHCHCHCH), 7.55 (dd,  $J=8.0/1.3$  Hz, 1 H, BrCCHCHCHCH), 7.70 (dd,  $J=7.7/1.7$  Hz, 1 H, BrCCHCHCHCH);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta=14.2$  ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_2$ ), 26.4 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 41.9 (CH), 46.6 ( $\text{CH}_2$ ), 47.7 ( $\text{CH}_2$ ), 48.7 ( $\text{CH}_2$ ), 52.4 ( $\text{CH}_2$ ), 54.3 ( $\text{CH}_2$ ), 60.3 ( $\text{CH}_2$ ), 60.6 (CH), 81.0 (C), 82.4 (C), 125.0 (CH), 125.1 (C), 125.4 (CH), 126.8 (CH), 129.1 (CH), 130.5 (CH), 133.1 (CH), 137.8 (C), 173.9 (C); IR (film):  $\tilde{\nu}=3060, 3032, 2937, 2864, 2805, 1731, 1660, 1588, 1568, 1466, 1440, 1368, 1347, 1311, 1281, 1261, 1223, 1181, 1152, 1131, 1095, 1046, 1026, 998, 974, 950, 868, 804, 795, 770, 747, 681, 652, 621$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{23}\text{H}_{29}\text{BrN}_2\text{O}_2$ : 445.1491, found: 445.1495.

**rac-[Ethyl (4R)-1-{4-(2-chlorophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4R)-19c) and rac-[ethyl (4S)-1-{4-(2-chlorophenyl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4S)-19c):**

$R_f=0.16$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=1.25$  (t,  $J=7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.43 (qd,  $J=11.6/3.7$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.67 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.77 (dp,  $J=11.4/3.9$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.89–1.99 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.02–2.29 (m, 3 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.41 (t,  $J=10.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.59 (tt,  $J=10.6/3.8$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.69 (t,  $J=5.7$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.79 (dbr,  $J=11.7$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.99–3.20 (m, 3 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 3.39–3.50 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 4.09–4.18 (m, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 5.03 (t,  $J=2.0$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 5.56–5.78 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 7.19–7.29 (m, 2 H, ClCCHCHCHCH), 7.33–7.41 (m, 1 H, ClCCHCHCHCH), 7.70 (dd,  $J=7.3/2.1$  Hz, 1 H, ClCCHCHCHCH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta=14.2$  ( $\text{CH}_3$ ), 24.5 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 41.9 (CH), 46.6 ( $\text{CH}_2$ ), 47.7 ( $\text{CH}_2$ ), 48.9 ( $\text{CH}_2$ ), 52.4 ( $\text{CH}_2$ ), 54.4 ( $\text{CH}_2$ ), 58.1 (CH), 60.4 ( $\text{CH}_2$ ), 81.1 (C), 82.2 (C), 125.0 (CH), 125.40 (CH), 126.2 (CH), 128.8 (CH), 129.8 (CH), 130.4 (CH), 134.5 (C), 136.2 (C), 174.0 (C); IR (film):  $\tilde{\nu}=3032, 2939, 2805, 1731, 1573, 1467, 1443, 1368, 1313, 1263, 1222, 1181, 1152, 1132, 1095, 1049, 1032, 999, 974, 950, 750, 706, 652$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{23}\text{H}_{29}\text{ClN}_2\text{O}_2$ : 401.1996, found: 401.1995.

**rac-[Ethyl (4R)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-(2-fluorophenyl)but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4R)-19d) and rac-[ethyl (4S)-1-{4-[3,6-dihydropyridin-1(2H)-yl]-4-(2-fluorophenyl)but-2-yn-1-yl}(3R)-piperidine-3-carboxylate] (rac-(3R,4S)-19d):**

$R_f=0.16$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.22$  (t,  $J=7.1$  Hz, 3 H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J=11.8/4.0$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.63 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.74 (dp,  $J=11.6/3.6$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.84–1.94 (m, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.00–2.20 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.24 (td,  $J=10.8/3.1$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.39 (t,  $J=10.5$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.55 (tt,  $J=10.1/3.7$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.66 (t,  $J=5.7$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.75 (dbr,  $J=11.2$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.94–3.16 (m, 3 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 3.41 (d,  $J=2.0$  Hz, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 4.09 (q,  $J=7.1$  Hz, 2 H,  $\text{OCH}_2\text{CH}_3$ ), 4.99 (t,  $J=2.0$  Hz, 1 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 5.66 (m, 2 H,  $\text{NCH}_2\text{CHCH}_2\text{H}_{\text{ax}}\text{H}_{\text{eq}}$ ), 7.06 (ddd,

$J=10.4/8.2/1.2$  Hz, 1 H, FCCCHCHCHCH), 7.15 (td,  $J=7.5/1.2$  Hz, 1 H, FCCCHCHCHCH), 7.25–7.36 (m, 1 H, FCCCHCHCHCH), 7.63 (tt,  $J=7.7/1.5$  Hz, 1 H, FCCCHCHCHCH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 47.0 ( $\text{CH}_2$ ), 48.1 ( $\text{CH}_2$ ), 49.4 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 55.2 ( $\text{CH}$ ), 55.3 ( $\text{CH}$ ), 60.8 ( $\text{CH}_2$ ), 80.7 ( $\text{C}$ ), 82.9 ( $\text{C}$ ), 116.0 (d,  $J_{\text{CF}}=22.1$  Hz, CH), 124.1 (d,  $J_{\text{CF}}=3.6$  Hz, CH), 125.5 ( $\text{CH}$ ), 125.9 ( $\text{CH}$ ), 126.3 (d,  $J_{\text{CF}}=13.1$  Hz, C), 130.0 (d,  $J_{\text{CF}}=8.4$  Hz, CH), 131.2 (d,  $J_{\text{CF}}=3.6$  Hz, CH), 161.3 (d,  $J_{\text{CF}}=247.7$  Hz, C), 174.4 (C);  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=-118.38$ ; IR (film):  $\tilde{\nu}=3432, 3034, 2940, 2866, 2807, 1731, 1659, 1615, 1588, 1489, 1456, 1393, 1368, 1317, 1270, 1233, 1181, 1153, 1132, 1094, 1073, 1046, 1030, 999, 974, 953, 857, 806, 795, 758, 712, 654, 619$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{23}\text{H}_{29}\text{FN}_2\text{O}_2$ : 385.2291, found: 385.2285.

***rac*-[Ethyl (4*R*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-[2-(trifluoromethyl)phenyl]but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19e) and *rac*-[ethyl (4*S*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-[2-(trifluoromethyl)phenyl]but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19e):**

$R_t=0.18$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.22$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.40 (qd,  $J=11.5/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.49–1.62 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.68–1.78 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.83–1.93 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.97–2.25 (m, 3H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.35 (t,  $J=10.6$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 1), 2.35 (t,  $J=10.6$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia 2), 2.49–2.62 (m, 2H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.64–2.76 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.95 (ddbr,  $J=11.1/3.7$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.98–3.15 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.37 (d,  $J=1.9$  Hz, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 4.09 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.87 (t,  $J=1.9$  Hz, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.55–5.78 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.42 (tbr,  $J=7.7$  Hz, 1H,  $\text{F}_3\text{CCCHCHCHCH}$ ), 7.57 (tbr,  $J=7.7$  Hz, 1H,  $\text{F}_3\text{CCCHCHCHCH}$ ), 7.67 (dbr,  $J=7.7$  Hz, 1H,  $\text{F}_3\text{CCCHCHCHCH}$ ), 7.96 (dbr,  $J=7.7$  Hz, 1H,  $\text{F}_3\text{CCCHCHCHCH}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 47.7 ( $\text{CH}_2$ ), 48.1 ( $\text{CH}_2$ ), 49.9 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 54.9 ( $\text{CH}_2$ ), 58.1 (q,  $J_{\text{CF}}=1.6$  Hz, CH), 60.8 ( $\text{CH}_2$ ), 81.8 (C), 83.6 (C), 125.1 (q,  $J_{\text{CF}}=274.3$  Hz, C), 125.5 (CH), 125.8 (CH), 126.9 (q,  $J_{\text{CF}}=5.8$  Hz, CH), 128.3 (CH), 128.8 (q,  $J_{\text{CF}}=30.3$  Hz, C), 131.1 (CH), 132.3 (CH), 139.0 (C), 174.3 (C);  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=-58.64$ ; IR (film):  $\tilde{\nu}=3035, 2941, 2806, 1731, 1660, 1607, 1585, 1451, 1393, 1368, 1312, 1264, 1223, 1181, 1156, 1129, 1058, 1036, 999, 975, 958, 948, 827, 770, 728, 666, 652$   $\text{cm}^{-1}$ ; HRMS-EI  $m/z$  calcd for  $\text{C}_{24}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_2$ : 434.2181, found: 434.2196.

***rac*-[Ethyl (4*R*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-methoxyphenyl)but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19f) and *rac*-[ethyl (4*S*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2-methoxyphenyl)but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19f):**

$R_t=0.29$  (PE/EtOAc 1:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta=1.18$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.18 (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.35 (qd,  $J=12.1/3.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.46–1.59 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.69 (dp,  $J=11.4/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.86 (dbr,  $J=13.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.95–2.23 (m, 3H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.34 (t,  $J=10.8$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.45–2.57 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.57–2.77 (m, 3H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.87–2.99 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.00–3.14 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.30–3.41 (m, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 3.76 (s, 3H,  $\text{OCH}_3$ ), 4.03–4.09 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.05 (s, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.45–5.74 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 6.81 (dd,  $J=8.3/1.1$  Hz, 1H,  $\text{MeOCCHCHCHCH}$ ), 6.88 (td,  $J=7.5/1.1$  Hz, 1H,  $\text{MeOCCHCHCHCH}$ ), 7.19 (td,  $J=7.8/1.8$  Hz, 1H,  $\text{MeOCCHCHCHCH}$ ), 7.52 (dd,  $J=7.5/1.7$  Hz, 1H,  $\text{MeOCCHCHCHCH}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 42.5 ( $\text{CH}$ ), 46.9 ( $\text{CH}_2$ ), 48.1 ( $\text{CH}_2$ ), 49.6 ( $\text{CH}_2$ ), 52.9 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 54.8 ( $\text{CH}$ ), 55.0 ( $\text{CH}_2$ ), 56.3 ( $\text{CH}_3$ ), 60.8 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 81.8 (C), 81.8 (C), 82.4 (C), 82.4 (C), 111.6 (CH), 120.4 (CH), 125.4 (CH), 126.3 (CH), 127.4 (C), 129.4 (CH), 130.6 (CH), 157.7 (C), 174.3 (CO), 174.4 (CO); IR (film):  $\tilde{\nu}=3031, 2939, 2804, 1731, 1659, 1600, 1587, 1491, 1464, 1440, 1393, 1368, 1317, 1287, 1246, 1226, 1181, 1152, 1132, 1095, 1048, 1030, 999, 974, 948, 906, 861, 755, 722, 653$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_3$ : 397.2491, found: 397.2489.

***rac*-[Ethyl (4*R*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3-methoxyphenyl)but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19g) and *rac*-[ethyl (4*S*)-1-(4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3-methoxyphenyl)but-2-yn-1-yl)(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19g):**

$R_t=0.30$  (PE/EtOAc 6:4);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.22$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J=12.0/4.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.65 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.69–1.80 (m, 1H,



NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.03–2.21 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.27 (td, *J*=10.9/3.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.41 (t, *J*=10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.51–2.66 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.77 (dbr, *J*=11.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.97–3.12 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.44 (d, *J*=1.9 Hz, 2H, NCHCCCH<sub>2</sub>N), 3.80 (s, 3H, OMe), 4.10 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.70 (t, *J*=2.0 Hz, 1H, NCHCCCH<sub>2</sub>N), 5.60–5.78 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.77–6.86 (m, 1H, CCHCHCHCOMe), 7.11–7.20 (m, 2H, CCHCOMe and CCHCHCHCOMe), 7.20–7.30 (m, 1H, CCHCHCHCOMe); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.1 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 42.5 (CH), 46.9 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 49.5 (CH<sub>2</sub>), 53.0 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 55.7 (CH<sub>3</sub>), 60.8 (CH<sub>2</sub>), 61.6 (CH), 81.2 (C), 83.3 (C), 113.5 (CH), 113.5 (CH), 114.4 (CH), 114.4 (CH), 121.2 (CH), 125.5 (CH), 126.19 (CH), 129.5 (CH), 141.0 (C), 160.2 (C), 174.4 (C); IR (film): ν̄=3031, 2939, 2911, 2866, 2832, 2807, 2746, 1731, 1658, 1600, 1586, 1487, 1465, 1451, 1435, 1393, 1368, 1347, 1315, 1274, 1248, 1226, 1182, 1153, 1133, 1095, 1047, 1030, 999, 975, 955, 935, 919, 865, 825, 802, 788, 759, 693, 655 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>3</sub>: 397.2491, found: 397.2482.

**rac-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (rac-(3*R*,4*R*)-19h) and rac-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (rac-(3*R*,4*S*)-19h):**

*R*<sub>T</sub>=0.09 (PE/EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd, *J*=11.3/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.79 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.94 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.98–2.19 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.24 (td, *J*=10.9/3.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.38 (t, *J*=10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.55 (tt, *J*=10.4/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.59–2.80 (m, 3H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.98 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.05–3.11 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.39 (d, *J*=2.0 Hz, 2H, NCHCCCH<sub>2</sub>N), 3.76 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.09 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.02 (t, *J*=2.0 Hz, 1H, NCHCCCH<sub>2</sub>N), 5.60–5.72 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.80 (dd, *J*=8.9/3.0 Hz, 1H, CCOMeCHCHCOMeCH), 6.85 (d, *J*=8.9 Hz, 1H, CCOMeCHCHCOMeCH), 7.15 (d, *J*=3.0 Hz, 1H, CCOMeCHCHCOMeCH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.1 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 42.5 (CH), 47.0 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 49.7 (CH<sub>2</sub>), 53.0 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 55.0 (CH), 55.0 (CH), 56.2 (CH<sub>3</sub>), 57.1 (CH<sub>3</sub>), 60.8 (CH<sub>2</sub>), 81.9 (C), 82.3 (C), 112.9 (CH), 112.9 (CH), 113.8 (CH), 113.8 (CH), 116.5 (CH), 116.5 (CH), 125.4 (CH), 126.2 (CH), 128.7 (C), 152.0 (C), 153.8 (C), 174.4 (C); IR (film): ν̄=3031, 2939, 2909, 2832, 2804, 2747, 1731, 1660, 1612, 1589, 1497, 1464, 1428, 1393, 1367, 1348, 1312, 1277, 1246, 1217, 1179, 1153, 1132, 1095, 1071, 1047, 1028, 999, 976, 883, 868, 808, 713, 703, 654 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>: 427.2597, found: 427.2587.

**rac-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (rac-(3*R*,4*R*)-19i) and rac-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(3,5-dimethoxyphenyl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (rac-(3*R*,4*S*)-19i):**

*R*<sub>T</sub>=0.18 (PE/EtOAc 1:1); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd, *J*=12.1/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.51–1.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.79 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.06–2.20 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.26 (td, *J*=10.9/3.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.40 (t, *J*=10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.51–2.66 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.77 (dbr, *J*=10.8 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.00 (dbr, *J*=10.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.06 (p, *J*=2.8 Hz, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.44 (d, *J*=2.0 Hz, 2H, NCHCCCH<sub>2</sub>N), 3.78 (s, 6H, OCH<sub>3</sub>), 4.09 (qd, *J*=7.1/1.2 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.65 (t, *J*=2.0 Hz, 1H, NCHCCCH<sub>2</sub>N), 5.63–5.75 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.37 (t, *J*=2.3 Hz, 1H, CCHCOMeCHCOMeCH), 6.77 (dt, *J*=2.3/0.8 Hz, 2H, CCHCOMeCHCOMeCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 42.5 (CH), 46.8 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 49.6 (CH<sub>2</sub>), 49.6 (CH<sub>2</sub>), 52.0 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 55.9 (CH<sub>3</sub>), 60.8 (CH<sub>2</sub>), 61.7 (CH), 81.2 (C), 83.2 (C), 100.0 (CH), 100.0 (CH), 106.8 (CH), 106.8 (CH), 125.5 (CH), 126.2 (CH), 141.9 (C), 161.2 (C), 174.4 (C); IR (film): ν̄=3031, 2939, 2835, 2807, 1731, 1659, 1596, 1460, 1427, 1393, 1367, 1336, 1315, 1298, 1261, 1244, 1204, 1154, 1133, 1095, 1064, 1053, 1029, 1001, 976, 955, 929, 858, 829, 794, 770, 730, 684, 647 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>4</sub>: 427.2597, found: 427.2586.

**rac**-[Ethyl (4*R*)-1-{4-(2-chloro-5-methoxyphenyl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*R*)-19*k*) and **rac**-[ethyl (4*S*)-1-{4-(2-chloro-5-methoxyphenyl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*S*)-19*k*):

$R_f=0.41$  (PE/EtOAc 6:4);  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.22$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.41 (qd,  $J=11.7/4.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.51–1.63 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.69–1.80 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.82–1.96 (m, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.99–2.21 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.25 (td,  $J=11.0/3.3$  Hz, 0.5H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.25 (td,  $J=11.0/3.3$  Hz, 0.5H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.39 (t,  $J=10.5$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 2.55 (tt,  $J=10.4/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$ ), 2.67 (t,  $J=5.7$  Hz, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.71–2.80 (m, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99 (dd<sub>br</sub>,  $J=12.3/3.3$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 3.01–3.19 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.42 (d,  $J=1.9$  Hz, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 3.80 (s, 3H,  $\text{OCH}_3$ ), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1 or dia2), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1 or dia2), 4.97 (t,  $J=1.9$  Hz, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.61–5.73 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 6.79 (dd,  $J=8.8/2.9$  Hz, 1H,  $\text{CICCHCHCOMeCHC}$ ), 7.26 (d,  $J=2.9$  Hz, 1H,  $\text{CICCHCHCOMeCHC}$ ), 7.27 (d,  $J=8.8$  Hz, 1H,  $\text{CICCHCHCOMeCHC}$ );  $^{13}\text{C NMR}$  (126 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 47.1 ( $\text{CH}_2$ ), 48.1 ( $\text{CH}_2$ ), 49.3 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 56.1 ( $\text{CH}_3$ ), 58.9 ( $\text{CH}$ ), 58.9 ( $\text{CH}$ ), 60.8 ( $\text{CH}_2$ ), 80.8 (C), 83.4 (C), 114.9 (CH), 114.9 (CH), 116.6 (CH), 116.6 (CH), 125.5 (CH), 126.0 (CH), 126.1 (C), 130.8 (CH), 137.9 (C), 137.9 (C), 158.6 (C), 174.3 (C); IR (film):  $\tilde{\nu}=3030, 2938, 2805, 1731, 1599, 1574, 1475, 1393, 1316, 1289, 1260, 1235, 1181, 1164, 1132, 1095, 1026, 1000, 976, 866, 803, 773$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for  $\text{C}_{24}\text{H}_{31}\text{ClN}_2\text{O}_3$ : 431.2101, found: 431.2094.

**rac**-[Ethyl (4*R*)-1-{4-([1,1'-biphenyl]-3-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*R*)-19*n*) and **rac**-[ethyl (4*S*)-1-{4-([1,1'-biphenyl]-3-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*S*)-19*n*):

$R_f=0.21$  (PE/EtOAc 7:3);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.21$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.22 (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.43 (qd,  $J=11.6/4.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.50–1.69 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.75 (dp,  $J=11.5/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.82–1.96 (m, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 2.04–2.24 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.29 (td,  $J=10.8/3.1$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.44 (t,  $J=10.4$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 2.51–2.72 (m, 3H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.73–2.87 (m, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.95–3.18 (m, 3H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.41–3.52 (m, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1 or dia2), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1 or dia2), 4.80 (t,  $J=2.0$  Hz, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.60–5.79 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.32–7.38 (m, 1H, ArH), 7.39–7.48 (m, 3H, ArH), 7.51–7.56 (m, 1H, ArH), 7.56–7.60 (m, 1H, ArH), 7.60–7.66 (m, 2H, ArH), 7.85 (t<sub>br</sub>,  $J=1.9$  Hz, 1H, ArH);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 42.5 (CH), 46.9 ( $\text{CH}_2$ ), 48.2 ( $\text{CH}_2$ ), 49.5 ( $\text{CH}_2$ ), 49.5 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 61.7 (CH), 81.1 (C), 81.2 (C), 83.5 (C), 125.5 (CH), 126.2 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 129.1 (CH), 129.3 (CH), 140.0 (C), 141.5 (C), 141.6 (C), 174.3 (C); IR (film):  $\tilde{\nu}=3059, 3031, 2939, 2866, 2807, 2747, 1949, 1885, 1731, 1659, 1599, 1574, 1478, 1467, 1452, 1419, 1368, 1348, 1317, 1274, 1250, 1223, 1181, 1152, 1133, 1095, 1048, 1029, 999, 974, 952, 901, 865, 809, 791, 752, 700, 656, 616$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for  $\text{C}_{29}\text{H}_{34}\text{N}_2\text{O}_2$ : 443.2699, found: 443.2690.

**rac**-[Ethyl (4*R*)-1-{4-([1,1'-biphenyl]-4-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*R*)-19*o*) and **rac**-[ethyl (4*S*)-1-{4-([1,1'-biphenyl]-4-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (**rac**-(3*R*,4*S*)-19*o*):

$R_f=0.18$  (PE/EtOAc 7:3);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.23$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.44 (qd,  $J=11.6/3.9$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 1.52–1.67 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.70–1.82 (m, 1H,  $\text{NCH}_2\text{CH}_{ax}H_{eq}\text{CH}_2\text{CH}$ ), 1.83–1.97 (m, 1H,  $\text{NCH}_2\text{CHCH}_{ax}H_{eq}$ ), 2.05–2.24 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.28 (td,  $J=10.9/3.1$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.43 (t,  $J=10.4$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$ ), 2.52–2.71 (m, 3H,  $\text{NCH}_2\text{CH}_{ax}\text{CH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.79 (d<sub>br</sub>,  $J=11.3$  Hz, 1H,  $\text{NCH}_{ax}H_{eq}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.94–3.17 (m, 3H,  $\text{NCH}_{ax}H_{eq}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 3.46 (d,  $J=2.0$  Hz, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 4.10 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.78 (t,  $J=2.0$  Hz, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.60–5.80 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.31–7.38 (m, 1H, ArH), 7.38–7.49 (m, 2H, ArH), 7.53–7.71 (m, 6H, ArH);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 25.2 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 42.5 (CH), 47.0 ( $\text{CH}_2$ ), 48.2 ( $\text{CH}_2$ ), 49.5 ( $\text{CH}_2$ ), 53.1 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 61.4 (CH), 81.1 (C), 81.1 (C), 83.5 (C), 83.52 (C), 125.5 (CH), 126.2 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 129.3 (CH), 129.4 (CH), 138.6 (C), 140.8 (C), 141.3 (C), 174.4 (C); IR (film):  $\tilde{\nu}=3424, 3030, 2938, 2806, 1730, 1599, 1486, 1465, 1448, 1367,$

1317, 1275, 1223, 1181, 1152, 1132, 1029, 1007, 998, 973, 860, 816, 790, 753, 697 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>: 443.2699, found: 443.2690.

***rac*-[Ethyl (4*R*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*p*) and *rac*-[ethyl (4*S*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*p*):**

*R*<sub>f</sub>=0.18 (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ=1.18–1.31 (m, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.33–1.50 (m, 1 H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.69 (m, 1 H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.82 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–2.09 (m, 3H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.09–2.45 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.45–2.66 (m, 2H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.66–2.75 (m, 4H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.33 (s, 1.1H, NCH<sub>2</sub>CCCH, atr-iso1), 3.43 (s, 0.9H, NCH<sub>2</sub>CCCH, atr-iso2), 4.02–4.23 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.36 (sbr, 0.55H, NCH<sub>2</sub>CCCH, atr-iso1), 4.91 (sbr, 0.45H, NCH<sub>2</sub>CCCH, atr-iso2), 5.48–5.68 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.80–7.76 (m, 13H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ=14.4 (CH<sub>3</sub>), 24.7 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 42.1 (CH), 46.6 (CH<sub>2</sub>), 46.6 (CH<sub>2</sub>), 47.2 (CH<sub>2</sub>), 47.9 (CH<sub>2</sub>), 47.9 (CH<sub>2</sub>), 48.4 (CH<sub>2</sub>), 48.4 (CH<sub>2</sub>), 48.5 (CH<sub>2</sub>), 52.4 (CH<sub>2</sub>), 52.4 (CH<sub>2</sub>), 52.6 (CH<sub>2</sub>), 52.6 (CH<sub>2</sub>), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 58.3 (CH), 58.3 (CH), 60.5 (CH<sub>2</sub>), 60.5 (CH<sub>2</sub>), 81.1 (C), 82.1 (C), 82.4 (C), 124.8 (CH), 125.0 (CH), 125.4 (CH), 125.7 (CH), 126.4 (CH), 126.5 (CH), 126.5 (CH), 126.6 (CH), 126.7 (CH), 126.9 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.6 (CH), 129.0 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 130.1 (CH), 130.6 (CH), 130.6 (CH), 131.3 (CH), 131.9 (CH), 132.0 (CH), 136.7 (C), 136.7 (C), 139.2 (C), 139.3 (C), 140.9 (C), 141.2 (C), 141.4 (C), 141.6 (C), 174.1 (C), 174.1 (C); IR (film): ν=3055, 3029, 2935, 2855, 2804, 2363, 2344, 1731, 1597, 1469, 1449, 1430, 1368, 1314, 1260, 1222, 1181, 1152, 1132, 1095, 1046, 1029, 998, 974, 948, 770, 753, 700 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>35</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>: 519.3012, found: 519.2999. Ratio of atropisomers is 45:55.

**Ethyl (4*R*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate ((3*R*,4*R*)-19*p*) and ethyl (4*S*)-1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate ((3*R*,4*S*)-19*p*):**

*R*<sub>f</sub>=0.27 (PE/EtOAc 6:4); [α]<sub>D</sub><sup>20.5</sup>=-0.59 (c=2.13 g/100 mL in chloroform); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub>, 373 K): δ=1.20 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.21 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.32–1.48 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.48–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.77–2.06 (m, 4H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.07–2.43 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.43–3.04 (m, 5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.19–3.45 (m, 2H, NCH<sub>2</sub>CCCH), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.09 (q, *J*=7.1 Hz, 1 H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.34 (sbr, 0.58H, NCH<sub>2</sub>CCCH, atr-iso1), 4.80 (sbr, 0.42H, NCH<sub>2</sub>CCCH, atr-iso2), 5.43–5.64 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.79–7.22 (m, 7H, ArH), 7.22–7.75 (m, 6H, ArH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 373 K): δ=14.4 (CH<sub>3</sub>), 23.3 (br, CH<sub>2</sub>), 26.0 (br, CH<sub>2</sub>), 40.6 (br, CH), 46.8 (CH<sub>2</sub>), 47.3 (CH<sub>2</sub>), 47.5 (CH<sub>2</sub>), 49.0 (br, CH<sub>2</sub>), 51.8 (CH<sub>2</sub>), 52.0 (CH<sub>2</sub>), 53.24 (br, CH<sub>2</sub>), 58.6 (CH), 61.0 (CH<sub>2</sub>), 125.1 (CH), 125.3 (CH), 126.7–128.0 (m, CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 129.3 (CH), 129.9 (CH), 130.1 (CH), 130.4 (CH), 130.7 (CH), 130.8 (CH), 131.6 (CH), 132.0 (CH), 132.3 (CH), 141.0 (C), 141.1 (C), 141.6 (C), 141.7 (C), 142.1 (C), 172.41 (C); IR (film): ν=3058, 3032, 2939, 2806, 1725, 1469, 1450, 1430, 1368, 1315, 1260, 1225, 1185, 1153, 1132, 1095, 1046, 1028, 1005, 974, 949, 887, 829, 807, 773, 746, 700, 625 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>35</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>: 519.3012, found: 519.3004. Ratio of atropisomers is 42:58.

***rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*q*) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*q*):**

*R*<sub>f</sub>=0.36 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd, *J*=11.9/4.2 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.80–2.03 (m, 3H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 1.91 (s, 3H, CH<sub>3</sub>), 1.97 (s, 3H, CH<sub>3</sub>), 2.10–2.27 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.36 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.48–2.59 (m, 2H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.61–2.77 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.78–2.88 (m, 1H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>),

2.97 (dd,  $J=10.8/3.4$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.38 (d,  $J=1.9$  Hz, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 4.09 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.20 (t,  $J=2.0$  Hz, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.44–5.64 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.00–7.10 (m, 3H, ArH), 7.10–7.18 (m, 1H, ArH), 7.32–7.40 (m, 2H, ArH), 7.71–7.80 (m, 1H, ArH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 21.2 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 27.1 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 47.3 ( $\text{CH}_2$ ), 48.2 ( $\text{CH}_2$ ), 48.6 ( $\text{CH}_2$ ), 53.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}$ ), 60.7 ( $\text{CH}_2$ ), 81.6 (C), 83.0 (C), 125.2 (CH), 126.1 (CH), 127.1 (CH), 127.2 (CH), 127.6 (CH), 127.6 (CH), 128.4 (CH), 129.4 (CH), 130.1 (CH), 135.6 (C), 137.4 (C), 138.5 (C), 140.7 (C), 141.8 (C), 174.4 (C), IR (film):  $\tilde{\nu}=3031, 2939, 2864, 2804, 1732, 1655, 1465, 1446, 1372, 1312, 1259, 1222, 1182, 1152, 1131, 1096, 1046, 1029, 1000, 974, 952, 863, 803, 765, 748, 732, 711, 652$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_2$ : 471.3012, found: 471.3003.

***rac*-[Ethyl (4*R*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19*r*) and *rac*-[ethyl (4*S*)-1-[4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19*r*):**

$R_f=0.31$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (500 MHz,  $\text{Tcl}_2$ ):  $\delta=0.96$  (d,  $J=6.8$  Hz, 1.71H,  $\text{CH}(\text{CH}_3)_2$ , atr-iso1), 1.03 (d,  $J=6.3$  Hz, 1.29H,  $\text{CH}(\text{CH}_3)_2$ , atr-iso2), 1.04 (d,  $J=6.1$  Hz, 1.29H,  $\text{CH}(\text{CH}_3)_2$ , atr-iso2), 1.07 (d,  $J=6.9$  Hz, 1.71H,  $\text{CH}(\text{CH}_3)_2$ , atr-iso1), 1.10–1.20 (m, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.21–1.40 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.40–1.57 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.58–1.73 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.75–2.04 (m, 3H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.04–2.16 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.16–2.35 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.35–2.77 (m, 5H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{CH}(\text{CH}_3)_2$ ), 2.79–3.00 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.25–3.37 (m, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 3.96–4.07 (m, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.09 (t,  $J=2.0$  Hz, 0.57H,  $\text{NCHCCCH}_2\text{N}$ , atr-iso1), 4.38 (t,  $J=2.0$  Hz, 0.43H,  $\text{NCHCCCH}_2\text{N}$ , atr-iso2), 5.35–5.65 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 6.98–7.17 (m, 3H, ArH), 7.17–7.38 (m, 4H, ArH), 7.65 (d,  $J=7.6$  Hz, 0.57H,  $\text{NCH}_2\text{CHCCHCCHCHCHCH}$ , atr-iso1), 7.71 (d,  $J=7.7$  Hz, 0.43H,  $\text{NCH}_2\text{CHCCHCCHCHCHCH}$ , atr-iso2);  $^{13}\text{C}$  NMR (126 MHz,  $\text{Tcl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ), 23.2 ( $\text{CH}_3$ ), 23.7 ( $\text{CH}_3$ ), 24.8 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_3$ ), 26.1 ( $\text{CH}_3$ ), 26.5 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 26.8 ( $\text{CH}_2$ ), 30.0 (CH), 30.4 (CH), 42.0 (CH), 45.9 ( $\text{CH}_2$ ), 47.0 ( $\text{CH}_2$ ), 48.0 ( $\text{CH}_2$ ), 48.0 ( $\text{CH}_2$ ), 48.9 ( $\text{CH}_2$ ), 50.0 ( $\text{CH}_2$ ), 52.4 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ), 52.6 ( $\text{CH}_2$ ), 52.6 ( $\text{CH}_2$ ), 54.4 ( $\text{CH}_2$ ), 54.5 ( $\text{CH}_2$ ), 54.6 ( $\text{CH}_2$ ), 58.1 (CH), 58.2 (CH), 60.7 ( $\text{CH}_2$ ), 60.7 ( $\text{CH}_2$ ), 81.4 (C), 82.2 (C), 82.8 (C), 83.3 (C), 124.9 (CH), 125.0 (CH), 125.2 (CH), 125.3 (CH), 125.8 (CH), 125.9 (CH), 127.1 (CH), 127.1 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 128.1 (CH), 129.0 (CH), 129.2 (CH), 129.6 (CH), 130.3 (CH), 130.6 (CH), 131.1 (CH), 137.1 (C), 137.2 (C), 138.9 (C), 139.2 (C), 141.7 (C), 142.0 (C), 146.9 (C), 147.9 (C), 174.2 (C), 174.3 (C), 174.3 (C); IR (film):  $\tilde{\nu}=3056, 3029, 2958, 2937, 2866, 2804, 1732, 1474, 1440, 1383, 1364, 1347, 1312, 1261, 1222, 1181, 1152, 1132, 1096, 1046, 1032, 1005, 974, 948, 866, 801, 756, 732$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{32}\text{H}_{40}\text{N}_2\text{O}_2$ : 485.3168, found: 485.3161. Ratio of atropisomers is 43:57.

***rac*-{Ethyl (4*R*)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,4*R*)-19*s*) and *rac*-{ethyl (4*S*)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]but-2-yn-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,4*S*)-19*s*):**

$R_f=0.24$  (PE/EtOAc 8:2);  $^1\text{H}$  NMR (400 MHz,  $\text{Tcl}_2$ , 393 K):  $\delta=1.21$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J=11.3/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.68 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.73 (dp,  $J=11.9/4.0$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.80–2.08 (m, 3H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.12–2.29 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.33 (dt,  $J=11.0/5.4$  Hz, 1H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.43 (t,  $J=10.7$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.47–2.66 (m, 2H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.66–2.94 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 2.94–3.09 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.30–3.49 (m, 2H,  $\text{NCHCCCH}_2\text{N}$ ), 4.10 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.31–4.48 (m, 1H,  $\text{NCHCCCH}_2\text{N}$ ), 5.42–5.64 (m, 2H,  $\text{NCH}_2\text{CHCHCH}_2\text{CH}_2$ ), 7.05–7.15 (m, 1H,  $\text{NCH}_2\text{CCCHCCHCHCHCH}$ ), 7.15–7.33 (m, 3H,  $\text{CICCHCCICHC}$  and  $\text{NCH}_2\text{CHCCHCCHCHCHCH}$  and  $\text{CICCHCCICHC}$ ), 7.36 (td,  $J=7.5/1.6$  Hz, 1H,  $\text{NCH}_2\text{CCCHCCHCHCHCH}$ ), 7.39–7.49 (m, 1H,  $\text{CICCHCCICHC}$ ), 7.70–7.88 (m, 1H,  $\text{NCH}_2\text{CCCHCCHCHCHCH}$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{Tcl}_2$ , 353 K):  $\delta=14.4$  ( $\text{CH}_3$ ), 24.1 ( $\text{CH}_2$ ), 26.2 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 41.5 (CH), 46.7 ( $\text{CH}_2$ ), 47.1 ( $\text{CH}_2$ ), 47.7 ( $\text{CH}_2$ ), 48.3 ( $\text{CH}_2$ ), 49.1 ( $\text{CH}_2$ ), 52.4 ( $\text{CH}_2$ ), 54.1 ( $\text{CH}_2$ ), 58.7 (CH), 58.8 (CH), 60.7 ( $\text{CH}_2$ ), 125.0 (CH), 125.0 (CH), 125.5 (CH), 126.4 (CH), 126.6 (CH), 127.7 (CH), 127.9 (CH), 128.1 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 129.5 (CH), 130.5 (CH), 130.8 (CH), 131.4 (CH), 133.9 (CH), 134.0 (C), 135.5 (C), 138.3 (C), 138.6 (C), 138.6 (C), 138.8 (C), 173.4 (C); IR (film):  $\tilde{\nu}=2926, 2805, 1731, 1587, 1551, 1464, 1444, 1375, 1314, 1223, 1181, 1152, 1132, 1100,$

1068, 1029, 1005, 974, 809, 763 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M+H*]<sup>+</sup> calcd for C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>: 511.1919, found: 511.1913. Ratio of atropisomers is 44:56.

***rac*-[Ethyl (4*R*)-1-{4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]}but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19t) and *rac*-[ethyl (4*S*)-1-{4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2*H*)-yl]}but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19t):**

*R*<sub>f</sub>=0.19 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub> 353 K): δ=1.19 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.38 (qd, *J*=11.3/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.70 (dp, *J*=11.5/3.6 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.79–2.00 (m, 3H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.20 (td, *J*=11.0/2.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.26–2.41 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.43–2.61 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub> and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.64–2.78 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.79–2.89 (m, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.96 (ddbr, *J*=10.4/3.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.37 (d, *J*=2.0 Hz, 2H, NCH<sub>2</sub>CCCH), 4.08 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.43 (t, *J*=2.0 Hz, 1H, NCH<sub>2</sub>CCCH), 5.43–5.62 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 6.73–6.90 (m, 2H, FCCCHF and FCCCH), 7.16 (dd, *J*=7.5/1.3 Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.29 (td, *J*=7.4/1.5 Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.32 (s<sub>br</sub>, 1H, FCCCHFCHCH), 7.35 (td, *J*=7.5/1.6 Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.76 (d, *J*=7.6 Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 353 K): δ=14.5 (CH<sub>3</sub>), 24.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 42.2 (CH), 46.5 (CH<sub>2</sub>), 47.9 (CH<sub>2</sub>), 48.6 (CH<sub>2</sub>), 52.6 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 58.9 (CH), 60.5 (CH<sub>2</sub>), 81.8 (C), 83.0 (C), 103.7 (t, <sup>2</sup>*J*<sub>CF</sub>=25.9 Hz, CH), 110.6 (dd, <sup>2/4</sup>*J*<sub>CF</sub>=20.9/3.9 Hz, CH), 125.0 (C and CH), 125.7 (CH), 127.6 (CH), 128.0 (CH), 129.2 (CH), 131.1 (CH), 132.8 (CH), 135.4 (C), 137.8 (C), 162.6 (dd, <sup>1/3</sup>*J*<sub>CF</sub>=248.2/11.6 Hz, C), 174.0 (C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, TCl<sub>2</sub>): δ=-111.13, -108.30; IR (film): ν=2939, 2804, 2360, 2341, 2035, 1730, 1618, 1593, 1509, 1479, 1446, 1419, 1367, 1314, 1264, 1225, 1182, 1152, 1138, 1096, 1027, 998, 962, 849, 764, 730 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M+H*]<sup>+</sup> calcd for C<sub>29</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>F<sub>2</sub>: 479.2510, found: 479.2498.

***rac*-[Ethyl (4*R*)-1-{4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]}but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19u) and *rac*-[ethyl (4*S*)-1-{4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]-4-[3,6-dihydropyridin-1(2*H*)-yl]}but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19u):**

*R*<sub>f</sub>=0.26 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.21 (td, *J*=7.1/1.3 Hz, 1.8H, OCH<sub>2</sub>CH<sub>3</sub>, atr-iso2), 1.22 (td, *J*=7.1/1.3 Hz, 1.2H, OCH<sub>2</sub>CH<sub>3</sub>, atr-iso1), 1.32–1.47 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–2.05 (m, 4H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.14–2.29 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.32–2.49 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.49–2.89 (m, 5H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub> and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 2.98 (dbr, *J*=10.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.33–3.48 (m, 2H, NCH<sub>2</sub>CCCH), 4.02–4.16 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.21 (t, *J*=1.6 Hz, 0.6H, NCH<sub>2</sub>CCCH, atr-iso2), 4.35–4.45 (m, 0.4H, NCH<sub>2</sub>CCCH, atr-iso1), 5.41–5.69 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCHCH<sub>2</sub>), 7.16 (dbr, *J*=7.5 Hz, 0.6H, NCHCCCH, atr-iso2), 7.19 (dbr, *J*=7.5 Hz, 0.4H, NCHCCCH, atr-iso1), 7.36 (td, *J*=7.5/1.3 Hz, 1H, NCHCCCHCH), 7.45 (td, *J*=7.5/1.3 Hz, 1H, NCHCCHCH), 7.54 (dbr, *J*=8.0 Hz, 0.4H, CF<sub>3</sub>CCHCH, atr-iso1), 7.67 (dbr, *J*=8.0 Hz, 0.6H, CF<sub>3</sub>CCHCH, atr-iso2), 7.71–7.80 (m, 1.2H, CF<sub>3</sub>CCHCH and NCHCCH, atr-iso2), 7.80–7.91 (m, 0.8H, CF<sub>3</sub>CCHCH and NCHCCH, atr-iso1), 8.00 (s, 1H, F<sub>3</sub>CCCHCCF<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 25.1 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 42.5 (CH), 46.6 (CH<sub>2</sub>), 47.5 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 48.9 (CH<sub>2</sub>), 53.0 (CH<sub>2</sub>), 53.1 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 59.1 (CH), 59.2 (CH), 60.8 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 80.1 (C), 81.4 (C), 83.6 (C), 84.4 (C), 123.0 (CH), 124.0 (q, <sup>1</sup>*J*<sub>CF</sub>=274.4 Hz, C), 124.2 (CH), 124.9 (CH), 125.2 (CH), 125.6 (CH), 125.9 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.5 (CH), 128.8 (CH), 128.90 (q, <sup>1</sup>*J*<sub>CF</sub>=256.3 Hz, C), 129.1 (CH), 129.3 (CH), 129.5 (q, <sup>2</sup>*J*<sub>CF</sub>=27.6 Hz, C), 130.0 (CH), 130.3 (q, <sup>2</sup>*J*<sub>CF</sub>=33.2 Hz, C), 130.50 (CH), 132.4 (CH), 135.7 (CH), 137.2 (C), 138.4 (C), 143.4 (C), 174.4 (C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=-57.9, -59.4, -63.1, -63.1; IR (film): ν=3034, 2939, 2808, 1732, 1625, 1578, 1467, 1447, 1344, 1287, 1275, 1178, 1132, 1084, 1064, 1048, 1029, 1007, 973, 948, 908, 844, 763, 729, 673 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M+H*]<sup>+</sup> calcd for C<sub>31</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>F<sub>6</sub>: 579.2446, found: 579.2437. Atropisomers 1 and 2 could be separated by column chromatography, however after isolation they equilibrate again to a ratio of ~ 40:60.

***rac*-[Ethyl (4*R*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*R*)-19v) and *rac*-[ethyl (4*S*)-1-{4-[3,6-dihydropyridin-1(2*H*)-yl]-4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)but-2-yn-1-yl}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,4*S*)-19v):**

$R_f=0.11$  (PE/EtOAc 6:4);  $^1\text{H NMR}$  (400 MHz,  $\text{Tcl}_2$ , 373 K):  $\delta=1.27$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.40–1.53 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.71 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.78 (dp,  $J=15.6/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.89–2.11 (m, 3H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CH}_2\text{CHCH}_2$ ), 2.28 (tbr,  $J=10.4$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.38–2.51 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CHCH}_2$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.51–2.68 (m, 2H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CHCH}_2$ ), 2.73–3.00 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CH}_2\text{CHCH}_2$ ), 3.04 (dbr,  $J=11.1$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.38–3.47 (m, 2H,  $\text{NCH}_2\text{CCCH}$ ), 3.71 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.16 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.49 (s, 1H,  $\text{NCH}_2\text{CCCH}$ ), 5.47–5.72 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CHCH}_2$ ), 6.50–6.59 (m, 2H, ArH), 7.09–7.26 (m, 2H, ArH), 7.30 (td,  $J=7.3/1.7$  Hz, 1H,  $\text{NCH}_2\text{CCCHCCHCH}$  or  $\text{NCH}_2\text{CCCHCCHCH}$ ), 7.34 (td,  $J=7.3/1.7$  Hz, 1H,  $\text{NCH}_2\text{CCCHCCHCH}$  or  $\text{NCH}_2\text{CCCHCCHCH}$ ), 7.79 (d,  $J=7.5$  Hz, 1H,  $\text{NCH}_2\text{CCCHCCH}$ );  $^{13}\text{C NMR}$  (126 MHz,  $\text{Tcl}_2$ ):  $\delta=14.5$  ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 42.0 (CH), 46.5 ( $\text{CH}_2$ ), 46.8 ( $\text{CH}_2$ ), 47.9 ( $\text{CH}_2$ ), 48.4 ( $\text{CH}_2$ ), 49.6 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ), 52.5 ( $\text{CH}_2$ ), 52.6 ( $\text{CH}_2$ ), 54.4 ( $\text{CH}_2$ ), 55.5 ( $\text{CH}_3$ ), 55.7 ( $\text{CH}_3$ ), 55.7 ( $\text{CH}_3$ ), 58.2 (CH), 58.2 (CH), 60.6 ( $\text{CH}_2$ ), 80.8 (C), 80.9 (C), 81.7 (C), 83.2 (C), 83.3 (C), 83.4 (C), 98.3 (CH), 98.7 (CH), 103.7 (CH), 104.2 (CH), 122.2 (C), 122.6 (C), 125.1 (CH), 125.8 (CH), 126.0 (CH), 126.7 (CH), 126.9 (CH), 127.1 (CH), 127.3 (CH), 128.3 (CH), 129.0 (CH), 130.9 (CH), 131.3 (CH), 132.8 (CH), 137.1 (C), 137.2 (C), 138.1 (C), 138.7 (C), 138.8 (C), 157.2 (C), 158.1 (C), 160.2 (C), 160.3 (C), 174.2 (C); IR (film):  $\tilde{\nu}=3029, 2937, 2833, 2803, 1730, 1612, 1581, 1511, 1465, 1438, 1413, 1305, 1280, 1207, 1182, 1158, 1132, 1094, 1032, 1002, 974, 933, 830, 795, 764, 732$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{31}\text{H}_{38}\text{N}_2\text{O}_4$ : 503.2910, found: 503.2901.

***rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R*<sub>a</sub>)-20b) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S*<sub>a</sub>)-20b):**

$R_f=0.34$  (PE/EtOAc 7:3);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta=1.23$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.23 (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.31–1.45 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.46–1.64 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.70 (dp,  $J=13.5/3.6$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.84–1.96 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.12 (td,  $J=11.0/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia2), 2.13 (td,  $J=11.0/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1), 2.26 (t,  $J=10.6$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2), 2.29 (t,  $J=10.6$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1), 2.53 (tt,  $J=10.3/3.8$  Hz, 0.5H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ , dia1), 2.54 (tt,  $J=10.3/3.8$  Hz, 0.5H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ , dia2), 2.72–2.87 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99 (dbr,  $J=11.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1), 3.05 (dbr,  $J=11.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2), 3.18 (dd,  $J=7.2/2.5$  Hz, 2H,  $\text{NCH}_2\text{CHCCH}$ ), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1), 4.10 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia2), 5.58 (q,  $J=7.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1), 5.58 (q,  $J=7.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia2), 6.56 (dt,  $J=6.4/2.4$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 7.03–7.09 (m, 1H,  $\text{BrCCHCHCHCHC}$ ), 7.23–7.29 (m, 1H,  $\text{BrCCHCHCHCHC}$ ), 7.45 (dd,  $J=7.9/1.7$  Hz, 1H,  $\text{BrCCHCHCHCHC}$ ), 7.53 (dd,  $J=8.0/1.2$  Hz, 1H,  $\text{BrCCHCHCHCHC}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ ):  $\delta=14.4$  ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 26.9 ( $\text{CH}_2$ ), 42.0 (CH), 42.0 (CH), 53.3 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 57.6 ( $\text{CH}_2$ ), 57.7 ( $\text{CH}_2$ ), 60.5 ( $\text{CH}_2$ ), 91.6 (CH), 93.9 (CH), 94.0 (CH), 122.6 (C), 127.5 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 133.1 (CH), 133.9 (C), 174.1 (C), 174.1 (C), 207.1 (C), 207.2 (C); IR (film):  $\tilde{\nu}=3058, 2940, 2855, 2796, 1949, 1731, 1589, 1562, 1474, 1439, 1367, 1342, 1309, 1276, 1217, 1181, 1152, 1134, 1095, 1023, 874, 763, 739$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{18}\text{H}_{22}\text{BrNO}_2$ : 364.0912, found: 364.0911.

***rac*-{Ethyl (*R*<sub>a</sub>)-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R*<sub>a</sub>)-20c) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S*<sub>a</sub>)-20c):**

$R_f=0.24$  (PE/EtOAc 7:3);  $^1\text{H NMR}$  (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.23$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.23 (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.38–1.50 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.50–1.61 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.68–1.78 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.85–1.95 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.12 (td,  $J=11.0/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia2), 2.13 (td,  $J=11.0/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1), 2.26 (t,  $J=10.9$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2), 2.29 (t,  $J=10.9$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1), 2.53 (tt,  $J=10.4/4.0$  Hz, 0.5H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ , dia1), 2.54 (tt,  $J=10.4/4.0$  Hz, 0.5H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ , dia2), 2.70–2.87 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.99 (ddbr,  $J=11.0/3.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1), 3.05 (ddbr,  $J=11.0/3.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2), 3.13–3.23 (m, 2H,  $\text{NCH}_2\text{CHCCH}$ ), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1), 4.10 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia2), 5.64

(q,  $J=6.7$  Hz, 1H, NCH<sub>2</sub>CHCCH), 6.61 (dt,  $J=6.4/2.5$  Hz, 1H, NCH<sub>2</sub>CHCCH), 7.14 (td,  $J=7.7/1.7$  Hz, 1H, CCHCHCHCHCCH), 7.21 (td,  $J=7.5/1.5$  Hz, 0.5H, CCHCHCHCHCCH, dia2), 7.22 (td,  $J=7.5/1.5$  Hz, 0.5H, CCHCHCHCHCCH, dia1), 7.34 (dd,  $J=8.0/1.3$  Hz, 1H, CCHCHCHCHCCH), 7.46 (dd,  $J=7.8/1.7$  Hz, 1H, CCHCHCHCHCCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.5 (CH), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 58.0 (CH<sub>2</sub>), 58.0 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 91.3 (CH), 91.3 (CH), 92.5 (CH), 92.5 (CH), 127.4 (CH), 128.5 (CH), 128.8 (CH), 130.2 (CH), 132.4 (C), 132.8 (C), 174.5 (C), 174.5 (C), 207.3 (C), 207.3 (C); IR (film):  $\tilde{\nu}=3063, 2978, 2940, 2856, 2797, 1949, 1731, 1590, 1567, 1477, 1467, 1442, 1388, 1367, 1342, 1309, 1275, 1217, 1181, 1152, 1134, 1095, 1049, 1033, 944, 875, 797, 763, 742, 705, 623$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>18</sub>H<sub>22</sub>ClNO<sub>2</sub>: 320.1417, found: 320.1410.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-{3R,R<sub>a</sub>}-20d) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-{3R,S<sub>a</sub>}-20d):**

$R_f=0.16$  (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=1.23$  (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.24 (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.39–1.49 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.85–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.12 (td,  $J=10.9/3.0$  Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.26 (t,  $J=10.6$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.29 (t,  $J=10.6$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.49–2.58 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.74–2.86 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.00 (dd,  $J=11.1/3.2$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.06 (dd,  $J=11.1/3.3$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.11–3.22 (m, 2H, NCH<sub>2</sub>CHCCH), 4.09 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.10 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.62 (q,  $J=7.0$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.62 (q,  $J=7.0$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.38 (dt,  $J=6.5/2.5$  Hz, 1H, NCH<sub>2</sub>CHCCH), 7.03 (ddd,  $J=10.6/8.2/1.3$  Hz, 1H, FCCHCHCHCH), 7.09 (tt,  $J=7.5/1.5$  Hz, 1H, FCCHCHCHCH), 7.15–7.21 (m, 1H, FCCHCHCHCH), 7.38 (td,  $J=7.7/1.7$  Hz, 1H, FCCHCHCHCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.5 (CH), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 58.0 (CH<sub>2</sub>), 58.1 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 87.3 (d, <sup>3</sup> $J_{CF}=5.8$  Hz, CH), 87.34 (d, <sup>3</sup> $J_{CF}=5.8$  Hz, CH), 92.2 (CH), 92.3 (CH), 116.0 (d, <sup>2</sup> $J_{CF}=21.4$  Hz, CH), 122.6 (d, <sup>2</sup> $J_{CF}=12.2$  Hz, C), 124.7 (d, <sup>4</sup> $J_{CF}=3.6$  Hz, CH), 128.7–128.9 (m, CH), 160.2 (d, <sup>1</sup> $J_{CF}=248.5$  Hz, C), 174.5 (C), 207.0 (d, <sup>4</sup> $J_{CF}=2.0$  Hz, C), 207.1 (d, <sup>4</sup> $J_{CF}=2.2$  Hz, C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=-120.1, -120.1$ ; IR (film):  $\tilde{\nu}=3418, 2941, 2800, 1951, 1730, 1583, 1493, 1457, 1367, 1343, 1310, 1233, 1180, 1152, 1134, 1094, 1031, 939, 876, 833, 788, 753$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>18</sub>H<sub>22</sub>FNO<sub>2</sub>: 304.1713, found: 304.1706.

***rac*-[Ethyl (R<sub>a</sub>)-1-[4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate] (*rac*-{3R,R<sub>a</sub>}-20e) and *rac*-[ethyl (S<sub>a</sub>)-1-[4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate] (*rac*-{3R,S<sub>a</sub>}-20e):**

$R_f=0.19$  (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=1.22$  (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.39–1.49 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.85–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.13 (td,  $J=10.6/3.0$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.14 (td,  $J=10.6/3.0$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.27 (t,  $J=10.3$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.29 (t,  $J=10.3$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.53 (tt,  $J=10.6/3.9$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.54 (tt,  $J=10.6/3.9$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.74–2.85 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.99 (dd,  $J=11.1/3.9$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.05 (dd,  $J=11.1/3.9$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.19 (dd,  $J=7.1/2.5$  Hz, 1H, NCH<sub>2</sub>CHCCH, dia2), 3.20 (dd,  $J=7.1/2.5$  Hz, 1H, NCH<sub>2</sub>CHCCH, dia1), 4.09 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.10 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.67 (q,  $J=6.9$  Hz, 1H, NCH<sub>2</sub>CHCCH), 6.49–6.57 (m, 1H, NCH<sub>2</sub>CHCCH), 7.30 (t,  $J=7.7$  Hz, 1H, F<sub>3</sub>CCCCHCHCHCH), 7.50 (t,  $J=7.7$  Hz, 1H, F<sub>3</sub>CCCCHCHCHCH), 7.58–7.67 (m, 2H, F<sub>3</sub>CCCCHCHCHCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.5 (CH), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 91.1 (q, <sup>4</sup> $J_{CF}=2.8$  Hz, CH), 91.13 (q, <sup>4</sup> $J_{CF}=2.8$  Hz, CH), 92.6 (CH), 92.6 (CH), 125.0 (q, <sup>1</sup> $J_{CF}=273.7$  Hz, C), 126.4 (q, <sup>3</sup> $J_{CF}=5.7$  Hz, CH), 126.9 (q, <sup>2</sup> $J_{CF}=30.1$  Hz, C), 127.2 (CH), 129.2 (CH), 129.3 (CH), 132.4 (CH), 133.7 (q, <sup>3</sup> $J_{CF}=1.4$  Hz, C), 174.5 (C), 207.5 (C), 207.6 (C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=-59.8$ ; IR (film):  $\tilde{\nu}=2941, 2856, 2801, 1950, 1731, 1605, 1579, 1494, 1454, 1367, 1316, 1262, 1207, 1157, 1121, 1097, 1058, 1034, 956, 867, 764$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>F<sub>3</sub>NO<sub>2</sub>: 354.1681, found: 354.1673.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*R<sub>a</sub>*}-20f) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*S<sub>a</sub>*}-20f):

*R<sub>f</sub>*=0.19 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.24 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.37–1.49 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.80 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.81–1.99 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.11 (td, *J*=10.9/3.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.24 (t, *J*=10.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.28 (t, *J*=10.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.45–2.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.70–2.90 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.00 (ddbr, *J*=11.1/3.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.07 (ddbr, *J*=11.1/3.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.09–3.21 (m, 2H, NCH<sub>2</sub>CHCCH), 3.83 (s, 3H, OCH<sub>3</sub>), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.10 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.54 (q, *J*=7.0 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.54 (dt, *J*=6.5/2.5 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.87 (dd, *J*=8.2, 1.1 Hz, 1H, CCHCHCHCHCOMe), 6.90 (td, *J*=7.5/1.1 Hz, 0.5H, CCHCHCHCHCOMe, dia2), 6.90 (td, *J*=7.5/1.1 Hz, 0.5H, CCHCHCHCHCOMe, dia1), 7.17 (td, *J*=7.4/1.8 Hz, 1H, CCHCHCHCHCOMe), 7.34 (dd, *J*=7.6/1.8 Hz, 1H, CCHCHCHCHCOMe); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 56.1 (CH<sub>3</sub>), 58.4 (CH<sub>2</sub>), 58.4 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 88.8 (CH), 88.9 (CH), 91.5 (CH), 91.5 (CH), 111.5 (CH), 121.2 (CH), 123.3 (C), 128.2 (CH), 128.5 (CH), 156.6 (C), 174.5 (C), 206.9 (C), 206.9 (C); IR (film): ν̄=2940, 2835, 2798, 1948, 1730, 1596, 1583, 1493, 1465, 1440, 1392, 1367, 1342, 1288, 1246, 1180, 1152, 1134, 1095, 1048, 1029, 932, 880, 822, 797, 750 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>25</sub>NO<sub>3</sub>: 316.1913, found: 316.1905.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*R<sub>a</sub>*}-20g) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*S<sub>a</sub>*}-20g):

*R<sub>f</sub>*=0.24 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.37–1.50 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.97 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.12 (td, *J*=10.8/3.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.14 (td, *J*=10.8/3.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.26 (t, *J*=11.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.29 (t, *J*=11.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.53 (tt, *J*=10.1/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.54 (tt, *J*=10.1/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.79 (dt, *J*=11.2/4.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.84 (dt, *J*=11.2/4.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 3.00 (ddbr, *J*=11.0/3.8 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.06 (ddbr, *J*=11.0/3.8 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.10–3.22 (m, 2H, NCH<sub>2</sub>CHCCH), 3.78 (s, 3H, OCH<sub>3</sub>), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.10 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.59 (q, *J*=7.3 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.59 (q, *J*=7.3 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.15 (dt, *J*=6.4/2.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.74 (ddt, *J*=8.0/2.6/0.7 Hz, 1H, CCHCHCHCOMe), 6.80–6.85 (m, 1H, CCHCOMe), 6.85–6.90 (m, 1H, CCHCHCHCOMe), 7.20 (t, *J*=8.0 Hz, 1H, CCHCHCHCOMe); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>), 55.6 (CH<sub>3</sub>), 55.7 (CH<sub>2</sub>), 55.7 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 92.3 (CH), 92.4 (CH), 94.9 (CH), 95.0 (CH), 112.2 (CH), 112.3 (CH), 113.3 (CH), 113.3 (CH), 119.8 (CH), 130.1 (CH), 136.5 (C), 160.5 (C), 174.5 (C), 206.5 (C), 206.5 (C); IR (film): ν̄=2940, 2854, 2833, 2803, 1949, 1730, 1598, 1582, 1553, 1530, 1512, 1490, 1467, 1453, 1440, 1408, 1367, 1343, 1311, 1263, 1222, 1181, 1153, 1134, 1094, 1047, 994, 880, 786, 754, 734, 687 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>25</sub>NO<sub>3</sub>: 316.1913, found: 316.1905.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*R<sub>a</sub>*}-20h) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (***rac***-{3*R*,*S<sub>a</sub>*}-20h):

*R<sub>f</sub>*=0.32 (PE/EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.37–1.50 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.72 (dp, *J*=11.0/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.84–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.06–2.19 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.26 (t, *J*=10.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.29 (t, *J*=10.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.48–2.59 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.79 (dtbr, *J*=11.3/4.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.84 (dtbr, *J*=11.3/4.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.99 (ddbr, *J*=11.0/3.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.05 (ddbr, *J*=11.0/3.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.08–3.23 (m, 2H, NCH<sub>2</sub>CHCCH), 3.73 (s, 1.5H, OCH<sub>3</sub>, dia2), 3.73 (s, 1.5H, OCH<sub>3</sub>, dia1), 3.78 (s, 3H, OCH<sub>3</sub>), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.56 (q, *J*=6.9 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.52 (dt, *J*=6.5/2.4 Hz, 0.5H, NCH<sub>2</sub>CHCCH,



dia2), 6.52 (dt,  $J=6.5/2.4$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 6.71 (dd,  $J=8.9/3.1$  Hz, 1H, CCOMeCHCHCOMeCH), 6.81 (d,  $J=8.9$  Hz, 1H, CCOMeCHCHCOMeCH), 6.89 (d,  $J=3.1$  Hz, 0.5H, CCOMeCHCHCOMeCH, dia2), 6.90 (d,  $J=3.1$  Hz, 0.5H, CCOMeCHCHCOMeCH, dia1); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.6 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 56.1 (CH<sub>3</sub>), 56.1 (CH<sub>3</sub>), 56.8 (CH<sub>3</sub>), 58.3 (CH<sub>2</sub>), 58.4 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 89.0 (CH), 89.0 (CH), 91.7 (CH), 91.8 (CH), 112.9 (CH), 113.0 (CH), 113.0 (CH), 113.0 (CH), 113.9 (CH), 113.9 (CH), 124.2 (C), 151.1 (C), 154.4 (C), 174.5 (C), 174.5 (C), 206.8 (C), 206.8 (C); IR (film):  $\tilde{\nu}=2939, 2832, 2802, 1948, 1729, 1606, 1501, 1465, 1427, 1412, 1366, 1342, 1308, 1280, 1244, 1214, 1179, 1152, 1133, 1094, 1047, 1027, 881, 860, 803, 713, 699$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>: 346.2018, found: 346.2011.

***rac*-{Ethyl (*R<sub>a</sub>*)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-{3*R*,*R<sub>a</sub>*}-20i) and *rac*-{ethyl (*S<sub>a</sub>*)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-{3*R*,*S<sub>a</sub>*}-20i):**

$R_f=0.31$  (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=1.22$  (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t,  $J=7.1$  Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.37–1.50 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.84–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.12 (td,  $J=10.6/3.0$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.15 (td,  $J=10.6/3.0$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.27 (t,  $J=11.2$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.30 (t,  $J=11.2$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.52 (tt,  $J=10.0/3.8$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.54 (tt,  $J=10.0/3.8$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.78 (dt<sub>br</sub>,  $J=11.1/3.8$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.84 (dt<sub>br</sub>,  $J=11.1/3.8$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.99 (dd<sub>br</sub>,  $J=11.0/3.4$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.06 (dd<sub>br</sub>,  $J=11.1/3.8$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.09–3.23 (m, 2H, NCH<sub>2</sub>CHCCH), 3.76 (s, 6H, OCH<sub>3</sub>), 4.09 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.09 (q,  $J=7.1$  Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.59 (q,  $J=6.7$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.59 (q,  $J=6.7$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.11 (dt,  $J=6.4/2.3$  Hz, 1H, NCH<sub>2</sub>CHCCH), 6.31 (t,  $J=2.3$  Hz, 1H, CCHCOMeCHCOMeCH), 6.44 (d,  $J=2.3$  Hz, 1H, CCHCOMeCHCOMeCH, dia2), 6.45 (d,  $J=2.3$  Hz, 1H, CCHCOMeCHCOMeCH, dia1); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.8 (CH<sub>3</sub>), 55.8 (CH<sub>3</sub>), 58.2 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 92.4 (CH), 92.5 (CH), 95.1 (CH), 95.1 (CH), 99.8 (CH), 99.9 (CH), 105.1 (CH), 105.1 (CH), 137.2 (C), 161.6 (C), 174.5 (C), 174.5 (C), 206.5 (C), 206.6 (C); IR (film):  $\tilde{\nu}=2939, 2835, 1948, 1729, 1603, 1593, 1466, 1458, 1432, 1397, 1365, 1339, 1313, 1295, 1204, 1153, 1094, 1064, 1030, 992, 876, 832, 678$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>: 346.2018, found: 346.2012.

***rac*-{Ethyl (*R<sub>a</sub>*)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-{3*R*,*R<sub>a</sub>*}-20j) and *rac*-{ethyl (*S<sub>a</sub>*)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylate} (*rac*-{3*R*,*S<sub>a</sub>*}-20j):**

$R_f=0.47$  (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=1.23$  (t,  $J=7.1$  Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.37–1.49 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.10 (td,  $J=11.0/3.5$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.11 (td,  $J=11.0/3.5$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.23 (t,  $J=11.1$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.25 (t,  $J=11.1$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.52 (tt,  $J=10.4/3.8$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.52 (tt,  $J=10.4/3.8$  Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.69–2.86 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.99 (d<sub>br</sub>,  $J=11.1$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.02 (d<sub>br</sub>,  $J=11.1$  Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.14–3.24 (m, 2H, NCH<sub>2</sub>CHCCH), 4.09 (q,  $J=7.1$  Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.49 (q,  $J=7.0$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.49 (q,  $J=7.0$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.46 (dt,  $J=6.6/2.8$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 6.47 (dt,  $J=6.6/2.8$  Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 7.10 (t,  $J=8.1$  Hz, 1H, ClCCHCHCH), 7.32 (d,  $J=8.1$  Hz, 2H, ClCCHCHCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta=14.6$  (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.5 (CH), 53.8 (CH<sub>2</sub>), 55.7 (CH<sub>2</sub>), 55.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 88.8 (CH), 88.8 (CH), 91.3 (CH), 91.3 (CH), 128.5 (CH), 129.2 (CH), 131.1 (C), 131.2 (C), 134.9 (C), 174.5 (C), 174.5 (C), 208.2 (C), 208.3 (C); IR (film):  $\tilde{\nu}=2978, 2940, 2866, 2794, 1955, 1731, 1578, 1557, 1467, 1450, 1435, 1392, 1367, 1343, 1310, 1259, 1217, 1183, 1152, 1134, 1096, 1031, 864, 832, 774, 747$  cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>18</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>2</sub>: 354.1028, found: 354.1025.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R<sub>a</sub>*)-20k) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S<sub>a</sub>*)-20k):

*R<sub>f</sub>*=0.31 (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.37–1.50 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.97 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.14 (td, *J*=11.1/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.15 (td, *J*=11.1/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.28 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.30 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.53 (tt, *J*=10.4/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.54 (tt, *J*=10.4/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.73–2.88 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.99 (dd<sub>br</sub>, *J*=11.0/2.9 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.04 (dd<sub>br</sub>, *J*=11.0/2.9 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.12–3.25 (m, 2H, NCH<sub>2</sub>CHCCH), 3.76 (s, 1.5H, OCH<sub>3</sub>, dia2), 3.76 (s, 1.5H, OCH<sub>3</sub>, dia1), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.65 (q, *J*=7.2 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.57 (dt, *J*=6.5/2.5 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.57 (dt, *J*=6.5/2.5 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 6.71 (dd, *J*=8.8/3.1 Hz, 1H, ClCCHCCHCOMeCH), 6.96 (d, *J*=2.0 Hz, 0.5H, ClCCHCCHCOMeCH, dia2), 6.97 (d, *J*=2.0 Hz, 0.5H, ClCCHCCHCOMeCH, dia1), 7.23 (d, *J*=8.8 Hz, 1H, ClCCHCCHCOMeCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 56.0 (CH<sub>3</sub>), 56.0 (CH<sub>3</sub>), 58.0 (CH<sub>2</sub>), 58.0 (CH<sub>2</sub>), 60.8 (CH<sub>2</sub>), 91.5 (CH), 91.5 (CH), 92.7 (CH), 92.7 (CH), 112.9 (CH), 113.0 (CH), 115.2 (CH), 115.3 (CH), 124.0 (C), 130.8 (CH), 130.8 (CH), 133.5 (C), 159.0 (C), 174.4 (C), 174.5 (C), 207.2 (C), 207.2 (C); IR (film): ν̄=2940, 2855, 2800, 1950, 1731, 1594, 1571, 1484, 1466, 1405, 1367, 1343, 1281, 1252, 1229, 1181, 1165, 1152, 1134, 1095, 1064, 1026, 877, 856, 808, 746, 691, 653 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>24</sub>ClNO<sub>3</sub>: 350.1523, found: 350.1518.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R<sub>a</sub>*)-20n) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S<sub>a</sub>*)-20n):

*R<sub>f</sub>*=0.23 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.21 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.22 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.45 (qd, *J*=11.7/4.1 Hz, 0.5H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>, dia2), 1.46 (qd, *J*=11.7/4.1 Hz, 0.5H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>, dia1), 1.51–1.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.80 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.84–1.97 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.14 (td, *J*=10.8/2.9 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.17 (td, *J*=10.8/2.9 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.30 (t, *J*=10.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.32 (t, *J*=10.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.54 (tt, *J*=10.3/3.9 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.55 (tt, *J*=10.3/3.9 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.75–2.87 (m, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.83–2.92 (m, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 3.01 (dd<sub>br</sub>, *J*=11.2/3.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.06 (dd<sub>br</sub>, *J*=10.7/3.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.11–3.25 (m, 2H, NCH<sub>2</sub>CHCCH), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.62 (q, *J*=6.8 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.63 (q, *J*=6.8 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.26 (dt, *J*=6.4/2.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.28 (dt, *J*=7.5/1.3 Hz, 0.5H, ArH, dia1), 7.28 (dt, *J*=7.5/1.3 Hz, 0.5H, ArH, dia2), 7.32–7.41 (m, 2H, ArH), 7.41–7.49 (m, 3H, ArH), 7.53 (t, *J*=1.7 Hz, 0.5H, ArH, dia2), 7.54 (t, *J*=1.7 Hz, 0.5H, ArH, dia1), 7.57–7.63 (m, 2H, ArH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 53.8 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.7 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 58.3 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 92.3 (CH), 92.6 (CH), 94.9 (CH), 94.9 (CH), 125.9 (CH), 126.0 (CH), 126.2 (CH), 126.2 (CH), 126.2 (CH), 127.6 (CH), 128.0 (CH), 129.3 (CH), 129.6 (CH), 129.6 (CH), 135.6 (C), 141.5 (C), 142.0 (C), 142.0 (C), 174.5 (C), 206.6 (C), 206.7 (C); IR (film): ν̄=3425, 3059, 3031, 2940, 2804, 1949, 1730, 1598, 1574, 1479, 1467, 1454, 1367, 1311, 1218, 1181, 1152, 1133, 1094, 1029, 894, 866, 802, 761, 736, 698 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>: 362.2120, found: 362.2114.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R<sub>a</sub>*)-20o) and ***rac***-{ethyl (*S<sub>a</sub>*)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S<sub>a</sub>*)-20o):

*R<sub>f</sub>*=0.22 (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.23 (t, *J*=7.2 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.24 (t, *J*=7.2 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.39–1.51 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.51–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.70–1.80 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.86–1.97 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.15 (td, *J*=11.0/2.8 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.15 (td, *J*=11.0/2.8 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.29 (t, *J*=11.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.31 (t, *J*=11.1 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.55 (tt, *J*=10.3/3.9 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1), 2.57 (tt, *J*=10.3/3.9 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia2), 2.74–2.83 (m, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.83–2.92 (m, 0.5H,

NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 3.02 (dbr, *J*=10.3 Hz, 0.5 H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.09 (dbr, *J*=10.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.13–3.25 (m, 2H, NCH<sub>2</sub>CHCCH), 4.10 (q, *J*=7.2 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.11 (q, *J*=7.2 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.63 (q, *J*=6.9 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1), 5.63 (q, *J*=6.9 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia2), 6.24 (dt, *J*=6.0/2.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.30–7.40 (m, 3H, ArH), 7.40–7.47 (m, 2H, ArH), 7.54–7.59 (m, 2H, ArH), 7.59–7.65 (m, 2H, ArH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 53.8 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 58.3 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 92.3 (CH), 92.4 (CH), 94.6 (CH), 94.6 (CH), 127.3 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 129.3 (CH), 134.2 (C), 140.1 (C), 141.2 (C), 174.5 (C), 174.5 (C), 206.7 (C), 206.7 (C); IR (film): ν̄=3432, 3030, 2940, 2805, 1947, 1730, 1600, 1518, 1487, 1467, 1451, 1367, 1312, 1218, 1182, 1152, 1134, 1095, 1030, 1007, 876, 842, 798, 769, 743, 723, 697 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>: 362.2120, found: 362.2113.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,R<sub>a</sub>)-20p) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,S<sub>a</sub>)-20p):**

*R*<sub>t</sub>=0.31 (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, TCl<sub>2</sub>): δ=1.16–1.30 (m, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.40 (q, *J*=12.4 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.46–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.61–1.82 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.96–2.10 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.09–2.27 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.38–2.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.62–2.83 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.83–3.16 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 3.89–4.28 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.24–5.50 (m, 1H, NCH<sub>2</sub>CHCCH), 5.90 (d, *J*=6.2 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.95–7.25 (m, 8H, ArH), 7.25–7.37 (m, 2H, ArH), 7.37–7.54 (m, 3H, ArH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>): δ=14.2 (CH<sub>3</sub>), 24.4 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 41.6 (CH), 52.6 (CH<sub>2</sub>), 52.8 (CH<sub>2</sub>), 54.4 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.3 (CH<sub>2</sub>), 57.4 (CH<sub>2</sub>), 60.3 (CH<sub>2</sub>), 90.5 (CH), 90.5 (CH), 92.5 (CH), 92.6 (CH), 126.2 (CH), 126.3 (CH), 126.7 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 129.4 (CH), 129.5 (CH), 129.9 (CH), 130.0 (CH), 130.9 (CH), 131.0 (CH), 131.0 (CH), 131.1 (CH), 132.1 (CH), 132.2 (CH), 138.9 (C), 139.4 (C), 140.9 (C), 140.9 (C), 141.2 (C), 174.0 (C), 206.2 (C); IR (film): ν̄=3057, 3021, 2939, 2868, 2795, 2359, 2342, 1947, 1731, 1597, 1490, 1471, 1450, 1366, 1310, 1218, 1180, 1151, 1133, 1094, 1031, 1008, 879, 767, 750, 699 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>31</sub>NO<sub>2</sub>: 438.2433, found: 438.2424. Ratio of atropisomers is 45:55.

**Ethyl (R<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate ((3R,R<sub>a</sub>)-20p) and Ethyl (S<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate ((3R,S<sub>a</sub>)-20p):**

*R*<sub>t</sub>=0.23 (PE/EtOAc 7:3); [α]<sub>D</sub><sup>21</sup>=+2.17° (c=2.205 g/100 mL in chloroform); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub>, 373K): δ=1.19 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.20 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.41 (qd, *J*=12.2/4.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.48–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.63–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.97 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.00–2.16 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.23 (t, *J*=10.7 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.26 (t, *J*=10.7 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.46–2.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.65–2.82 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.82–3.23 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 5.34 (q, *J*=6.0 Hz, 1H, NCH<sub>2</sub>CHCCH), 5.85–6.02 (m, 1H, NCH<sub>2</sub>CHCCH), 6.89–7.20 (m, 8H, ArH), 7.21–7.30 (m, 2H, ArH), 7.31–7.48 (m, 3H, ArH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 393K): δ=14.2 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>), 21.9 (br, CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 39.0 (br, CH), 51.7 (br, CH<sub>2</sub>), 52.6 (br, CH<sub>2</sub>), 56.7 (br, CH<sub>2</sub>), 61.5 (CH<sub>2</sub>), 84.1 (br, CH), 95.3 (CH), 126.7 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 129.7 (CH), 130.4 (CH), 130.7 (br, C), 131.2 (CH), 131.6 (CH), 139.2 (C), 140.8 (C), 141.4 (br, C), 141.7 (br, C), 171.2 (br, C), 209.8 (br, C); IR (film): ν̄=3057, 3020, 2978, 2940, 2855, 2795, 1947, 1731, 1597, 1490, 1472, 1450, 1388, 1366, 1342, 1310, 1218, 1180, 1151, 1134, 1095, 1046, 1031, 1008, 948, 912, 878, 797, 768, 750, 699, 631, 614 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>31</sub>NO<sub>2</sub>: 438.2433, found: 438.2426. Ratio of atropisomers is 44:56.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,R<sub>a</sub>)-20q) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,S<sub>a</sub>)-20q):**

*R*<sub>t</sub>=0.34 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.21 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.23 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.41 (qd, *J*=11.6/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.60 (m, 1H,

NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.76 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–1.93 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.95 (s, 3H, CH<sub>3</sub>), 1.96 (s, 3H, CH<sub>3</sub>), 2.05 (td, *J*=11.0/2.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.07 (td, *J*=11.0/2.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.20 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.43–2.57 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.68–2.83 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.89–3.12 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 4.07 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.43 (q, *J*=6.9 Hz, 1H, NCH<sub>2</sub>CHCCH), 5.74 (dt, *J*=6.4/2.5 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.03 (dd, *J*=7.4/1.6 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH), 7.07–7.13 (m, 2H, ArH), 7.13–7.19 (m, 1H, ArH), 7.26 (td, *J*=7.4/1.4 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH), 7.31 (td, *J*=7.5/1.3 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia2), 7.32 (td, *J*=7.5/1.3 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1), 7.53 (dd, *J*=7.7/1.2 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>), 20.8 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.6 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 58.3 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 91.5 (CH), 91.6 (CH), 92.3 (CH), 92.3 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 130.1 (CH), 132.9 (C), 136.8 (C), 136.9 (C), 139.5 (C), 140.6 (C), 174.5 (C), 206.8 (C), 206.8 (C); IR (film): ν=3059, 3020, 2940, 2855, 2795, 1946, 1729, 1598, 1580, 1466, 1443, 1376, 1309, 1260, 1216, 1179, 1151, 1133, 1094, 1029, 954, 878, 798, 761, 711, 677 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>2</sub>: 390.2433, found: 390.2426.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,R<sub>a</sub>)-20r) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,S<sub>a</sub>)-20r):**

*R*<sub>t</sub>=0.32 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.01–1.09 (m, 3H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.09–1.18 (m, 3H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.18–1.30 (m, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.32–1.46 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.63–1.79 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.81–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.01–2.15 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.15–2.31 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.41–2.59 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.62–2.85 (m, 2H, CH(CH<sub>3</sub>)<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.89–3.17 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 4.02–4.14 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.41–5.53 (m, 1H, NCH<sub>2</sub>CHCCH), 5.81–5.88 (m, 1H, NCH<sub>2</sub>CHCCH), 7.03–7.10 (m, 1H, ArH), 7.14 (dd, *J*=7.6/1.5 Hz, 1H, ArH), 7.17–7.27 (m, 2H, ArH), 7.27–7.42 (m, 3H, ArH), 7.48–7.56 (m, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>), 24.7 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 30.5 (CH), 42.5 (CH), 53.6 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.5 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 58.1 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 58.2 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 91.5 (CH), 91.8 (CH), 91.6 (CH), 91.8 (CH), 92.9 (CH), 93.0 (CH), 93.0 (CH), 125.8 (CH), 125.9 (CH), 125.9 (CH), 126.9 (CH), 127.2 (CH), 127.2 (CH), 127.3 (CH), 127.9 (CH), 128.5 (CH), 130.4 (CH), 130.5 (CH), 130.7 (CH), 130.7 (CH), 133.2 (C), 133.3 (C), 139.8 (C), 139.9 (C), 140.4 (C), 140.5 (C), 147.6 (C), 147.7 (C), 174.5 (C), 206.6 (C), 206.7 (C), 206.6 (C), 206.8 (C); IR (film): ν=3059, 3022, 2960, 2868, 2795, 1948, 1731, 1596, 1496, 1479, 1469, 1444, 1384, 1364, 1343, 1310, 1261, 1218, 1181, 1152, 1134, 1095, 1047, 1033, 1005, 880, 794, 756 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>27</sub>H<sub>33</sub>NO<sub>2</sub>: 404.2590, found: 404.2580. Ratio of atropisomers is 49:51.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,R<sub>a</sub>)-20s) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylate} (*rac*-(3R,S<sub>a</sub>)-20s):**

*R*<sub>t</sub>=0.38 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub>, 373K): δ=1.19 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.20 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.35–1.48 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.48–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.64–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.04–2.19 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.28 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.43–2.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.66–2.86 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.91–3.16 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.09 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.43 (q, *J*=6.8 Hz, 1H, NCH<sub>2</sub>CHCCH), 5.88 (dt, *J*=5.4/2.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.09 (dd, *J*=7.6/1.2 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH), 7.16 (d, *J*=8.2 Hz, 1H, ClCCHCClCHCHC), 7.21 (td, *J*=7.6/1.2 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH), 7.26 (dd, *J*=8.2/2.1 Hz, 1H, ClCCHCClCHCHC), 7.30 (td, *J*=7.6/1.2 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCHCHCH), 7.42–7.49 (m, 2H, ClCCHCClCHCHC and ClCCHCClCHCHC and NCH<sub>2</sub>CHCCHCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 373K): δ=14.4 (CH<sub>3</sub>), 24.3 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 41.7 (br, CH), 53.1 (CH<sub>2</sub>), 54.8 (br, CH<sub>2</sub>), 57.4 (CH<sub>2</sub>), 60.5 (CH<sub>2</sub>), 90.3 (br, CH), 93.0 (br, CH), 127.0 (br, CH), 127.2 (CH), 127.7 (CH), 128.6 (CH), 129.6 (CH), 130.4 (CH), 132.7 (CH), 132.7 (C), 134.3 (C), 134.8 (C), 136.8 (C), 138.6 (C), 173.5 (C), 207.2 (br, C); IR (film): ν=3058, 2978, 2940, 2866, 2796, 2362, 1947, 1731, 1599, 1586, 1550, 1496, 1467, 1442, 1373, 1342, 1309, 1275, 1217, 1180, 1152,

1135, 1100, 1068, 1046, 1031, 1004, 865, 823, 804, 758, 701  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{Cl}_2\text{NO}_2$ : 430.1341, found: 430.1340. Ratio of atropisomers is ~ 50:50.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R,R<sub>a</sub>*)-20t) and *rac*-{ethyl (*S<sub>a</sub>*)-1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R,S<sub>a</sub>*)-20t):

$R_f=0.37$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{TC}_2$ , 353K):  $\delta=1.18$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.20 (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.40 (dq,  $J=11.0/4.0$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.46–1.62 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.62–1.74 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.80–1.94 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.07 (td,  $J=10.7/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia2), 2.09 (td,  $J=10.7/3.1$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1), 2.23 (t,  $J=10.8$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2), 2.24 (t,  $J=10.8$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1), 2.42–2.61 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.63–2.81 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.90–3.02 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.02–3.15 (m, 2H,  $\text{NCH}_2\text{CHCCH}$ ), 4.06 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1), 4.08 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia2), 5.45 (q,  $J=6.8$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 5.92–6.02 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 6.80–6.96 (m, 2H,  $\text{FCCHCF}$  and  $\text{FCCHCH}$ ), 7.12–7.26 (m, 3H,  $\text{NCH}_2\text{CHCCHCCCHCHCHCH}$  and  $\text{NCH}_2\text{CHCCHCCCHCHCHCH}$  and  $\text{FCCHCFCHCHC}$ ), 7.26–7.33 (m, 1H,  $\text{NCH}_2\text{CHCCHCCCHCHCHCH}$ ), 7.47 (dd,  $J=7.8/1.0$  Hz, 1H,  $\text{NCH}_2\text{CHCCHCCCHCHCHCH}$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{TC}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ), 24.7 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 41.9 ( $\text{CH}$ ), 53.1 ( $\text{CH}_2$ ), 53.2 ( $\text{CH}_2$ ), 54.9 ( $\text{CH}_2$ ), 57.7 ( $\text{CH}_2$ ), 60.8 ( $\text{CH}_2$ ), 91.3 ( $\text{CH}$ ), 92.7 ( $\text{CH}$ ), 104.4 (t,  $^2J_{\text{CF}}=25.7$  Hz, CH), 111.7 (dd,  $^2/4J_{\text{CF}}=21.1/3.7$  Hz, CH), 124.4 (dd,  $^2/4J_{\text{CF}}=16.8/3.8$  Hz, C), 127.2 ( $\text{CH}$ ), 127.6 ( $\text{CH}$ ), 128.7 ( $\text{CH}$ ), 131.2 ( $\text{CH}$ ), 133.0 (dd,  $^3J_{\text{CF}}=9.4/5.0$  Hz, CH), 133.0 (C), 133.2 (C), 159.8 (dd,  $^1/3J_{\text{CF}}=249.4/12.2$  Hz, C), 162.70 (dd,  $^1/3J_{\text{CF}}=248.6/11.4$  Hz, C), 174.3 (C), 206.9 (C);  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{TC}_2$ , 393 K):  $\delta=-109.8$ ,  $-109.3$  (d,  $^4J_{\text{FF}}=7.5$  Hz); IR (film):  $\tilde{\nu}=3062$ , 2939, 2801, 1948, 1730, 1619, 1592, 1509, 1484, 1467, 1447, 1420, 1367, 1302, 1264, 1220, 1181, 1151, 1139, 1096, 1030, 1009, 963, 850, 819, 759  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{F}_2\text{NO}_2$ : 398.1932, found: 398.1925.

***rac***-[Ethyl (*R<sub>a</sub>*)-1-{4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R,R<sub>a</sub>*)-20u) and *rac*-[ethyl (*S<sub>a</sub>*)-1-{4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R,S<sub>a</sub>*)-20u):

$R_f=0.28$  (PE/EtOAc 7:3);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.20$  (t,  $J=7.1$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia1), 1.22 (td,  $J=7.1/1.6$  Hz, 1.5H,  $\text{OCH}_2\text{CH}_3$ , dia2), 1.41 (qd,  $J=11.2/3.6$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.46–1.60 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.64–1.76 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.82–1.94 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.99–2.12 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.13–2.26 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.42–2.56 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.63–2.80 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.88–3.08 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCCH}$ ), 4.07 (qd,  $J=7.1/0.9$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia1), 4.09 (q,  $J=7.1$  Hz, 1H,  $\text{OCH}_2\text{CH}_3$ , dia2), 5.39 (q,  $J=6.9$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 5.42 (q,  $J=6.9$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 5.73 (dt,  $J=6.2/2.5$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 7.14 (dbr,  $J=7.6$  Hz, 1H,  $\text{NCH}_2\text{CHCCHCCCH}$ ), 7.26 (td,  $J=7.5/1.2$  Hz, 1H,  $\text{NCH}_2\text{CHCCHCCCHCH}$ ), 7.39 (td,  $J=7.7/1.4$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCHCCCHCH}$ , dia2), 7.40 (td,  $J=7.7/1.4$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCHCCCHCH}$ , dia1), 7.45 (dbr,  $J=6.9$  Hz, 0.5H,  $\text{CF}_3\text{CCHCH}$ , dia1 or dia2), 7.47 (dbr,  $J=6.9$  Hz, 0.5H,  $\text{CF}_3\text{CCHCH}$ , dia1 or dia2), 7.49–7.54 (m, 1H,  $\text{NCH}_2\text{CHCCHCCCH}$ ), 7.86 (d,  $J=8.0$  Hz, 1H,  $\text{CF}_3\text{CCHCH}$ ), 8.04 (s, 1H,  $\text{F}_3\text{CCCHCCF}_3$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ), 14.6 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 25.2 ( $\text{CH}_2$ ), 27.3 ( $\text{CH}_2$ ), 27.4 ( $\text{CH}_2$ ), 42.5 ( $\text{CH}$ ), 42.5 ( $\text{CH}$ ), 53.6 ( $\text{CH}_2$ ), 53.7 ( $\text{CH}_2$ ), 53.8 ( $\text{CH}_2$ ), 55.4 ( $\text{CH}_2$ ), 55.5 ( $\text{CH}_2$ ), 55.6 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 60.7 ( $\text{CH}_2$ ), 91.9 ( $\text{CH}$ ), 92.0 ( $\text{CH}$ ), 92.1 ( $\text{CH}$ ), 92.7 ( $\text{CH}$ ), 92.7 ( $\text{CH}$ ), 92.8 ( $\text{CH}$ ), 123.9 (q,  $^1J_{\text{CF}}=274.4$  Hz, C), 123.7–124.1 (m, CH), 124.2 (q,  $^1J_{\text{CF}}=273.0$  Hz, C), 126.6 ( $\text{CH}$ ), 127.6 ( $\text{CH}$ ), 127.7 ( $\text{CH}$ ), 128.6–129.0 (m, CH), 129.3 ( $\text{CH}$ ), 130.2 ( $\text{CH}$ ), 130.5 (C), 130.8 (C), 133.1 (C), 133.2 (C), 133.8 (CH), 133.8 (CH), 134.0 (CH), 134.0 (CH), 136.2 (C), 136.2 (C), 144.4 (C), 174.5 (C), 174.5 (C), 206.8 (C), 206.8 (C), 206.8 (C), 206.8 (C);  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=-59.4$ ,  $-59.4$ ,  $-59.4$ ,  $-59.4$ ,  $-63.1$ ,  $-63.1$ ; IR (film):  $\tilde{\nu}=2940$ , 2802, 1948, 1732, 1625, 1577, 1508, 1467, 1447, 1344, 1277, 1177, 1133, 1083, 1065, 1031, 1006, 911, 847, 759, 671  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{26}\text{H}_{26}\text{F}_6\text{NO}_2$ : 498.1868, found: 498.1857. Ratio of atropisomers is ~ 50:50.

***rac*-{Ethyl (R<sub>a</sub>)-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylate} (*rac*-(3R,R<sub>a</sub>)-20v) and *rac*-{ethyl (S<sub>a</sub>)-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylate} (*rac*-(3R,S<sub>a</sub>)-20v):**

*R*<sub>f</sub>=0.26 (PE/EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.24 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.43 (qd, *J*=11.7/3.8 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.48–1.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.84–1.94 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.08 (td, *J*=10.9/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 2.09 (td, *J*=10.9/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.23 (t, *J*=10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.44–2.60 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.67–2.88 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.98 (ddbr, *J*=11.0/3.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 3.03 (ddbr, *J*=11.1/3.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 3.06–3.17 (m, 2H, NCH<sub>2</sub>CHCCH), 3.74 (s, 3H, OCH<sub>3</sub>), 3.85 (s, 3H, OCH<sub>3</sub>), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 4.10 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 5.49 (q, *J*=6.9 Hz, 1H, NCH<sub>2</sub>CHCCH), 5.98 (dt, *J*=6.5/2.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.53–6.59 (m, 2H, CCCCHCHCOMeCHCOMe and CCCCHCHCOMeCHCOMe), 7.01–7.08 (m, 1H, CCCCHCHCOMeCHCOMe), 7.13–7.18 (m, 1H, CHCCHCHCHCHC), 7.21 (td, *J*=7.4/1.4 Hz, 1H, CHCCHCHCHCHC), 7.27 (td, *J*=7.5/1.7 Hz, 0.5H, CHCCHCHCHCHC, dia2), 7.27 (td, *J*=7.5/1.7 Hz, 0.5H, CHCCHCHCHCHC, dia1), 7.49 (dd, *J*=7.7/1.4 Hz, 1H, CHCCHCHCHCHC); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.6 (CH<sub>3</sub>), 14.6 (CH<sub>3</sub>), 25.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 42.5 (CH), 42.6 (CH), 53.7 (CH<sub>2</sub>), 53.7 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 55.6 (CH<sub>2</sub>), 56.0 (CH<sub>3</sub>), 56.0 (CH<sub>3</sub>), 58.3 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 91.6 (CH), 91.7 (CH), 93.3 (CH), 93.3 (CH), 99.1 (CH), 105.0 (CH), 122.7 (C), 127.0 (CH), 127.2 (CH), 127.8 (CH), 131.5 (CH), 132.3 (CH), 133.8 (C), 137.5 (C), 158.2 (C), 161.3 (C), 174.5 (C), 174.5 (C), 206.6 (C), 206.6 (C); IR (film): ν̄=2939, 2834, 2796, 1947, 1730, 1611, 1581, 1511, 1483, 1465, 1438, 1414, 1366, 1306, 1282, 1242, 1208, 1182, 1158, 1134, 1094, 1033, 1002, 933, 917, 879, 834, 798, 760 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>31</sub>NO<sub>4</sub>: 422.2331, found: 422.2321.

***rac*-[(R<sub>a</sub>)-1-(4-Phenylbuta-2,3-dien-1-yl)](3R)-piperidine-3-carboxylic acid] (*rac*-(3R,R<sub>a</sub>)-21a) and *rac*-[(S<sub>a</sub>)-1-(4-phenylbuta-2,3-dien-1-yl)](3R)-piperidine-3-carboxylic acid] (*rac*-(3R,S<sub>a</sub>)-21a):**

mp: 68 °C; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O, 1M NaOD): δ=1.00–1.20 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.23–1.40 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.41–1.55 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.62 (t, *J*=11.7 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 1.69 (t, *J*=11.7 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 1.78 (dbr, *J*=12.4 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.89 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 1.95 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.13–2.30 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.55–2.73 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.73–2.84 (m, 1H, NCH<sub>2</sub>CHCCH), 2.83–2.93 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.92–3.09 (m, 1H, NCH<sub>2</sub>CHCCH), 5.34–5.45 (m, 1H, NCH<sub>2</sub>CHCCH), 5.89–5.97 (m, 1H, NCH<sub>2</sub>CHCCH), 6.81–6.97 (m, 1H, ArH), 6.97–7.19 (m, 4H, ArH); <sup>13</sup>C NMR (126 MHz, D<sub>2</sub>O, 1M NaOD): δ=24.1 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 44.7 (CH), 51.9 (CH<sub>2</sub>), 52.0 (CH<sub>2</sub>), 55.7 (CH<sub>2</sub>), 55.9 (CH<sub>2</sub>), 56.6 (CH<sub>2</sub>), 56.9 (CH<sub>2</sub>), 90.3 (CH), 90.6 (CH), 94.3 (CH), 94.3 (CH), 126.7 (CH), 126.9 (CH), 127.0 (CH), 128.7 (CH), 128.7 (CH), 134.0 (C), 134.1 (C), 182.8 (C), 182.8 (C), 206.1 (C), 206.1 (C); IR (KBr): ν̄=3433, 3030, 2939, 2861, 2795, 2360, 2343, 1951, 1709, 1596, 1495, 1458, 1388, 1340, 1195, 1153, 1094, 1072, 1028, 957, 914, 875, 776, 725, 692, 631 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>19</sub>NO<sub>2</sub>: 258.1494, found: 258.1489.

***rac*-{[(R<sub>a</sub>)-1-[4-(2-Bromophenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid} (*rac*-(3R,R<sub>a</sub>)-21b) and *rac*-{[(S<sub>a</sub>)-1-[4-(2-bromophenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid} (*rac*-(3R,S<sub>a</sub>)-21b):**

mp: 75 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.37 (qd, *J*=12.7/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.52–1.69 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.82 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.94–2.11 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.17 (t, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 and dia2), 2.35–2.49 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.90–3.03 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.12–3.27 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.71 (q, *J*=6.7 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.63 (dt, *J*=6.3/2.3 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.05–7.12 (m, 1H, BrCCHCHCHCHC or BrCCHCHCHCHC), 7.26–7.33 (m, 1H, BrCCHCHCHCHC), 7.44–7.50 (m, 1H, BrCCHCHCHCHC or BrCCHCHCHCHC), 7.53 (dt, *J*=8.1/1.4 Hz, 1H, BrCCHCHCHCHC); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.5 (CH), 46.5 (CH), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 92.0 (CH), 92.1 (CH), 94.4 (CH), 94.5 (CH), 123.1 (C), 123.2 (C), 128.8 (CH), 128.9 (CH), 129.6 (CH), 129.6 (CH), 129.6 (CH), 129.7 (CH), 134.0 (CH), 134.1 (CH), 134.9 (C), 182.6 (C), 208.3 (C), 208.4 (C); IR (KBr): ν̄=3429, 2936, 2858, 2795, 2518, 2360, 2341, 1951, 1710, 1588, 1560, 1474, 1438, 1395, 1339, 1307, 1276, 1221, 1194, 1153, 1094, 1044, 1022, 955, 874, 765, 742, 669, 623 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>18</sub>BrNO<sub>2</sub>: 336.0599, found: 336.0594.

***rac*-{(*R*<sub>a</sub>)-1-[4-(2-Chlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-21c) and *rac*-{(*S*<sub>a</sub>)-1-[4-(2-chlorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-21c):**

mp: 46-49 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.38 (qd, *J*=12.7/4.2 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.53–1.69 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.81 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.93–2.11 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.16 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.18 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.35–2.47 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.93 (dbr, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.98 (dbr, *J*=11.2 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.10–3.25 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.71 (q, *J*=7.3 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.71 (q, *J*=7.3 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 6.62 (dt, *J*=6.6/2.3 Hz, 1H, NCH<sub>2</sub>CHCCH), 7.17 (td, *J*=7.6/1.8 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.17 (td, *J*=7.6/1.8 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.25 (td, *J*=7.8/1.4 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.26 (td, *J*=7.8/1.4 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.34 (dd, *J*=7.8/1.5 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.35 (dd, *J*=7.8/1.5 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.46 (dd, *J*=7.8/1.7 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2), 7.47 (dd, *J*=7.8/1.7 Hz, 0.5H, CCHCHCHCHCCL, dia1 or dia2); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 91.7 (CH), 91.8 (CH), 91.9 (CH), 92.1 (CH), 128.3 (CH), 128.3 (CH), 129.4 (CH), 129.4 (CH), 129.5 (CH), 129.5 (CH), 130.7 (CH), 130.8 (CH), 132.9 (C), 133.0 (C), 133.1 (C), 182.7 (C), 182.8 (C), 208.3 (C), 208.4 (C); IR (KBr): ν=3424, 3059, 2940, 2861, 2798, 2522, 1952, 1710, 1589, 1568, 1478, 1442, 1395, 1340, 1307, 1277, 1222, 1196, 1153, 1131, 1094, 1049, 1034, 952, 876, 818, 766, 746, 705, 624 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>18</sub>ClNO<sub>2</sub>: 292.1104, found: 292.1099.

***rac*-{(*R*<sub>a</sub>)-1-[4-(2-Fluorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>)-21d) and *rac*-{(*S*<sub>a</sub>)-1-[4-(2-fluorophenyl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>)-21d):**

mp: 36-46 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.31–1.44 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.53–1.68 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.70–1.81 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.93–2.10 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.15 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.19 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.36–2.48 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.94 (dbr, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.00 (dbr, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.12–3.24 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.67 (q, *J*=7.2 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.68 (q, *J*=7.2 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 6.36–6.44 (m, 1H, NCH<sub>2</sub>CHCCH), 7.01–7.08 (m, 1H, FCCCHCHCHCH), 7.09–7.15 (m, 1H, FCCCHCHCHCH), 7.17–7.24 (m, 1H, FCCCHCHCHCH), 7.35–7.43 (m, 1H, FCCCHCHCHCH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.5 (CH), 46.5 (CH), 54.3 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 87.8 (d, <sup>3</sup>*J*<sub>CF</sub>=6.7 Hz, CH), 87.9 (d, <sup>3</sup>*J*<sub>CF</sub>=6.7 Hz, CH), 91.6 (CH), 91.7 (CH), 116.5 (d, <sup>2</sup>*J*<sub>CF</sub>=21.8 Hz, CH), 116.5 (d, <sup>2</sup>*J*<sub>CF</sub>=21.8 Hz, CH), 122.9 (d, <sup>1</sup>*J*<sub>CF</sub>=12.1 Hz, C), 122.9 (d, <sup>2</sup>*J*<sub>CF</sub>=12.1 Hz, C), 125.5 (d, <sup>4</sup>*J*<sub>CF</sub>=4.0 Hz, CH), 125.5 (d, <sup>4</sup>*J*<sub>CF</sub>=4.0 Hz, CH), 129.4 (d, <sup>3</sup>*J*<sub>CF</sub>=3.2 Hz, CH), 129.5 (d, <sup>3</sup>*J*<sub>CF</sub>=3.2 Hz, CH), 129.7 (d, <sup>3</sup>*J*<sub>CF</sub>=3.6 Hz, CH), 129.7 (d, <sup>3</sup>*J*<sub>CF</sub>=3.6 Hz, CH), 161.0 (d, <sup>1</sup>*J*<sub>CF</sub>=248.0 Hz, C), 161.0 (d, <sup>1</sup>*J*<sub>CF</sub>=248.0 Hz, C), 182.7 (C), 182.7 (C), 208.1 (d, <sup>4</sup>*J*<sub>CF</sub>=1.9 Hz, C), 208.3 (d, <sup>4</sup>*J*<sub>CF</sub>=1.9 Hz, C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, MeOD): δ=-121.6, -121.4; IR (KBr): ν=3419, 2940, 1954, 1582, 1493, 1456, 1400, 1341, 1272, 1233, 1177, 1152, 1090, 1033, 955, 880, 833, 753, 696, 669, 622, 530 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>18</sub>FNO<sub>2</sub>: 276.1400, found: 276.1393.

***rac*-[(*R*<sub>a</sub>)-1-{4-[2-(Trifluoromethyl)phenyl]buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*R*<sub>a</sub>)-21e) and *rac*-[(*S*<sub>a</sub>)-1-{4-[2-(trifluoromethyl)phenyl]buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*S*<sub>a</sub>)-21e):**

mp: 49 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.38 (qd, *J*=12.7/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.69 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.82 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.90–2.12 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.17 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.18 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.34–2.49 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.89–3.01 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.07–3.27 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.75 (q, *J*=7.0 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.47–6.57 (m, 1H, NCH<sub>2</sub>CHCCH), 7.35 (t, *J*=7.6 Hz, 1H, F<sub>3</sub>CCCCHCHCHCH), 7.52–7.60 (m, 1H, F<sub>3</sub>CCCCHCHCHCH), 7.62–7.70 (m, 2H, F<sub>3</sub>CCCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.5 (CH), 46.5 (CH), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.4 (CH<sub>2</sub>), 58.5 (CH<sub>2</sub>), 91.4–91.7 (m, CH), 92.1 (CH), 92.2 (CH), 125.8 (q, <sup>1</sup>*J*<sub>CF</sub>=273.6 Hz, C), 126.9 (q, <sup>3</sup>*J*<sub>CF</sub>=5.9 Hz, CH), 126.9 (q, <sup>3</sup>*J*<sub>CF</sub>=5.8 Hz, CH), 127.6 (q, <sup>2</sup>*J*<sub>CF</sub>=29.9 Hz, C), 127.6 (q,

$^2J_{CF}=30.1$  Hz, C), 128.2 (CH), 128.2 (CH), 130.0 (CH), 130.0 (CH), 133.3 (CH), 133.4 (CH), 134.0 (C), 182.7 (C), 208.5 (C), 208.6 (C);  $^{19}\text{F}$  { $^1\text{H}$ } NMR (376 MHz, MeOD, NaOD):  $\delta=-60.9$ ,  $-60.9$ ; IR (KBr):  $\tilde{\nu}=3427$ , 3044, 2946, 2865, 2805, 1955, 1712, 1580, 1495, 1454, 1395, 1316, 1264, 1207, 1160, 1119, 1058, 1035, 956, 872, 765, 720, 662, 635, 596  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}_2$ : 326.1368, found: 326.1360.

***rac*-{(R<sub>a</sub>)-1-[4-(2-Methoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,R<sub>a</sub>)-21f}) and ***rac*-{(S<sub>a</sub>)-1-[4-(2-methoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,S<sub>a</sub>)-21f}):

mp: 50 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.30$ – $1.44$  (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),  $1.52$ – $1.69$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.69$ – $1.81$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.93$ – $2.10$  (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ),  $2.14$  (t,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2),  $2.17$  (t,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2),  $2.36$ – $2.49$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ),  $2.94$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $3.01$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $3.16$  (td,  $J=7.6/2.4$  Hz, 2H,  $\text{NCH}_2\text{CHCCH}$ ),  $3.18$ – $3.27$  (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ),  $3.83$  (s, 3H,  $\text{OCH}_3$ ),  $5.57$  (q,  $J=6.9$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ),  $6.51$ – $6.57$  (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ),  $6.88$  (td,  $J=7.7/2.6$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $6.88$  (td,  $J=7.7/2.6$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $6.93$  (dd,  $J=8.3/1.4$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $6.93$  (dd,  $J=8.3/1.4$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $7.16$  (td,  $J=5.7/1.7$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $7.17$  (td,  $J=5.7/1.7$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $7.30$  (dd,  $J=5.7/1.7$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2),  $7.31$  (dd,  $J=5.7/1.7$  Hz, 0.5H,  $\text{CCHCHCHCHCOMe}$ , dia1 or dia2);  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ),  $26.0$  ( $\text{CH}_2$ ),  $29.4$  ( $\text{CH}_2$ ),  $46.5$  (CH),  $46.5$  (CH),  $54.4$  ( $\text{CH}_2$ ),  $54.5$  ( $\text{CH}_2$ ),  $56.1$  ( $\text{CH}_3$ ),  $57.8$  ( $\text{CH}_2$ ),  $57.9$  ( $\text{CH}_2$ ),  $59.1$  ( $\text{CH}_2$ ),  $59.2$  ( $\text{CH}_2$ ),  $89.6$  (CH),  $89.6$  (CH),  $90.6$  (CH),  $90.8$  (CH),  $112.1$  (CH),  $112.1$  (CH),  $121.8$  (CH),  $121.8$  (CH),  $123.6$  (C),  $128.7$  (CH),  $128.8$  (CH),  $129.3$  (CH),  $129.3$  (CH),  $157.5$  (C),  $182.7$  (C),  $182.7$  (C),  $208.0$  (C),  $208.1$  (C); IR (KBr):  $\tilde{\nu}=3424$ , 2941, 1952, 1582, 1494, 1466, 1394, 1289, 1247, 1161, 1119, 1099, 1048, 1025, 954, 883, 822, 755, 632  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_3$ : 288.1600, found: 288.1593.

***rac*-{(R<sub>a</sub>)-1-[4-(3-Methoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,R<sub>a</sub>)-21g}) and ***rac*-{(S<sub>a</sub>)-1-[4-(3-methoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,S<sub>a</sub>)-21g}):

mp: 47 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.31$  (qt,  $J=12.7/3.9$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),  $1.46$ – $1.62$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.62$ – $1.73$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.87$ – $2.04$  (m, 2H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),  $2.08$  (t,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2),  $2.13$  (t,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2),  $2.27$ – $2.43$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ),  $2.87$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $2.97$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $3.02$ – $3.20$  (m, 3H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ),  $3.70$  (s, 1.5H,  $\text{OCH}_3$ , dia1 or dia2),  $3.70$  (s, 1.5H,  $\text{OCH}_3$ , dia1 or dia2),  $5.56$  (q,  $J=7.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2),  $5.57$  (q,  $J=7.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2),  $6.12$ – $6.18$  (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ),  $6.68$  (dt,  $J=8.0/2.7$  Hz, 1H,  $\text{CCHCHCHCOMe}$ ),  $6.73$ – $6.84$  (m, 2H,  $\text{CCHCOMe}$  and  $\text{CCHCHCHCOMe}$ ),  $7.12$  (t,  $J=8.0$  Hz, 1H,  $\text{CCHCHCHCOMe}$ );  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ),  $26.1$  ( $\text{CH}_2$ ),  $29.4$  ( $\text{CH}_2$ ),  $46.5$  (CH),  $46.6$  (CH),  $54.4$  ( $\text{CH}_2$ ),  $54.5$  ( $\text{CH}_2$ ),  $55.6$  ( $\text{CH}_3$ ),  $55.7$  ( $\text{CH}_3$ ),  $57.7$  ( $\text{CH}_2$ ),  $58.0$  ( $\text{CH}_2$ ),  $58.8$  ( $\text{CH}_2$ ),  $59.0$  ( $\text{CH}_2$ ),  $91.5$  (CH),  $91.7$  (CH),  $95.6$  (CH),  $112.6$  (CH),  $112.8$  (CH),  $114.0$  (CH),  $114.1$  (CH),  $120.4$  (CH),  $130.6$  (CH),  $137.0$  (C),  $137.0$  (C),  $161.4$  (C),  $182.6$  (C),  $182.6$  (C),  $207.5$  (C),  $207.7$  (C); IR (KBr):  $\tilde{\nu}=3426$ , 2927, 2855, 1952, 1710, 1597, 1490, 1467, 1385, 1260, 1155, 1044, 880, 784, 754, 687  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_3$ : 288.1600, found: 288.1593.

***rac*-{(R<sub>a</sub>)-1-[4-(2,5-Dimethoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,R<sub>a</sub>)-21h}) and ***rac*-{(S<sub>a</sub>)-1-[4-(2,5-dimethoxyphenyl)buta-2,3-dien-1-yl]}(3R)-piperidine-3-carboxylic acid** (*rac*-{(3R,S<sub>a</sub>)-21h}):

mp: 74 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.38$  (qt,  $J=12.7/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),  $1.52$ – $1.69$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.69$ – $1.83$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ),  $1.91$ – $2.13$  (m, 2H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ),  $2.14$  (t,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1),  $2.20$  (t,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia2),  $2.32$ – $2.50$  (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ),  $2.93$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $3.05$  (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2),  $3.08$ – $3.26$  (m, 3H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ),  $3.72$  (s, 1.5H,  $\text{OCH}_3$ , dia1 or dia2),  $3.72$  (s, 1.5H,  $\text{OCH}_3$ , dia1 or dia2),  $3.78$  (s, 3H,  $\text{OCH}_3$ ),  $5.60$  (q,  $J=7.1$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2),



5.61 (q,  $J=7.1$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 6.48–6.58 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 6.73 (dd,  $J=9.0/3.2$  Hz, 0.5H,  $\text{CCOMeCHCHCOMeCH}$ , dia1 or dia2), 6.74 (dd,  $J=9.0/3.2$  Hz, 0.5H,  $\text{CCOMeCHCHCOMeCH}$ , dia1 or dia2), 6.83–6.93 (m, 2H,  $\text{CCOMeCHCHCOMeCH}$ );  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 46.5 (CH), 46.6 (CH), 54.3 ( $\text{CH}_2$ ), 54.5 ( $\text{CH}_2$ ), 56.1 ( $\text{CH}_3$ ), 56.2 ( $\text{CH}_3$ ), 56.8 ( $\text{CH}_3$ ), 56.9 ( $\text{CH}_3$ ), 57.6 ( $\text{CH}_2$ ), 58.0 ( $\text{CH}_2$ ), 58.9 ( $\text{CH}_2$ ), 59.2 ( $\text{CH}_2$ ), 89.7 (CH), 89.7 (CH), 90.9 (CH), 91.3 (CH), 113.4 (CH), 113.5 (CH), 113.7 (CH), 114.7 (CH), 114.9 (CH), 124.5 (C), 124.5 (C), 152.0 (C), 152.0 (C), 155.2 (C), 155.2 (C), 182.6 (C), 182.6 (C), 207.8 (C), 208.0 (C); IR (KBr):  $\tilde{\nu}=3426, 2995, 2939, 2858, 2833, 2488, 1950, 1712, 1605, 1585, 1501, 1465, 1412, 1340, 1280, 1245, 1214, 1179, 1159, 1129, 1095, 1045, 1023, 953, 882, 803, 713, 699$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_4$ : 318.1705, found: 318.1698.

***rac*-{(R<sub>a</sub>)-1-[4-(3,5-Dimethoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,R<sub>a</sub>)-21i) and *rac*-{(S<sub>a</sub>)-1-[4-(3,5-dimethoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,S<sub>a</sub>)-21i):**

mp: 39 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.38$  (qt,  $J=12.7/4.3$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.61 (qq,  $J=12.7/4.1$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.69–1.81 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.93–2.26 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.36–2.49 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.93 (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1), 3.05 (dbr,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia2), 3.08–3.26 (m, 3H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.75 (s, 6H,  $\text{OCH}_3$ ), 5.59–5.68 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 6.14–6.21 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 6.31 (t,  $J=2.3$  Hz, 0.5H,  $\text{CCHCOMeCHCOMeCH}$ , dia1 or dia2), 6.32 (t,  $J=2.3$  Hz, 0.5H,  $\text{CCHCOMeCHCOMeCH}$ , dia1 or dia2), 6.41–6.50 (m, 2H,  $\text{CCHCOMeCHCOMeCH}$ );  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 46.5 (CH), 46.6 (CH), 54.4 ( $\text{CH}_2$ ), 54.5 ( $\text{CH}_2$ ), 55.8 ( $\text{CH}_3$ ), 55.9 ( $\text{CH}_3$ ), 57.6 ( $\text{CH}_2$ ), 58.0 ( $\text{CH}_2$ ), 58.8 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}_2$ ), 91.6 (CH), 91.8 (CH), 95.8 (CH), 100.5 (CH), 100.6 (CH), 105.7 (CH), 105.7 (CH), 137.6 (C), 162.5 (C), 182.6 (C), 182.6 (C), 207.6 (C), 207.8 (C); IR (KBr):  $\tilde{\nu}=3418, 2996, 2939, 2837, 2492, 1951, 1712, 1603, 1593, 1470, 1433, 1401, 1340, 1314, 1296, 1204, 1154, 1094, 1064, 991, 945, 927, 877, 833, 679$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_4$ : 318.1705, found: 318.1698.

***rac*-{(R<sub>a</sub>)-1-[4-(2,6-Dichlorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,R<sub>a</sub>)-21j) and *rac*-{(S<sub>a</sub>)-1-[4-(2,6-dichlorophenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,S<sub>a</sub>)-21j):**

mp: 62 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.36$  (qd,  $J=12.9/2.6$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.37 (qd,  $J=12.9/2.6$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.59 (qt,  $J=12.9/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.67–1.81 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.93–2.09 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.13 (t,  $J=11.2$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.19 (t,  $J=11.2$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.33–2.49 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.87–3.00 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.10–3.28 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCCH}$ ), 5.54 (q,  $J=7.0$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 5.56 (q,  $J=7.0$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 6.44–6.52 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 7.18 (t,  $J=8.1$  Hz, 0.5H,  $\text{CICCHCHCH}$ , dia1 or dia2), 7.18 (t,  $J=8.1$  Hz, 0.5H,  $\text{CICCHCHCH}$ , dia1 or dia2), 7.37 (d,  $J=8.1$  Hz, 1H,  $\text{CICCHCHCH}$ , dia1 or dia2), 7.37 (d,  $J=8.1$  Hz, 1H,  $\text{CICCHCHCH}$ , dia1 or dia2);  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 46.5 (CH), 46.5 (CH), 54.3 ( $\text{CH}_2$ ), 54.7 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 58.0 ( $\text{CH}_2$ ), 58.4 ( $\text{CH}_2$ ), 58.6 ( $\text{CH}_2$ ), 89.2 (CH), 89.3 (CH), 90.6 (CH), 90.8 (CH), 129.6 (CH), 129.7 (CH), 129.9 (CH), 131.5 (C), 135.5 (C), 182.7 (C), 209.3 (C), 209.4 (C); IR (KBr):  $\tilde{\nu}=3441, 2939, 2862, 2795, 2524, 1955, 1711, 1578, 1557, 1468, 1451, 1435, 1396, 1339, 1308, 1215, 1184, 1152, 1089, 1043, 959, 872, 832, 773, 688, 668, 650$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{16}\text{H}_{17}\text{Cl}_2\text{NO}_2$ : 326.0715, found: 326.0709.

***rac*-{(R<sub>a</sub>)-1-[4-(2-Chloro-5-methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,R<sub>a</sub>)-21k) and *rac*-{(S<sub>a</sub>)-1-[4-(2-chloro-5-methoxyphenyl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-{(3R,S<sub>a</sub>)-21k):**

mp: 41 °C;  $^1\text{H}$  NMR (500 MHz, MeOD, NaOD):  $\delta=1.37$  (qd,  $J=12.8/4.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.38 (qd,  $J=12.8/4.2$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.53–1.69 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.69–1.81 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.93–2.07 (m, 1.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.10 (td,  $J=11.8/2.9$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.16 (t,  $J=12.7$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.21 (t,  $J=12.7$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.35–2.48 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.93 (dbr,  $J=11.2$  Hz, 0.5H,

NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.02 (dbr, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.10–3.28 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 3.76 (s, 1.5H, OCH<sub>3</sub>, dia1 or dia2), 3.77 (s, 1.5H, OCH<sub>3</sub>, dia1 or dia2), 5.72 (q, *J*=7.2 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.73 (q, *J*=7.2 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 6.58 (dt, *J*=6.4/2.3 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.76 (dd, *J*=8.8/3.0 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2), 6.77 (dd, *J*=8.8/3.0 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2), 6.96 (d, *J*=3.0 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2), 6.97 (d, *J*=3.0 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2), 7.23 (d, *J*=8.8 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2), 7.24 (d, *J*=8.8 Hz, 0.5H, CICCHCHCOMeCH, dia1 or dia2); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.5 (CH), 46.6 (CH), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 56.1 (CH<sub>3</sub>), 56.2 (CH<sub>3</sub>), 57.6 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 92.0 (CH), 92.0 (CH), 92.1 (CH), 92.3 (CH), 113.3 (CH), 113.5 (CH), 116.1 (CH), 116.3 (CH), 124.5 (C), 124.6 (C), 131.4 (CH), 131.5 (CH), 133.8 (C), 133.9 (C), 160.0 (C), 160.0 (C), 182.6 (C), 182.6 (C), 208.1 (C), 208.3 (C); IR (KBr): ν̄=3424, 2937, 2859, 1952, 1718, 1686, 1594, 1571, 1560, 1484, 1405, 1341, 1284, 1230, 1166, 1063, 1024, 876, 805, 745, 669, 653, 600 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>17</sub>H<sub>20</sub>ClNO<sub>3</sub>: 322.1210, found: 322.1204.

***rac*-{(*R*<sub>a</sub>)-1-[4-(Naphthalen-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>-211)) and *rac*-{(*S*<sub>a</sub>)-1-[4-(naphthalen-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>-211)):**

mp: 43 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.39 (qt, *J*=12.8/4.0 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.63 (pt, *J*=13.1/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.71–1.83 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.97–2.14 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.18 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.22 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.38–2.51 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.98 (dbr, *J*=11.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.05 (dbr, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 3.19–3.28 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.72 (q, *J*=7.1 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.40–6.49 (m, 1H, NCH<sub>2</sub>CHCCH), 7.35–7.54 (m, 3H, ArH), 7.69 (s, 1H, ArH), 7.74–7.85 (m, 3H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 46.5 (CH), 46.6 (CH), 54.4 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 58.9 (CH<sub>2</sub>), 59.0 (CH<sub>2</sub>), 91.8 (CH), 91.9 (CH), 95.9 (CH), 95.9 (CH), 125.6 (CH), 125.7 (CH), 126.7 (CH), 126.7 (CH), 126.8 (CH), 126.8 (CH), 127.3 (CH), 127.3 (CH), 128.7 (CH), 128.7 (CH), 128.7 (CH), 128.8 (CH), 129.3 (CH), 129.3 (CH), 133.1 (C), 134.2 (C), 135.2 (C), 182.7 (C), 182.7 (C), 208.1 (C), 208.2 (C); IR (KBr): ν̄=3443, 3053, 2939, 2860, 2803, 2542, 1949, 1710, 1597, 1508, 1467, 1449, 1394, 1335, 1275, 1214, 1198, 1153, 1128, 1094, 1043, 1016, 950, 895, 859, 819, 755, 739, 476 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>2</sub>: 308.1651, found: 308.1644.

***rac*-{(*R*<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>-21m)) and *rac*-{(*S*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>-21m)):**

mp: 76 °C; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, 1M NaOD, 333 K): δ=1.43 (qd, *J*=12.6/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.53–1.72 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.72–1.85 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.93–2.04 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.04–2.15 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.20–2.33 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.45–2.58 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.90 (d, *J*=11.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1), 2.98 (d, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia2), 3.02–3.12 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.12–3.30 (m, 2H, NCH<sub>2</sub>CHCCH), 5.49–5.70 (m, 1H, NCH<sub>2</sub>CHCCH), 6.12–6.32 (m, 1H, NCH<sub>2</sub>CHCCH), 7.10–7.48 (m, 8H, ArH), 7.51–7.64 (m, 1H, ArH); <sup>13</sup>C NMR (101 MHz, D<sub>2</sub>O, 1M NaOD, 333 K): δ=25.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 45.9 (CH), 53.1 (CH<sub>2</sub>), 53.2 (CH<sub>2</sub>), 57.1 (CH<sub>2</sub>), 57.2 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 90.9 (CH), 90.9 (CH), 93.3 (CH), 93.4 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 130.2 (CH), 130.9 (CH), 132.2 (C), 132.3 (C), 141.1 (C), 141.5 (C), 183.2 (C), 207.5 (C); IR (KBr): ν̄=3422, 3056, 3025, 2937, 2860, 2795, 2537, 2360, 2342, 1949, 1712, 1595, 1480, 1450, 1435, 1396, 1340, 1308, 1222, 1190, 1154, 1096, 1073, 1048, 1008, 882, 771, 747, 702, 668, 632, 616 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>23</sub>NO<sub>2</sub>: 334.1807, found: 334.1802.

***rac*-{(*R*<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-3-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*R*<sub>a</sub>-21n)) and *rac*-{(*S*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-3-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid} (*rac*-(3*R*,*S*<sub>a</sub>-21n)):**

mp: 73 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.38 (qt, *J*=12.7/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.54–1.69 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.70–1.80 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.93–2.06 (m, 1.5H,

$\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.11 (td,  $J=11.6/2.9$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 2.16 (t,  $J=11.4$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.25 (t,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.37–2.48 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.94 (dbr,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 3.07 (dbr,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 3.11–3.29 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCCH}$ ), 5.67 (q,  $J=7.4$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 5.69 (q,  $J=7.4$  Hz, 0.5H,  $\text{NCH}_2\text{CHCCH}$ , dia1 or dia2), 6.33 (dt,  $J=6.4/2.3$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 7.25–7.30 (m, 1H, ArH), 7.31–7.35 (m, 1H, ArH), 7.38 (tt,  $J=7.7/0.6$  Hz, 1H, ArH), 7.40–7.46 (m, 3H, ArH), 7.50–7.53 (m, 1H, ArH), 7.54–7.60 (m, 2H, ArH);  $^{13}\text{C}$  NMR (126 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 46.5 (CH), 54.2 ( $\text{CH}_2$ ), 54.6 ( $\text{CH}_2$ ), 57.7 ( $\text{CH}_2$ ), 58.1 ( $\text{CH}_2$ ), 58.8 ( $\text{CH}_2$ ), 59.1 ( $\text{CH}_2$ ), 91.4 (CH), 92.0 (CH), 95.6 (CH), 95.6 (CH), 126.4 (CH), 126.4 (CH), 126.7 (CH), 126.8 (CH), 126.8 (CH), 126.8 (CH), 128.0 (CH), 128.0 (CH), 128.5 (CH), 128.5 (CH), 129.9 (CH), 129.9 (CH), 130.3 (CH), 136.1 (C), 142.2 (C), 142.2 (C), 142.9 (C), 182.7 (C), 182.8 (C), 207.7 (C), 207.9 (C); IR (KBr):  $\tilde{\nu}=3420, 3057, 3031, 2938, 2862, 2802, 2530, 1952, 1708, 1596, 1479, 1454, 1439, 1395, 1340, 1310, 1246, 1152, 1092, 1075, 1048, 1022, 955, 895, 875, 804, 763, 698, 669, 645, 615, 597$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{22}\text{H}_{23}\text{NO}_2$ : 334.1807, found: 334.1800.

***rac*-{(*R*<sub>a</sub>)-1-[4-([1,1'-Biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-{3*R*,*R*<sub>a</sub>}-21o) and *rac*-{(*S*<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-{3*R*,*S*<sub>a</sub>}-21o):**

mp: 65 °C;  $^1\text{H}$  NMR (500 MHz, MeOD, NaOD):  $\delta=1.38$  (qd,  $J=12.9/2.3$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.39 (qd,  $J=12.9/2.3$  Hz, 0.5H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ , dia1 or dia2), 1.54–1.70 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.70–1.82 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.96–2.12 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.18 (t,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.19 (t,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.43 (dt,  $J=15.4/7.7/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.96 (dbr,  $J=11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 3.02 (dbr,  $J=11.5$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 3.13–3.23 (m, 2.5H,  $\text{NCH}_2\text{CHCCH}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 3.23–3.29 (m, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 5.67 (q,  $J=7.2$  Hz, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 6.24–6.34 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 7.28–7.34 (m, 1H, ArH), 7.34–7.39 (m, 2H, ArH), 7.39–7.45 (m, 2H, ArH), 7.53–7.64 (m, 4H, ArH);  $^{13}\text{C}$  NMR (126 MHz, MeOD, NaOD):  $\delta=26.0$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 46.5 (CH), 46.5 (CH), 54.5 ( $\text{CH}_2$ ), 54.5 ( $\text{CH}_2$ ), 57.8 ( $\text{CH}_2$ ), 57.9 ( $\text{CH}_2$ ), 58.9 ( $\text{CH}_2$ ), 59.0 ( $\text{CH}_2$ ), 91.6 (CH), 91.7 (CH), 95.3 (CH), 127.8 (CH), 128.2 (CH), 128.3–128.4 (CH), 129.9 (CH), 134.6 (C), 134.6 (C), 141.1 (C), 141.1 (C), 142.0 (C), 182.7 (C), 182.7 (C), 207.8 (C), 207.8 (C); IR (KBr):  $\tilde{\nu}=3406, 3056, 3029, 2939, 2863, 2800, 2538, 1950, 1701, 1578, 1486, 1467, 1450, 1395, 1341, 1275, 1152, 1092, 1075, 1040, 1006, 955, 876, 843, 770, 747, 723, 696, 625, 551, 502$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{22}\text{H}_{23}\text{NO}_2$ : 334.1807, found: 334.1800.

***rac*-{(*R*<sub>a</sub>)-1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-{3*R*,*R*<sub>a</sub>}-21p) and *rac*-{(*S*<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]}(3*R*)-piperidine-3-carboxylic acid} (*rac*-{3*R*,*S*<sub>a</sub>}-21p):**

mp: 95 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta=1.30$ –1.42 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.47–1.64 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.65–1.76 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.82–2.02 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.02–2.18 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.32–2.43 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.73–2.98 (m, 2H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$  and  $\text{NCH}_2\text{CHCCH}$ ), 2.98–3.16 (m, 2H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCCH}$ ), 5.32–5.43 (m, 1H,  $\text{NCH}_2\text{CHCCH}$ ), 5.81–5.88 (m, 0.55H,  $\text{NCH}_2\text{CHCCH}$ , atr-iso1), 5.90–5.96 (m, 0.45H,  $\text{NCH}_2\text{CHCCH}$ , atr-iso2), 6.98–7.23 (m, 8H, ArH), 7.23–7.35 (m, 2H, ArH), 7.38–7.51 (m, 3H, ArH);  $^{13}\text{C}$  NMR (101 MHz, MeOD, NaOD):  $\delta=25.9$  ( $\text{CH}_2$ ), 26.0 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 46.4 (CH), 46.5 (CH), 53.8 ( $\text{CH}_2$ ), 53.9 ( $\text{CH}_2$ ), 54.4 ( $\text{CH}_2$ ), 54.6 ( $\text{CH}_2$ ), 57.8 ( $\text{CH}_2$ ), 57.8 ( $\text{CH}_2$ ), 58.7 ( $\text{CH}_2$ ), 58.8 ( $\text{CH}_2$ ), 90.4 (CH), 90.8 (CH), 91.1 (CH), 93.5 (CH), 93.6 (CH), 93.8 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.0 (CH), 130.6 (CH), 130.7 (CH), 131.1 (CH), 131.1 (CH), 132.1 (CH), 132.2 (CH), 133.4 (CH), 133.5 (CH), 140.6 (C), 141.3 (C), 142.6 (C), 142.7 (C), 182.7 (C), 207.9 (C), 208.0 (C); IR (KBr):  $\tilde{\nu}=3438, 3055, 3020, 2936, 2856, 2795, 2360, 1948, 1711, 1594, 1490, 1472, 1449, 1432, 1399, 1339, 1307, 1221, 1191, 1155, 1094, 1074, 1044, 1008, 948, 913, 878, 769, 749, 699, 632, 615, 565$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{28}\text{H}_{27}\text{NO}_2$ : 410.2120, found: 410.2115. Ratio of atropisomers is 45:55.

**(R<sub>a</sub>)-1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid ((3R,R<sub>a</sub>)-21p) and (S<sub>a</sub>)-1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid ((3R,S<sub>a</sub>)-21p):**

mp: 96 °C; [ $\alpha$ ]<sub>D</sub><sup>22</sup>=+8.57 ° (c=0.573 g/100 mL in chloroform); <sup>1</sup>H NMR (400 MHz, MeOD, NaOD):  $\delta$ =1.25–1.43 (m, 1H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>), 1.45–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.64–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.79–2.02 (m, 2H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub> and NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.02–2.19 (m, 1H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>), 2.29–2.47 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub></sub>CH<sub>2</sub>), 2.69–3.19 (m, 4H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCCH and NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>), 5.31–5.44 (m, 1H, NCH<sub>2</sub>CHCCH), 5.79–5.89 (m, 0.56H, NCH<sub>2</sub>CHCCH, atr-iso1), 5.89–5.96 (m, 0.44H, NCH<sub>2</sub>CHCCH, atr-iso2), 6.95–7.22 (m, 8H, ArH), 7.22–7.34 (m, 2H, ArH), 7.34–7.51 (m, 3H, ArH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD):  $\delta$ =25.9 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 46.5 (CH), 46.5 (CH), 53.9 (CH<sub>2</sub>), 54.2 (CH<sub>2</sub>), 54.4 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 57.6 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.5 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 58.9 (CH<sub>2</sub>), 90.4 (CH), 90.8 (CH), 90.8 (CH), 91.1 (CH), 93.5 (CH), 93.6 (CH), 93.7 (CH), 93.8 (CH), 127.5 (CH), 127.5 (CH), 127.5 (CH), 127.6 (CH), 128.0 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 130.6 (CH), 130.7 (CH), 131.1 (CH), 131.1 (CH), 132.0 (CH), 132.1 (CH), 132.1 (CH), 132.2 (CH), 133.4 (C), 133.5 (C), 140.6 (C), 141.2 (C), 141.3 (C), 142.6 (C), 142.7 (C), 142.8 (C), 142.9 (C), 142.9 (C), 182.7 (C), 207.8 (C), 207.9 (C), 207.9 (C), 208.0 (C); IR (KBr):  $\tilde{\nu}$ =3423, 3057, 2927, 2852, 2614, 2539, 1950, 1584, 1490, 1472, 1449, 1431, 1396, 1153, 1093, 1073, 1008, 950, 914, 879, 796, 767, 750, 700, 632, 614, 564, 541, 515, 469 cm<sup>-1</sup>; HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>27</sub>NO<sub>2</sub>: 410.2120, found: 410.2111. Ratio of atropisomers 44:56. HPLC analytics: Chiralpak ZWIX(+) Daicel, 150x3 mm, 3  $\mu$ m, 0.2 mL/min, 18EtOH/80dioxane/2H<sub>2</sub>O with 50 mM formic acid and 25 mM DEA, ratio of enantiomers: 81% (3R,R<sub>a</sub>)-21p/(3R,S<sub>a</sub>)-21p and 19% (3S,R<sub>a</sub>)-21p/(3S,S<sub>a</sub>)-21p.

**rac-((R<sub>a</sub>)-1-[4-(2',6'-Dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid) (rac-(3R,R<sub>a</sub>)-21q) and rac-((S<sub>a</sub>)-1-[4-(2',6'-dimethyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid) (rac-(3R,S<sub>a</sub>)-21q):**

mp: 64 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD):  $\delta$ =1.34 (qd, *J*=12.8/3.9 Hz, 0.5H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>, dia1 or dia2), 1.35 (qd, *J*=12.8/3.9 Hz, 0.5H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>, dia1 or dia2), 1.48–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.65–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.92 (s, 3H, CH<sub>3</sub>), 1.93 (s, 3H, CH<sub>3</sub>), 1.93–2.02 (m, 2H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub> and NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.05 (t, *J*=11.4 Hz, 0.5H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>, dia1 or dia2), 2.14 (t, *J*=11.3 Hz, 0.5H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>, dia1 or dia2), 2.31–2.45 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub></sub>CH<sub>2</sub>), 2.87 (dbr, *J*=11.1 Hz, 0.5H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.92 (dbr, *J*=11.1 Hz, 0.5H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.94–3.10 (m, 2H, NCH<sub>2</sub>CHCCH), 3.10–3.20 (m, 1H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>), 5.43 (q, *J*=7.0 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.44 (q, *J*=7.0 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.71–5.80 (m, 1H, NCH<sub>2</sub>CHCCH), 6.98 (dd, *J*=7.5/1.6 Hz, 0.5H, NCH<sub>2</sub>CHCCHCHCHCHCH, dia1 or dia2), 6.99 (dd, *J*=7.5/1.6 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.05–7.12 (m, 2H, ArH), 7.12–7.18 (m, 1H, ArH), 7.27 (td, *J*=7.4/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.28 (td, *J*=7.4/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.32 (td, *J*=7.6/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.33 (td, *J*=7.6/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.50 (dd, *J*=7.8/1.4 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2), 7.52 (dd, *J*=7.8/1.4 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCHCH, dia1 or dia2); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD):  $\delta$ =20.7 (CH<sub>3</sub>), 20.7 (CH<sub>3</sub>), 26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 54.2 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.9 (CH<sub>2</sub>), 59.1 (CH<sub>2</sub>), 90.8 (CH), 90.9 (CH), 92.9 (CH), 92.9 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.6 (CH), 130.6 (CH), 130.7 (CH), 133.2 (C), 133.2 (C), 137.2 (C), 137.2 (C), 137.3 (C), 140.4 (C), 140.4 (C), 141.3 (C), 141.3 (C), 182.7 (C), 207.8 (C), 207.9 (C); IR (KBr):  $\tilde{\nu}$ =3434, 3059, 3018, 2941, 2858, 2796, 2533, 1948, 1712, 1579, 1466, 1444, 1377, 1340, 1308, 1220, 1192, 1154, 1133, 1094, 1044, 1003, 951, 918, 879, 761, 677, 630 cm<sup>-1</sup>; HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>: 362.2120, found: 362.2113.

**rac-((R<sub>a</sub>)-1-[4-(2'-Isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid) (rac-(3R,R<sub>a</sub>)-21r) and rac-((S<sub>a</sub>)-1-[4-(2'-isopropyl-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid) (rac-(3R,S<sub>a</sub>)-21r):**

mp: 86 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD):  $\delta$ =0.99–1.09 (m, 3H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.10–1.20 (m, 3H, CH(CH<sub>3</sub>)<sub>2</sub>), 1.29–1.42 (m, 1H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>), 1.49–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.66–1.80 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH), 1.90–2.04 (m, 2H, NCH<sub>2</sub>CHCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub> and NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.04–2.21 (m, 1H, NCH<sub>H<sub>ax</sub>H<sub>eq</sub></sub>CHCH<sub>2</sub>), 2.30–2.47 (m, 1H, NCH<sub>2</sub>CH<sub>H<sub>ax</sub></sub>CH<sub>2</sub>), 2.63–2.78 (m, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 2.82–

2.98 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.98–3.24 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 5.39–5.59 (m, 1H, NCH<sub>2</sub>CHCCH), 5.77–5.88 (m, 1H, NCH<sub>2</sub>CHCCH), 6.97–7.05 (m, 1H, ArH), 7.05–7.15 (m, 1H, ArH), 7.16–7.27 (m, 2H, ArH), 7.27–7.44 (m, 3H, ArH), 7.44–7.56 (m, 1H, NCH<sub>2</sub>CHCCHCC<sub>H</sub>CHCHCH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=23.6 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>), 23.7 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 24.8 (CH<sub>3</sub>), 26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 31.1 (CH), 31.1 (CH), 46.4 (CH), 46.4 (CH), 46.5 (CH), 46.5 (CH), 54.2 (CH<sub>2</sub>), 54.2 (CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 58.9 (CH<sub>2</sub>), 59.0 (CH<sub>2</sub>), 90.9 (CH), 91.1 (CH), 91.1 (CH), 91.3 (CH), 93.5 (CH), 93.5 (CH), 93.6 (CH), 93.6 (CH), 126.3 (CH), 126.4 (CH), 126.4 (CH), 126.5 (CH), 126.5 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 130.8 (CH), 130.8 (CH), 131.0 (CH), 131.2 (CH), 131.2 (CH), 133.5 (C), 133.6 (C), 133.6 (C), 140.6 (C), 140.6 (C), 140.7 (C), 140.7 (C), 141.2 (C), 141.3 (C), 141.3 (C), 141.3 (C), 148.1 (C), 148.2 (C), 182.6 (C), 182.7 (C), 182.7 (C), 207.6 (C), 207.7 (C), 207.8 (C), 207.9 (C); IR (KBr): ν=3427, 3057, 3020, 2959, 2866, 2796, 2532, 1948, 1712, 1594, 1496, 1478, 1442, 1400, 1384, 1362, 1341, 1308, 1220, 1193, 1154, 1133, 1095, 1045, 1034, 1005, 948, 880, 757, 631, 537 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>29</sub>NO<sub>2</sub>: 376.2277, found: 376.2270. Ratio of atropisomers is 49:51.

***rac*-{(R<sub>a</sub>)-1-[4-(2',4'-Dichloro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-(3R,R<sub>a</sub>)-21s) and *rac*-{(S<sub>a</sub>)-1-[4-(2',4'-dichloro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-(3R,S<sub>a</sub>)-21s):**

mp: 100 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.06–1.23 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.30–1.45 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.46–1.61 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.73–1.82 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.82–2.00 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.08–2.28 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.62–2.75 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.75–2.91 (m, 2H, NCH<sub>2</sub>CHCCH), 2.94 (d<sub>br</sub>, *J*=10.8 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.20–5.32 (m, 1H, NCH<sub>2</sub>CHCCH), 5.61–5.77 (m, 1H, NCH<sub>2</sub>CHCCH), 6.91 (d, *J*=7.6 Hz, 1H, ClCCHCH), 7.00–7.12 (m, 2H, ClCCHCH and NCH<sub>2</sub>CHCCHCCHCHCH), 7.12–7.24 (m, 2H, NCH<sub>2</sub>CHCCHCCHCH and NCH<sub>2</sub>CHCCHCCHCCH), 7.24–7.33 (m, 1H, NCH<sub>2</sub>CHCCHCCH), 7.36 (s, 1H, ClCCHCH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 54.2 (CH<sub>2</sub>), 54.2 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 91.0 (CH), 91.1 (CH), 91.2 (CH), 91.3 (CH), 93.2 (CH), 93.2 (CH), 93.3 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 128.5 (CH), 129.6 (CH), 129.7 (CH), 130.1 (CH), 130.2 (CH), 131.1 (CH), 131.1 (CH), 131.2 (CH), 133.6 (C), 133.7 (C), 133.8 (CH), 133.8 (CH), 133.9 (CH), 135.3 (C), 135.6 (C), 135.7 (C), 135.7 (C), 137.8 (C), 137.9 (C), 137.9 (C), 139.8 (C), 182.7 (C), 208.0 (C), 208.0 (C), 208.1 (C), 208.1 (C); IR (KBr): ν=3432, 3057, 2938, 2859, 2797, 2529, 2361, 2342, 1950, 1717, 1586, 1468, 1443, 1399, 1375, 1340, 1305, 1220, 1193, 1153, 1139, 1101, 1069, 1044, 1004, 951, 867, 824, 805, 759, 701, 629, 576 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>2</sub>: 402.1028, found: 402.1022. Ratio of atropisomers is ~ 50:50.

***rac*-{(R<sub>a</sub>)-1-[4-(2',4'-Difluoro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-(3R,R<sub>a</sub>)-21t) and *rac*-{(S<sub>a</sub>)-1-[4-(2',4'-difluoro[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3R)-piperidine-3-carboxylic acid} (*rac*-(3R,S<sub>a</sub>)-21t):**

mp: 80 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.25–1.43 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.67 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.83 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.91–2.05 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.09 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.15 (t, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.39 (tt, *J*=12.1/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1 or dia2), 2.41 (tt, *J*=12.1/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1 or dia2), 2.85–2.98 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.01–3.12 (m, 2H, NCH<sub>2</sub>CHCCH), 3.12–3.21 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.52 (q, *J*=7.2 Hz, 1H, NCH<sub>2</sub>CHCCH), 5.99 (d<sub>br</sub>, *J*=6.4 Hz, 1H, NCH<sub>2</sub>CHCCH), 6.98–7.09 (m, 2H, FCCHCF and FCCHCH), 7.14–7.21 (m, 1H, NCH<sub>2</sub>CHCCHCCHCHCH), 7.21–7.33 (m, 2H, FCCHCH and NCH<sub>2</sub>CHCCHCCHCHCH), 7.36 (td, *J*=7.7/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCH, dia1 or dia2), 7.37 (td, *J*=7.7/1.5 Hz, 0.5H, NCH<sub>2</sub>CHCCHCCHCHCH, dia1 or dia2), 7.47–7.55 (m, 1H, NCH<sub>2</sub>CHCCHCCHCCH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 54.3 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 57.7 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 58.8 (CH<sub>2</sub>), 91.2 (CH), 91.4 (CH), 93.3 (CH), 104.8 (t, <sup>2</sup>*J*<sub>CF</sub>=26.1 Hz, CH), 112.3 (dd, <sup>2</sup>/<sub>4</sub>*J*<sub>CF</sub>=21.4/3.7 Hz, CH), 125.8 (dd, <sup>2</sup>/<sub>4</sub>*J*<sub>CF</sub>=17.0/2.4 Hz, C), 128.0 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 129.5 (CH), 129.6 (CH), 131.8 (CH), 131.8 (CH), 134.1 (dd, <sup>2</sup>/<sub>4</sub>*J*<sub>CF</sub>=9.8/4.6 Hz, CH), 134.4 (C), 134.5 (C), 161.1 (dd, <sup>1</sup>/<sub>3</sub>*J*<sub>CF</sub>=236.7/11.8 Hz, C), 163.5 (dd, <sup>1</sup>/<sub>3</sub>*J*<sub>CF</sub>=248.2/12.2 Hz, C), 182.6 (C), 182.7 (C), 208.0 (C), 208.0 (C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, MeOD, NaOD): δ=-111.9, -112.9, -112.9; IR (KBr): ν=3442, 3062, 2934, 2855, 2360, 2341, 1951, 1712, 1619, 1592, 1509, 1484, 1448, 1419, 1340, 1302, 1264, 1222, 1139, 1098, 1046, 1009,

963, 850, 820, 760, 737, 714, 668, 630, 613, 590, 559 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>2</sub>: 370.1619, found: 370.1608.

***rac*-[(*R<sub>a</sub>*)-1-{4-[2',4'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl}(3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*R<sub>a</sub>*)-21u) and *rac*-[(*S<sub>a</sub>*)-1-{4-[2',4'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl]buta-2,3-dien-1-yl}(3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*S<sub>a</sub>*)-21u):**

mp: 90 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.22–1.43 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.45–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.79 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.87–2.01 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.03 (t, *J*=11.5 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.13 (t<sub>br</sub>, *J*=11.3 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.35 (tt, *J*=12.2/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1 or dia2), 2.38 (tt, *J*=12.2/3.8 Hz, 0.5H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>, dia1 or dia2), 2.73–3.05 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCCH), 3.10 (d<sub>br</sub>, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.28–5.45 (m, 1H, NCH<sub>2</sub>CHCCH), 5.75–5.85 (m, 1H, NCH<sub>2</sub>CHCCH), 7.14 (d, *J*=7.6 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCCH), 7.27 (t, *J*=7.6 Hz, 1H, NCH<sub>2</sub>CHCCHCCHCCHCCH), 7.36–7.45 (m, 1H, NCH<sub>2</sub>CHCCHCCHCCHCCH), 7.45–7.57 (m, 2H, NCH<sub>2</sub>CHCCHCCHCCH and CF<sub>3</sub>CCHCCH), 7.99 (d, *J*=8.2 Hz, 1H, CF<sub>3</sub>CCHCCH), 8.06 (s, 1H, F<sub>3</sub>CCCHCCHCF<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=25.9 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 46.4 (CH), 46.5 (CH), 54.1 (CH<sub>2</sub>), 54.7 (CH<sub>2</sub>), 57.6 (CH<sub>2</sub>), 57.6 (CH<sub>2</sub>), 57.8 (CH<sub>2</sub>), 58.6 (CH<sub>2</sub>), 58.7 (CH<sub>2</sub>), 91.0 (CH), 91.0 (CH), 91.2 (CH), 91.3 (CH), 93.4 (CH), 93.5 (CH), 124.0–124.4 (m, CH), 124.9 (q, <sup>1</sup>*J*<sub>C-F</sub>=248.1 Hz, C), 126.2 (q, <sup>2</sup>*J*<sub>C-F</sub>=30.8 Hz, C), 127.4 (CH), 128.3–128.9 (m, CH), 129.4 (q, <sup>1</sup>*J*<sub>C-F</sub>=247.4 Hz, C), 129.7–129.9 (m, CH), 130.0 (CH), 130.0 (CH), 130.7–131.0 (m, CH), 131.5 (q, <sup>2</sup>*J*<sub>C-F</sub>=33.6 Hz, C), 133.5 (C), 133.5 (C), 134.8 (CH), 135.0 (CH), 135.0 (CH), 137.1 (C), 137.1 (C), 145.3–145.6 (m, C), 182.7 (C), 182.7 (C), 208.0 (C), 208.1 (C), 208.1 (C), 208.2 (C); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, MeOD, NaOD): δ=-60.4, -60.4, -60.4, -60.4, -64.2, -64.3, IR (KBr): ν=3427, 3064, 2943, 2861, 2800, 1952, 1713, 1625, 1579, 1484, 1469, 1447, 1403, 1345, 1277, 1178, 1132, 1083, 1065, 1047, 1006, 952, 912, 868, 848, 759, 731, 715, 672, 647, 629, 587 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>24</sub>H<sub>21</sub>F<sub>6</sub>NO<sub>2</sub>: 470.1555, found: 470.1546. Ratio of atropisomers is ~ 50:50.

***rac*-[(*R<sub>a</sub>*)-1-[4-(2',4'-Dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*R<sub>a</sub>*)-21v) and *rac*-[(*S<sub>a</sub>*)-1-[4-(2',4'-dimethoxy-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl](3*R*)-piperidine-3-carboxylic acid] (*rac*-(3*R*,*S<sub>a</sub>*)-21v):**

mp: 94 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.14–1.28 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.33–1.51 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.51–1.65 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.74–1.89 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 1.93 (t, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1), 2.00 (t, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia2), 2.17–2.33 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.74 (d<sub>br</sub>, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.81 (d<sub>br</sub>, *J*=11.4 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.85–3.07 (m, 3H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub> and NCH<sub>2</sub>CHCCH), 3.56 (s, 3H, OCH<sub>3</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 5.34 (q, *J*=7.1 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.35 (q, *J*=7.1 Hz, 0.5H, NCH<sub>2</sub>CHCCH, dia1 or dia2), 5.73–5.85 (m, 1H, NCH<sub>2</sub>CHCCH), 6.39–6.50 (m, 2H, CCCCHCHCOMeCHCOMe and CCCCHCHCOMeCHCOMe), 6.84 (d, *J*=8.1 Hz, 1H, CCCCHCHCOMeCHCOMe), 6.90–6.98 (m, 1H, CHCCHCHCHCHC), 7.02 (td, *J*=7.6/1.6 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2), 7.03 (td, *J*=7.6/1.6 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2), 7.09 (td, *J*=7.6/1.6 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2), 7.10 (td, *J*=7.6/1.6 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2), 7.28 (dd, *J*=7.6/1.4 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2), 7.30 (dd, *J*=7.6/1.4 Hz, 0.5H, CHCCHCHCHCHC, dia1 or dia2); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 46.5 (CH), 46.5 (CH), 54.2 (CH<sub>2</sub>), 54.6 (CH<sub>2</sub>), 55.9 (CH<sub>3</sub>), 55.9 (CH<sub>3</sub>), 57.8 (CH<sub>2</sub>), 59.0 (CH<sub>2</sub>), 59.2 (CH<sub>2</sub>), 90.7 (CH), 91.0 (CH), 94.1 (CH), 94.1 (CH), 99.6 (CH), 105.8 (CH), 123.6 (C), 123.6 (C), 127.5 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.2 (CH), 132.0 (CH), 132.0 (CH), 132.8 (CH), 134.1 (C), 138.5 (C), 138.5 (C), 159.1 (C), 162.3 (C), 182.7 (C), 182.7 (C), 207.6 (C), 207.7 (C); IR (KBr): ν=3431, 3057, 2998, 2936, 2859, 2834, 1948, 1710, 1611, 1580, 1511, 1484, 1464, 1453, 1438, 1413, 1339, 1306, 1282, 1241, 1207, 1158, 1133, 1093, 1051, 1032, 1002, 933, 917, 879, 832, 799, 761, 634 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>4</sub>: 394.2018, found: 394.2010.

**Methyl 1-(prop-2-yn-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (22):**

*R*<sub>t</sub>=0.10 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=2.29 (t, *J*=2.5 Hz, 1H, NCH<sub>2</sub>C≡CH), 2.31–2.39 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 2.61 (t, *J*=5.7 Hz, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.26 (td, *J*=2.9/2.0 Hz, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.44 (d, *J*=2.5 Hz, 2H, NCH<sub>2</sub>C≡CH), 3.71 (s, 3H, OCH<sub>3</sub>), 6.96 (tt, *J*=4.0/2.0 Hz, 1H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=27.2 (CH<sub>2</sub>), 46.9 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 50.4 (CH<sub>2</sub>),

51.9 (CH<sub>3</sub>), 73.4 (CH), 79.3 (C), 129.5 (C), 137.9 (CH), 166.6 (C); IR (film):  $\tilde{\nu}$ =3292, 2951, 2914, 2812, 1714, 1657, 1463, 1436, 1399, 1351, 1324, 1264, 1195, 1127, 1090, 1056, 1043, 1000, 975, 901, 848, 786, 766, 720 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub>: 180.1025, found: 180.1018.

***rac*-[Methyl 1-{4-([1,1':2',1''-terphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}-1,2,5,6-tetrahydropyridine-3-carboxylate] (*rac*-23p):**

$R_f$ =0.53 (DCM, 5% MeOH); <sup>1</sup>H NMR (400 MHz, T<sub>cl2</sub>):  $\delta$ =1.67–2.07 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.09–2.43 (m, 4H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.47 (t,  $J$ =5.6 Hz, 1.08H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso1), 2.57 (t,  $J$ =5.6 Hz, 0.92H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso2), 2.63–2.86 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.09–3.18 (m, 1.08H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso1), 3.20–3.26 (m, 0.92H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso2), 3.32–3.36 (m, 1.08H, NCH<sub>2</sub>CCCHN, atr-iso1), 3.43–3.51 (m, 0.92H, NCH<sub>2</sub>CCCHN, atr-iso2), 3.65 (s, 1.62H, OCH<sub>3</sub>, atr-iso1), 3.66 (s, 1.38H, OCH<sub>3</sub>, atr-iso2), 4.27 (t,  $J$ =1.9 Hz, 0.54H, NCH<sub>2</sub>CCCHN, atr-iso1), 4.82 (t,  $J$ =2.0 Hz, 0.46H, NCH<sub>2</sub>CCCHN, atr-iso2), 5.41–5.60 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.72–7.20 (m, 8H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub> and ArH), 7.21–7.66 (m, 6H, ArH); <sup>13</sup>C NMR (101 MHz, T<sub>cl2</sub>):  $\delta$ =26.6 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 46.8 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 47.1 (CH<sub>2</sub>), 47.1 (CH<sub>2</sub>), 47.7 (CH<sub>2</sub>), 47.9 (CH<sub>2</sub>), 48.4 (CH<sub>2</sub>), 48.7 (CH<sub>2</sub>), 50.1 (CH<sub>2</sub>), 50.3 (CH<sub>2</sub>), 52.0 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 58.2 (CH), 58.3 (CH), 80.9 (C), 82.2 (C), 82.4 (C), 82.5 (C), 125.2 (CH), 125.3 (CH), 125.7 (CH), 125.9 (CH), 126.6–127.0 (m, CH), 127.1 (CH), 127.4 (CH), 127.8 (CH), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.7 (CH), 129.1 (CH), 129.2 (C), 129.2 (C), 129.9 (CH), 129.9 (CH), 130.3 (CH), 130.6 (CH), 130.8 (CH), 131.4 (CH), 132.1 (CH), 136.4 (C), 136.7 (C), 138.2 (CH), 138.2 (CH), 139.3 (C), 139.4 (C), 140.9 (C), 141.2 (C), 141.4 (C), 141.6 (C), 141.7 (C), 141.7 (C), 166.5 (C); IR (film):  $\tilde{\nu}$ =3056, 3029, 2909, 2806, 1715, 1656, 1598, 1469, 1432, 1396, 1351, 1322, 1261, 1193, 1125, 1090, 1074, 1055, 1042, 998, 973, 948, 753, 719, 700 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>34</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>: 503.2699, found: 503.2690. Ratio of atropisomers is 46:54.

***rac*-[Methyl 1-{4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}-1,2,5,6-tetrahydropyridine-3-carboxylate] (*rac*-23s):**

$R_f$ =0.23 (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, T<sub>cl2</sub>):  $\delta$ =1.71–2.01 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.13–2.49 (m, 4H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.56 (t,  $J$ =6.0 Hz, 0.86H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso2), 2.57 (t,  $J$ =6.0 Hz, 1.14H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>, atr-iso1), 2.61–2.88 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.16–3.28 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.47 (d,  $J$ =1.9 Hz, 0.86H, NCH<sub>2</sub>CCCHN, atr-iso2), 3.49 (d,  $J$ =1.9 Hz, 1.14H, NCH<sub>2</sub>CCCHN, atr-iso1), 3.65 (s, 1.71H, OCH<sub>3</sub>, atr-iso1), 3.65 (s, 1.29H, OCH<sub>3</sub>, atr-iso2), 4.26 (t,  $J$ =1.9 Hz, 0.57H, NCH<sub>2</sub>CCCHN, atr-iso1), 4.33 (t,  $J$ =1.9 Hz, 0.43H, NCH<sub>2</sub>CCCHN, atr-iso2), 5.34–5.64 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.92 (tt,  $J$ =3.8/2.1 Hz, 1H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 7.07 (dd,  $J$ =7.4/1.6 Hz, 0.57H, NCHCCHCHCHCH, atr-iso1), 7.09 (dd,  $J$ =7.4/1.6 Hz, 0.43H, NCHCCHCHCHCH, atr-iso2), 7.13 (d,  $J$ =8.2 Hz, 0.43H, ClCCCH, atr-iso2), 7.16 (dd,  $J$ =8.3/2.1 Hz, 0.57H, ClCCCHCH, atr-iso1), 7.20 (dd,  $J$ =8.3/2.1 Hz, 0.43H, ClCCCHCH, atr-iso2), 7.24–7.37 (m, 2.57H, NCHCCHCHCH and ClCCCH, atr-iso1), 7.38 (d,  $J$ =2.1 Hz, 0.57H, ClCCCHCl, atr-iso1), 7.40 (d,  $J$ =2.1 Hz, 0.43H, ClCCCHCl, atr-iso2), 7.67 (d<sub>br</sub>,  $J$ =7.5 Hz, 0.57H, NCHCCH, atr-iso1), 7.74 (d<sub>br</sub>,  $J$ =7.6 Hz, 0.43H, NCHCCH, atr-iso2); <sup>13</sup>C NMR (101 MHz, T<sub>cl2</sub>):  $\delta$ =26.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 46.6 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 47.9 (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 49.1 (CH<sub>2</sub>), 50.2 (CH<sub>2</sub>), 52.1 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 58.7 (CH), 81.3 (C), 82.0 (C), 82.4 (C), 82.7 (C), 125.1 (CH), 125.1 (CH), 125.6 (CH), 125.7 (CH), 126.4 (CH), 126.6 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.7–129.4 (m, CH), 130.5 (CH), 130.7 (CH), 133.6 (C), 133.8 (C), 131.2 (CH), 134.0 (CH), 133.7 (C), 135.5 (C), 138.1 (C), 138.2 (CH), 138.5 (C), 138.8 (C), 166.5 (C); IR (film):  $\tilde{\nu}$ =3030, 2948, 2909, 2806, 1716, 1656, 1587, 1551, 1463, 1438, 1376, 1350, 1320, 1262, 1193, 1127, 1100, 1067, 1055, 1042, 1004, 973, 949, 864, 809, 786, 764, 720, 704, 650 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 495.1606, found: 495.1600. Ratio of atropisomers is 43:57.

***rac*-[Methyl 1-{4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)-4-[3,6-dihydropyridin-1(2H)-yl]but-2-yn-1-yl}-1,2,5,6-tetrahydropyridine-3-carboxylate] (*rac*-23t):**

$R_f$ =0.24 (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, T<sub>cl2</sub>, 353 K):  $\delta$ =1.84–1.97 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.24–2.38 (m, 3H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.42–2.53 (m, 1H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.61 (t,  $J$ =5.7 Hz, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 2.64–2.76 (m, 1H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 2.77–2.89 (m, 1H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 3.22–3.31 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.50 (d,  $J$ =1.9 Hz, 2H, NCH<sub>2</sub>CCCHN), 3.68 (s, 3H, OCH<sub>3</sub>), 4.43 (t,  $J$ =1.9 Hz, 1H, NCH<sub>2</sub>CCCHN), 5.42–5.62 (m, 2H, NCH<sub>2</sub>CHCHCH<sub>2</sub>CH<sub>2</sub>), 6.76–6.87 (m, 2H, FCCHCFCHCHC and FCCHCFCHCHC), 6.92

(tt,  $J=3.9/1.9$  Hz, 1H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 7.16 (dd,  $J=7.5/1.6$  Hz, 1H, NCHCCCHCHCHCH), 7.29 (td,  $J=7.4/1.5$  Hz, 1H, NCHCCCHCHCHCH), 7.32 (s<sub>br</sub>, 1H, FCCHCFCHCHC), 7.35 (td,  $J=7.5/1.6$  Hz, 1H, NCHCCCHCHCHCH), 7.76 (dd,  $J=7.6/1.5$  Hz, 1H, NCHCCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 353 K):  $\delta=26.6$  (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 46.5 (CH<sub>2</sub>), 47.0 (CH<sub>2</sub>), 48.0 (CH<sub>2</sub>), 48.6 (CH<sub>2</sub>), 50.3 (CH<sub>2</sub>), 51.7 (CH<sub>3</sub>), 58.9 (CH), 81.7 (C), 82.9 (C), 103.7 (t, <sup>2</sup> $J_{CF}=26.1$  Hz, CH), 110.6 (dd, <sup>2/4</sup> $J_{CF}=20.9/3.7$  Hz, CH), 124.9 (dd, <sup>2/4</sup> $J_{CF}=17.0/3.9$  Hz, C), 125.0 (CH), 125.7 (CH), 127.6 (CH), 128.0 (CH), 129.2 (CH), 129.5 (C), 131.1 (CH), 132.8 (br, CH), 135.5 (C), 137.7 (CH), 137.8 (C), 162.6 (dd, <sup>1/3</sup> $J_{CF}=248.2/11.7$  Hz, C), 166.3 (C); <sup>19</sup>F NMR {<sup>1</sup>H} (376 MHz, TCl<sub>2</sub>, 353 K):  $\delta=-111.1$ , -109.3; IR (film):  $\tilde{\nu}=3032$ , 2910, 2808, 1715, 1657, 1620, 1593, 1510, 1480, 1462, 1437, 1420, 1396, 1351, 1321, 1263, 1194, 1138, 1099, 1055, 1042, 1000, 963, 950, 887, 849, 816, 786, 764, 746, 731, 718, 652 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>28</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: 463.2197, found: 463.2190.

**rac-{Methyl 1-[4-([1,1':2',1''-terphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (rac-24p):**

$R_f=0.38$  (PE/EtOAc 1:1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta=2.28-2.40$  (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 2.45–2.69 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.08 (dd,  $J=7.3/2.3$  Hz, 1.08H, NCH<sub>2</sub>CHCCH, atr-iso1), 3.12–3.36 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub> and 0.92H, NCH<sub>2</sub>CHCCH, atr-iso2), 3.73 (s, 1.38H, OCH<sub>3</sub>, atr-iso2), 3.73 (s, 1.62H, OCH<sub>3</sub>, atr-iso1), 5.41 (q,  $J=7.1$  Hz, 0.46H, NCH<sub>2</sub>CHCCH, atr-iso2), 5.43 (q,  $J=7.1$  Hz, 0.54H, NCH<sub>2</sub>CHCCH, atr-iso1), 5.97 (dt,  $J=6.4/2.3$  Hz, 0.54H, NCH<sub>2</sub>CHCCH, atr-iso1), 6.04 (dt,  $J=6.4/2.4$  Hz, 0.46H, NCH<sub>2</sub>CHCCH, atr-iso2), 6.92–7.60 (m, 14H, ArH and NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta=26.7$  (CH<sub>2</sub>), 48.1 (CH<sub>2</sub>), 48.3 (CH<sub>2</sub>), 51.0 (CH<sub>2</sub>), 51.2 (CH<sub>2</sub>), 51.7 (CH<sub>3</sub>), 56.8 (CH<sub>2</sub>), 57.0 (CH<sub>2</sub>), 90.4 (CH), 90.8 (CH), 93.0 (CH), 93.1 (CH), 126.5 (CH), 126.5 (CH), 126.6 (CH), 126.6 (CH), 127.0 (CH), 127.2 (CH), 127.3 (CH), 127.3 (CH), 127.4 (CH), 127.8 (CH), 127.9 (CH), 127.9 (CH), 128.0 (CH), 129.1 (C), 129.2 (C), 129.7 (CH), 129.8 (CH), 130.2 (CH), 130.3 (CH), 131.2 (CH), 131.3 (CH), 131.4 (CH), 131.2 (CH), 132.4 (C), 132.4 (C), 138.0 (CH), 139.3 (C), 139.9 (C), 141.3 (C), 141.4 (C), 141.6 (C), 141.6 (C), 166.4 (C), 166.4 (C), 206.7 (C), 206.9 (C); IR (film):  $\tilde{\nu}=3057$ , 3021, 2949, 2917, 2802, 2237, 1947, 1714, 1656, 1598, 1490, 1472, 1435, 1397, 1354, 1337, 1311, 1264, 1193, 1126, 1090, 1056, 1044, 1006, 969, 950, 886, 801, 769, 745, 719, 700 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>27</sub>NO<sub>2</sub>: 422.2120, found: 422.2112. Ratio of atropisomers is 46:54.

**rac-{Methyl 1-[4-(2',4'-dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (rac-24s):**

$R_f=0.26$  (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub>, 353K):  $\delta=2.19-2.39$  (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 2.42–2.70 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.09–3.36 (m, 4H, NCH<sub>2</sub>CHCCH and NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.68 (s, 3H, OCH<sub>3</sub>), 5.46 (q,  $J=6.7$  Hz, 1H, NCH<sub>2</sub>CHCCH), 5.89 (dt,  $J=6.5/2.4$  Hz, 1H, NCH<sub>2</sub>CHCCH), 6.93 (tt,  $J=3.9/1.9$  Hz, 1H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 7.10 (dd,  $J=7.6/1.1$  Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.16 (d,  $J=8.2$  Hz, 1H, ClCCHCClCHCHC), 7.21 (td,  $J=7.5/1.2$  Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.26 (dd,  $J=8.2/2.1$  Hz, 1H, ClCCHCClCHCHC), 7.31 (td,  $J=7.6/1.4$  Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.42–7.49 (m, 2H, ClCCHCClCHCHC and NCH<sub>2</sub>CHCCHCCCHCHCHCH); <sup>13</sup>C NMR (101 MHz, TCl<sub>2</sub>, 353K):  $\delta=26.4$  (CH<sub>2</sub>), 48.2 (CH<sub>2</sub>), 50.9 (CH<sub>2</sub>), 51.7 (CH<sub>3</sub>), 56.6 (CH<sub>2</sub>), 90.9 (CH), 93.0 (CH), 127.0 (CH), 127.2 (CH), 127.7 (CH), 128.7 (CH), 129.6 (CH), 130.4 (CH), 132.7 (CH), 132.9 (C), 134.3 (C), 134.8 (C), 136.8 (C), 137.9 (CH), 138.5 (C), 166.3 (C), 207.2 (C); IR (film):  $\tilde{\nu}=2922$ , 2802, 1946, 1714, 1656, 1586, 1550, 1467, 1438, 1375, 1353, 1263, 1193, 1128, 1101, 1069, 1044, 1004, 876, 826, 804, 787, 761, 720 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>2</sub>: 414.1028, found: 414.1022. Ratio of atropisomers ~ 50:50.

**rac-{Methyl 1-[4-(2',4'-difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylate} (rac-24t):**

$R_f=0.16$  (*n*-Pentan/Et<sub>2</sub>O 1:1); <sup>1</sup>H NMR (400 MHz, TCl<sub>2</sub>, 373K):  $\delta=2.21-2.40$  (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 2.49–2.69 (m, 2H, NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.10–3.35 (m, 4H, NCH<sub>2</sub>CHCCH and NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 3.69 (s, 3H, OCH<sub>3</sub>), 5.50 (q,  $J=6.8$  Hz, 1H, NCH<sub>2</sub>CHCCH), 5.96–6.06 (m, 1H, NCH<sub>2</sub>CHCCH), 6.82–6.96 (m, 3H, FCCHCFCHCHC and FCCHCFCHCHC and NCH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>), 7.13–7.26 (m, 3H, NCH<sub>2</sub>CHCCHCCCHCHCHCH and NCH<sub>2</sub>CHCCHCCCHCHCHCH and FCCHCFCHCHC), 7.31 (td,  $J=7.5/1.6$  Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH), 7.49 (dd,  $J=7.9/1.0$  Hz, 1H, NCH<sub>2</sub>CHCCHCCCHCHCHCH); <sup>13</sup>C NMR (126 MHz, TCl<sub>2</sub>):  $\delta=26.8$  (CH<sub>2</sub>), 48.3 (CH<sub>2</sub>), 51.1 (CH<sub>2</sub>), 52.1 (CH<sub>3</sub>), 56.9 (CH<sub>2</sub>), 91.5 (CH), 92.8 (CH), 104.4 (t, <sup>2</sup> $J_{CF}=25.8$  Hz, CH), 111.7 (dd, <sup>2/4</sup> $J_{CF}=21.0/3.7$  Hz, CH), 124.4 (dd, <sup>2/4</sup> $J_{CF}=16.4/3.8$  Hz, C), 127.2 (CH), 127.6 (CH), 128.7 (CH), 129.1 (C), 131.2 (CH), 133.0 (dd,



$^3J_{CF}=9.2/5.0$  Hz, CH), 133.0 (C), 133.2 (C), 138.5 (CH), 159.8 (dd,  $^{1/3}J_{CF}=249.8/13.1$  Hz, C), 162.7 (dd,  $^{1/3}J_{CF}=248.6/11.4$  Hz, C), 166.6 (C), 206.9 (C);  $^{19}F$  { $^1H$ } NMR (376 MHz,  $CD_2Cl_2$ ):  $\delta=-110.3, -110.2, -109.9, 109.9$ ; IR (film):  $\tilde{\nu}=3061, 2950, 2919, 2802, 1948, 1714, 1657, 1619, 1592, 1509, 1484, 1463, 1436, 1420, 1354, 1337, 1264, 1193, 1139, 1101, 1090, 1045, 1009, 963, 879, 850, 820, 761, 718$   $cm^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $C_{23}H_{21}F_2NO_2$ : 382.1619, found: 382.1615.

***rac*-{1-[4-([1,1':2',1''-Terphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-25p):**

mp: 105 °C;  $^1H$  NMR (400 MHz,  $CD_2Cl_2$ ):  $\delta=2.16-2.48$  (m, 2H,  $NCH_2CCHCH_2CH_2$ ), 2.51–2.84 (m, 2H,  $NCH_2CCHCH_2CH_2$ ), 3.01–3.51 (m, 4H,  $NCH_2CCHCH_2CH_2$  and  $NCH_2CHCCH$ ), 5.47 (q,  $J=6.8$  Hz, 0.46H,  $NCH_2CHCCH$ , atr-iso2), 5.49 (q,  $J=6.8$  Hz, 0.54H,  $NCH_2CHCCH$ , atr-iso1), 5.97 (dt,  $J=6.4/2.1$  Hz, 0.54H,  $NCH_2CHCCH$ , atr-iso1), 6.03 (dt,  $J=6.4/2.1$  Hz, 0.46H,  $NCH_2CHCCH$ , atr-iso2), 6.89 (s<sub>br</sub>, 1H,  $NCH_2CCHCH_2CH_2$ ), 6.99–7.24 (m, 8H, ArH), 7.24–7.58 (m, 5H, ArH);  $^{13}C$  NMR (101 MHz,  $CD_2Cl_2$ ):  $\delta=25.6$  ( $CH_2$ ), 25.8 ( $CH_2$ ), 47.6 ( $CH_2$ ), 47.8 ( $CH_2$ ), 50.8 ( $CH_2$ ), 51.0 ( $CH_2$ ), 56.1 ( $CH_2$ ), 56.3 ( $CH_2$ ), 89.5 (CH), 90.0 (CH), 93.6 (CH), 93.7 (CH), 127.0 (CH), 127.0 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 130.1 (CH), 130.2 (C), 130.7 (CH), 130.7 (CH), 131.6 (CH), 131.7 (CH), 131.8 (CH), 132.5 (C), 132.6 (C), 136.4 (CH), 139.6 (C), 140.5 (C), 141.8 (C), 141.9 (C), 142.0 (C), 142.0 (C), 169.3 (C), 169.6 (C), 207.6 (C), 207.9 (C); IR (KBr):  $\tilde{\nu}=3424, 3057, 3019, 2925, 2585, 1951, 1669, 1654, 1577, 1490, 1472, 1431, 1385, 1350, 1261, 1188, 1158, 1117, 1073, 1008, 955, 913, 883, 769, 749, 700, 633, 614, 565$   $cm^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $C_{28}H_{25}NO_2$ : 408.1964, found: 408.1955. Ratio of atropisomers is 46:54.

***rac*-{1-[4-(2',4'-Dichloro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-25s):**

mp: 104 °C;  $^1H$  NMR (500 MHz,  $CD_2Cl_2$ ):  $\delta=2.07-2.42$  (m, 2H,  $NCH_2CCHCH_2CH_2$ ), 2.43–2.71 (m, 2H,  $NCH_2CCHCH_2CH_2$ ), 3.10–3.53 (m, 4H,  $NCH_2CHCCH$  and  $NCH_2CCHCH_2CH_2$ ), 5.41–5.69 (m, 1H,  $NCH_2CHCCH$ ), 5.88 (s<sub>br</sub>, 1H,  $NCH_2CHCCH$ ), 6.85 (s<sub>br</sub>, 1H,  $NCH_2CCHCH_2CH_2$ ), 6.98–7.62 (m, 7H, ArH);  $^{13}C$  NMR (126 MHz,  $CD_2Cl_2$ ):  $\delta=26.4$  ( $CH_2$ ), 48.1 ( $CH_2$ ), 51.7 ( $CH_2$ ), 56.6 ( $CH_2$ ), 91.2 (CH), 92.9 (CH), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.7 (CH), 129.1 (CH), 129.8 (CH), 130.6 (CH), 133.1 (C and CH), 134.5 (C), 134.9 (C), 134.9 (C), 137.0 (C), 138.6 (C), 170.6 (C), 207.4 (C); IR (KBr):  $\tilde{\nu}=3445, 2926, 1950, 1653, 1560, 1507, 1498, 1467, 1441, 1385, 1101, 1068, 1042, 1004, 866, 826, 804, 759, 733, 700, 658, 629, 577$   $cm^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $C_{22}H_{19}Cl_2NO_2$ : 400.0871, found: 400.0864. Ratio of atropisomers is ~ 50:50.

***rac*-{1-[4-(2',4'-Difluoro-[1,1'-biphenyl]-2-yl)buta-2,3-dien-1-yl]-1,2,5,6-tetrahydropyridine-3-carboxylic acid} (*rac*-25t):**

mp: 72-77 °C;  $^1H$  NMR (400 MHz,  $CD_2Cl_2$ ):  $\delta=2.24-2.40$  (m, 2H,  $NCH_2CCHCH_2CH_2$ ), 2.68 (t,  $J=5.8$  Hz, 2H,  $NCH_2CCHCH_2CH_2$ ), 3.22–3.44 (m, 4H,  $NCH_2CHCCH$  and  $NCH_2CCHCH_2CH_2$ ), 5.59 (q,  $J=7.0$  Hz, 1H,  $NCH_2CHCCH$ ), 5.99–6.10 (m, 1H,  $NCH_2CHCCH$ ), 6.70 (s, 1H, COOH), 6.83–6.88 (m, 1H,  $NCH_2CCHCH_2CH_2$ ), 6.88–7.00 (m, 2H,  $FCCHCFCHCHC$  and  $FCCHCFCHCHC$ ), 7.16–7.29 (m, 3H,  $NCH_2CHCCHCCCHCHCHCH$  and  $NCH_2CHCCHCCCHCHCHCH$  and  $FCCHCFCHCHC$ ), 7.34 (td,  $J=7.6/1.4$  Hz, 1H,  $NCH_2CHCCHCCCHCHCHCHCH$ ), 7.52 (dd,  $J=7.7/1.0$  Hz, 1H,  $NCH_2CHCCHCCCHCHCHCHCH$ );  $^{13}C$  NMR (101 MHz,  $CD_2Cl_2$ ):  $\delta=25.7$  ( $CH_2$ ), 47.9 ( $CH_2$ ), 51.0 ( $CH_2$ ), 56.2 ( $CH_2$ ), 90.3 (CH), 93.3 (CH), 104.5 (t,  $^3J_{CF}=25.9$  Hz, CH), 111.9 (dd,  $^{2/4}J_{CF}=21.1/3.8$  Hz, CH), 124.8 (dd,  $^{2/4}J_{CF}=16.5/3.8$  Hz, C), 127.5 (CH), 127.9 (CH), 129.0 (CH), 130.1 (C), 131.3 (CH), 133.1 (C), 133.3 (dd,  $^2J_{CF}=9.5/4.8$  Hz, CH), 133.6 (C), 136.2 (CH), 160.2 (dd,  $^{1/3}J_{CF}=248.2/11.8$  Hz, C), 163.2 (dd,  $^{1/3}J_{CF}=248.3/11.5$  Hz, C), 169.8 (C), 207.8 (C);  $^{19}F$  { $^1H$ } NMR (376 MHz,  $CD_2Cl_2$ ):  $\delta=-111.5, -111.5, -110.9, -110.9$ ; IR (KBr):  $\tilde{\nu}=3427, 3063, 2910, 2798, 1949, 1661, 1618, 1592, 1568, 1509, 1484, 1447, 1419, 1398, 1361, 1339, 1264, 1193, 1139, 1101, 1042, 1009, 963, 880, 851, 820, 760, 736, 715, 668, 631, 613, 290, 559, 457$   $cm^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $C_{22}H_{19}F_2NO_2$ : 368.1462, found: 368.1457.

### **3.3 Third Publication: “Synthesis and Biological Evaluation of Nipecotic Acid Derivatives as GABA Uptake Inhibitors with Terminally Double-Substituted Allenic Spacers”**

#### *3.3.1 Summary of the Results*

In summary, a new series of nipecotic acid derivatives, featuring a four- and five-carbon atom allenic spacer connecting the nitrogen of the polar nipecotic acid head with up to two lipophilic aromatic residues, has been synthesized. The parent compounds, characterized as nipecotic acids bearing a buta-2,3-dien-1-yl and penta-3,4-dien-1-yl residue at the amino nitrogen, respectively, have been synthesized via a two-step, allyl(*tert*-butyl)amine mediated ATA reaction and a subsequent ester hydrolysis. For the synthesis of the envisaged nipecotic acid derivatives characterized by an allenic carbon chain originating from the amino nitrogen of the amino acid subunit linking the latter with two terminal substituents, mainly aryl residues, a CuI-catalyzed cross-coupling of diaryldiazomethanes and nipecotic acid derived terminal alkynes was used as key step by which variously substituted diaryl subunits were implemented in the target compounds. A similar synthesis method, whereat the diaryldiazomethanes were replaced by *N*-tosylhydrazones, has been applied to incorporate non-diaryl substrates, such as 6-methoxy-1-tetralone, into the terminal position of the corresponding allenic spacer and to synthesize nipecotic acid derived compounds with an elongated, i.e. a five-carbon atom allenic spacer with a single terminal substituent. In contrast to the preceding study, in which nipecotic acid derivatives with an allenic four-carbon atom chain, terminally un- or monosubstituted, have been investigated successfully, an elongation of the spacer to five-carbon atoms resulted in nipecotic acid derivatives, either un- or monosubstituted at the terminal position of the allenic carbon chain, that exhibit a substantially lower stability. Hence, solely the nipecotic acid derivatives with

a terminally disubstituted allenic four- and five-carbon atom spacer, have been characterized regarding their inhibitory potency at mGAT1-4 and binding affinity for mGAT1.

As a result, nipecotic acid derivatives equipped with a shorter terminally disubstituted allenic four-carbon atom spacer have been identified to possess generally higher biological activity at mGAT1-4 than their analogues with a terminally disubstituted allenic five-carbon atom spacer. Among the biologically investigated compounds, nipecotic acid derivative *rac*-**32d** (**Scheme 4** in the manuscript), exhibiting two 4-chlorophenyl residues connected via a four-carbon atom allenyl spacer to the amino nitrogen of the polar nipecotic acid head, was identified as highly potent mGAT1 and mGAT4 inhibitor. The *R* enantiomer (*R*)-**32d** displays an inhibitory potency at mGAT1 that is in the range of the known, therapeutically used inhibitor tiagabine. For the enantiopure *S* isomer (*S*)-**32d** pIC<sub>50</sub> values amounting to 6.59 ± 0.01 at mGAT4 and 6.49 ± 0.10 for the human equivalent hGAT-3 have been determined, which are significantly higher than that of the benchmark mGAT4 inhibitor (*S*)-SNAP-5114. However, the subtype selectivity of (*S*)-**32d** for mGAT4 over the other three subtypes is less pronounced. The combination of a rigid allenic spacer with a diaryl residue as lipophilic domain in compound (*S*)-**32d** represents a novel structural motif for this kind of bioactive compound. While diaryl moieties are well known as lipophilic domains of mGAT1 inhibitors, it is to our knowledge unprecedented for mGAT4 inhibitors with high potencies. Hence, the herein described compounds could serve as useful starting points for further structure-activity relationship studies of mGAT4 inhibitors and facilitate the design of new ligands with higher potencies and better selectivities at this molecular target.

### 3.3.2 Declaration of contributions

The synthesis of all described compounds as well as the evaluation of all corresponding analytical data were accomplished by myself. The practical performance of the biological testing and the determination of the  $pK_i$  values and  $pIC_{50}$  values were performed by the technical assistants Silke Duesing-Kropp, Miriam Sandner, and Tanja Franz under the supervision of Dr. Georg Höfner. I wrote the manuscript and generated all graphics and tables, supported by Prof. Dr. Klaus T. Wanner. The manuscript was corrected by Prof. Dr. Klaus T. Wanner.

# Synthesis and Biological Evaluation of Nipecotic Acid Derivatives with Terminally Double-Substituted Allenic Spacers

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## Abstract

A new series of nipecotic acid derivatives, featuring a four- and five-carbon atom allenic spacer connecting the nitrogen of the polar nipecotic acid head with up to two aromatic residues, has been synthesized and characterized regarding their inhibitory potency at mGAT1-4 and binding affinity for mGAT1. Among the investigated compounds a highly potent mGAT4 inhibitor has been identified, which is defined as nipecotic acid derivative with a four-carbon atom allenic spacer terminally carrying two 4-chlorophenyl residues. The *S* enantiomer of this compound, 1-[4,4-bis(4-chlorophenyl)penta-3,4-dien-1-yl]-(*S*)-piperidine-3-carboxylic acid [(*S*)-**33d**], displays potencies in the higher nanomolar range at mGAT4 and its human equivalent hGAT-3 with pIC<sub>50</sub>s of 6.59 ± 0.01 and 6.49 ± 0.10, respectively, which are significantly higher than that of the well-known mGAT4 inhibitor (*S*)-SNAP-5114. For the synthesis of the studied nipecotic acid derivatives with terminally substituted allenic spacer a Cu<sup>I</sup>-catalyzed cross-coupling of diaryldiazomethanes or *N*-tosylhydrazones with nipecotic acid derived terminal alkynes was used as key step by which variously substituted diaryl and monoaryl residues were attached at the allene terminus of the spacer.

## Introduction

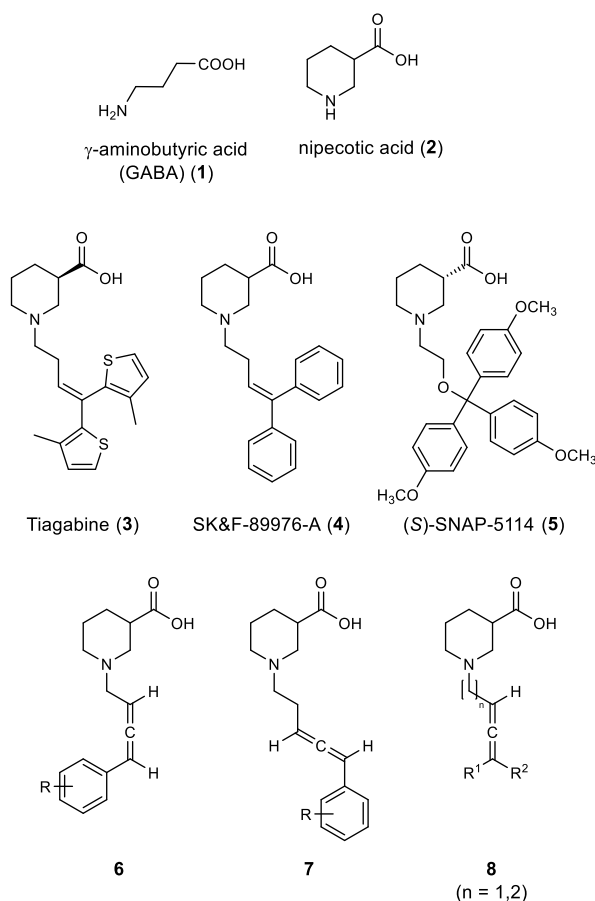
$\gamma$ -Aminobutyric acid (GABA) (1, Figure 1), the major inhibitory neurotransmitter in the mammalian central nervous system (CNS), plays a central role in normal brain function. The uptake of GABA into neurons and glial cells mediated by GABA transporters (GATs) is an important part of the GABAergic system. Targeting the individual stages of GABA signaling to overcome a dysregulation of GABA neurotransmission has become a valuable strategy for the potential therapy of related diseases such as epilepsy, Parkinson's disease, Huntington's disease, schizophrenia, and Alzheimer's disease.<sup>[1]</sup> Through inhibition of the enzymatic breakdown of GABA, inhibition of the GABA transport proteins, or direct agonism at the GABA<sub>A</sub> receptors, an increased GABAergic activity might be achieved.<sup>[2],[3],[4]</sup> The antiepileptic drug vigabatrine, for instance, improves the GABA level by acting as a suicide inhibitor of GABA transaminase, an enzyme, that is responsible for the metabolic degradation of GABA. The enhancement of GABA neurotransmission through allosteric modulation of GABA<sub>A</sub> receptors can be achieved by the use of benzodiazepines and barbiturates, which are amongst the most commonly used GABAergic drugs today. GABA transporters (GATs) mediate the transport of synaptically released GABA from the extracellular to the intracellular side of glial and neuronal cells. Inhibition of these transporters leads to enhanced GABA signaling as a consequence of increased extracellular GABA levels, which has been shown to be effective in the treatment of seizures in epileptic disorders. There are four different GABA transporter subtypes belonging to the solute carrier 6 family (SLC6), which use the co-transport of sodium ions as driving force for the translocation of their substrates against chemical gradients.<sup>[5]</sup> The subtypes cloned from mouse brain are termed as mGAT1, mGAT2, mGAT3, and mGAT4,<sup>[6]</sup> whereas the human derived GABA transporters are named as hGAT-1, hBGT-1, hGAT-2, and hGAT-3, respectively. This nomenclature is also

adopted by the Human Genome Organization (HUGO).<sup>[7]</sup> mGAT1 and mGAT4 are almost exclusively expressed around the synaptic cleft, whereupon mGAT1 is primarily located in presynaptic neuronal membranes, and mGAT4 is mainly located in astrocytes. mGAT1 is considered to be the most important transporter subtype for neuronal GABA uptake, which makes it an interesting drug target. Nipecotic acid (**2**, Figure 1), a cyclic GABA analogue, has subsequently been used as lead structure in the efforts to synthesize potent GAT inhibitors. Among them, tiagabine (**3**, Figure 1) is the only currently approved antiepileptic drug that addresses mGAT1 with high affinity and subtype selectivity. However, it has the disadvantage of occasionally observed side effects, which seem to be inherently coupled with the function of mGAT1.<sup>[8],[9]</sup> Therefore other GAT subtypes, in particular mGAT4, has gained increasing research interest.<sup>[10],[11],[12]</sup> Although plenty of highly potent and subtype selective inhibitors are available for mGAT1, the lack of similar potent inhibitors for mGAT4 still retards its pharmacological elucidation. The first prototypic mGAT4 inhibitor with moderate potency and selectivity is represented by (S)-SNAP-5114 (**5**, Figure 1).<sup>[13]</sup> However, the application of (S)-SNAP-5114 (**5**) *in vivo* is limited due to its low brain uptake and modest chemical stability.<sup>[14]</sup> In addition, its selectivity is not sufficiently pronounced to exclude effects on other GABA transporter subtypes. Hence, the development of more potent and selective mGAT4 inhibitors would help to gain deeper insights in the physiological roles and therapeutic potential of inhibitors of this transporter. Besides, there is still a need for mGAT1 inhibitors with more favorable pharmacokinetic properties than tiagabine (**3**), which is used as an add-on therapeutic agent for epilepsy,<sup>[15]</sup> and that possess also less side effects, such as dizziness, asthenia, nervousness, tremor, diarrhea, and depression, than **3**.<sup>[16]</sup>

Owing to the unique structural features, related to the presence of two in perpendicular planes located  $\pi$  bonds, allenes are important and useful building blocks in organic

synthesis. Many natural products with interesting biological activity, containing an allene moiety, have been identified.<sup>[17],[18]</sup> The interest in this scaffold is constantly growing, due to its intrinsic three-carbon axial chirality, less-hindered linear structure and high substituent-loading ability. Recently, a compound class characterized by a four-carbon atom allenic spacer connecting the nitrogen of the nipecotic acid subunit with an aromatic residue (**6**, Figure 1) has been synthesized in our group and investigated regarding its biological activities at mGAT1-4. As a result, new mGAT1 inhibitors with good inhibitory potencies and subtype selectivities have been identified among these nipecotic acid derivatives with a terminally mono-substituted allenic spacer.<sup>[19]</sup> In continuation of this study, we now aimed at the synthesis and biological characterization of related compounds **7** with a five-carbon atom allenic spacer with a single terminal substituent (Figure 1) and nipecotic acid derivatives with an allenic four- and five-carbon atom spacer with two terminal substituents **8** (Figure 1). Regarding the latter class of compounds, it was of interest to introduce two lipophilic aryl residues, like those present in SK&F-89976 (**4**, Figure 1), which are known to be favorable for enhanced potency at and selectivity for mGAT1.





**Figure 1.** Structures of GABA (1), selected GAT inhibitors (2-5) and nipecotic acid derivatives with allenic spacer (6-8).

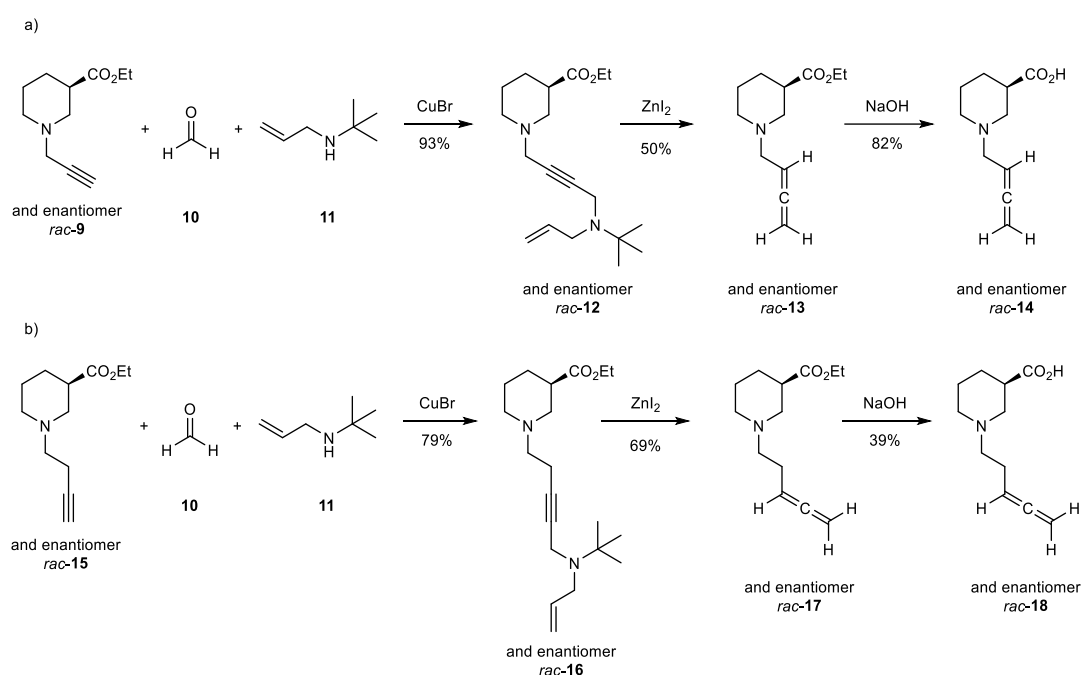
## Results and Discussion

### Chemistry

#### Synthesis of Parent Compounds

The synthesis of parent compounds *rac*-14 and *rac*-18 (Scheme 1), bearing a four- and five-carbon atom N-substituent with a terminal allene unit, respectively, has been accomplished by allenylation of the respective terminal alkynes *rac*-9 and *rac*-15 (ATA reaction). Following a recently published two-step-procedure,<sup>[20]</sup> at first the propargylic amines *rac*-12 and *rac*-16 (Scheme 1) were synthesized via Cu<sup>I</sup>-catalyzed aldehyde-alkyne-amine coupling. Thus, upon reaction of terminal alkynes *rac*-9 and *rac*-15 with paraformaldehyde and allyl(*tert*-butyl)amine in the presence of CuBr, propargylic amines *rac*-12 and *rac*-16 were obtained in yields of 93% and 79%, respectively

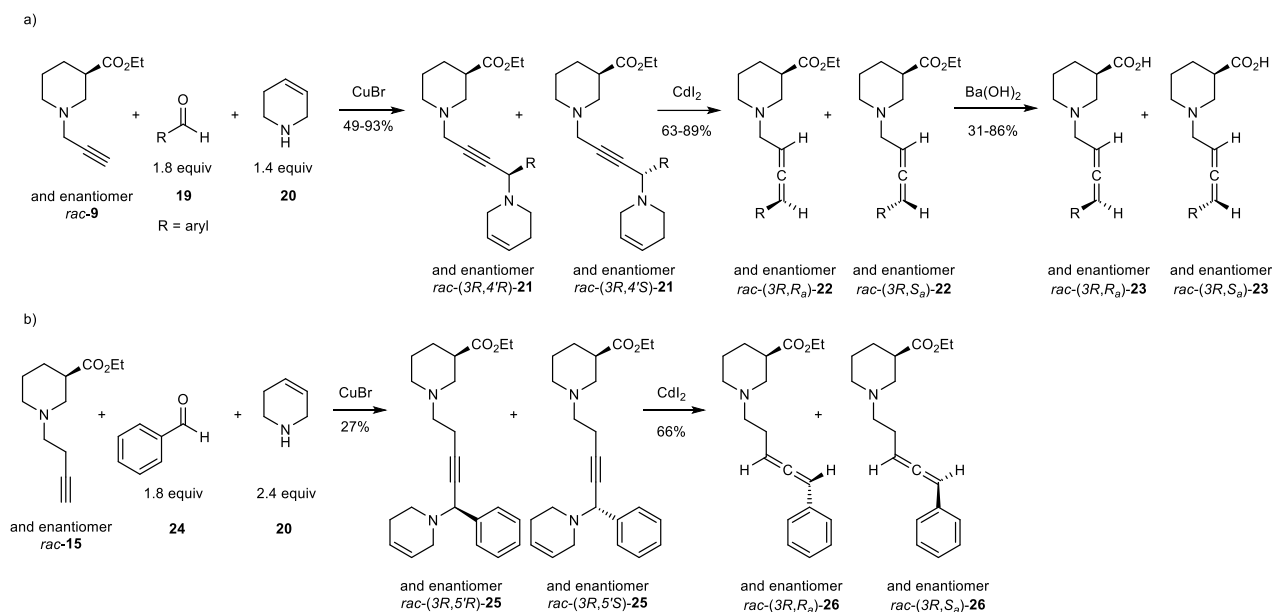
(Scheme 1). Subsequent treatment of *rac-12* and *rac-16* with  $ZnI_2$  led to the corresponding terminal allenes *rac-13* and *rac-17* in yields of 50% and 69%, respectively (Scheme 1). Finally, after hydrolysis of the carboxylic acid ester functions of the nipecotic acid ester derivatives *rac-13* and *rac-17* under basic conditions, the desired nipecotic acid derived terminal allenes *rac-14* and *rac-18*, respectively, were obtained. Parent compound *rac-18* seems to be prone to side reactions under the conditions employed for the hydrolysis and the subsequent workup. Hence, this compound was considered as too labile for biological studies. Since parent compound *rac-14* was obtained in a higher yield after hydrolysis (*rac-14*: 82%; *rac-18*: 39%; Scheme 1), this stability difference is likely to be due to the length of the allenic N-substituent.



**Scheme 1.** Synthesis route to nipecotic acid derived parent compounds *rac-14* and *rac-18* with four- and five-carbon atom comprising N-substituents with an allene moiety.

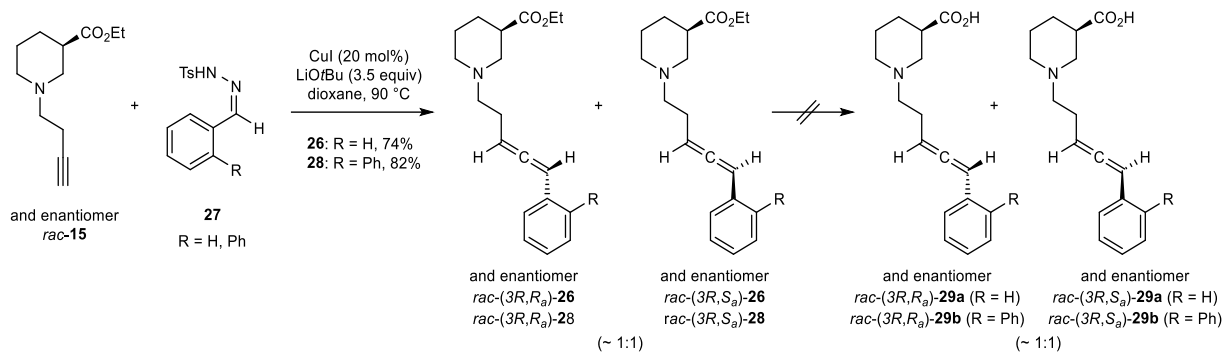
## *Synthesis of Nipecotic Acid Derivatives with a Terminally Substituted Five-Carbon Atom Allenic Spacer*

Various derivatives of parent compound *rac*-**14**, as e.g. represented by the mixture of the racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**23**/*rac*-(3*R*,*S*<sub>a</sub>)-**23** in Scheme 2a, exhibiting a four-carbon atom allenic spacer, have been successfully synthesized as previously reported by us, by applying the ATA reaction method with terminal alkyne *rac*-**9** as starting material. For the preparation of these recently described compounds a procedure similar to the synthesis route outlined in Scheme 1 has been employed, whereby, however, 1,2,5,6-tetrahydropyridine (**20**) served as amine and CdI<sub>2</sub> as catalyst (Scheme 2a).<sup>[19]</sup> Unfortunately, when this method was applied to the syntheses of derivatives of parent compound *rac*-**18**, exhibiting the longer five-carbon atom allenic spacer, the yields of the intermediate propargylic amines were comparatively low [17% with alkyne *rac*-**15**, benzaldehyde (**24**) and **20**]. Although the conversion of propargylic amines *rac*-(3*R*,5'*R*)-**25**/*rac*-(3*R*,5'*S*)-**25** to the corresponding allenes *rac*-(3*R*,*R*<sub>a</sub>)-**26**/*rac*-(3*R*,*S*<sub>a</sub>)-**26** provided good yields (Scheme 2b), further optimization experiments could not improve the yield of the intermediate propargylic amines *rac*-(3*R*,5'*R*)-**25**/*rac*-(3*R*,5'*S*)-**25** above 27% (Scheme 2b), which was considered insufficient for the intended purpose. Therefore, an alternative synthesis route had to be found, whereupon the copper catalyzed coupling of *N*-tosylhydrazones with terminal alkynes via a Cu<sup>I</sup> carbene migratory insertion mechanism appeared as a promising method, since it should rapidly lead to substituted allenes from simple and readily available starting materials.<sup>[21],[22]</sup>



**Scheme 2.** Synthesis of nipecotic acid derivatives with terminally mono-substituted allenic spacer via allenylation of terminal alkynes; a) nipecotic acid derivatives with four-carbon atom allenic spacer, b) nipecotic acid derivative with five-carbon atom allenic spacer. All racemic diastereomers have been obtained as ~ 1:1 mixtures.

When the aforementioned Cu<sup>I</sup>-catalyzed cross-coupling reaction was applied to alkyne *rac-15* and the *N*-tosylhydrazone (**27**) of benzaldehyde and of [1,1'-biphenyl]-2-carbaldehyde, respectively, the desired nipecotic acid derivatives *rac*-(3*R*,*R*<sub>a</sub>)-**26**/*rac*-(3*R*,*S*<sub>a</sub>)-**26** and *rac*-(3*R*,*R*<sub>a</sub>)-**28**/*rac*-(3*R*,*S*<sub>a</sub>)-**28** with a five-carbon atom allenic spacer were obtained in high yields (Scheme 3). In both cases, products represented ~ 1:1 mixtures of racemic diastereomers. Unfortunately, upon attempts to transform *rac*-(3*R*,*R*<sub>a</sub>)-**26**/*rac*-(3*R*,*S*<sub>a</sub>)-**26** and *rac*-(3*R*,*R*<sub>a</sub>)-**28**/*rac*-(3*R*,*S*<sub>a</sub>)-**28** into the free amino acids *rac*-(3*R*,*R*<sub>a</sub>)-**29**/*rac*-(3*R*,*S*<sub>a</sub>)-**29** under basic or acidic conditions, no such product could be isolated. This behavior is in line with the low stability observed for parent compound *rac-18* (Scheme 1), and indicates for the investigated free amino acids that the nipecotic acid derivatives with a five-carbon atom allenic spacer are more prone than their analogues with a four-carbon atom allenic spacer to side reactions.

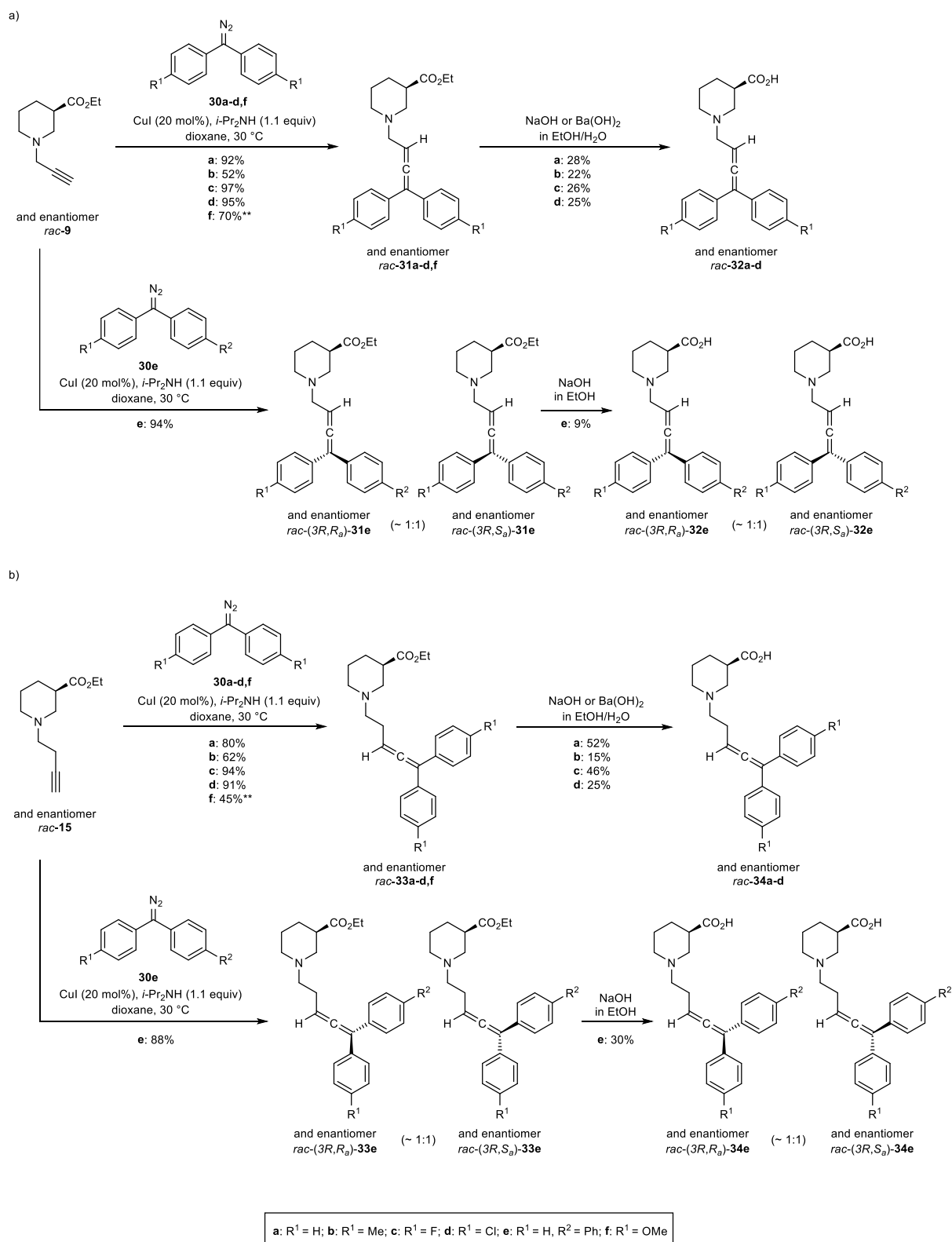


**Scheme 3.** Synthesis of nipecotic acid derivatives *rac*-(3*R*,*R*<sub>a</sub>)-26/*rac*-(3*R*,*S*<sub>a</sub>)-26 and *rac*-(3*R*,*R*<sub>a</sub>)-28/*rac*-(3*R*,*S*<sub>a</sub>)-28 with terminally mono-substituted five-carbon atom allenic spacer as ~ 1:1 mixture of racemic diastereomers via *N*-tosylhydrazones.<sup>[22]</sup>

### Synthesis of Nipecotic Acid Derivatives with Terminally Double-Substituted Four- and Five-Carbon Atom Allenic Spacers

For ketone-alkyne-amine coupling reactions (KA<sup>2</sup> coupling), in which ketones are used as substrates instead of aldehydes, according to literature harsher reaction conditions, i.e. higher temperature, are required,<sup>[23].<sup>[24]</sup></sup> which is most likely to be attributed to the lower reactivity and higher steric demand of ketones as compared to aldehydes. However, in our case all attempts to generate ketone derived propargylic amine intermediates for the allenylation of terminal alkynes (such as *rac*-9), with the intention to generate nipecotic acid derivatives with terminally double substituted allenic spacers, failed in generating the desired amino methylation products. Hence, the Cu<sup>I</sup> carbene migratory insertion process, that had already delivered the desired allenic products *rac*-(3*R*,*R*<sub>a</sub>)-26/*rac*-(3*R*,*S*<sub>a</sub>)-26 and *rac*-(3*R*,*R*<sub>a</sub>)-28/*rac*-(3*R*,*S*<sub>a</sub>)-28 in excellent yields (Scheme 3), seemed to be a very promising alternative for the synthesis of nipecotic acid derivatives with a terminally double-substituted four- and five-carbon atom allenic spacer, too. However, Wang et al. have demonstrated that substantially better yields of 1,3,3-trisubstituted allenes are obtained, when diaryldiazomethanes instead of *N*-tosylhydrazones are applied for the Cu<sup>I</sup>-catalyzed coupling of terminal alkynes.<sup>[25]</sup> Hence, this method was used in the attempts to synthesize the desired

nipecotic acid derivatives with a terminally double-substituted allenic four- and five-carbon atom spacer (Scheme 4). The required diaryldiazomethanes **30a-f** were synthesized in a general procedure via the hydrazones of the corresponding ketones. Cu<sup>I</sup>-catalyzed coupling of diaryldiazomethanes **30a-d,f** with terminal alkynes *rac*-**9** and *rac*-**15**, respectively, in the presence of *i*-Pr<sub>2</sub>NH provided finally the desired 1,3,3-trisubstituted allenes *rac*-**31a-d,f** and *rac*-**33a-d,f** in yields up to 97%. When diazomethane **30e** exhibiting two different aryl residues was employed with *rac*-**9** and *rac*-**15** in this reaction, accordingly, *rac*-(3*R*,*R*<sub>a</sub>)-**31e**/*rac*-(3*R*,*S*<sub>a</sub>)-**31e** and *rac*-(3*R*,*R*<sub>a</sub>)-**33e**/*rac*-(3*R*,*S*<sub>a</sub>)-**33e** as ~ 1:1 mixture of racemic diastereomers were obtained [yield: *rac*-(3*R*,*R*<sub>a</sub>)-**31e**/*rac*-(3*R*,*S*<sub>a</sub>)-**31e**: 94%; *rac*-(3*R*,*R*<sub>a</sub>)-**33e**/*rac*-(3*R*,*S*<sub>a</sub>)-**33e**: 88%]. Subsequent hydrolysis under basic conditions delivered the corresponding free amino acids *rac*-**32a-d**, *rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e**, *rac*-**34a-d** and *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e** in yields up to 52% (Scheme 4). Accordingly, the enantiopure compounds (*R*)-**32d** and (*S*)-**32d** had been synthesized applying terminal alkynes (*R*)-**9** and (*S*)-**9**, respectively, as starting material [yields: (*R*)-**32d**: 51%, (*S*)-**32d**: 68%].

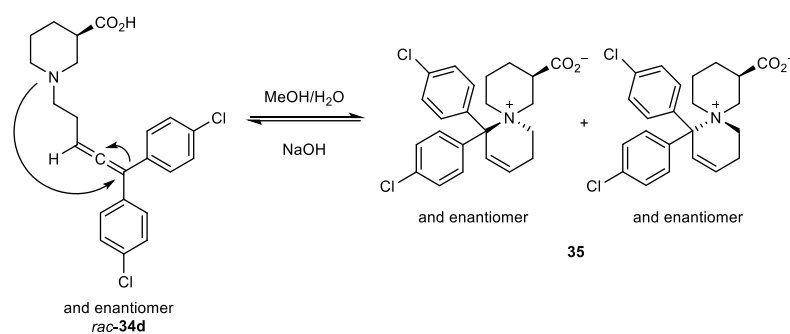


**Scheme 4.** Synthesis of nipecotic acid derivatives with terminally double-substituted allenic spacer via  $\text{Cu}^I$ -catalyzed cross-coupling of diaryldiazomethanes **30a-f** and terminal alkynes *rac-9* and *rac-15*. \*\*decomposition after isolation.

Nipecotic acid derivatives *rac-34a-d* and *rac-(3R,R<sub>a</sub>)-34e/rac-(3R,S<sub>a</sub>)-34e* with an allenic five-carbon atom spacer, were found to be prone to side reactions during RP-MPLC purification and subsequent freeze drying. Without recognizable differences in reaction performance the decomposition tendency is varying within this series of nipecotic acid derivatives, whereby these compounds distinguish from their more stable analogues [*rac-32a-d*, *rac-(3R,R<sub>a</sub>)-32e/rac-(3R,S<sub>a</sub>)-32e*] only by the length of the allenic spacer. The substituents on the two phenyl residues were observed to have an influence on the decomposition tendency. For compound *rac-34d* for example, complete decomposition was observed and by means of <sup>1</sup>H NMR of isolated side product **35** (see supporting information), the most prominent side reaction was potentially identified as a reversible cyclization reaction (Scheme 5). Side product **35** exists as a mixture of racemic diastereomers. Thus, NMR signals could not be clearly assigned, whereby the proposed structure is not completely confirmed. In literature, related allene involved 6-endo-trig cyclization reactions have already been described.<sup>[26]</sup> Whereas compound *rac-34d*, exhibiting a *p*-chloro substituent at both phenyl groups, had completely decomposed to **35** after MPLC purification in a MeOH/H<sub>2</sub>O solvent mixture and subsequent lyophilisation, no decomposition has been observed for nipecotic acid derivative *rac-34c*, bearing *p*-fluoro substituents. Fortunately, after repeating the synthesis under identical reaction conditions, compound *rac-34d* could already be isolated in pure form after aqueous workup and the MPLC purification step - likely to be responsible together with the freeze drying for the decomposition - could be skipped. With compound *rac-34d* in hand, further experiments have been performed to investigate its tendency to decompose during the required incubation time in the applied incubation buffers for uptake (Tris-NaCl buffer) and binding assays (Krebs buffer). For this purpose, a 100 μM solution of *rac-34d* in buffer solution, containing 1% DMSO was stirred for 40 min, respectively 35 min, at

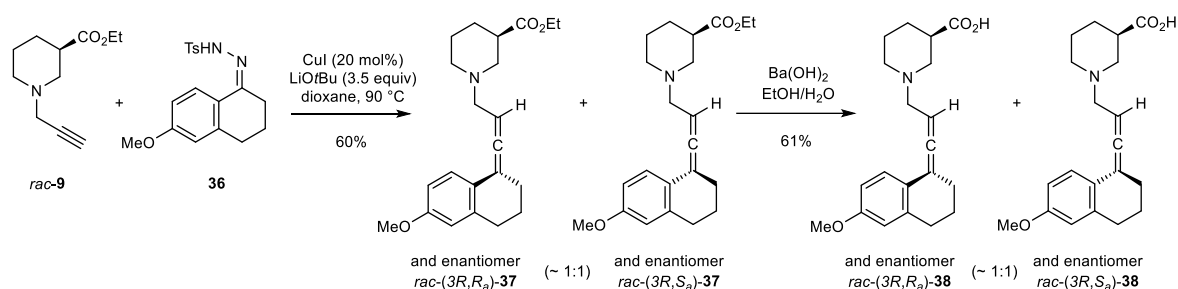


37 °C and was quenched by ether extraction. <sup>1</sup>H NMR analysis of the extracted residue revealed that no decomposition had occurred and therefore results of the following biological studies can be assumed to result from the allenic compound *rac-35d*. Nipecotic acid derivative *rac-34d* displayed the highest tendency to undergo decomposition, thus for the nipecotic acid derivatives *rac-34a-c,e*, being considered as the more stable analogues, the same can be assumed.



**Scheme 5.** Proposed reversible 6-endo cyclization of nipecotic acid derivative *rac-34b* to side product **35**.

When applying ketones other than diaryl-ketones, the coupling procedure via *N*-tosylhydrazones was used (Scheme 6). Reaction of the *N*-tosylhydrazone of 6-methoxy-1-tetralone (**36**) with terminal alkyne *rac-9* under copper catalysis delivered the corresponding mixture of nipecotic acid derivatives *rac*-(3*R*,*R*<sub>a</sub>)-**38** and *rac*-(3*R*,*S*<sub>a</sub>)-**38** in 61% yield.



**Scheme 6.** Synthesis of nipecotic acid derivatives *rac*-(3*R*,*R*<sub>a</sub>)-**38** and *rac*-(3*R*,*S*<sub>a</sub>)-**38** with terminally double-substituted four-carbon atom allenic spacer as ~ 1:1 mixture of racemic diastereomers via *N*-tosylhydrazone **37**.

## Biological Evaluations

For synthesized nipecotic acid derivatives *rac-14*, *rac-32a-d*, *rac-(3R,R<sub>a</sub>)-32e/rac-(3R,S<sub>a</sub>)-32e*, *rac-34a-d*, *rac-(3R,R<sub>a</sub>)-34e/rac-(3R,S<sub>a</sub>)-34e* and *rac-(3R,R<sub>a</sub>)-38/rac-(3R,S<sub>a</sub>)-38* binding affinities for mGAT1 ( $pK_i$  values) were determined in MS Binding Assays with NO711 as native MS marker.<sup>[27]</sup> In addition, their functional activity was characterized as  $pIC_{50}$  values in [<sup>3</sup>H]GABA-Uptake-Assays on HEK293 cells stably expressing the individual mouse GABA transporters mGAT1-mGAT4.<sup>[28]</sup> Compounds *rac-(3R,R<sub>a</sub>)-32e/rac-(3R,S<sub>a</sub>)-32e*, *rac-(3R,R<sub>a</sub>)-34e/rac-(3R,S<sub>a</sub>)-34e* and *rac-(3R,R<sub>a</sub>)-38/rac-(3R,S<sub>a</sub>)-38* have been tested as ~ 1:1 mixtures of racemic diastereomers as which they had been formed. The biological results for each of the stereoisomers, i.e. enantiomers and diastereomers, will most likely differ from the results of the mixture. Hence, the derived structure-activity relationships for these compounds should be regarded as estimates.

At first, parent compound *rac-14*, bearing an allenic four-carbon atom residue attached to the nitrogen of the nipecotic acid serving as spacer in the more elaborate compounds, was analyzed regarding its biological activity. Compared to (*RS*)-nipecotic acid (**2**:  $pIC_{50} = 4.88 \pm 0.07$ ) the inhibitory potency of *rac-14* is one log unit lower at mGAT1 (*rac-14*:  $pIC_{50} = 3.89$ , Table 1, entry 1). Furthermore, compound *rac-14* exhibits some but low subtype selectivity for mGAT1. Introducing phenyl groups at the terminal position of the allenic four-carbon atom residue resulted in nipecotic acid derived *rac-32a* as a close analogue to the known mGAT1 inhibitor SK&F-89976-A (**4**) from which it differs only by an additional double bond transforming the mono- into a di-unsaturated allenic spacer. Due to this substitution, the inhibitory potency at mGAT1 increased to  $pIC_{50} = 5.13 \pm 0.11$  (*rac-32a*, Table 1, entry 2), which is now in the range of that of (*RS*)-nipecotic acid. The mGAT1 inhibitory potency of compound *rac-32a*,

equipped with an allenyl spacer, is, however, about one log unit lower than that of SK&F-89976-A, possessing an alkenyl spacer (**4**:  $pIC_{50} = 6.16 \pm 0.05$ , Table 1, entry 16), what might be explained by the different flexibility and geometry of both spacer types. Since the nature of the spacer seems to influence the inhibitory potency, in addition to *rac*-**32a** with a four-carbon atom allenic spacer also compound *rac*-**34a** with an extended five-carbon atom allenic spacer has been studied. This spacer extension, however, led to a decrease in mGAT1 inhibition of 0.52 log units (*rac*-**34a**:  $pIC_{50} = 4.61 \pm 0.00$ , Table 1, entry 3). The introduction of methyl groups in *para*-position of both phenyl residues in *rac*-**32a** and *rac*-**34a** led to a slight increase of about 0.24 log units for the derivative with a five-carbon atom allenic spacer (*rac*-**34b**:  $pIC_{50} = 4.85 \pm 0.05$ , Table 1, entry 5), whereas the mGAT1 inhibition potency of the derivative with a four-carbon atom allenic spacer remained unchanged compared to *rac*-**32a** (*rac*-**32b**:  $pIC_{50} = 5.19 \pm 0.02$ , Table 1, entry 4). An increase in inhibitory potency at mGAT1 was observed when in *rac*-**32b**, with the four-carbon atom allenic spacer, the methyl groups were replaced by fluorine substituents resulting in compound *rac*-**32c** with a  $pIC_{50}$  of  $5.97 \pm 0.10$  (Table 1, entry 6). In contrast, the inhibitory potency of related compound *rac*-**34c** with an extended five-carbon atom allenic spacer did not increase with fluorine instead of the methyl substituents, it remained more or less unchanged (*rac*-**32c**:  $pIC_{50} = 4.89 \pm 0.09$ , Table 1, entry 7). The so far described nipecotic acid derivatives with a terminally double-substituted allenic four- and five-carbon atom spacer *rac*-**32a-c** and *rac*-**34a-c** displayed a subtype preference for mGAT1. This is least distinct for compound *rac*-**32b** for which the inhibitory potency at mGAT3 and mGAT4 is only slightly lower than at mGAT1 and further slowly declines for mGAT2.

An additional gain in mGAT1 inhibition of about 0.5 log units was observed when *p*-chlorine instead of *p*-fluorine is present in the terminal phenyl rings, resulting in *rac*-**32d** with  $pIC_{50} = 6.43 \pm 0.07$  (Table 1, entry 8). Surprisingly, for this compound not only the

inhibitory potency at mGAT1 increased but also at mGAT4 which increase was even distinctly higher (~ 1.5 log units as compared to 0.5 log units for mGAT1), leading to a very good pIC<sub>50</sub> value of 6.08 ± 0.05 (Table 1, entry 8). The pIC<sub>50</sub> values of mGAT4 benchmark inhibitor (S)-SNAP-5114 (**5**) displayed in Table 1 are based on repetitive testing over several years of (S)-SNAP-5114 as a reference mGAT4 inhibitor in our laboratory, leading to continuously updated mean values (pIC<sub>50</sub> = 5.65 ± 0.02 at mGAT4, Table 1, entry 17). Thus, when *rac*-**32d** was characterized in [<sup>3</sup>H]GABA-Uptake-Assays on HEK293 cells stably expressing mGAT4 in parallel also (S)-SNAP-5114 as a reference was studied, what allows a direct comparison of the inhibitory potency of *rac*-**32d** with (S)-SNAP-5114 (**5**). The obtained pIC<sub>50</sub> value of (S)-SNAP-5114 (**5**) in this experiment was found to be 6.09 ± 0.09, and thus relatively high. Hence, considering the SEM, the pIC<sub>50</sub> value of *rac*-**32d** at this transporter subtype (*rac*-**32d**: pIC<sub>50</sub> = 6.08 ± 0.05 at mGAT4, Table 1, entry 8) is identical with that of (S)-SNAP-5114 (**5**). However, compound *rac*-**32d** possesses no distinct subtype selectivity for mGAT4, due to its even higher inhibitory potency at mGAT1.

For mGAT1 inhibitors delineated from nipecotic acid, it is well known that the biological activity resides mainly in the *R* enantiomer, whereas for mGAT4 inhibitors the *S* enantiomer is more active. Hence, the enantiopure *R* and *S* isomers of *rac*-**32d** had been synthesized and characterized with the intention to further increase mGAT1 and mGAT4 inhibitory potency and subtype selectivity. As expected, compared to the racemate, the isomer (*R*)-**32d** possesses an increased mGAT1 activity [(*R*)-**32d**: pIC<sub>50</sub> = 6.81 ± 0.03, Table 1, entry 9], which is in the range of the known inhibitor tiagabine (**3**: pIC<sub>50</sub> = 6.88 ± 0.12, Table 1, entry 15), whereas mGAT4 inhibition is reduced [(*R*)-**32d**: pIC<sub>50</sub> = 5.70 ± 0.11, Table 1, entry 9]. The opposite is true for isomer (*S*)-**32d**, for which the inhibitory potency at mGAT1 is lower [(*S*)-**32d**: pIC<sub>50</sub> = 5.87 ± 0.11, Table 1, entry 10] and at mGAT4 increased to a distinguished pIC<sub>50</sub> value of 6.59 ± 0.01

(Table 1, entry 10), which is now significantly higher than that of (*S*)-SNAP-5114 (**5**,  $pIC_{50} = 6.09 \pm 0.09$ ). The lipophilic domain of (*S*)-**32d** is derived from a diaryl moiety. While such a structural motif is well known as lipophilic domain of mGAT1 inhibitors, it is to our knowledge unprecedented for mGAT4 inhibitors with high potencies. Regarding the subtype selectivity of (*S*)-**32d** for mGAT4 over mGAT1 and mGAT3 the difference of the  $pIC_{50}$  values is about 0.6-0.7 log units, which indicates that in *in vivo* studies a mixed pharmacological profile influenced by the latter GABA transporter subtypes cannot be excluded. The poor subtype selectivity for mGAT4 over mGAT3 is, however, a problem frequently observed for mGAT4 inhibitors.<sup>[28],[29],[30],[32]</sup> Isomer (*R*)-**32d** is at least one order of magnitude more potent towards mGAT1 than towards mGAT2, mGAT3 and mGAT4, respectively, indicating a reasonable subtype selectivity over the other subtypes. In order to confirm potencies and to establish  $pIC_{50}$  values also at the human equivalent of mGAT4, compounds *rac*-**32d**, (*R*)-**32d**, and (*S*)-**32d** were additionally characterized at hGAT-3 in competitive MS based GABA transport experiments (MS Transport Assays)<sup>[31],[32]</sup> utilizing COS cells stably expressing hGAT-3. The results obtained in these experiments reassured the high inhibitory potencies of *rac*-**32d** and (*S*)-**32d** at hGAT-3 [*rac*-**32d**:  $pIC_{50} = 6.35 \pm 0.02$ , Table 1, entry 8; (*S*)-**32d**:  $pIC_{50} = 6.49 \pm 0.10$ , Table 1, entry 10], with (*S*)-**32d** possessing a slightly higher  $pIC_{50}$  value than *rac*-**32d**. Accordingly, the inhibitory potency of (*R*)-**32d** [(*R*)-**32d**:  $pIC_{50} = 5.62 \pm 0.06$ , Table 1, entry 9] is lower than that of the racemic compound *rac*-**32d** and even more than that of its enantiomer (*S*)-**32d**. In nipecotic acid derivative *rac*-**34d** (Table 1, entry 11) the extension of the allenic spacer to five carbons resulted in a loss of activity at all four transporter subtypes compared to compound *rac*-**32d**, equipped with the four-carbon atom allenic spacer.

In an effort to further elucidate structural influences, two different diaryl residues, a phenyl and a 4'-biphenyl moiety, had been introduced as lipophilic domains at the







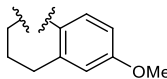
termini of the allenic spacer of the nipecotic acid derivatives. This resulted in *rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e** as derivatives with a four-carbon atom allenic spacer and *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e** as derivatives with a five-carbon atom allenic spacer, respectively, which had been obtained as ~ 1:1 mixture of racemic diastereomers and also characterized with regard to their biological activity as such. At the subtypes mGAT1-3 both compound mixtures displayed a pIC<sub>50</sub> value of around 5, though for mGAT4 inhibition, the derivative possessing the shorter allenyl spacer is about 0.45 log units more active than the derivative with extended spacer [*rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e**: pIC<sub>50</sub> = 5.35 ± 0.12, Table 1, entry 12; *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e**: pIC<sub>50</sub> = 4.90 ± 0.08, Table 1, entry 13]. The mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e** with a four-carbon atom allenic spacer has almost equal potencies at all four GABA transporter subtypes, whereas *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e** with a five-carbon atom allenic spacer is slightly more potent towards mGAT1 than towards mGAT2-4. The moderate to good potencies at mGAT4 have been confirmed at hGAT-3, at which even higher pIC<sub>50</sub> values for both compounds have been obtained [*rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e**: pIC<sub>50</sub> = 5.78 ± 0.11, Table 1, entry 12; *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e**: pIC<sub>50</sub> = 5.21 ± 0.08, Table 1, entry 13].

Finally, to mimic one of the anisole groups of (S)-SNAP-5114 (**5**), the nipecotic acid derived ~ 1:1 mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**38**/*rac*-(3*R*,*S*<sub>a</sub>)-**38** with a four-carbon atom allenic spacer of which the terminal allene carbon is embedded in the lipophilic ring system has been synthesized. Contrary to the expected results, with pIC<sub>50</sub> values below 4.87 at all four transporter subtypes, this compound mixture is amongst the least potent inhibitors in this study (Table 1, entry 14).

To sum up the influence of the allenic spacer length, the shorter four-carbon atom spacer is more favored, except for the at the terminal allene moiety unsymmetrical

substituted compound mixtures *rac*-(3*R*,*R*<sub>a</sub>)-**32e**/*rac*-(3*R*,*S*<sub>a</sub>)-**32e** and *rac*-(3*R*,*R*<sub>a</sub>)-**34e**/*rac*-(3*R*,*S*<sub>a</sub>)-**34e**, where the inhibitory potency at mGAT1-3 is not influenced by the spacer length. The inhibitory potencies of most of the studied compounds at mGAT1 (pI<sub>C</sub><sub>50</sub>) were about a half to one log unit lower than the corresponding p*K*<sub>i</sub> values. Such a difference between pI<sub>C</sub><sub>50</sub> and p*K*<sub>i</sub> values is a common phenomenon constantly observed for mGAT1 inhibitors when characterized in this test system.<sup>[33],[34],[35],[36],[37]</sup> The conclusions drawn for the above discussed pI<sub>C</sub><sub>50</sub> values at mGAT1 are equally well supported by the observed p*K*<sub>i</sub> values.

**Table 1:** Nipecotic acid derived GAT inhibitors containing terminally double-substituted allenic spacers and their inhibitory potencies at mGAT1-4 (hGAT-3) and binding affinities for mGAT1.

Entry	Compd	R <sup>1</sup>	R <sup>2</sup>	n	pK <sub>i</sub> <sup>e</sup>				
					mGAT1 <sup>f</sup>	mGAT1 <sup>f</sup>	mGAT2 <sup>f</sup>	mGAT3 <sup>f</sup>	mGAT4 <sup>f</sup> (hGAT-3) <sup>g</sup>
1	<i>rac</i> - <b>14</b> <sup>a</sup>	H	-	1	3.58 ± 0.03	3.89	3.32	88%	94%
2	<i>rac</i> - <b>32a</b> <sup>a</sup>		-	1	5.93 ± 0.06	5.13 ± 0.11	80%	78%	82%
3	<i>rac</i> - <b>34a</b> <sup>a</sup>			2	5.26 ± 0.03	4.61 ± 0.00	3.75	3.89	64%
4	<i>rac</i> - <b>32b</b> <sup>a</sup>		-	1	5.86 ± 0.05	5.19 ± 0.02	4.56	4.98 ± 0.05	4.94 ± 0.07
5	<i>rac</i> - <b>34b</b> <sup>a</sup>			2	5.80 ± 0.08	4.85 ± 0.05	4.09	4.23	4.08
6	<i>rac</i> - <b>32c</b> <sup>a</sup>		-	1	6.25 ± 0.04	5.97 ± 0.10	4.10	4.16	4.52
7	<i>rac</i> - <b>34c</b> <sup>a</sup>			2	5.49 ± 0.06	4.89 ± 0.09	63%	50%	63%
8	<i>rac</i> - <b>32d</b> <sup>a</sup>		-	1	6.81 ± 0.05	6.43 ± 0.07	5.12 ± 0.06	5.53 ± 0.08	6.08 ± 0.05 (6.35 ± 0.02) <sup>g</sup>
9	( <i>R</i> )- <b>32d</b> <sup>b</sup>				6.99 ± 0.06	6.81 ± 0.03	4.80 ± 0.10	5.38 ± 0.08	5.70 ± 0.11 (5.62 ± 0.06) <sup>g</sup>
10	( <i>S</i> )- <b>32d</b> <sup>c</sup>				5.60 ± 0.10	5.87 ± 0.11	5.39 ± 0.03	5.96 ± 0.04	6.59 ± 0.01 (6.49 ± 0.10) <sup>g</sup>
11	<i>rac</i> - <b>34d</b> <sup>a</sup>				2	6.20 ± 0.10	5.72 ± 0.10	4.92	4.55 ± 0.07
12	<i>rac</i> -(3 <i>R</i> , <i>R</i> <sub>a</sub> )- <b>32e</b> / <i>rac</i> -(3 <i>R</i> , <i>S</i> <sub>a</sub> )- <b>32e</b> <sup>d</sup>			1	5.91 ± 0.05	5.30 ± 0.12	5.19 ± 0.08	5.08 ± 0.12	5.35 ± 0.12 (5.78 ± 0.11) <sup>g</sup>
13	<i>rac</i> -(3 <i>R</i> , <i>R</i> <sub>a</sub> )- <b>34e</b> / <i>rac</i> -(3 <i>R</i> , <i>S</i> <sub>a</sub> )- <b>34e</b> <sup>d</sup>			2	6.05 ± 0.09	5.33 ± 0.07	4.91 ± 0.12	4.99 ± 0.04	4.90 ± 0.08 (5.21 ± 0.08) <sup>g</sup>
14	<i>rac</i> -(3 <i>R</i> , <i>R</i> <sub>a</sub> )- <b>38</b> / <i>rac</i> -(3 <i>R</i> , <i>S</i> <sub>a</sub> )- <b>38</b> <sup>d</sup>			1	4.23	4.87	81%	75%	70%
15	tiagabine ( <b>3</b> )				7.43 ± 0.11 <sup>h</sup>	6.88 ± 0.12 <sup>i</sup>	52%/100 μM <sup>i</sup>	64%/100 μM <sup>i</sup>	73%/100 μM <sup>i</sup> (78%/250 μM) <sup>i,g</sup>
16	SK&F-89976-A ( <b>4</b> )				6.73 ± 0.02 <sup>h</sup>	6.16 ± 0.05 <sup>i</sup>	3.43 ± 0.07 <sup>i</sup>	3.71 ± 0.04 <sup>i</sup>	3.56 ± 0.06 <sup>i</sup> (3.00 ± 0.06) <sup>i,g</sup>
17	(S)-SNAP-5114 ( <b>5</b> )				4.56 ± 0.02 <sup>j</sup>	4.07 ± 0.09 <sup>k</sup>	63%/100 μM <sup>k</sup>	5.29 ± 0.04 <sup>k</sup>	5.65 ± 0.02 <sup>k</sup> (5.48 ± 0.10) <sup>k,g</sup>

<sup>a</sup> Compounds were tested as racemates. <sup>b</sup> %ee=77.7. <sup>c</sup> %ee=95.4. <sup>d</sup> Investigated as ~ 1:1 mixture of diastereomeric compounds in racemic form. <sup>e</sup> Data are the mean ± SEM of three or more independent experiments, each performed in triplicate. In case of low inhibitory potencies percentages are given that represent remaining GABA uptake in presence of 100 μM test compound (except for tiagabine (**3**) at hGAT-3, which was applied in a concentration of 250 μM). <sup>f</sup> Results of [<sup>3</sup>H]GABA uptake assays performed with HEK cells stably expressing mGAT1-mGAT4 in our laboratory. <sup>g</sup> Results of MS Transport Assays performed with COS cells stably expressing hGAT-3 in our laboratory. <sup>h</sup> Values from reference literature<sup>[38]</sup>. <sup>i</sup> Values from reference literature<sup>[28]</sup> (mGAT1-mGAT4) and reference literature<sup>[32]</sup> (hGAT-3). <sup>j</sup> Value from reference literature<sup>[39]</sup>. <sup>k</sup> Values from reference literature<sup>[40]</sup>.



## Conclusion

In summary, a new series of nipecotic acid derived GABA uptake inhibitors, characterized by an allenic four- and five-carbon atom spacer, bearing lipophilic aryl residues at the spacer terminus, has been synthesized and biologically characterized. Compounds equipped with the shorter four-carbon atom allenic spacer have been identified to possess higher biological activity than those with an allenic five-carbon atom spacer. The synthesis of nipecotic acid derivatives with terminally double-substituted allenic spacers was accomplished by two efficient cross-coupling reactions, whereby diaryl ketones as starting material have been implemented in Cu<sup>I</sup>-catalyzed cross-couplings of related ketone derived diaryldiazomethanes with nipecotic acid derived terminal alkynes, and substrates like 6-methoxy-1-tetralone have been transformed in an analogue cross-coupling reaction via the corresponding *N*-tosylhydrazones. The latter cross-coupling method has also been applied for the synthesis of nipecotic acid derivatives with a terminally mono-substituted allenic five-carbon atom spacer attached to the amino nitrogen. Among the biologically investigated compounds derivative *rac*-**32d**, exhibiting two 4-chlorophenyl residues connected via the four-carbon atom allenic spacer with the amino nitrogen of the polar nipecotic acid head, was identified as highly potent mGAT1 and mGAT4 inhibitor. The *R* enantiomer (*R*)-**32d** displays an inhibitory potency at mGAT1 that is in the range of the known inhibitor tiagabine (**3**). For the enantiopure *S* isomer (*S*)-**32d** pIC<sub>50</sub> values of 6.59 ± 0.01 at mGAT4 and 6.49 ± 0.10 for the human equivalent hGAT-3 have been determined, which are significantly higher than that of the benchmark mGAT4 inhibitor (*S*)-SNAP-5114 (**5**). The combination of a rigid allenyl spacer with a diaryl residue as lipophilic domain in compound (*S*)-**32d** possesses a novel structural scaffold for this kind of bioactive compounds. Unfortunately, the subtype selectivity of (*S*)-**32d** for mGAT4 over the other three subtypes is not very pronounced. Hence, there is still a

lack of highly selective mGAT4 inhibitors that would allow to elucidate the pharmacological role of this GABA transporter subtype. The herein described compounds represent a new structural motif for mGAT4 inhibitors, which could serve as useful starting points for the further expansion of structure-activity relationships of mGAT4 inhibitors and facilitate the design of new ligands with higher potencies and better selectivities at this molecular target.

## Experimental Section

All commercially available reagents were used without further purification. Unless otherwise noted, all reactions were performed in oven dried glassware under moisture-free conditions and argon- or nitrogen atmosphere. Toluene and 1,4-dioxane were dried over sodium and distilled under nitrogen. Chlorobenzene was dried over CaCl<sub>2</sub>, distilled under nitrogen atmosphere and stored over molecular sieves (4 Å) under nitrogen atmosphere prior to use. For chromatographic purposes only distilled solvents were used (EtOAc, *iso*-hexane/PE 42-62 °C, dichloromethane/DCM, MeOH, *n*-pentane, Et<sub>2</sub>O, H<sub>2</sub>O). Flash column chromatography was performed using silica gel (grading 0.035-0.070 mm). Thin layer chromatography (TLC) was carried out on precoated silica gel F<sub>254</sub> glass plates. Preparative MPLC was performed using a Büchi instrument (C-605 binary pump system, C-630 UV detector at 254 nm and C-660 fraction collector) and a Sepacore glass column B-685 (26x230 mm) equipped with YMC Gel SIL-HG (12 nm, 5-20 µm) for straight phase and YMC Gel Triart Prep C18-S (12 nm, S-20 µm) for reverse phase. NMR spectra were recorded on a JNMNR-GX (JEOL) at room temperature (unless otherwise noted) on 400 MHz (<sup>1</sup>H NMR: 400 MHz, <sup>13</sup>C NMR: 101 MHz) and 500 MHz (<sup>1</sup>H NMR: 500 MHz, <sup>13</sup>C NMR: 126 MHz) spectrometers. These NMR spectrometers were also used for DEPT, HMQC, HMBC and COSY experiments. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts were referenced to the deuterated solvent signals and the coupling constants were stated with an accuracy of 0.5 Hz. MestreNova software was used for further analysis of the NMR data. Broadened signals in <sup>1</sup>H NMR spectra were supplemented by the index “br” (*s*<sub>br</sub>, *d*<sub>br</sub>, *t*<sub>br</sub>) and signals from mixtures of diastereomeric compounds in racemic form were labeled as “dia1” or “dia2”. IR spectra were recorded with a FT-IR spectrometer and Spectrum v2.00 software was used for analysis. Samples were measured either as KBr pellets or as films on NaCl plates. High resolution mass spectrometry was carried out with a LTQ FT Ultra mass spectrometer (ThermoFinnigan). Optical rotations were determined by a 241 MC Polarimeter ADP440+ at λ=589 cm<sup>-1</sup>. Purity testing of biologically tested compounds *rac*-**14**, *rac*-**34a** and *rac*-**34d** was done by Quantitative <sup>1</sup>H NMR (qHNMR)<sup>[41],[42]</sup> and purity was determined as ≥95%. QHNMR data based on peak area ratios are determined under conditions that assure complete relaxation. For qHNMR the internal standard maleic acid (TraceCERT®, Sigma Aldrich, Lot#BCBM8127V: purity 99.94%) was dissolved in MeOD. The purity was calculated using the purity calculator of MestreNova NMR software (MestreLab Research S.L.). For compounds *rac*-**32a**, *rac*-**32b**, *rac*-**32c**, *rac*-**32d**, (*R*)-**32d**, (*S*)-**32d**, *rac*-(*3R,R<sub>a</sub>*)-**32e**/*rac*-(*3R,S<sub>a</sub>*)-**32e**, *rac*-**34b**, *rac*-**34c**, *rac*-(*3R,R<sub>a</sub>*)-**34e**/*rac*-(*3R,S<sub>a</sub>*)-**34e**, and *rac*-(*3R,R<sub>a</sub>*)-**38**/*rac*-(*3R,S<sub>a</sub>*)-**38** purity testing was done by means of analytical HPLC on an

Agilent 1100 instrument (G1329A ALS autosampler, G1316A column compartment, G1314A VWD detector, G1312A binary pump, G1379A degasser), equipped with a Lichrospher 100 RP-18 (5  $\mu\text{m}$ ) in a LiChroCART 250-4 column, with elution at 0.5 mL/min with ammonium formate buffer (10 mM, pH 6.8) to MeOH 20:80 and purity was determined as  $\geq 95\%$ .

**General Procedure for the N-Alkylation (GP1):** N-alkylation was performed employing a synthesis route similar to a procedure described in literature.<sup>[43]</sup> Alkyne (1.00 equiv) and amine (1.20 equiv) were dissolved in acetone (2 mL/mmol) and  $\text{Na}_2\text{CO}_3$  (2.50 equiv) and NaI (0.50 equiv) were added. The reaction mixture was refluxed for 72 h and the reaction was monitored by TLC. For quenching, DCM (5 mL/mmol) and water (5 mL/mmol) were added and the product was extracted with DCM. The combined organic phases were then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under vacuum. The crude product was purified by flash column chromatography to afford the desired alkyne.

**General Procedure for the Synthesis of Tosylhydrazones (27, 36) by Literature Procedure<sup>[44]</sup> (GP2):** A solution of pure  $\text{TsNHNH}_2$  (1 equiv) in methanol (1 mL/mmol) was stirred and heated to 60  $^\circ\text{C}$  until the  $\text{TsNHNH}_2$  dissolved. The mixture was cooled to rt. Then the corresponding aldehyde (1 equiv) was dropped slowly to the mixture. The crude product could be obtained as needle shaped crystals. The colorless crystals were collected by filtration and washed with PE and were then dried under vacuum to afford the desired product.

**General Procedure for the Preparation of Diaryldiazomethanes 30a-f by Literature Procedure<sup>[45]</sup> (GP3):** Hydrazine monohydrate (80% purity) was added to a solution of diarylmethanone in ethanol. Then, aqueous HCl (37%, 0.50 mL/20 mmol ketone) was added and the mixture was heated to reflux overnight. After cooling to room temperature, the diarylmethanone hydrazone was precipitated as needle shaped crystals. Filtration of the crude mixture gave pure diarylmethanone hydrazones. A mixture of diarylmethanone hydrazone (10.0 mmol, 1.0 equiv), anhydrous  $\text{MgSO}_4$  (1.00 g) and 30.0 mL DCM was cooled to 0  $^\circ\text{C}$ . To this rapidly stirred mixture activated  $\text{MnO}_2$ <sup>[46]</sup> (3.04 g, 35.0 mmol, 3.5 equiv) was added in one portion. The reaction mixture was warmed to room temperature and kept stirring for 8 h and then the solid was filtered off with a celite pad and washed with DCM. After removal of the solvent under reduced pressure, the residual was purified by column chromatography (pretreated with PE/ $\text{Et}_3\text{N}$  10:1) with PE/ $\text{Et}_3\text{N}$  20:1 as the eluent to afford diaryldiazomethanes **30a-f** as purple solid or oil.

**General Procedure for the Synthesis of Allenes via N-Tosylhydrazones (GP4):<sup>[47]</sup>** Under argon atmosphere, the alkyne (1 equiv) was added to a mixture of CuI (0.2 equiv),  $\text{Li}^t\text{OBu}$  (3.5 equiv), and *N*-tosylhydrazone (2.2 equiv) in 1,4-dioxane (5 mL/0.4 mmol). The solution was stirred at 90  $^\circ\text{C}$  for 1 h, and the progress of the reaction was monitored by TLC. Upon completion of the reaction, the mixture was cooled to rt and was filtered through a short silica gel column eluting with EtOAc. The solvent was removed in vacuum to leave a crude product mixture, which was purified by column chromatography to afford the pure allene.

**General Procedure for the  $\text{Cu}^I$ -Catalyzed Cross-Coupling of Diaryldiazomethanes and Terminal Alkynes (GP5):<sup>[45]</sup>** Under nitrogen atmosphere, diaryldiazomethane (1.0 equiv) was added to a mixture of CuI (0.2 equiv), *i*- $\text{Pr}_2\text{NH}$  (1.1 equiv) and terminal alkyne (1.0 equiv) in 1,4-dioxane (1.0 mL). The solution was stirred at 30  $^\circ\text{C}$  for 1 h and the progress of the reaction was monitored by TLC. Upon

completion of the reaction, indicated by a color change from purple to yellow/brown, the reaction mixture was cooled down to room temperature and filtered through a short pad of aluminum oxide by using EtOAc as the eluent. The solvent was removed in vacuum to leave a crude mixture, which was purified by column chromatography to afford the desired allenic product.

**General Procedure for the Ester Hydrolysis with NaOH (GP6):**<sup>[48]</sup> The ester was dissolved in EtOH (5.0 mL/mmol) and 2N NaOH (1.5 mL/mmol, 3 equiv) was added. The mixture was stirred at rt and controlled via TLC (EtOAc). The solvent was then completely removed under reduced pressure. Phosphate buffer (pH 7) was then added to the solid residue until the pH was adjusted to 7 (indicator paper). After freeze drying, Et<sub>2</sub>O was added to the solid residue and the resulting suspension was filtrated. Subsequently, the filter cake was washed several times with Et<sub>2</sub>O. The solvent was then completely removed under reduced pressure and the remaining oil was dissolved in water and freeze dried, to obtain the free amino acid as white to yellow amorphous powder.

**General Procedure for the Ester Hydrolysis with Ba(OH)<sub>2</sub> (GP7):**<sup>[49]</sup> The ester (1 equiv) was dissolved in EtOH/H<sub>2</sub>O (2:1) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (2 equiv) was added. The suspension was then stirred at rt overnight. After completion of the reaction CO<sub>2</sub> was bubbled through the suspension until no further BaCO<sub>3</sub> precipitated. The suspension was then filtered through a syringe filter (25mm) and the filtrate was purified by RP-MPLC. After freeze drying the corresponding free amino acid could be obtained as white to yellow amorphous powder.

**Ethyl 1-(prop-2-yn-1-yl)-(3S)-piperidine-3-carboxylate (S-9):** GP1 was followed applying propargyl bromide solution (80 wt% in xylene, 0.56 mL, 5.0 mmol), ethyl (S)-piperidine-3-carboxylate (943 mg, 6.0 mmol), acetone (10 mL), Na<sub>2</sub>CO<sub>3</sub> (1.33 g, 12.5 mmol) and NaI (375 mg, 2.50 mmol). The crude product was purified by column chromatography (PE/EtOAc 8:2) to afford the desired alkyne **S-9** as pale yellow oil (973 mg, >99%): *R*<sub>f</sub>=0.18 (PE/EtOAc 8:2); [ $\alpha$ ]<sub>D</sub><sup>22</sup> = -7.2 (c=1.76 g/100 mL in chloroform); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =1.23 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd, *J*=11.7/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.69–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.94 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.20 (td, *J*=10.9/3.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.27 (t, *J*=2.4 Hz, 1H, NCH<sub>2</sub>C $\equiv$ CH), 2.34 (t, *J*=10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.53 (tt, *J*=10.4/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.71 (dt<sub>br</sub>, *J*=11.2/4.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.94 (dd<sub>br</sub>, *J*=10.9/4.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.29 (d, *J*=2.4 Hz, 2H, NCH<sub>2</sub>C $\equiv$ CH), 4.09 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  = 14.6, 25.1, 27.0, 42.4, 47.7, 52.8, 54.8, 60.8, 73.2, 79.6, 174.4; IR (film):  $\tilde{\nu}$ =3291, 2980, 2941, 2860, 2807, 1731, 1468, 1450, 1393, 1368, 1348, 1311, 1262, 1223, 1183, 1153, 1134, 1095, 1047, 1031, 1003, 979, 956, 936, 900, 864, 792, 625 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>17</sub>NO<sub>2</sub>: 196.1338, found: 196.1331.

**rac-[Ethyl 1-(but-3-yn-1-yl)piperidine-3-carboxylate] (rac-15):** GP1 was followed applying 4-bromo-1-butin (1.00 eq, 1.94 mL, 20.0 mmol), ethyl nipecotate (1.20 eq, 3.74 mL, 24.0 mmol), acetone (40 mL), Na<sub>2</sub>CO<sub>3</sub> (2.50 eq, 5.30 g, 50.0 mmol) and NaI (0.50 eq, 1.50 g, 10.0 mmol). The crude product was purified by column chromatography (PE/EtOAc 8:2) to afford the desired alkyne **rac-15** as pale yellow oil (3.22 g, 77%): *R*<sub>f</sub>=0.20 (PE/EtOAc 8:2); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ =1.25 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.38–1.51 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.51–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.88–1.96 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.97 (t, *J*=2.7 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CCH), 2.07 (td, *J*=11.0/3.1 Hz, 1H,

$\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.23 (t,  $J=10.6$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.34–2.41 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 2.55 (tt,  $J=10.6/3.9$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.57–2.66 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 2.73–2.81 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.94–3.02 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 4.13 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta=14.2$  (1C,  $\text{OCH}_2\text{CH}_3$ ), 16.7 (1C,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 24.5 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 26.9 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 41.8 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 53.4 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 55.1 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 57.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 60.3 (1C,  $\text{OCH}_2\text{CH}_3$ ), 69.0 (1C,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 82.8 (1C,  $\text{NCH}_2\text{CH}_2\text{CCH}$ ), 174.1 (1C, CO); IR (film):  $\tilde{\nu}=3297, 2945, 2856, 2812, 2118, 1731, 1469, 1447, 1371, 1311, 1273, 1214, 1181, 1154, 1134, 1102, 1033$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{12}\text{H}_{19}\text{NO}_2$ : 210.1494, found: 210.1489.

***rac*-[Ethyl 1-{5-[allyl(*tert*-butyl)amino]pent-3-yn-1-yl}piperidine-3-carboxylate] (*rac*-16):** This modified procedure based on a procedure described by Yu et al.<sup>[50]</sup> To a Schlenk flask was added CuBr (65 mg, 0.45 mmol, 0.15 equiv) and molecular sieve (4Å). Toluene anhyd. (15 mL, 5.00 mL/mmol) was then added, followed by paraformaldehyde (171 mg, 5.40 mmol, 1.80 equiv), *N*-allyl-*N*-*tert*-butylamine (0.63 mL, 4.2 mmol, 1.4 equiv) and alkyne *rac*-15 (628 mg, 3.00 mmol, 1.00 equiv). The reaction mixture was stirred at rt overnight. The completion of the reaction was monitored by TLC. The reaction mixture was then filtrated, washed with EtOAc and concentrated under vacuum. The crude product was purified by column chromatography (PE/EtOAc 1:1) to afford the desired propargylic amine *rac*-16 as pale yellow oil (791 mg, 79%):  $R_f=0.26$  (PE/EtOAc 1:1);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta=1.16$  (s, 9H, *t*-Bu), 1.25 (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.42 (qd,  $J=11.8/3.8$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.49–1.64 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.72 (dp,  $J=13.3/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.88–1.99 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 2.05 (td,  $J=11.0/3.0$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.20 (t,  $J=10.7$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.31–2.41 (m, 2H,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 2.47–2.62 (m, 3H,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$  and  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.78 (dt,  $J=10.5/4.0$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.94–3.04 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.27 (dt,  $J=6.5/1.3$  Hz, 2H,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 3.44 (t,  $J=2.2$  Hz, 2H,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 4.13 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.09 (ddt,  $J=10.0/2.2/1.2$  Hz, 1H,  $\text{NCH}_2\text{CH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.23 (ddt,  $J=17.1/2.2/1.4$  Hz, 1H,  $\text{NCH}_2\text{CH}=\text{CH}_{\text{trans}}\text{H}_{\text{cis}}$ ), 5.82 (ddt,  $J=17.1/10.0/6.5$  Hz, 1H,  $\text{NCH}_2\text{CH}=\text{CH}_2$ );  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta=14.2$  (1C,  $\text{OCH}_2\text{CH}_3$ ), 17.2 (1C,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 24.6 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 26.9 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 27.7 (3C,  $\text{NC}(\text{CH}_3)_3$ ), 36.6 (1C,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 41.9 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 50.0 (1C,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 53.4 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 54.9 (1C,  $\text{NC}(\text{CH}_3)_3$ ), 55.1 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 57.7 (1C,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 60.3 (1C,  $\text{OCH}_2\text{CH}_3$ ), 79.0 (1C,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 82.2 (1C,  $\text{NCH}_2\text{CCCH}_2\text{CH}_2\text{N}$ ), 116.7 (1C,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 137.5 (1C,  $\text{NCH}_2\text{CH}=\text{CH}_2$ ), 174.1 (1C, CO); IR (film):  $\tilde{\nu}=3416, 2971, 2814, 2359, 2337, 1732, 1641, 1467, 1445, 1390, 1364, 1309, 1270, 1203, 1179, 1153, 1133, 1101, 1032, 994, 916$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{20}\text{H}_{34}\text{N}_2\text{O}_2$ : 335.2699, found: 335.2698.

***rac*-[Ethyl 1-(penta-3,4-dien-1-yl)piperidine-3-carboxylate] (*rac*-17):** To a Schlenk tube  $\text{ZnI}_2$  (107 mg, 0.336 mmol, 0.800 equiv) was added. The  $\text{ZnI}_2$  was then heated with a heat gun under vacuum until the pale yellow solid turned to darker yellow. Chlorobenzene anhyd (8.0 mL/mmol) was added, followed by propargylic amine *rac*-16 (140 mg, 0.420 mmol, 1.00 equiv). The reaction mixture was stirred at 100 °C for 30 min and the reaction was monitored by TLC. After cooling to rt, the reaction mixture was directly purified by column chromatography (PE/EtOAc 1:1) to afford the desired allene *rac*-17 as pale yellow oil (64.4 mg, 69%):  $R_f=0.35$  (PE/EtOAc 1:1);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta=1.25$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.44 (qd,  $J=11.4/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.53–1.66 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.73 (dp,  $J=13.4/3.9$  Hz,

1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.90–1.99 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.02 (td, *J*=11.1/3.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.14–2.25 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.43–2.50 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 2.52–2.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.76–2.82 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.01 (d<sub>br</sub>, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.13 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.67 (dt, *J*=6.7/3.2 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 5.11 (p, *J*=6.7 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ=14.2 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.6 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>), 25.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 27.0 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 41.9 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 53.7 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 55.4 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 58.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 60.3 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 75.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 87.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 174.2 (1C, CO), 208.6 (1C, CHCCH<sub>2</sub>); IR (film): ν̄=3425, 2942, 2856, 2805, 1956, 1732, 1641, 1468, 1444, 1371, 1311, 1273, 1211, 1180, 1153, 1101, 1031, 844 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>13</sub>H<sub>21</sub>NO<sub>2</sub>: 224.1651, found: 224.1645.

***rac*-[1-(Penta-3,4-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-18):** GP6 was followed using nipecotic acid ester *rac*-17 (0.30 mmol, 67 mg), EtOH (1.0 mL) and 2M NaOH (2 equiv, 0.30 mL) for 2.75 h. The crude compound was purified by RP-MPLC (MeOH/H<sub>2</sub>O 3:7) to obtain the free amino acid *rac*-18 as colorless viscous oil (23 mg, 39%): <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.35 (qd, *J*=12.8/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.59 (qt, *J*=12.8/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.94 (td, *J*=11.8/2.8 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 1.96–2.01 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.04 (t, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.15–2.28 (m, 2H, CH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>N), 2.38 (tt, *J*=11.8/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.42–2.49 (m, 2H, CH<sub>2</sub>CCHCH<sub>2</sub>CH<sub>2</sub>N), 2.89 (d<sub>br</sub>, *J*=10.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.12 (ddt, *J*=11.3/3.5/1.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.68 (dt, *J*=6.6/3.2 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 5.12 (p, *J*=6.8 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=25.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 26.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 29.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.1 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 75.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 88.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH<sub>2</sub>), 182.8 (1C, CO), 210.1 (1C, CH<sub>2</sub>CHCCH<sub>2</sub>); IR (film): ν̄=3385, 2956, 1956, 1585, 1450, 1391, 1150, 1076, 857 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>11</sub>H<sub>17</sub>NO<sub>2</sub>: 196.1338, found: 196.1331.

***rac*-[Ethyl (*R*<sub>a</sub>)-1-(5-phenylpenta-3,4-dien-1-yl)-(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*R*<sub>a</sub>)-26) and *rac*-[ethyl (*S*<sub>a</sub>)-1-(5-phenylpenta-3,4-dien-1-yl)-(3*R*)-piperidine-3-carboxylate] (*rac*-(3*R*,*S*<sub>a</sub>)-26):** GP4 was followed applying alkyne *rac*-15 (84 mg, 0.40 mmol), CuI (15 mg, 0.080 mmol), Li<sup>t</sup>OBu (112 mg, 1.40 mmol), and *N*-benzylidene-4-methylbenzenesulfonohydrazide (241 mg, 0.880 mmol) in 1,4-dioxane (5 mL). The solution was stirred at 90 °C for 40 min. Purification by column chromatography (DCM/MeOH 98:2) afforded the desired allenes *rac*-(3*R*,*R*<sub>a</sub>)-26 and *rac*-(3*R*,*S*<sub>a</sub>)-26 as ~ 1:1 mixture of racemic diastereomers as yellow viscous oil (88.7 mg, 74%): *R*<sub>f</sub>=0.20 (PE/EtOAc 8:2); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ=1.19–1.30 (m, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.37–1.50 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.91–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.98–2.05 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.15–2.20 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.28–2.37 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 2.46–2.63 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.77–2.80 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.96–3.06 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.07–4.16 (m, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.58 (q, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 6.13 (dt, *J*=6.2/3.0 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 7.14–7.22 (m, 1H, ArH), 7.23–7.36 (m, 4H, ArH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ=14.2 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.6 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 26.3 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or

dia2), 26.3 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 27.0 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 27.0 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 41.9 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 42.0 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 53.7 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 53.8 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 55.4 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 55.5 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 58.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 60.3 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 60.3 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 92.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 94.9 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 94.9 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 126.6 (2C, ArC), 126.7 (1C, ArC), 128.5 (2C, ArC), 134.8 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 134.8 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 174.2 (0.5C, CO, dia1 or dia2), 174.2 (0.5C, CO, dia1 or dia2), 205.3 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 205.3 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2); IR (film):  $\tilde{\nu}$ =3061, 3030, 2936, 2855, 2807, 1948, 1730, 1598, 1495, 1459, 1370, 1300, 1273, 1210, 1179, 1151, 1134, 1100, 1072, 1029, 962, 911, 874, 776, 722, 692, 650, 629 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>25</sub>NO<sub>2</sub>: 300.1964, found: 300.1956.

***rac***-{Ethyl (*R<sub>a</sub>*)-1-[5-([1,1'-biphenyl]-2-yl)penta-3,4-dien-1-yl]-(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*R<sub>a</sub>*)-**28**) and *rac*-{ethyl (*S<sub>a</sub>*)-1-[5-([1,1'-biphenyl]-2-yl)penta-3,4-dien-1-yl]-(3*R*)-piperidine-3-carboxylate} (*rac*-(3*R*,*S<sub>a</sub>*)-**28**): GP4 was followed applying alkyne *rac*-**15** (84 mg, 0.40 mmol), CuI (15 mg, 0.08 mmol), Li<sup>t</sup>OBu (112 mg, 1.40 mmol), and *N'*-([1,1'-biphenyl]-2-ylmethylene)-4-methylbenzenesulfonohydrazide (308 mg, 0.880 mmol) in 1,4-dioxane (5 mL). The solution was stirred at 90 °C for 40 min. Purification by column chromatography (PE/EtOAc 8:2) afforded the desired allenes *rac*-(3*R*,*R<sub>a</sub>*)-**28** and *rac*-(3*R*,*S<sub>a</sub>*)-**28** as ~ 1:1 mixture of racemic diastereomers as yellow viscous oil (122 mg, 82%): *R<sub>f</sub>*=0.36 (PE/EtOAc 7:3); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =1.21 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.22 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.34–1.47 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.59 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.60–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–1.93 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.99 (td, *J*=11.3/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.02 (td, *J*=11.3/3.0 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 2.16 (t, *J*=10.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.26 (q, *J*=6.9 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 2.27 (q, *J*=6.9 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 2.40–2.57 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.62–2.82 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.93 (d<sub>br</sub>, *J*=10.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 2.96 (d<sub>br</sub>, *J*=10.6 Hz, 0.5H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>, dia1 or dia2), 4.07 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.08 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 5.53 (q, *J*=6.7 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 6.15 (dt, *J*=6.2/3.0 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCCH), 7.19–7.26 (m, 2H, ArH), 7.26–7.32 (m, 1H, ArH), 7.32–7.38 (m, 3H, ArH), 7.38–7.45 (m, 2H, ArH), 7.57 (dd, *J*=8.0/0.8 Hz, 1H, ArH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =14.4 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 25.1 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 26.8 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 26.8 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 27.4 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 27.4 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 42.3 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 42.4 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 54.1 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 55.9 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 56.0 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 58.4 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 58.4 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 60.5 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 60.5 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 93.0 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH or NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 93.0 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH or NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 93.1 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH or NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 93.1 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CHCCH or NCH<sub>2</sub>CH<sub>2</sub>CHCCH, dia1 or dia2), 126.9 (1C, ArC), 127.4 (1C, ArC), 127.7 (0.5C, ArC, dia1 or dia2), 127.7 (0.5C, ArC, dia1 or dia2), 127.8 (0.5C, ArC, dia1 or dia2), 127.8 (0.5C, ArC, dia1 or dia2), 128.5 (2C, ArC), 130.1 (2C, ArC),

130.5 (0.5C, ArC, dia1 or dia2), 130.5 (0.5C, ArC, dia1 or dia2), 132.6 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 132.6 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 140.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 140.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 141.3 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 141.3 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 174.4 (0.5C, CO, dia1 or dia2), 174.4 (0.5C, CO, dia1 or dia2), 206.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =3058, 3026, 2940, 2854, 2804, 1947, 1730, 1596, 1499, 1480, 1467, 1436, 1370, 1304, 1210, 1179, 1152, 1102, 1032, 1009, 881, 770, 746, 702 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>25</sub>H<sub>29</sub>NO<sub>2</sub>: 376.2277, found: 376.2271.

***rac*-[Ethyl 1-(4,4-diphenylbuta-2,3-dien-1-yl)piperidine-3-carboxylate] (*rac*-31a):**

GP5 was followed using alkyne *rac*-9 (98 mg, 0.50 mmol), CuI (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and (diazomethylene)dibenzene (97 mg, 0.50 mmol) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-31a was afforded as yellow viscous oil (167 mg, 92%):  $R_f$ =0.18 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =1.21 (t,  $J$ =7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.42 (qd,  $J$ =11.5/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.83–1.94 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.10 (td,  $J$ =10.9/3.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.25 (t,  $J$ =10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.52 (tt,  $J$ =10.4/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.73–2.85 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.02 (dd<sub>br</sub>,  $J$ =11.2/3.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.23 (d,  $J$ =7.0 Hz, 2H, NCH<sub>2</sub>CHCC), 4.07 (q,  $J$ =7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.72 (t,  $J$ =7.0 Hz, 1H, NCH<sub>2</sub>CHCC), 7.24–7.31 (m, 2H, ArH), 7.33 (d,  $J$ =4.5 Hz, 8H, ArH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 25.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.6 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.8 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.4 (1C, NCH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.8 (1C, NCH<sub>2</sub>CHCC), 110.4 (1C, NCH<sub>2</sub>CHCC), 127.7 (2C, ArC), 128.9 (4C, ArC), 129.0 (2C, ArC), 129.0 (2C, ArC), 137.4 (1C, ArC<sub>q</sub>), 137.4 (1C, ArC<sub>q</sub>), 174.5 (1C, CO), 206.7 (1C, NCH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =3057, 3026, 2939, 2866, 2807, 1943, 1731, 1597, 1492, 1466, 1451, 1442, 1367, 1310, 1223, 1180, 1151, 1133, 1095, 1074, 1030, 998, 921, 902, 863, 768, 695 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>: 362.2120, found: 362.2113.

***rac*-[Ethyl 1-(4,4-di-*p*-tolylbuta-2,3-dien-1-yl)piperidine-3-carboxylate] (*rac*-31b):**

GP5 was followed using alkyne *rac*-9 (98 mg, 0.50 mmol), CuI (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(methylbenzene) (111 mg, 0.50 mmol) in 1,4-dioxane (2.5 mL) for 30 min. After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-31b was afforded as yellow viscous oil (103 mg, 52%):  $R_f$ =0.27 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>):  $\delta$ =1.15 (t,  $J$ =7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.33 (qd,  $J$ =11.8/3.8 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.41–1.55 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.58–1.71 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.76–1.93 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.02 (t<sub>br</sub>,  $J$ =10.9 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.16 (t,  $J$ =10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.28 (s, 6H, CH<sub>3</sub>), 2.39–2.62 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.76 (d<sub>br</sub>,  $J$ =7.8 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.99 (d<sub>br</sub>,  $J$ =10.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.16 (d,  $J$ =7.1 Hz, 2H, NCH<sub>2</sub>CHCC), 4.02 (q,  $J$ =7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.62 (t,  $J$ =7.1 Hz, 1H, NCH<sub>2</sub>CHCC), 7.07 (d,  $J$ =8.2 Hz, 4H, ArH), 7.15 (d,  $J$ =8.2 Hz, 4H, ArH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>):  $\delta$ =14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 21.6 (2C, CH<sub>3</sub>), 24.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.2 (1C, NCH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.0 (1C, NCH<sub>2</sub>CHCC), 109.8 (1C, NCH<sub>2</sub>CHCC), 128.7 (2C, ArC), 128.7 (2C, ArC), 129.4 (4C, ArC), 134.0 (2C, ArC<sub>q</sub>), 137.2 (2C, ArC<sub>q</sub>), 174.5 (1C, CO), 206.2 (1C, NCH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =3023, 2940, 2866, 2804, 2237, 1941, 1731, 1509, 1466, 1451, 1368, 1310, 1278, 1223, 1181, 1151, 1133, 1095, 1031, 1005, 949, 911, 887,



863, 822, 781, 745, 720, 702  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{26}\text{H}_{31}\text{NO}_2$ : 390.2433, found: 390.2424.

***rac*-{Ethyl 1-[4,4-bis(4-fluorophenyl)buta-2,3-dien-1-yl]piperidine-3-carboxylate}** (***rac*-31c**): GP5 was followed using alkyne *rac*-9 (98 mg, 0.50 mmol), CuI (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(fluorobenzene) (115 mg, 0.500 mmol) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-31c was afforded as pale yellow oil (192 mg, 97%):  $R_f$ =0.43 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>):  $\delta$ =1.14 (t,  $J$ =7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.32 (qd,  $J$ =11.9/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.40–1.54 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.55–1.70 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.78–1.90 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.00 (td,  $J$ =11.1/3.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.14 (t,  $J$ =10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.45 (tt,  $J$ =10.6/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.70 (d<sub>br</sub>,  $J$ =11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.93 (dd<sub>br</sub>,  $J$ =11.1/3.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.15 (d,  $J$ =7.1 Hz, 2H, NCH<sub>2</sub>CHCC), 4.01 (q,  $J$ =7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.65 (t,  $J$ =7.1 Hz, 1H, NCH<sub>2</sub>CHCC), 6.90–7.02 (m, 4H, FCCH), 7.18–7.25 (m, 4H, FCCHCH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>):  $\delta$ =14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.0 (1C, NCH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.6 (1C, NCH<sub>2</sub>CHCC), 108.4 (1C, NCH<sub>2</sub>CHCC), 115.7 (d<sub>CF</sub>, <sup>2</sup> $J_{CF}$ =21.5 Hz, 4C, FCCH), 130.2 (d<sub>CF</sub>, <sup>3</sup> $J_{CF}$ =3.9 Hz, 2C, FCCHCH), 130.3 (d<sub>CF</sub>, <sup>3</sup> $J_{CF}$ =3.9 Hz, 2C, FCCHCH), 132.8 (d<sub>CF</sub>, <sup>4</sup> $J_{CF}$ =1.8 Hz, 1C, FCCHCHC), 132.9 (d<sub>CF</sub>, <sup>4</sup> $J_{CF}$ =1.8 Hz, 1C, FCCHCHC), 162.27 (d<sub>CF</sub>, <sup>1</sup> $J_{CF}$ =246.5 Hz, 2C, FC), 174.4 (1C, CO), 206.2 (1C, NCH<sub>2</sub>CHCC); <sup>19</sup>F NMR (376 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>):  $\delta$ =-114.59–-114.33 (m); IR (film):  $\tilde{\nu}$ =2940, 2803, 1941, 1731, 1601, 1505, 1469, 1455, 1372, 1298, 1281, 1223, 1180, 1155, 1133, 1094, 1030, 911, 838, 800, 723  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{F}_2\text{NO}_2$ : 398.1932, found: 398.1919.

***rac*-{Ethyl 1-[4,4-bis(4-chlorophenyl)buta-2,3-dien-1-yl]piperidine-3-carboxylate}** (***rac*-31d**): GP5 was followed using alkyne *rac*-9 (98 mg, 0.50 mmol), CuI (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(chlorobenzene) (203 mg, crude compound) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-31d was afforded as yellow viscous oil (204 mg, 95%):  $R_f$ =0.57 (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =1.21 (t,  $J$ =7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd,  $J$ =11.3/3.7 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.60 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.84–1.94 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.09 (td,  $J$ =10.8/3.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.23 (t,  $J$ =10.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.50 (tt,  $J$ =10.3/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.71–2.80 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.98 (dd<sub>br</sub>,  $J$ =11.2/3.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.22 (dd,  $J$ =7.0/1.6 Hz, 2H, NCH<sub>2</sub>CHCC), 4.08 (q,  $J$ =7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.75 (t,  $J$ =7.0 Hz, 1H, NCH<sub>2</sub>CHCC), 7.23–7.29 (m, 4H, ArH), 7.29–7.35 (m, 4H, ArH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 25.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.7 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.1 (1C, NCH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 92.6 (1C, NCH<sub>2</sub>CHCC), 108.8 (1C, NCH<sub>2</sub>CHCC), 129.1 (4C, ArC), 130.2 (2C, ArC), 130.3 (2C, ArC), 133.5 (1C, ArC<sub>q</sub>), 133.6 (1C, ArC<sub>q</sub>), 135.6 (1C, ArC<sub>q</sub>), 135.7 (1C, ArC<sub>q</sub>), 174.4 (1C, CO), 206.6 (1C, NCH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =2941, 2867, 2801, 2238, 1941, 1728, 1590, 1489, 1467, 1452, 1415, 1396, 1368, 1309, 1274, 1223, 1182, 1152, 1134, 1091, 1047, 1030, 1014, 949, 909, 887, 832, 746, 702  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{25}\text{Cl}_2\text{NO}_2$ : 430.1341, found: 430.1338.

**rac**-{Ethyl (R<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)-4-phenylbuta-2,3-dien-1-yl]-(3R)-piperidine-3-carboxylate} (**rac**-(3R,R<sub>a</sub>)-**31e**) and **rac**-{ethyl (S<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)-4-phenylbuta-2,3-dien-1-yl]-(3R)-piperidine-3-carboxylate} (**rac**-(3R,S<sub>a</sub>)-**31e**): GP5 was followed using alkyne **rac**-**9** (98 mg, 0.50 mmol), Cul (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4-[diazo(phenyl)methyl]-1,1'-biphenyl (135 mg, 0.50 mmol) in 1,4-dioxane (2.5 mL) for 40 min. After purification by column chromatography (gradient elution PE/EtOAc 9:1 to PE/EtOAc 7:3) pure **rac**-(3R,R<sub>a</sub>)-**31e** and **rac**-(3R,S<sub>a</sub>)-**31e** were obtained as ~ 1:1 mixture of racemic diastereomers as yellow viscous oil (205 mg, 94%): *R*<sub>f</sub>=0.19 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=1.14 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.14 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.34 (qd, *J*=12.0/3.5 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.43–1.53 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.60–1.71 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.78–1.91 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.04 (tbr, *J*=11.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.19 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.40–2.55 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.76 (dbr, *J*=9.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.99 (dbr, *J*=11.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.21 (d, *J*=7.0 Hz, 2H, NCH<sub>2</sub>CHCC), 4.01 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.01 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 5.71 (t, *J*=7.0 Hz, 1H, NCH<sub>2</sub>CHCC), 7.26–7.41 (m, 10H, ArH), 7.48–7.59 (m, 4H, ArH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.3 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 53.4 (0.5C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH, dia1 or dia2), 55.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.1 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2), 58.1 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.3 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2), 91.4 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2), 109.9 (1C, NCH<sub>2</sub>CHCC), 127.2 (2C, ArC), 127.3 (2C, ArC), 127.7 (1C, ArC), 127.7 (1C, ArC), 128.8 (2C, ArC), 128.9 (1C, ArC), 128.9 (1C, ArC), 129.1 (1C, ArC), 129.1 (1C, ArC), 129.2 (2C, ArC), 135.9 (1C, ArC<sub>q</sub>), 136.8 (1C, ArC<sub>q</sub>), 140.0 (1C, ArC<sub>q</sub>), 140.7 (1C, ArC<sub>q</sub>), 174.4 (1C, CO), 206.6 (1C, NCH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =3424, 3057, 3028, 2939, 2803, 1943, 1730, 1598, 1486, 1466, 1447, 1367, 1310, 1222, 1180, 1151, 1133, 1094, 1030, 1007, 906, 841, 767, 729, 697 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>30</sub>H<sub>31</sub>NO<sub>2</sub>: 438.2433, found: 438.2421.

**rac**-{Ethyl 1-[4,4-bis(4-methoxyphenyl)buta-2,3-dien-1-yl]piperidine-3-carboxylate} (**rac**-**31f**). GP5 was followed using alkyne **rac**-**9** (98 mg, 0.50 mmol), Cul (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.080 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(methoxybenzene) (650 mg, crude compound) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 7:3) pure **rac**-**31f** was afforded as yellow viscous oil (148 mg, 70%): *R*<sub>f</sub>=0.34 (PE/EtOAc 6:4); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=1.22 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.40 (qd, *J*=12.1/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.49–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.78 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.87–1.98 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.02–2.15 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.24 (t, *J*=10.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.47–2.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.82 (dbr, *J*=11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.06 (dbr, *J*=10.9 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.23 (d, *J*=7.0 Hz, 2H, NCH<sub>2</sub>CHCC), 3.81 (s, 6H, OCH<sub>3</sub>), 4.09 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.69 (t, *J*=7.0 Hz, 1H, NCH<sub>2</sub>CHCC), 6.80–6.96 (m, 4H, ArH), 7.17–7.35 (m, 4H, ArH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=14.2 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 26.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 41.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 52.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.8 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 55.3 (2C, OCH<sub>3</sub>), 57.9 (1C, NCH<sub>2</sub>CHCC), 60.3 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 90.4 (1C, NCH<sub>2</sub>CHCC), 108.8 (1C, NCH<sub>2</sub>CHCC), 113.7 (4C, ArC), 128.9 (2C, ArC<sub>q</sub>), 129.4 (2C, ArC), 129.4 (2C, ArC), 158.6 (2C, COCH<sub>3</sub>), 174.0 (1C, CO), 205.6 (1C, NCH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =2938, 2835, 1729, 1606, 1578, 1508, 1464, 1442, 1368, 1295, 1248, 1175, 1151, 1134, 1095,

1034, 833  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{26}\text{H}_{31}\text{NO}_4$ : 422.2331, found: 422.2328.

***rac*-[1-(4,4-Diphenylbuta-2,3-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-32a):** GP7 was followed using nipecotic acid ester *rac*-31a (171 mg, 0.472 mmol) and  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (298 mg, 0.944 mmol) in 3.4 mL EtOH/ $\text{H}_2\text{O}$  (2:1) overnight. After purification by RP-MPLC (MeOH/ $\text{H}_2\text{O}$  7:3) the desired amino acid *rac*-32a was afforded as pale yellow amorphous solid (43.6 mg, 28%): mp: -;  $^1\text{H}$  NMR (500 MHz, MeOD, NaOD):  $\delta$ =1.24 (qd,  $J$ =12.5/3.1 Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.39–1.53 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.53–1.63 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.80–1.95 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.08 (t,  $J$ =11.1 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.30 (tbr,  $J$ =7.3 Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.82 (d,  $J$ =11.2 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.01–3.18 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCC}$ ), 5.65 (t,  $J$ =7.3 Hz, 1H,  $\text{NCH}_2\text{CHCC}$ ), 7.19 (m, 10H, ArH);  $^{13}\text{C}$  NMR (126 MHz, MeOD, NaOD):  $\delta$ =26.0 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 29.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 46.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 54.4 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 58.1 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 59.1 (1C,  $\text{NCH}_2\text{CHCC}$ ), 91.1 (1C,  $\text{NCH}_2\text{CHCC}$ ), 111.4 (1C,  $\text{NCH}_2\text{CHCC}$ ), 128.4 (1C, ArC), 128.4 (1C, ArC), 129.4–129.6 (m, 8C, ArC), 137.9 (1C, ArC<sub>q</sub>), 138.0 (1C, ArC<sub>q</sub>), 182.6 (1C, CO), 207.6 (1C,  $\text{NCH}_2\text{CHCC}$ ); IR (KBr):  $\tilde{\nu}$ =3418, 3057, 3027, 2937, 2858, 2804, 1945, 1560, 1492, 1466, 1451, 1442, 1407, 1333, 1155, 1093, 1074, 1030, 1000, 961, 922, 903, 769, 695, 630, 611  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{22}\text{H}_{23}\text{NO}_2$ : 334.1807, found: 334.1801.

***rac*-[1-(4,4-Di-*p*-tolylbuta-2,3-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-32b):** GP7 was followed using nipecotic acid ester *rac*-31b (92.3 mg, 0.237 mmol) and  $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (150 mg, 0.474 mmol) in 1.5 mL EtOH/ $\text{H}_2\text{O}$  (2:1) for 6 h. After purification by RP-MPLC (MeOH/ $\text{H}_2\text{O}$  7:3) the desired amino acid *rac*-32b was afforded as white amorphous solid (19.2 mg, 22%): mp: 101 °C;  $^1\text{H}$  NMR (400 MHz, MeOD):  $\delta$ =1.36 (qd,  $J$ =12.7/4.4 Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.65 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.65–1.75 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.91–2.05 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.19 (t,  $J$ =11.2 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.33 (s, 3H,  $\text{CH}_3$ ), 2.34 (s, 3H,  $\text{CH}_3$ ), 2.42 (tt,  $J$ =11.6/3.8 Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.93 (dbr,  $J$ =11.4 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.13–3.30 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCC}$ ), 5.71 (t,  $J$ =7.3 Hz, 1H,  $\text{NCH}_2\text{CHCC}$ ), 6.99–7.31 (m, 8H, ArH);  $^{13}\text{C}$  NMR (126 MHz, MeOD):  $\delta$ =21.2 (2C,  $\text{CH}_3$ ), 26.0 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 29.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 46.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 54.4 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 58.1 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 59.3 (1C,  $\text{NCH}_2\text{CHCC}$ ), 90.8 (1C,  $\text{NCH}_2\text{CHCC}$ ), 111.1 (1C,  $\text{NCH}_2\text{CHCC}$ ), 129.4 (2C, ArC), 129.4 (2C, ArC), 130.1 (2C, ArC), 130.1 (2C, ArC), 135.0 (1C, ArC<sub>q</sub>), 135.1 (1C, ArC<sub>q</sub>), 138.2 (1C, ArC<sub>q</sub>), 138.3 (1C, ArC<sub>q</sub>), 182.7 (1C, CO), 207.4 (1C,  $\text{NCH}_2\text{CHCC}$ ); IR (KBr):  $\tilde{\nu}$ =3387, 3026, 2922, 1932, 1603, 1508, 1447, 1374, 1362, 1336, 1309, 1279, 1258, 1210, 1178, 1149, 1108, 1059, 1017, 959, 938, 912, 872, 855, 829, 820, 783, 725, 668, 647, 610, 591, 526  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{24}\text{H}_{27}\text{NO}_2$ : 362.2120, found: 362.2112.

***rac*-[1-[4,4-Bis(4-fluorophenyl)buta-2,3-dien-1-yl]piperidine-3-carboxylic acid] (*rac*-32c):** GP6 was followed using nipecotic acid ester *rac*-31c (0.425 mmol, 169 mg), EtOH (2.1 mL) and 2M NaOH (0.64 mL) for 40 min. The desired amino acid *rac*-32c was obtained as pale yellow amorphous solid (40.4 mg, 26%): mp: 77 °C;  $^1\text{H}$  NMR (400 MHz, MeOD, NaOD):  $\delta$ =1.11 (qd,  $J$ =12.7/4.1 Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.33 (qt,  $J$ =13.1/4.0 Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.40–1.52 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.67–1.81 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 1.92 (t,  $J$ =11.3 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.16 (tt,  $J$ =11.8/3.8 Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.66 (dbr,  $J$ =11.2 Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.90–2.97 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.99 (dd,  $J$ =7.3/2.0

Hz, 2H, NCH<sub>2</sub>CHCC), 5.53 (t, *J*=7.3 Hz, 1H, NCH<sub>2</sub>CHCC), 6.76–6.92 (m, 4H, FCCH), 6.98–7.12 (m, 4H, FCCHCH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 29.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.6 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.0 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.0 (1C, NCH<sub>2</sub>CHCC), 91.6 (1C, NCH<sub>2</sub>CHCC), 109.6 (1C, NCH<sub>2</sub>CHCC), 116.4 (dd<sub>CF</sub>, <sup>2</sup>*J*<sub>CF</sub>=21.9/2.0 Hz, 4C, FCCH), 131.2 (dd<sub>CF</sub>, <sup>3</sup>*J*<sub>CF</sub>=8.1/3.0 Hz, 4C, FCCHCH), 134.0 (t<sub>CF</sub>, <sup>4</sup>*J*<sub>CF</sub>=3.8 Hz, 2C, FCCHCHC), 163.7 (d<sub>CF</sub>, <sup>1</sup>*J*<sub>CF</sub>=245.5 Hz, 2C, FC), 182.7 (1C, CO), 207.4 (1C, NCH<sub>2</sub>CHCC); <sup>19</sup>F NMR (376 MHz, MeOD, NaOD): δ=-116.9, -117.0; IR (KBr): ν̄=3447, 3048, 2940, 2863, 2802, 1944, 1715, 1601, 1505, 1467, 1451, 1400, 1338, 1298, 1282, 1224, 1156, 1095, 1013, 911, 838, 800, 724, 606, 584 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>F<sub>2</sub>NO<sub>2</sub>: 370.1619, found: 370.1610.

***rac*-{1-[4,4-Bis(4-chlorophenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylic acid} (*rac*-32d):** GP6 was followed using nipecotic acid ester *rac*-31d (0.470 mmol, 202 mg), EtOH (2.35 mL) and 2M NaOH (0.71 mL) for 1.5 h. The desired amino acid *rac*-32d was obtained as pale yellow amorphous solid (46.8 mg, 25%): mp: 91 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.36 (qd, *J*=12.7/4.1 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.58 (qt, *J*=13.0/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.76 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.94–2.06 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.18 (t, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.41 (tt, *J*=11.7/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.90 (dbr, *J*=11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.14–3.22 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.26 (dd, *J*=7.3/2.0 Hz, 2H, NCH<sub>2</sub>CHCC), 5.83 (t, *J*=7.3 Hz, 1H, NCH<sub>2</sub>CHCC), 7.21–7.32 (m, 4H, ArH), 7.32–7.42 (m, 4H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 29.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.0 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.7 (1C, NCH<sub>2</sub>CHCC), 92.1 (1C, NCH<sub>2</sub>CHCC), 109.7 (1C, NCH<sub>2</sub>CHCC), 129.8 (2C, ArC), 129.8 (2C, ArC), 130.9 (2C, ArC), 130.9 (2C, ArC), 134.4 (1C, ArC<sub>q</sub>), 134.4 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 182.7 (1C, CO), 207.5 (1C, CH<sub>2</sub>CHCC); IR (KBr): ν̄=3433, 3030, 2938, 2860, 2796, 2522, 1942, 1712, 1589, 1489, 1451, 1396, 1334, 1300, 1222, 1191, 1153, 1090, 1044, 1013, 959, 909, 868, 831, 783, 747, 722, 702, 638, 612, 535, 509, 460 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>2</sub>: 402.1028, found: 402.1020.

**1-[4,4-Bis(4-chlorophenyl)penta-3,4-dien-1-yl]-(*R*)-piperidine-3-carboxylic acid ((*R*)-32d):** GP6 was followed using the corresponding nipecotic acid ester (0.480 mmol, 207 mg), EtOH (2.4 mL) and 2M NaOH (0.72 mL) for 1.5 h. The desired amino acid (*R*)-32d was obtained as pale yellow amorphous solid (99.0 mg, 51%): mp: 85 °C; [α]<sub>D</sub><sup>22</sup>=+15.2 (c=0.90 g/100 mL in chloroform); <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.36 (qd, *J*=12.7/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.53–1.64 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.66–1.75 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.94–2.06 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.18 (t, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.41 (tt, *J*=11.7/3.3 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.90 (dbr, *J*=11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.19 (dbr, *J*=11.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.25 (dd, *J*=7.3/1.3 Hz, 2H, NCH<sub>2</sub>CHCC), 5.83 (t, *J*=7.3 Hz, 1H, NCH<sub>2</sub>CHCC), 7.24–7.31 (m, 4H, ArH), 7.32–7.41 (m, 4H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 29.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.6 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.0 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.7 (1C, NCH<sub>2</sub>CHCC), 92.1 (1C, NCH<sub>2</sub>CHCC), 109.7 (1C, NCH<sub>2</sub>CHCC), 129.8 (2C, ArC), 129.8 (2C, ArC), 130.9 (2C, ArC), 130.9 (2C, ArC), 134.4 (1C, ArC<sub>q</sub>), 134.4 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 182.6 (1C, CO), 207.5 (1C, CH<sub>2</sub>CHCC); IR (KBr): ν̄=3426, 3030, 2938, 2862, 2797, 2531, 1942, 1711, 1589, 1489, 1451, 1396, 1333, 1300, 1222, 1192, 1152, 1090, 1044, 1013, 959, 909, 868, 831, 769, 747, 722, 702, 638, 612, 534, 508, 460 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>22</sub>H<sub>21</sub>Cl<sub>2</sub>NO<sub>2</sub>: 402.1028, found: 402.1021.

**1-[4,4-Bis(4-chlorophenyl)penta-3,4-dien-1-yl]-(S)-piperidine-3-carboxylic acid ((S)-32d)**: GP6 was followed using the corresponding nipecotic acid ester (0.480 mmol, 207 mg), EtOH (2.4 mL) and 2M NaOH (0.72 mL) for 1.5 h. The desired amino acid (S)-32d was obtained as pale yellow amorphous solid (130 mg, 68%): mp: 86 °C;  $[\alpha]_D^{22} = -18.4$  (c=0.90 g/100 mL in chloroform);  $^1\text{H NMR}$  (400 MHz, MeOD, NaOD):  $\delta = 1.36$  (qd,  $J = 12.6/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.58 (qt,  $J = 12.8/4.0$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.66–1.76 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.93–2.06 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.18 (t,  $J = 11.2$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.41 (tt,  $J = 11.6/3.7$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.90 (dbr,  $J = 11.2$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.18 (ddbr,  $J = 11.1/3.5$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.25 (dd,  $J = 7.3/1.3$  Hz, 2H,  $\text{NCH}_2\text{CHCC}$ ), 5.83 (t,  $J = 7.3$  Hz, 1H,  $\text{NCH}_2\text{CHCC}$ ), 7.24–7.31 (m, 4H, ArH), 7.31–7.40 (m, 4H, ArH);  $^{13}\text{C NMR}$  (126 MHz, MeOD, NaOD):  $\delta = 26.0$  (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 29.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 46.5 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 54.5 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 57.9 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 58.7 (1C,  $\text{NCH}_2\text{CHCC}$ ), 92.1 (1C,  $\text{NCH}_2\text{CHCC}$ ), 109.7 (1C,  $\text{NCH}_2\text{CHCC}$ ), 129.8 (2C, ArC), 129.8 (2C, ArC), 130.9 (2C, ArC), 130.9 (2C, ArC), 134.4 (1C, ArC<sub>q</sub>), 134.4 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 136.3 (1C, ArC<sub>q</sub>), 182.7 (1C, CO), 207.5 (1C,  $\text{CH}_2\text{CHCC}$ ); IR (KBr):  $\tilde{\nu} = 3428, 3030, 2936, 2858, 2797, 2528, 1943, 1708, 1589, 1489, 1450, 1396, 1333, 1300, 1276, 1222, 1192, 1152, 1090, 1044, 1013, 959, 909, 867, 831, 770, 746, 722, 702, 670, 638, 612, 535, 509, 462$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$   $[M+H]^+$  calcd for  $\text{C}_{22}\text{H}_{21}\text{Cl}_2\text{NO}_2$ : 402.1028, found: 402.1022.

**rac-((R<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)-4-phenylbuta-2,3-dien-1-yl]-(3R)-piperidine-3-carboxylic acid} (rac-(3R,R<sub>a</sub>)-32e) and rac-((S<sub>a</sub>)-1-[4-([1,1'-biphenyl]-4-yl)-4-phenylbuta-2,3-dien-1-yl]-(3R)-piperidine-3-carboxylic acid} (rac-(3R,S<sub>a</sub>)-32e)**. GP6 was followed using nipecotic acid esters *rac*-(3R,R<sub>a</sub>)-31e and *rac*-(3R,S<sub>a</sub>)-31e (0.423 mmol, 185 mg), EtOH (2.1 mL) and 2M NaOH (0.63 mL) for 2 h. The desired amino acids *rac*-(3R,R<sub>a</sub>)-32e and *rac*-(3R,S<sub>a</sub>)-32e were obtained as ~ 1:1 mixture of racemic diastereomers as pale yellow amorphous solid (16.2 mg, 9%): mp: 109 °C;  $^1\text{H NMR}$  (400 MHz, MeOD, NaOD):  $\delta = 1.37$  (qd,  $J = 12.7/4.2$  Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.51–1.67 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.67–1.79 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.93–2.10 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.21 (t,  $J = 11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.23 (t,  $J = 11.3$  Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.43 (tt,  $J = 11.6/3.8$  Hz, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.96 (dbr,  $J = 11.3$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.17–3.30 (m, 3H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$  and  $\text{NCH}_2\text{CHCC}$ ), 5.80 (t,  $J = 7.3$  Hz, 0.5H,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 5.81 (t,  $J = 7.3$  Hz, 0.5H,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 7.22–7.47 (m, 10H, ArH), 7.53–7.70 (m, 4H, ArH);  $^{13}\text{C NMR}$  (126 MHz, MeOD, NaOD):  $\delta = 26.0$  (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 29.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 46.6 (0.5C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 46.6 (0.5C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 54.4 (0.5C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 54.5 (0.5C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ , dia1 or dia2), 58.0 (0.5C,  $\text{NCH}_2\text{CHCH}_2$ , dia1 or dia2), 58.1 (0.5C,  $\text{NCH}_2\text{CHCH}_2$ , dia1 or dia2), 59.1 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 59.2 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 91.2 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 91.3 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 111.1 (1C,  $\text{NCH}_2\text{CHCC}$ ), 127.9 (2C, ArC), 128.0 (1C, ArC), 128.0 (1C, ArC), 128.4 (0.5C, ArC, dia1 or dia2), 128.4 (0.5C, ArC, dia1 or dia2), 128.5 (0.5C, ArC, dia1 or dia2), 128.5 (0.5C, ArC, dia1 or dia2), 129.6 (1C, ArC), 129.6 (1C, ArC), 129.6 (1C, ArC), 129.6 (1C, ArC), 129.9 (1C, ArC), 129.9 (2C, ArC), 129.9 (1C, ArC), 136.9 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 136.9 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 137.9 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 137.9 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 141.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 141.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 141.9 (1C, ArC<sub>q</sub>), 182.7 (1C, CO), 207.7 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 207.7 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2); IR (KBr):  $\tilde{\nu} = 3423, 3055, 3027, 2936, 2857, 2800, 1942, 1708, 1597, 1578, 1486, 1466, 1447, 1405, 1334, 1309, 1224, 1191, 1155, 1133, 1094,$

1074, 1040, 1007, 963, 907, 841, 767, 729, 697, 630 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>28</sub>H<sub>27</sub>NO<sub>2</sub>: 410.2120, found: 410.2110.

**rac-[Ethyl 1-(5,5-diphenylpenta-3,4-dien-1-yl)piperidine-3-carboxylate] (rac-33a):** GP5 was followed using alkyne *rac-15* (105 mg, 0.500 mmol), Cul (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and (diazomethylene)dibenzene (97 mg, 0.50 mmol) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac-33a* was afforded as yellow viscous oil (151 mg, 80%): *R*<sub>f</sub>=0.28 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=1.22 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.33–1.44 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.45–1.56 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.61–1.72 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.82–1.92 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.99 (td, *J*=10.9/2.9 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.15 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.36 (q, *J*=6.8 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.41–2.59 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.68–2.81 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.96 (d<sub>br</sub>, *J*=11.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.07 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.72 (t, *J*=6.8 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.15–7.27 (m, 2H, ArH), 7.27–7.41 (m, 8H, ArH); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ=14.4 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 25.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 56.0 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 60.5 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 92.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 110.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 127.4 (2C, ArC), 128.7 (4C, ArC), 128.8 (4C, ArC), 137.5 (2C, ArC<sub>q</sub>), 174.4 (1C, CO), 205.9 (1C, CH<sub>2</sub>CHCC); IR (film): ν̄=3057, 3025, 2940, 2854, 2806, 1943, 1731, 1597, 1492, 1467, 1452, 1442, 1370, 1310, 1273, 1210, 1178, 1151, 1100, 1031, 768, 695 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>25</sub>H<sub>29</sub>NO<sub>2</sub>: 376.2277, found: 376.2272.

**rac-[Ethyl 1-(5,5-di-*p*-tolylpenta-3,4-dien-1-yl)piperidine-3-carboxylate] (rac-33b):** GP5 was followed using alkyne *rac-15* (105 mg, 0.500 mmol), Cul (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(methylbenzene) (111 mg, 0.500 mmol) in 1,4-dioxane (2.5 mL) for 30 min. After purification by column chromatography (PE/EtOAc 8:2) pure *rac-33b* was afforded as yellow viscous oil (124 mg, 62%): *R*<sub>f</sub>=0.20 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=1.16 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.32 (qd, *J*=11.9/3.8 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.38–1.52 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.52–1.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.75–1.87 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.91 (t<sub>br</sub>, *J*=10.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.07 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.28 (s, 8H, NCH<sub>2</sub>CH<sub>2</sub>CHCC and CH<sub>3</sub>), 2.35–2.55 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.69 (d<sub>br</sub>, *J*=11.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.90 (d<sub>br</sub>, *J*=11.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.02 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.60 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.07 (d, *J*=8.0 Hz, 4H, ArH), 7.17 (d, *J*=8.0 Hz, 4H, ArH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 21.6 (2C, CH<sub>3</sub>), 24.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 26.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.6 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 92.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 109.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 128.6 (2C, ArC), 128.6 (2C, ArC), 129.4 (4C, ArC), 134.3 (2C, ArC<sub>q</sub>), 137.0 (2C, ArC<sub>q</sub>), 174.6 (1C, CO), 205.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (film): ν̄=3022, 2939, 2857, 2805, 1940, 1731, 1508, 1468, 1445, 1370, 1308, 1275, 1210, 1179, 1151, 1133, 1100, 1033, 910, 862, 822, 720 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+*H*]<sup>+</sup> calcd for C<sub>27</sub>H<sub>33</sub>NO<sub>2</sub>: 404.2590, found: 404.2579.

**rac-{Ethyl 1-[5,5-bis(4-fluorophenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylate} (rac-33c):** GP5 was followed using alkyne *rac-15* (105 mg, 0.500 mmol), Cul (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(fluorobenzene) (115 mg, 0.500 mmol) in 1,4-dioxane (2.5 mL).

After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-**33c** was afforded as pale yellow oil (194 mg, 94%):  $R_f=0.21$  (PE/EtOAc 7:3);  $^1\text{H NMR}$  (400 MHz,  $\text{C}_2\text{D}_2\text{Cl}_4$ ):  $\delta=1.15$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.23–1.49 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.54–1.68 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.76–1.86 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.91 (td,  $J=10.6/2.3$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.07 (t,  $J=10.6$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.29 (q,  $J=7.0$  Hz, 2H,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 2.34–2.52 (m, 3H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 2.67 (dbr,  $J=10.9$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.88 (dbr,  $J=10.3$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 4.01 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.64 (t,  $J=6.6$  Hz, 1H,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 6.91–7.01 (m, 4H,  $\text{FCCH}$ ), 7.16–7.29 (m, 4H,  $\text{FCCHCH}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{C}_2\text{D}_2\text{Cl}_4$ ):  $\delta=14.4$  (1C,  $\text{OCH}_2\text{CH}_3$ ), 24.7 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 26.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 27.1 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 41.9 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 53.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 55.4 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 57.9 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 60.5 (1C,  $\text{OCH}_2\text{CH}_3$ ), 93.0 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 108.1 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 115.4 ( $d_{\text{CF}}$ ,  $^2J_{\text{CF}}=21.4$  Hz, 4C,  $\text{FCCH}$ ), 130.0 ( $d_{\text{CF}}$ ,  $^3J_{\text{CF}}=8.0$  Hz, 2C,  $\text{FCCHCH}$ ), 130.3 ( $d_{\text{CF}}$ ,  $^3J_{\text{CF}}=8.0$  Hz, 2C,  $\text{FCCHCH}$ ), 133.0 ( $d_{\text{CF}}$ ,  $^4J_{\text{CF}}=2.8$  Hz, 2C,  $\text{FCCHCHC}$ ), 162.0 ( $d_{\text{CF}}$ ,  $^1J_{\text{CF}}=245.9$  Hz, 2C,  $\text{FC}$ ), 174.4 (1C,  $\text{CO}$ ), 205.3 (1C,  $\text{CH}_2\text{CHCC}$ );  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{C}_2\text{D}_2\text{Cl}_4$ ):  $\delta=-114.8$ ; IR (film):  $\tilde{\nu}=2941, 2855, 2806, 1942, 1893, 1731, 1601, 1505, 1468, 1446, 1370, 1299, 1279, 1222, 1179, 1156, 1134, 1096, 1032, 1014, 911, 838, 800, 723$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{25}\text{H}_{27}\text{F}_2\text{NO}_2$ : 412.2088, found: 412.2078.

***rac*-{Ethyl 1-[5,5-bis(4-chlorophenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylate} (*rac*-**33d**)**: GP5 was followed using alkyne *rac*-**15** (105 mg, 0.500 mmol),  $\text{CuI}$  (19 mg, 0.10 mmol),  $i\text{-Pr}_2\text{NH}$  (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(chlorobenzene) (303 mg, crude compound) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-**33d** was afforded as yellow viscous oil (203 mg, 91%):  $R_f=0.50$  (PE/EtOAc 6:4);  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=1.22$  (t,  $J=7.1$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 1.32–1.55 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.63–1.72 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.83–1.92 (m, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.99 (td,  $J=10.9/3.0$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.14 (t,  $J=10.6$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 2.29–2.39 (m, 2H,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 2.39–2.54 (m, 3H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$  and  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 2.67–2.79 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.94 (dbr,  $J=11.6$  Hz, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 4.08 (q,  $J=7.1$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 5.76 (t,  $J=6.7$  Hz, 1H,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 7.24–7.30 (m, 4H,  $\text{ArH}$ ), 7.30–7.35 (m, 4H,  $\text{ArH}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta=14.6$  (1C,  $\text{OCH}_2\text{CH}_3$ ), 25.2 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 27.1 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 27.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 42.5 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 53.5 (1C,  $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 56.1 (1C,  $\text{NCH}_2\text{CHCH}_2$ ), 58.3 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 60.7 (1C,  $\text{OCH}_2\text{CH}_3$ ), 93.9 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 108.6 (1C,  $\text{NCH}_2\text{CH}_2\text{CHCC}$ ), 129.0 (4C,  $\text{ArC}$ ), 130.2 (2C,  $\text{ArC}$ ), 130.2 (2C,  $\text{ArC}$ ), 133.3 (2C,  $\text{ArC}_q$ ), 136.0 (1C,  $\text{ArC}_q$ ), 136.0 (1C,  $\text{ArC}_q$ ), 174.5 (1C,  $\text{CO}$ ), 206.1 (1C,  $\text{CH}_2\text{CHCC}$ ); IR (film):  $\tilde{\nu}=2941, 2855, 2807, 2361, 2230, 1941, 1727, 1590, 1489, 1467, 1444, 1396, 1370, 1303, 1274, 1181, 1152, 1133, 1090, 1032, 1014, 949, 909, 887, 832, 795, 746, 721, 702$   $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{25}\text{H}_{27}\text{Cl}_2\text{NO}_2$ : 444.1497, found: 444.1495.

***rac*-{Ethyl (*R*<sub>a</sub>)-1-[5-([1,1'-biphenyl]-4-yl)-5-phenylpenta-3,4-dien-1-yl]-(3*R*)-piperidine-3-carboxylate} (*rac*-(*3R,R*<sub>a</sub>)-**33e**) and *rac*-{ethyl (*S*<sub>a</sub>)-1-[5-([1,1'-biphenyl]-4-yl)-5-phenylpenta-3,4-dien-1-yl]-(3*R*)-piperidine-3-carboxylate} (*rac*-(*3R,S*<sub>a</sub>)-**33e**)**: GP5 was followed using alkyne *rac*-**15** (105 mg, 0.500 mmol),  $\text{CuI}$  (19 mg, 0.10 mmol),  $i\text{-Pr}_2\text{NH}$  (0.08 mL, 0.55 mmol) and 4-(diazo(phenyl)methyl)-1,1'-biphenyl (135 mg, 0.50 mmol) in 1,4-dioxane (2.5 mL) for 1 h. After purification by column chromatography (gradient elution PE/EtOAc 9:1 to PE/EtOAc 7:3) pure *rac*-

(3*R*,*R*<sub>a</sub>)-**33e** and *rac*-(3*R*,*S*<sub>a</sub>)-**33e** were obtained as ~ 1:1 mixture of racemic diastereomers as yellow viscous oil (198 mg, 88%): *R*<sub>f</sub>=0.14 (PE/EtOAc 8:2); <sup>1</sup>H NMR (400 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=1.15 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.16 (t, *J*=7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 1.32 (qd, *J*=11.7/3.7 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.38–1.52 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.53–1.67 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.76–1.88 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.93 (tbr, *J*=10.8 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.09 (t, *J*=10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.33 (q, *J*=7.1 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.38–2.56 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.71 (dbr, *J*=11.1 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.92 (dbr, *J*=11.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 4.01 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 4.02 (q, *J*=7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1 or dia2), 5.69 (t, *J*=7.1 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.18–7.45 (m, 10H, ArH), 7.45–7.63 (m, 4H, ArH); <sup>13</sup>C NMR (101 MHz, C<sub>2</sub>D<sub>2</sub>Cl<sub>4</sub>): δ=14.6 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 26.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC or NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 42.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.6 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 92.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 109.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 127.3 (2C, ArC), 127.3 (2C, ArC), 127.5 (1C, ArC), 127.7 (1C, ArC), 128.7 (2C, ArC), 128.9 (1C, ArC), 128.9 (1C, ArC), 129.1 (1C, ArC), 129.1 (1C, ArC), 129.2 (2C, ArC), 136.3 (1C, ArC<sub>q</sub>), 137.1 (1C, ArC<sub>q</sub>), 139.8 (1C, ArC<sub>q</sub>), 140.8 (1C, ArC<sub>q</sub>), 174.6 (1C, CO), 206.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =3057, 3028, 2940, 2854, 2804, 1940, 1730, 1598, 1519, 1486, 1468, 1446, 1370, 1310, 1273, 1210, 1178, 1151, 1133, 1100, 1074, 1030, 1007, 964, 906, 842, 799, 767, 728, 697 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>31</sub>H<sub>33</sub>NO<sub>2</sub>: 452.2590, found: 452.2578.

***rac*-[Ethyl 1-[5,5-bis(4-methoxyphenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylate] (*rac*-33f)**: GP5 was followed using alkyne *rac*-**15** (105 mg, 0.500 mmol), CuI (19 mg, 0.10 mmol), *i*-Pr<sub>2</sub>NH (0.08 mL, 0.55 mmol) and 4,4'-(diazomethylene)bis(methoxybenzene) (520 mg, crude compound) in 1,4-dioxane (2.5 mL). After purification by column chromatography (PE/EtOAc 8:2) pure *rac*-**33f** was afforded as yellow viscous oil (97.7 mg, 45%): *R*<sub>f</sub>=0.24 (PE/EtOAc 7:3); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ=1.24 (t, *J*=7.1 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (qd, *J*=12.0/4.0 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.47–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.64–1.76 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.87–2.08 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.17 (t, *J*=10.7 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.36 (q, *J*=7.2 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.45–2.66 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.80 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.02 (dbr, *J*=11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.82 (s, 6H, OCH<sub>3</sub>), 4.12 (q, *J*=7.1 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 5.65 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 6.78–6.94 (m, 4H, ArH), 7.17–7.35 (m, 4H, ArH); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ=14.2 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 24.6 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 26.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 27.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 41.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 53.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 55.3 (2C, OCH<sub>3</sub>), 55.4 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 58.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 60.3 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.8 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 109.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 113.7 (4C, ArC), 129.5 (4C, ArC), 129.6 (2C, ArC<sub>q</sub>), 158.7 (2C, COCH<sub>3</sub>), 174.2 (1C, CO), 204.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (film):  $\tilde{\nu}$ =2938, 2835, 2805, 1940, 1730, 1606, 1578, 1508, 1464, 1442, 1370, 1296, 1247, 1174, 1152, 1106, 1034, 963, 935, 910, 833, 807, 779, 730 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>27</sub>H<sub>33</sub>NO<sub>4</sub>: 436.2488, found: 436.2486.

***rac*-[1-(5,5-Diphenylpenta-3,4-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-34a)**: GP7 was followed using nipecotic acid ester *rac*-**33a** (93.9 mg, 0.250 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (158 mg, 0.500 mmol) in 1.8 mL EtOH/H<sub>2</sub>O (2:1) for 25 h. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acid *rac*-**34a** was



afforded as white amorphous solid (45.3 mg, 52%): mp: 41 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.13 (qd, *J*=13.5/4.4 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.36 (qt, *J*=12.9/3.8 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.43–1.55 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.67–1.82 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.86 (t, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.11–2.30 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.32–2.43 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.71 (dbr, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.95 (dbr, *J*=11.0 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.55 (t, *J*=6.7 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.00–7.19 (m, 10H, ArH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 29.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 92.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 111.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 128.2 (2C, ArC), 129.4 (4C, ArC), 129.4 (4C, ArC), 138.3 (2C, ArC<sub>q</sub>), 182.7 (1C, CO), 206.7 (1C, CH<sub>2</sub>CHCC); IR (KBr): ν̄=3433, 3056, 3026, 2938, 2857, 2805, 2525, 2368, 2345, 1944, 1708, 1597, 1491, 1451, 1442, 1389, 1310, 1278, 1218, 1188, 1155, 1101, 1074, 1030, 921, 902, 770, 696, 630 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>25</sub>NO<sub>2</sub>: 348.1964, found: 348.1958; average purity by qHNMR (internal calibrant: maleic acid Lot#BCBM8127V): 99%.

***rac*-[1-(5,5-Di-*p*-tolylpenta-3,4-dien-1-yl)piperidine-3-carboxylic acid] (*rac*-34b):** GP7 was followed using nipecotic acid ester *rac*-33b (109 mg, 0.269 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (170 mg, 0.538 mmol) in 1.5 mL EtOH/H<sub>2</sub>O (2:1) for 5 h. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 7:3) the desired amino acid *rac*-34b was afforded as white amorphous solid (14.6 mg, 15%): mp: 54 °C; <sup>1</sup>H NMR (500 MHz, MeOD): δ=1.33 (qd, *J*=13.0/4.4 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.51–1.63 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.64–1.74 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.93 (td, *J*=11.8/2.9 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 1.97–2.03 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.05 (t, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.33 (s, 6H, CH<sub>3</sub>), 2.35–2.45 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCC and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.52–2.61 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.90 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.16 (dbr, *J*=11.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.69 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.11–7.23 (m, 8H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD): δ=21.2 (2C, CH<sub>3</sub>), 26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 29.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 92.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 111.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 129.3 (4C, ArC), 130.0 (4C, ArC), 135.5 (2C, ArC<sub>q</sub>), 138.0 (2C, ArC<sub>q</sub>), 182.7 (1C, CO), 206.4 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (KBr): ν̄=3432, 3021, 2922, 2858, 1942, 1702, 1593, 1509, 1449, 1386, 1308, 1181, 1153, 1108, 1020, 910, 822, 796, 783, 720, 668, 611, 584, 514, 462 cm<sup>-1</sup>; HRMS-ESI *m/z* [*M*+H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>29</sub>NO<sub>2</sub>: 376.2277, found: 376.2266.

***rac*-{1-[5,5-Bis(4-fluorophenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylic acid} (*rac*-34c):** GP7 was followed using nipecotic acid ester *rac*-33c (194 mg, 0.472 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (298 mg, 0.944 mmol) in 3.0 mL EtOH/H<sub>2</sub>O (2:1) overnight. After purification by RP-MPLC (gradient elution with MeOH/H<sub>2</sub>O 6:4 to MeOH/H<sub>2</sub>O 7:3) the desired amino acid *rac*-34c was afforded as white amorphous solid (82.4 mg, 46%): mp: 62 °C; <sup>1</sup>H NMR (400 MHz, MeOD, NaOD): δ=1.33 (qd, *J*=12.8/4.2 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.55 (qt, *J*=12.8/3.9 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.63–1.76 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.86–2.01 (m, 2H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH and NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.05 (t, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.32–2.47 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.50–2.61 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.90 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.08–3.19 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.77 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.01–7.14 (m, 4H, FCCH), 7.22–7.37 (m, 4H, FCCH); <sup>13</sup>C NMR (101 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.2

(1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 29.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 93.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 109.7 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 116.3 (d<sub>CF</sub>, <sup>2</sup>J<sub>CF</sub>=21.8 Hz, 2C, FCCHCHC), 116.3 (d<sub>CF</sub>, <sup>2</sup>J<sub>CF</sub>=21.8 Hz, 2C, FCCHCHC), 131.1 (d<sub>CF</sub>, <sup>3</sup>J<sub>CF</sub>=8.0 Hz, 4C, FCCHCHC), 134.4 (d<sub>CF</sub>, <sup>4</sup>J<sub>CF</sub>=3.4 Hz, 2C, FCCHCHC), 163.5 (d<sub>CF</sub>, <sup>1</sup>J<sub>CF</sub>=245.3 Hz, 2C, FC), 182.8 (1C, CO), 206.5 (1C, CH<sub>2</sub>CHCC); <sup>19</sup>F NMR (376 MHz, MeOD, NaOD): δ=-116.5, -116.6; IR (KBr): ν̄=3422, 3044, 2942, 2861, 2804, 2494, 2027, 1944, 1896, 1711, 1600, 1505, 1468, 1450, 1390, 1298, 1281, 1222, 1156, 1096, 1013, 911, 838, 799, 767, 724, 606, 582, 550, 519, 490 cm<sup>-1</sup>; HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>23</sub>F<sub>2</sub>NO<sub>2</sub>: 384.1775, found: 384.1766.

***rac*-{1-[5,5-Bis(4-chlorophenyl)penta-3,4-dien-1-yl]piperidine-3-carboxylic acid} (*rac*-34d):** GP6 was followed using nipecotic acid ester *rac*-33d (0.510 mmol, 227 mg), EtOH (2.55 mL) and 2M NaOH (0.77 mL) for 45 min. The desired amino acid *rac*-34d was obtained as colorless amorphous solid (53.2 mg, 25%): mp: 79 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.01 (qd, *J*=12.7/3.9 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.15–1.30 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.30–1.42 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.55–1.69 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 1.72 (t, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 1.99–2.16 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCC and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.23 (t, *J*=7.7 Hz, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.57 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.82 (dbr, *J*=11.2 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.49 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 6.95 (d, *J*=8.1 Hz, 4H, ArH), 7.02 (d, *J*=8.1 Hz, 4H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 29.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.2 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 94.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 109.6 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 129.7 (2C, ArC), 129.7 (2C, ArC), 130.8 (4C, ArC), 134.2 (2C, ArC<sub>q</sub>), 136.7 (2C, ArC<sub>q</sub>), 182.8 (1C, CO), 206.8 (1C, CH<sub>2</sub>CHCC); IR (KBr): ν̄=3435, 2936, 2855, 2803, 1941, 1711, 1590, 1488, 1450, 1396, 1299, 1218, 1154, 1090, 1013, 909, 832, 745, 722, 701, 639, 613, 595, 532, 511, 461 cm<sup>-1</sup>; HRMS-ESI *m/z* [M+H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>23</sub>Cl<sub>2</sub>NO<sub>2</sub>: 416.1184, found: 416.1178; average purity by qHNMR (internal calibrant: maleic acid Lot#BCBM8127V): 98%.

***rac*-{(R<sub>a</sub>)-1-[5-([1,1'-biphenyl]-4-yl)-5-phenylpenta-3,4-dien-1-yl]-(3R)-piperidine-3-carboxylic acid} (*rac*-(3R,R<sub>a</sub>)-34e) and *rac*-{(S<sub>a</sub>)-1-[5-([1,1'-biphenyl]-4-yl)-5-phenylpenta-3,4-dien-1-yl]-(3R)-piperidine-3-carboxylic acid} (*rac*-(3R,S<sub>a</sub>)-34e):** GP6 was followed using nipecotic acid esters *rac*-(3R,R<sub>a</sub>)-33e and *rac*-(3R,S<sub>a</sub>)-33e (0.202 mmol, 91.2 mg), EtOH (1.0 mL) and 2M NaOH (0.30 mL) for 2.5 h. The desired amino acids *rac*-(3R,R<sub>a</sub>)-34e and *rac*-(3R,S<sub>a</sub>)-34e were obtained as ~ 1:1 mixture of racemic diastereomers as yellow amorphous solid (25.6 mg, 30%): mp: 86 °C; <sup>1</sup>H NMR (500 MHz, MeOD, NaOD): δ=1.34 (qd, *J*=12.8/4.2 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.57 (qt, *J*=13.0/4.0 Hz, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.65–1.73 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.91–2.02 (m, 2H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub> and NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.07 (t, *J*=11.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.33–2.51 (m, 3H, NCH<sub>2</sub>CH<sub>2</sub>CHCC and NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub>), 2.54–2.64 (m, 2H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 2.92 (dbr, *J*=11.3 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 3.16 (ddbr, *J*=10.5/3.5 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 5.79 (t, *J*=6.6 Hz, 1H, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 7.24–7.47 (m, 10H, ArH), 7.57–7.66 (m, 4H, ArH); <sup>13</sup>C NMR (126 MHz, MeOD, NaOD): δ=26.0 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 27.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 29.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 46.3 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 54.9 (1C, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 58.3 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>), 59.5 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 93.1 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 111.2 (1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC), 127.9 (2C, ArC), 128.0 (2C, ArC), 128.3 (1C, ArC), 128.4 (1C, ArC), 129.5 (2C, ArC), 129.5 (2C, ArC), 129.8 (2C, ArC), 129.9 (2C, ArC), 137.3 (1C, ArC<sub>q</sub>), 138.3 (1C, ArC<sub>q</sub>), 141.3 (1C, ArC<sub>q</sub>), 142.0 (1C, ArC<sub>q</sub>), 182.8 (1C, CO), 206.9

(1C, NCH<sub>2</sub>CH<sub>2</sub>CHCC); IR (KBr):  $\tilde{\nu}$ =3422, 3054, 3027, 2931, 2855, 2802, 1943, 1711, 1655, 1598, 1485, 1446, 1390, 1312, 1279, 1183, 1154, 1101, 1074, 1029, 1007, 907, 842, 768, 729, 697, 629 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>29</sub>H<sub>29</sub>NO<sub>2</sub>: 424.2277, found: 424.2269.

**rac-[Ethyl (R<sub>a</sub>)-1-{3-[6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene]allyl}-(3R)-piperidine-3-carboxylate] (rac-(3R,R<sub>a</sub>)-37) and rac-[ethyl (S<sub>a</sub>)-1-{3-[6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene]allyl}-(3R)-piperidine-3-carboxylate] (rac-(3R,S<sub>a</sub>)-37):** GP4 was followed applying alkyne *rac*-9 (98 mg, 0.50 mmol), Cul (19 mg, 0.10 mmol), Li<sup>t</sup>OBu (140 mg, 1.75 mmol), and *N'*-[6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene]-4-methylbenzenesulfonohydrazide (379 mg, 1.10 mmol) in 1,4-dioxane (5.0 mL). The solution was stirred at 90 °C for 1 h. After purification by column chromatography (PE/EtOAc 7:3) *rac*-(3R,R<sub>a</sub>)-37 and *rac*-(3R,S<sub>a</sub>)-37 were obtained as ~ 1:1 mixture of racemic diastereomers as yellow oil (107 mg, 60%):  $R_f$ =0.35 (PE/EtOAc 6:4); <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =1.23 (t,  $J$ =7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 1.24 (t,  $J$ =7.1 Hz, 1.5H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 1.43 (qd,  $J$ =11.8/4.0 Hz, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 1.50–1.66 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.68–1.77 (m, 1H, NCH<sub>2</sub>CH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH), 1.86 (p,  $J$ =6.2 Hz, 2H, NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 1.89–1.95 (m, 1H, NCH<sub>2</sub>CHCH<sub>ax</sub>H<sub>eq</sub>), 2.10 (td,  $J$ =11.0/2.4 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.23 (t,  $J$ =10.6 Hz, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 2.46–2.59 (m, 3H, NCH<sub>2</sub>CH<sub>ax</sub>CH<sub>2</sub> and NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.77 (t,  $J$ =6.2 Hz, 2H, NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 2.78–2.87 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CH<sub>2</sub>CH<sub>2</sub>CH), 2.98–3.08 (m, 1H, NCH<sub>ax</sub>H<sub>eq</sub>CHCH<sub>2</sub>), 3.09 (d,  $J$ =6.9 Hz, 1H, NCH<sub>2</sub>CHCC, dia2), 3.10 (d,  $J$ =6.9 Hz, 1H, NCH<sub>2</sub>CHCC, dia1), 3.76 (s, 3H, OCH<sub>3</sub>), 4.10 (q,  $J$ =7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 4.10 (q,  $J$ =7.1 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 5.45 (tt,  $J$ =6.9/3.0 Hz, 1H, NCH<sub>2</sub>CHCC), 6.62 (d,  $J$ =2.8 Hz, 1H, CCCHCOCH<sub>3</sub>), 6.68 (dt,  $J$ =8.6/2.8 Hz, 1H, CH<sub>3</sub>OCCHCH), 7.33 (d,  $J$ =8.6 Hz, 1H, CH<sub>3</sub>OCCHCH); <sup>13</sup>C NMR (126 MHz, CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$ =14.6 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia2), 14.6 (0.5C, OCH<sub>2</sub>CH<sub>3</sub>, dia1), 23.6 (1C, NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 25.2 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1), 25.3 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia2), 27.4 (1C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 29.7 (1C, NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 30.9 (1C, NCH<sub>2</sub>CHCCCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>), 42.6 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 42.6 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 53.7 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 53.8 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 55.6 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 55.7 (0.5C, NCH<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, dia1 or dia2), 55.7 (1C, OCH<sub>3</sub>), 58.9 (0.5C, NCH<sub>2</sub>CHCC, dia1), 58.9 (0.5C, NCH<sub>2</sub>CHCC, dia2), 60.7 (1C, OCH<sub>2</sub>CH<sub>3</sub>), 91.2 (0.5C, NCH<sub>2</sub>CHCC, dia1), 91.2 (0.5C, NCH<sub>2</sub>CHCC, dia2), 101.9 (0.5C, NCH<sub>2</sub>CHCC, dia2), 101.9 (0.5C, NCH<sub>2</sub>CHCC, dia1), 113.2 (1C, CH<sub>3</sub>OCCHCH), 113.8 (1C, CCCHCOCH<sub>3</sub>), 124.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 124.5 (0.5C, ArC<sub>q</sub>, dia1 or dia2), 128.6 (1C, CH<sub>3</sub>OCCHCH), 138.5 (1C, ArC<sub>q</sub>), 158.9 (1C, COCH<sub>3</sub>), 174.6 (0.5C, CO, dia1 or dia2), 174.6 (0.5C, CO, dia1 or dia2), 202.6 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2), 202.6 (0.5C, NCH<sub>2</sub>CHCC, dia1 or dia2); IR (film):  $\tilde{\nu}$ =2937, 2862, 2834, 2796, 1946, 1730, 1607, 1571, 1498, 1466, 1441, 1366, 1319, 1261, 1245, 1180, 1152, 1132, 1111, 1094, 1068, 1033, 884, 836, 809 cm<sup>-1</sup>; HRMS-ESI  $m/z$  [ $M+H$ ]<sup>+</sup> calcd for C<sub>22</sub>H<sub>29</sub>NO<sub>3</sub>: 356.2226, found: 356.2221.

**rac-[(R<sub>a</sub>)-1-{3-[6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene]allyl}-(3R)-piperidine-3-carboxylic acid] (rac-(3R,R<sub>a</sub>)-38) and rac-[(S<sub>a</sub>)-1-{3-[6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene]allyl}-(3R)-piperidine-3-carboxylic acid] (rac-(3R,S<sub>a</sub>)-38):** GP7 was followed using nipecotic acid esters *rac*-(3R,R<sub>a</sub>)-37 and *rac*-(3R,S<sub>a</sub>)-37 (107 mg, 0.300 mmol) and Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (189 mg, 0.600 mmol) in 2.1 mL EtOH/H<sub>2</sub>O (2:1) for 24 h. After purification by RP-MPLC (MeOH/H<sub>2</sub>O 6:4) the desired amino acids *rac*-(3R,R<sub>a</sub>)-38 and *rac*-(3R,S<sub>a</sub>)-38 were obtained as ~ 1:1 mixture of racemic diastereomers as pale yellow amorphous solid (59.6 mg, 61%): mp.: 115.2 °C;

$^1\text{H}$  NMR (400 MHz, MeOD):  $\delta$ =1.37 (qd,  $J$ =12.7/4.0 Hz, 1H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$ ), 1.54–1.69 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.70–1.80 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}$ ), 1.85 (p,  $J$ =6.1 Hz, 2H,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 1.95–2.07 (m, 2H,  $\text{NCH}_2\text{CHCH}_{\text{ax}}\text{H}_{\text{eq}}$  and  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 2.13 (t,  $J$ =11.4 Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.16 (t,  $J$ =11.4 Hz, 0.5H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ , dia1 or dia2), 2.35–2.48 (m, 1H,  $\text{NCH}_2\text{CH}_{\text{ax}}\text{CH}_2$ ), 2.48–2.61 (m, 2H,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 2.76 (t,  $J$ =6.1 Hz, 2H,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 2.92–3.05 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CH}_2\text{CH}_2\text{CH}$ ), 3.05–3.18 (m, 2H,  $\text{NCH}_2\text{CHCC}$ ), 3.18–3.28 (m, 1H,  $\text{NCH}_{\text{ax}}\text{H}_{\text{eq}}\text{CHCH}_2$ ), 3.75 (s, 3H,  $\text{OCH}_3$ ), 5.40–5.56 (m, 1H,  $\text{NCH}_2\text{CHCC}$ ), 6.63 (d,  $J$ =2.6 Hz, 0.5H,  $\text{CCCHCOCH}_3$ , dia1 or dia2), 6.63 (d,  $J$ =2.4 Hz, 0.5H,  $\text{CCCHCOCH}_3$ , dia1 or dia2), 6.69 (dd,  $J$ =8.6/2.6 Hz, 0.5H,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 6.71 (dd,  $J$ =8.6/2.6 Hz, 0.5H,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 7.29 (d,  $J$ =8.6 Hz, 0.5H,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 7.32 (d,  $J$ =8.6 Hz, 0.5H,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2);  $^{13}\text{C}$  NMR (101 MHz, MeOD):  $\delta$ =24.2 (1C,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 26.0 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 26.0 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 29.4 (1C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 30.2 (1C,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 31.4 (1C,  $\text{NCH}_2\text{CHCCCH}_2\text{CH}_2\text{CH}_2$ ), 46.5 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 46.6 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 54.3 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 54.5 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 55.6 (1C,  $\text{OCH}_3$ ), 57.8 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 57.9 (0.5C,  $\text{NCH}_2\text{CHCH}_2\text{CH}_2\text{CH}_2$ , dia1 or dia2), 59.6 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 59.7 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 90.6 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 90.6 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 103.0 (1C,  $\text{NCH}_2\text{CHCC}$ ), 113.8 (0.5C,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 113.8 (0.5C,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 114.4 (0.5C,  $\text{CCCHCOCH}_3$ , dia1 or dia2), 114.4 (0.5C,  $\text{CCCHCOCH}_3$ , dia1 or dia2), 124.7 (0.5C,  $\text{ArC}_q$ , dia1 or dia2), 124.7 (0.5C,  $\text{ArC}_q$ , dia1 or dia2), 129.2 (0.5C,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 129.3 (0.5C,  $\text{CH}_3\text{OCCHCH}$ , dia1 or dia2), 139.0 (0.5C,  $\text{ArC}_q$ , dia1 or dia2), 139.1 (0.5C,  $\text{ArC}_q$ , dia1 or dia2), 160.0 (1C,  $\text{COCH}_3$ ), 182.7 (1C,  $\text{CO}$ ), 203.8 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2), 203.8 (0.5C,  $\text{NCH}_2\text{CHCC}$ , dia1 or dia2); IR (KBr):  $\tilde{\nu}$ =3433, 2935, 2860, 2835, 2525, 1946, 1715, 1606, 1571, 1498, 1465, 1452, 1394, 1320, 1271, 1246, 1195, 1154, 1125, 1067, 1035, 953, 884, 837, 820, 766, 718, 668, 565  $\text{cm}^{-1}$ ; HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{20}\text{H}_{25}\text{NO}_3$ : 328.1913, found: 328.1907.

**Keywords:** allene moiety · GABA uptake inhibitors · mGAT4 · nipecotic acid

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# Supporting Information

## Synthesis and Biological Evaluation of Nipecotic Acid Derivatives with Terminally Double-Substituted Allenic Spacers

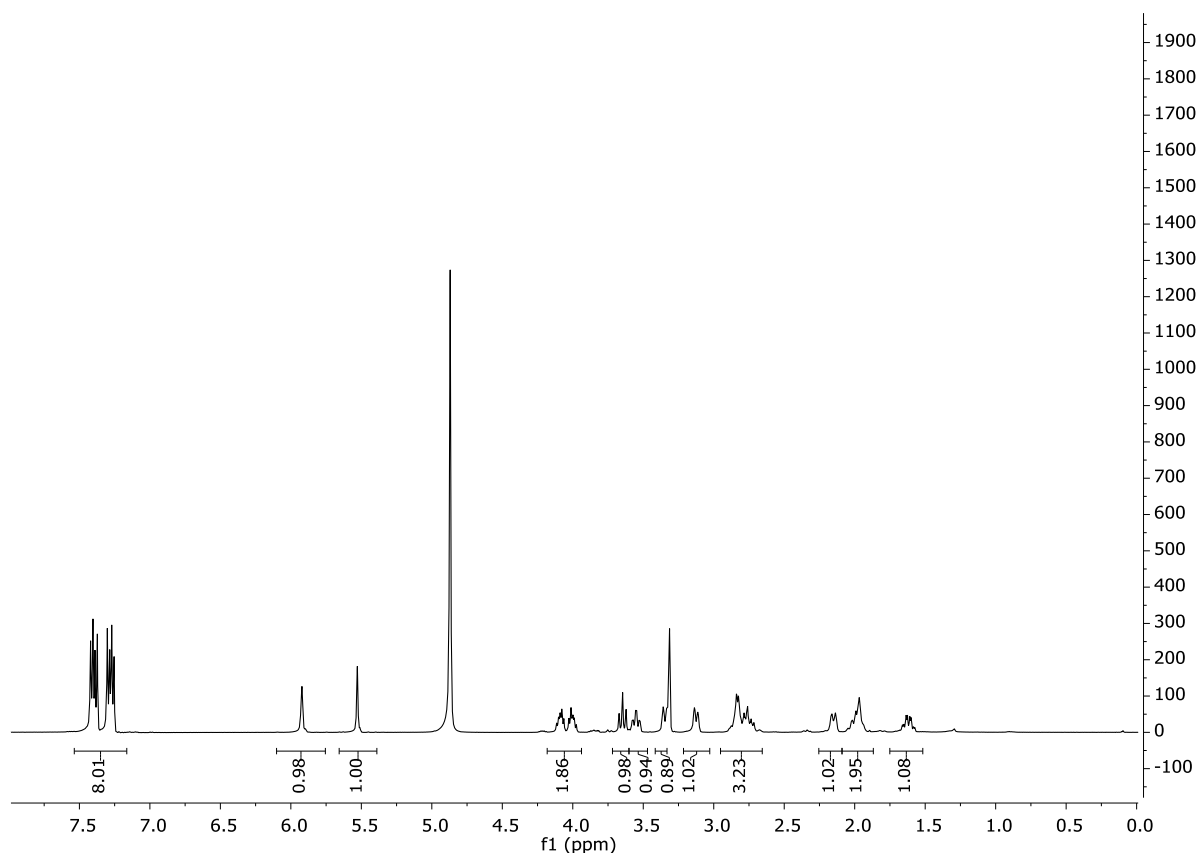
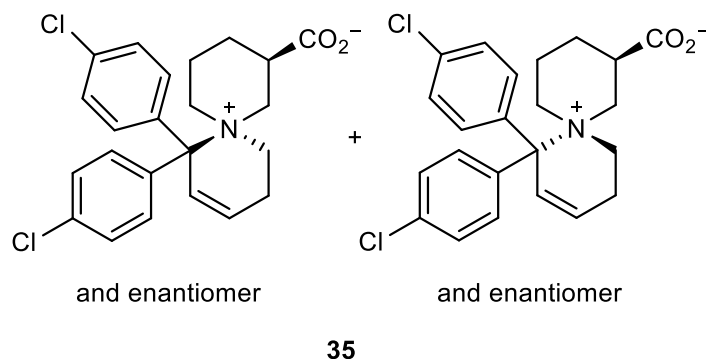
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NMR spectra of decomposition product **35**:



**SI-Figure 1.**  $^1\text{H-NMR}$  of compound **35** in MeOD.

$^1\text{H NMR}$  (500 MHz, MeOD):  $\delta$ =1.62 (qd,  $J$ =12.9/4.8 Hz, 1H,  $\text{CH}_2$ ), 1.87–2.08 (m, 2H,  $\text{CH}_2$ ), 2.15 (d,  $J$ =12.5 Hz, 1H,  $\text{CH}_2$ ), 2.64–2.92 (m, 3H,  $\text{CH}_2$  and  $\text{CH}$ ), 3.13 (d,  $J$ =11.7 Hz, 1H,  $\text{CH}_2$ ), 3.33–3.39 (m, 1H,  $\text{CH}_2$ ), 3.55 (td,  $J$ =12.3/4.3 Hz, 1H,  $\text{CH}_2$ ), 3.65 (t,  $J$ =12.4 Hz, 1H,  $\text{CH}_2$ ), 3.95–4.14 (m, 2H,  $\text{CH}_2$ ), 5.53 (s, 1H,  $\text{CH}$ ), 5.88–5.97 (m, 1H,  $\text{CH}$ ), 7.21–7.35 (m, 4H, ArH), 7.35–7.48 (m, 4H, ArH);  $^{13}\text{C NMR}$  (126 MHz, MeOD):  $\delta$ =20.8 (1C,  $\text{CH}_2$ ), 24.9 (1C,  $\text{CH}_2$ ), 26.5 (1C,  $\text{CH}_2$ ), 40.7 (1C,  $\text{CH}$ ), 45.2 (1C,  $\text{CH}$ ), 59.1 (1C,  $\text{CH}_2$ ), 59.5 (1C,  $\text{CH}_2$ ), 61.2 (1C,  $\text{CH}_2$ ), 128.9 (2C, ArC), 128.9 (2C, ArC), 129.3 (1C,  $\text{CH}$ ), 129.9 (2C, ArC), 130.0 (2C, ArC), 133.3 (1C, C), 133.4 (1C, C), 138.5 (1C, C), 138.8 (1C, C), 150.8 (1C, C), 176.2 (1C, C). The assignment was done by means of 2D NMR spectra (HMQC, COSY, DEPT). HRMS-ESI  $m/z$  [ $M+H$ ] $^+$  calcd for  $\text{C}_{23}\text{H}_{23}\text{Cl}_2\text{NO}_2$ : 416.1184, found: 416.1172.

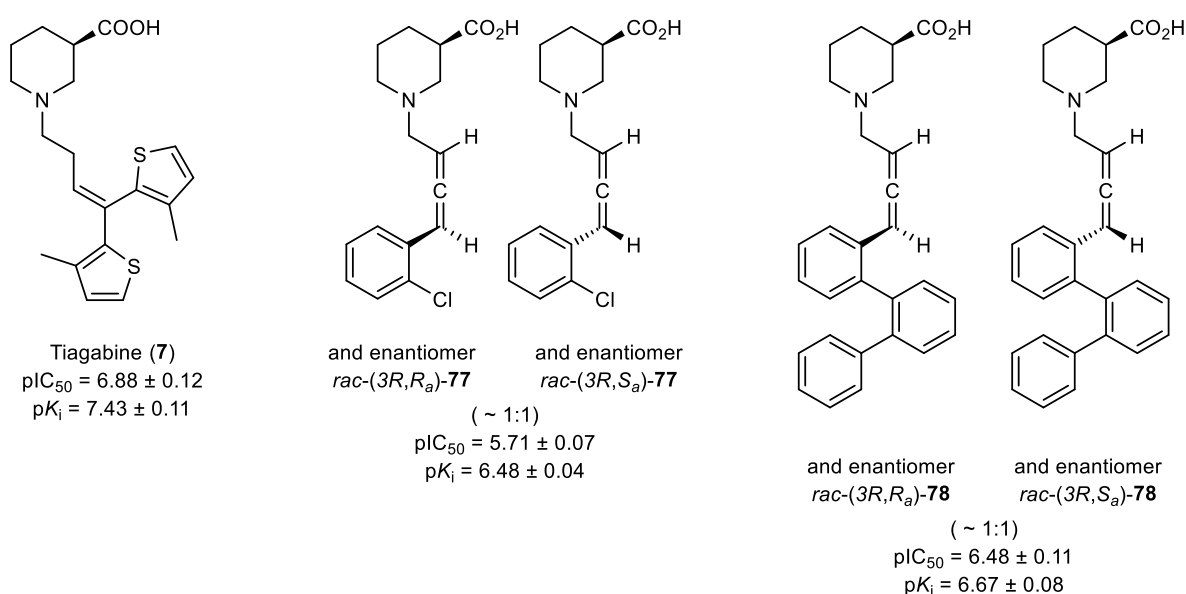


## 4 Conclusion and Summary

Within the first study, a new synthesis procedure was developed giving flexible access to a wide range of nipecotic acid derivatives with terminally substituted and unsubstituted allenic spacers as lipophilic N-substituents. Through studying the synthesis of terminal and 1,3-disubstituted allenes from amino methylation precursors via [1,5]-hydride transfer reactions under  $\text{CdI}_2$  catalysis, deeper insights of how the electronic, conformational and especially the steric properties of different secondary amines serving as hydride donors influence this reaction step, have been gained. With allyl(*tert*-butyl)amine a new hydride donor has been found that due to its high steric demand reduces the reaction limiting complexation of the hydride donor nitrogen by the Lewis acid catalyst and thus delivers excellent yields when used as mediator in terminal allene synthesis. In addition, 1,2,5,6-tetrahydropyridine has also been identified as high performing hydride donor in ATA (allenylation of terminal alkynes) reactions delivering 1,3-disubstituted allenes in high yields.

In the first series of nipecotic acid and guvacine derivatives that is defined by a terminally monosubstituted allenic four-carbon atom spacer connecting the polar amino acid head via the amino nitrogen with various aromatic residues, such as phenyls and 2-biphenyls, several very promising mGAT1 inhibitors have been identified. The target compounds were synthesized via the previously developed 1,2,5,6-tetrahydropyridine mediated ATA procedure, delivering the allene products in good to excellent yields up to 95%. This procedure allowed to easily vary the lipophilic residue attached to the allene termini of the desired compounds. Due to the presence of two stereogenic centers, a chiral center at the nipecotic acid and a chiral axis arising from the allene moiety, the synthesis yielded the nipecotic acid derivatives as a mixture of racemic diastereomers, the ratio of which amounted to approximately 1:1. As these

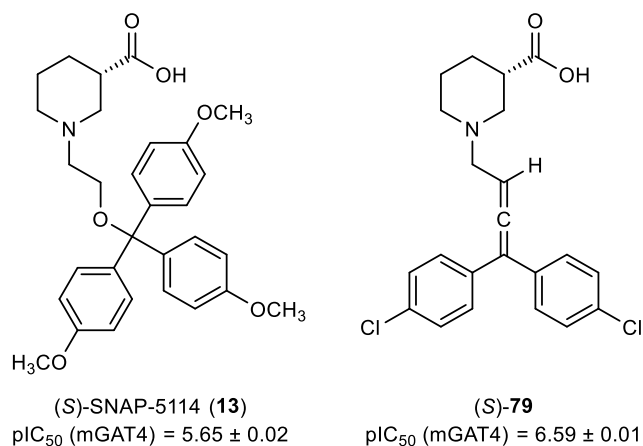
mixtures of diastereomers were highly difficult to separate, on the stage of the amino acid esters and the free amino acids, they were directly, i.e. as ~1:1 mixtures, used for biological testing. The small *o*-chlorophenyl residue and the larger *o*-terphenyl residue are considered as the most interesting implemented aromatic domains of this study. The mGAT1 binding affinity of the corresponding nipecotic acid derivatives *rac*-(3*R*,*R*<sub>a</sub>)-**77**/*rac*-(3*R*,*S*<sub>a</sub>)-**77** and *rac*-(3*R*,*R*<sub>a</sub>)-**78**/*rac*-(3*R*,*S*<sub>a</sub>)-**78** (**Figure 10**), representing ~ 1:1 mixtures of racemic diastereomers, has been determined as  $pK_i = 6.48$  and  $pK_i = 6.67$ , respectively. For the (*R*)-nipecotic acid derived form of **78**, (3*R*,*R*<sub>a</sub>)-**78**/(3*R*,*S*<sub>a</sub>)-**78**, the inhibitory potency in [<sup>3</sup>H]GABA-Uptake-Assays has been determined as  $pIC_{50} = 6.78$ , being in the range of the known mGAT1 inhibitor tiagabine (**7**, **Figure 10**). With guvacine instead of nipecotic acid as polar subunit in **78**, a slightly lower inhibitory potency at mGAT1 and an equally high binding affinity for mGAT1 has been observed ( $pIC_{50} = 6.46$ ;  $pK_i = 7.07$ ). Due to the lower molecular weight and higher polarity of the racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** as compared to tiagabine (**7**), especially this compound appears to be very promising for the further development of mGAT1 selective inhibitors as potential antiepileptic drugs.



**Figure 10:** Structure of the known mGAT1 inhibitor tiagabine and structures of new identified mGAT1 inhibitors.

In an additional study, the new compound class has been complemented with nipecotic acid derivatives exhibiting an extended, i.e. allenic five-carbon atom chain attached to the amino nitrogen of the polar amino acid head being terminally either, un-, mono-, or disubstituted, whereat compounds with terminally disubstituted allenic spacer have been synthesized with a shorter four-carbon atom spacer, too. The synthesis of the corresponding compounds has been achieved via a copper-catalyzed cross coupling reaction of nipecotic acid derived terminal alkynes with diaryldiazomethanes or *N*-tosylhydrazones for the introduction of diaryl and monoaryl residues as lipophilic domains.

As a result, among the various biologically investigated nipecotic acid derived compounds with a terminally disubstituted allenic spacer a highly potent mGAT4 inhibitor has been identified. For the enantiopure *S* isomer (*S*)-**79** (**Figure 11**) pIC<sub>50</sub> values of 6.59 at mGAT4 and 6.49 for the human equivalent hGAT-3 have been determined, which are significantly higher than that of the benchmark mGAT4 inhibitor (*S*)-SNAP-5114 (**13**, **Figure 11**). The lipophilic domain of (*S*)-**79** is derived from a diaryl moiety. While such a structural motif is well known as lipophilic domain of mGAT1 inhibitors, it is to our knowledge unprecedented for mGAT4 inhibitors with high potencies. Hence, the combination of the rigid allenyl spacer, the resulting new ligand orientation and the diaryl residue as lipophilic domain represents a new structural motif for mGAT4 inhibitors.

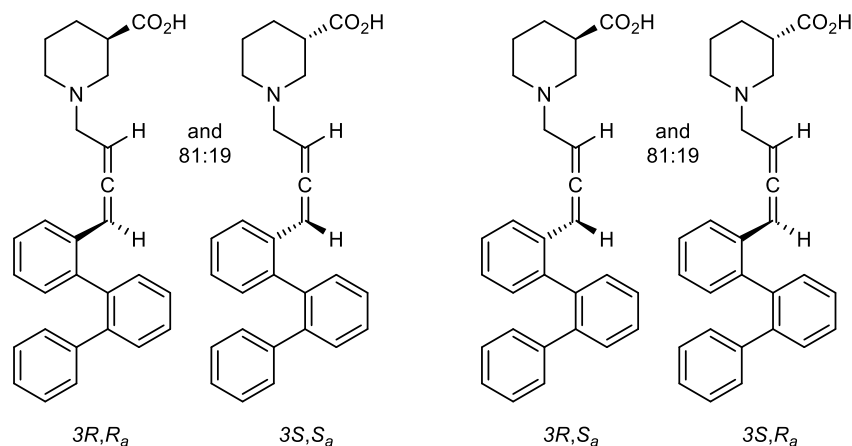


**Figure 11:** Structure of benchmark mGAT4 inhibitor (S)-SNAP-5114 (**13**) and structure of newly identified mGAT4 inhibitor (S)-**79**.

Overall, the herein introduced compounds might represent useful tools for further progressions in search of novel mGAT1 and mGAT4 selective inhibitors that one day possibly may serve as final active substances for the successful treatment of neurological diseases.

## 5 Further Experiments

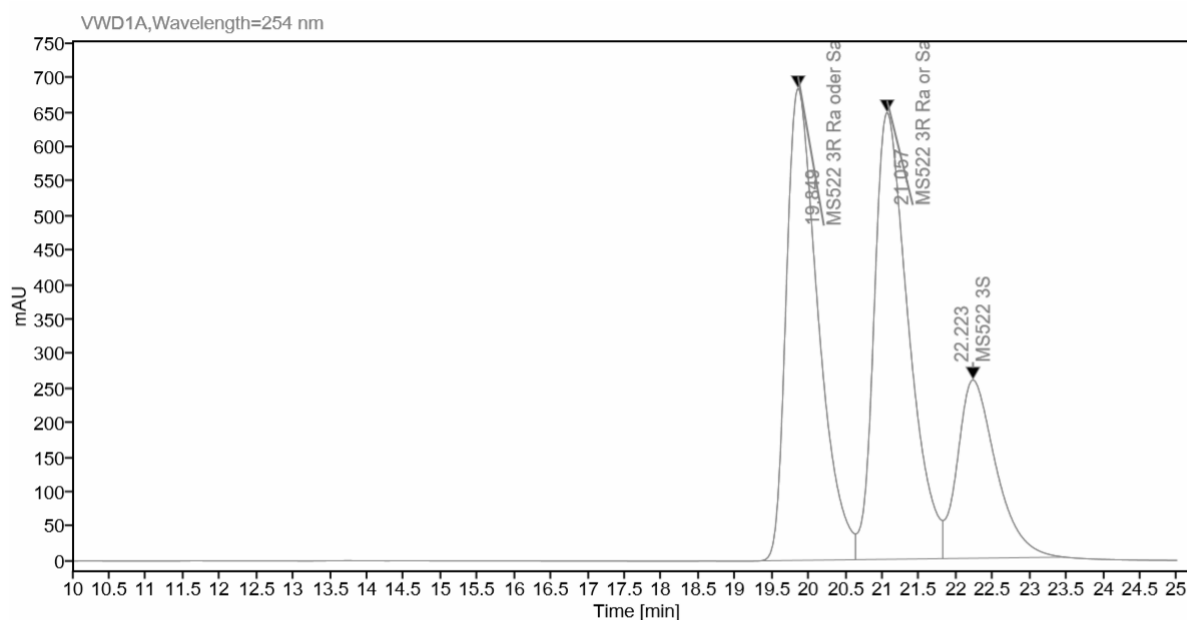
### 5.1 Separation of Diastereomers via Analytical HPLC



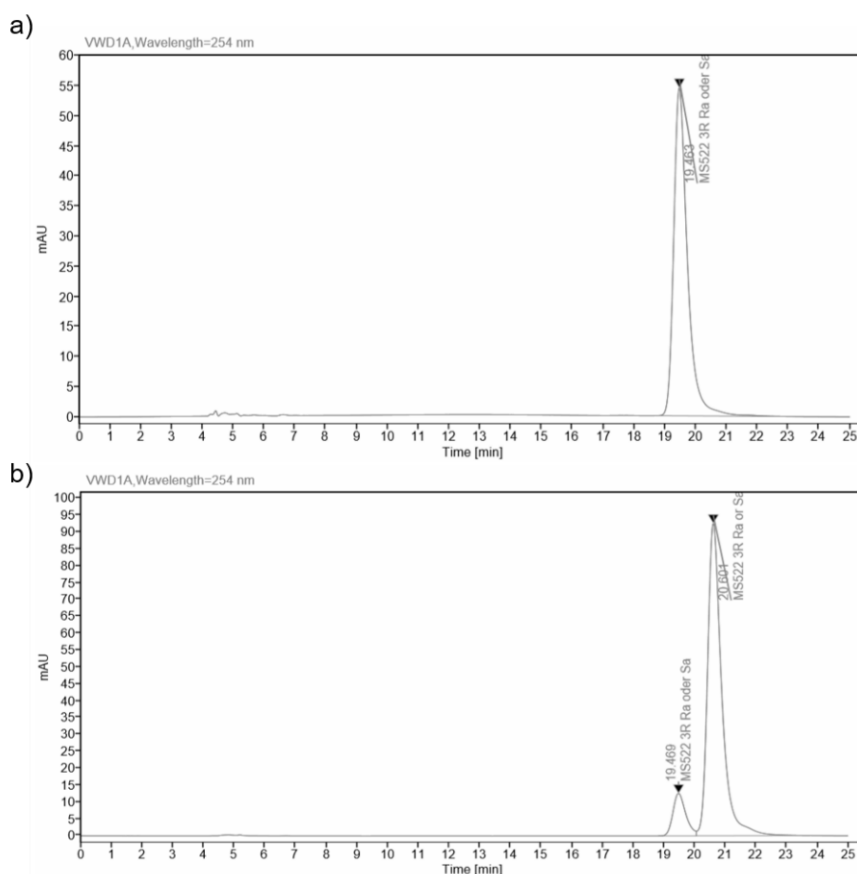
**Figure 12:** Mixture of diastereomers (3R,R<sub>a</sub>)-21p and (3R,S<sub>a</sub>)-21p, containing 19% of the enantiomers (3S,R<sub>a</sub>)-21p and (3S,S<sub>a</sub>)-21p (from the publication "Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1"; M. Schaarschmidt, G. Höfner, K. T. Wanner, *ChemMedChem* 2019, accepted article).

For the separation of the diastereomers (3R,R<sub>a</sub>)-21p and (3R,S<sub>a</sub>)-21p (Figure 12, containing 19% of the corresponding enantiomers (3S,R<sub>a</sub>)-21p and (3S,S<sub>a</sub>)-21p) HPLC method development has been performed. In Figure 13 the HPLC conditions, under which the best separation result has been achieved, are described, whereat the desired diastereomers (3R,R<sub>a</sub>)-21p and (3R,S<sub>a</sub>)-21p have been characterized as the first two peaks (peaks could not be assigned). The assignment of the (*R*)-nipecotic acid derivatives (3R,R<sub>a</sub>)-21p and (3R,S<sub>a</sub>)-21p and (*S*)-nipecotic acid derivatives (3S,R<sub>a</sub>)-21p and (3S,S<sub>a</sub>)-21p has been concluded by comparing the peak areas of the chromatogram shown in Figure 13 with the HPLC chromatogram of the mixture of the racemic diastereomers *rac*-(3R,R<sub>a</sub>)-21p and *rac*-(3R,S<sub>a</sub>)-21p obtained under the same conditions. The synthesis of the mixture of diastereomers (3R,R<sub>a</sub>)-21p and (3R,S<sub>a</sub>)-21p was performed by applying the commercially available (*R*)-ethyl nipecotate as starting material, thus peaks with larger areas were assigned to the (*R*)-nipecotic acid derivatives and the smaller third peak was assigned to the mixture of (*S*)-nipecotic acid

derivatives  $(3S,R_a)$ -**21p** and  $(3S,S_a)$ -**21p**, originating from a contamination of the starting material  $(R)$ -ethyl nipecotate. Through repeated fraction collection on the analytical column Chiralpak ZWIX(+) applying the developed HPLC method, minor amounts (less than 1 mg) of separated diastereomer (Peak 1,  $(3R,R_a)$ -**21p** or  $(3R,S_a)$ -**21p**) have been obtained (**Figure 14a**). However, NMR analysis revealed that the solvent additives formic acid and triethylamine could not be completely removed. For the second diastereomer (Peak 2,  $(3R,R_a)$ -**21p** or  $(3R,S_a)$ -**21p**) only a partially separation has been obtained after repeated fraction collection (**Figure 14b**).

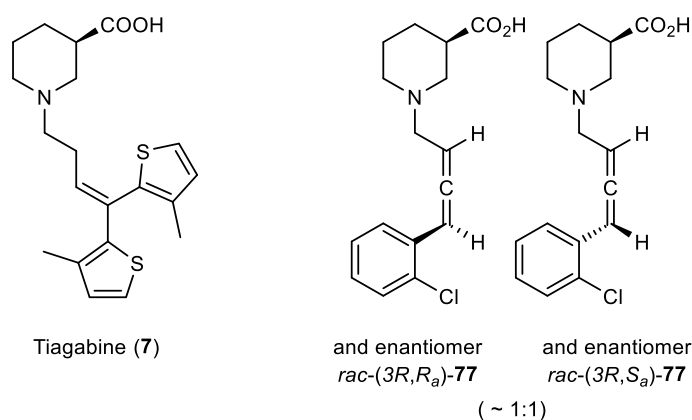


**Figure 13:** HPLC separation method; mobile phase: EtOH/MeOH/ACN 30:20:50 (v/v/v), 50mM FA, 25mM TEA; 0.2 mL/min; Chiralpak ZWIX(+), injection volume: 2  $\mu$ L (1 mg/mL).



**Figure 14:** Repeated fraction collection (cutting fractions every 20 seconds) led to complete separation of the first peak, displayed in chromatogram a), and partial separation of the second peak, displayed in chromatogram b); mobile phase: EtOH/MeOH/ACN 30:20:50 (v/v/v), 50mM FA, 25mM TEA; 0.2 mL/min; Chiralpak ZWIX(+).

## 5.2 Determination of $\log D$ Values



**Figure 15:** Selected compounds for the determination of  $\log D$ .

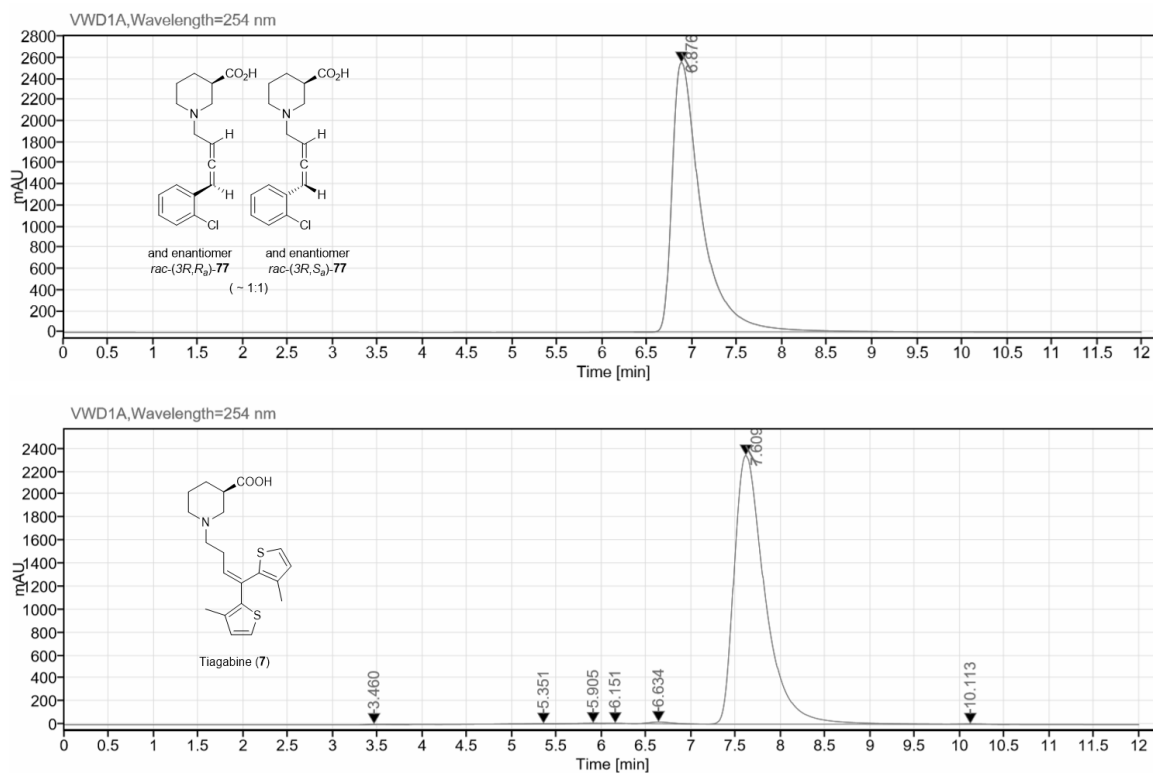
The mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-77 and *rac*-(3*R*,*S*<sub>a</sub>)-77 (**Figure 15**), which was among the most promising test compounds synthesized, displayed

moderate inhibitory potency at mGAT1 ( $pK_i = 6.48 \pm 0.04$ ;  $pIC_{50} = 5.71 \pm 0.07$ ). Compared to the known mGAT1 inhibitor tiagabine (**7**, **Figure 15**, MW = 375,55 g/mol) the mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** (MW = 291,78 g/mol) has a significantly reduced molecular weight, what is thought to facilitate the penetration across the blood-brain barrier, being an important criterion for CNS drugs.<sup>72</sup> Another important descriptor for CNS penetration is lipophilicity, whereat for better brain permeation the logD values should best be between 0 and 3.<sup>72</sup> Hence, for better evaluation of the capability of *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** to cross the blood-brain barrier, it appears obvious to determine the corresponding logD value. Within this experiment the logD value of tiagabine (**7**) has been determined as well, for comparability reasons.

For the determination of the logD values the Eppendorf Shake-Flask method described in literature has been employed.<sup>73</sup> To 100  $\mu$ L, 300  $\mu$ L, and 400  $\mu$ L of a 1 mg/mL solution of the analyte in 100 mM phosphate buffer (pH 7.4) were added 400  $\mu$ L, 200  $\mu$ L, and 100  $\mu$ L of 100 mM phosphate buffer (pH 7.4) and 500  $\mu$ L of octan-1-ol. The logD determination for each of the concentrations were performed in triplicate. All Eppendorf vials were Vortex mixed and shaken on a reciprocal shaker for 15 minutes, with repeated Vortex mixing after 5 minutes. After centrifugation, both phases were manually separated. The octan-1-ol phase was diluted with methanol (1+9). Both phases, the diluted octan-1-ol phase and the buffer phase were then diluted with mobile phase (1+9) and transferred into HPLC vials. Each phase was analyzed by HPLC and the logD values derived from the peak area ratios for the analyte in each phase. The applied analytical RP-HPLC method is described in **Figure 16**. As a result, the logD value of the mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** has been determined as  $\log D = 0.54 \pm 0.02$  at pH 7.4 (calculated in MarvinSketch:<sup>74</sup>



logD = 0.8 at pH 7.4) and the logD value of tiagabine (**7**) has been determined as logD =  $1.47 \pm 0.04$  at pH 7.4 (calculated in MarvinSketch:<sup>74</sup> logD = 2.6 at pH 7.4). Consequently, the mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** is more polar than tiagabine (**7**).



**Figure 16:** Chromatograms of the mixture of racemic diastereomers *rac*-(3*R*,*R*<sub>a</sub>)-**77** and *rac*-(3*R*,*S*<sub>a</sub>)-**77** (top) and tiagabine (**7**, bottom); mobile phase: 80% MeOH, 20% ammonium formate (10 mM, pH 6.8), 0.5 mL/min, injection volume 10  $\mu$ L (1 mg/mL), column: Lichrospher 100 RP-18 (5  $\mu$ m), LiChroCART 250-4.

## 6 List of Abbreviations

ATA reaction	allenylation of terminal alkynes
A <sup>3</sup> coupling	aldehyde-alkyne-amine reaction
BBB	blood-brain barrier
CNS	central nervous system
GABA	γ-aminobutyric acid
GABA-T	GABA transaminase
GAD	glutamic acid decarboxylase
GAT	GABA transporter
HPLC	high performance liquid chromatography
HUGO	human genome organization
IC <sub>50</sub>	half maximal inhibitory concentration
<i>K<sub>i</sub></i>	inhibition constant
LeuT	leucine transporter
mGAT1-4	murine γ-aminobutyric acid transporter subtype 1-4
NMR	nuclear magnetic resonance
NSS	neurotransmitter-sodium-symporters
RP	reverse phase
SAR	structure-activity relationship
SLC	solute carrier
TM	transmembrane helix
VGAT	vesicular neurotransmitter transporter
WHO	world health organization

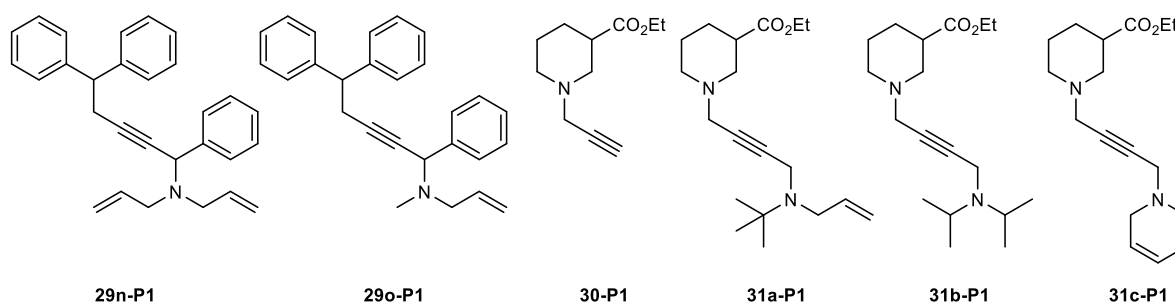
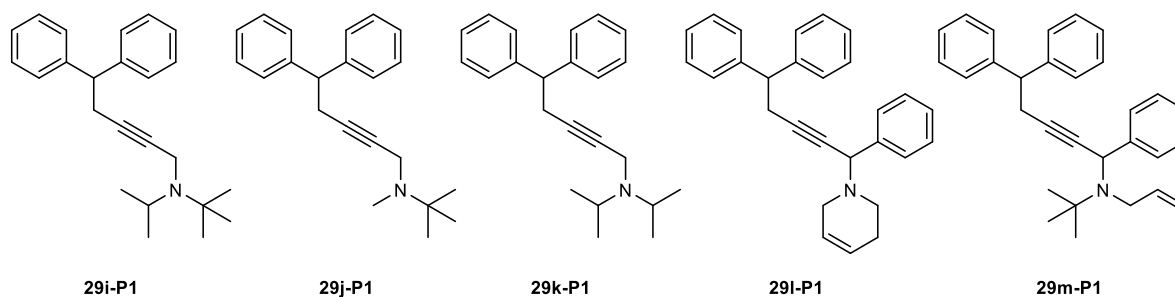
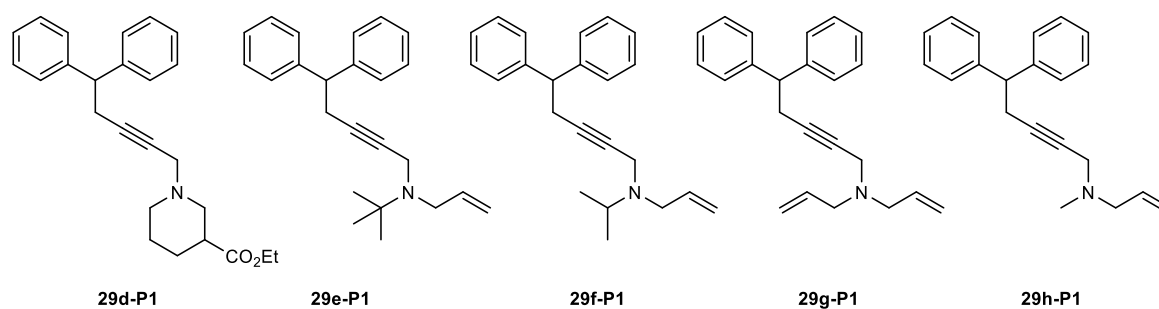
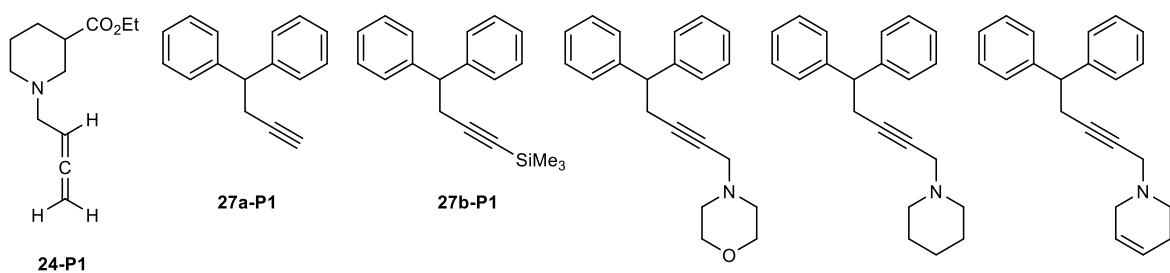
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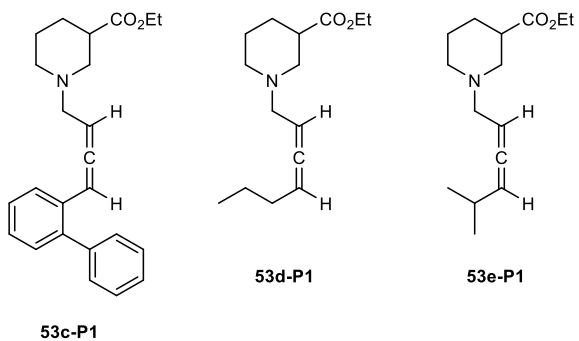
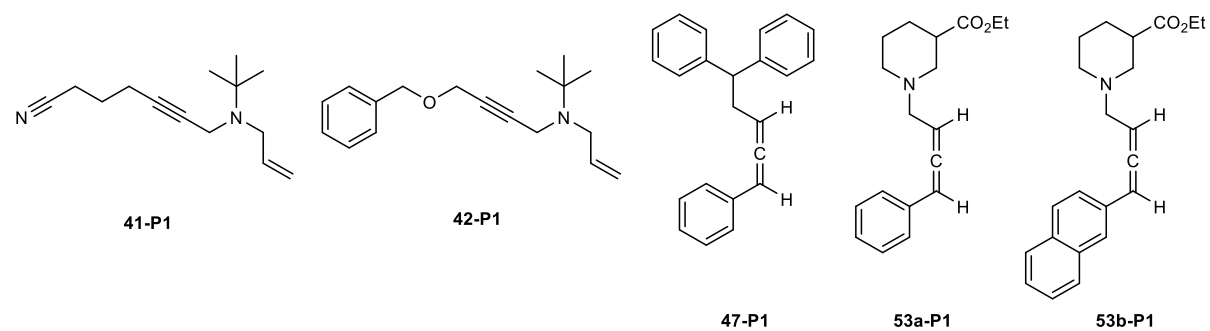
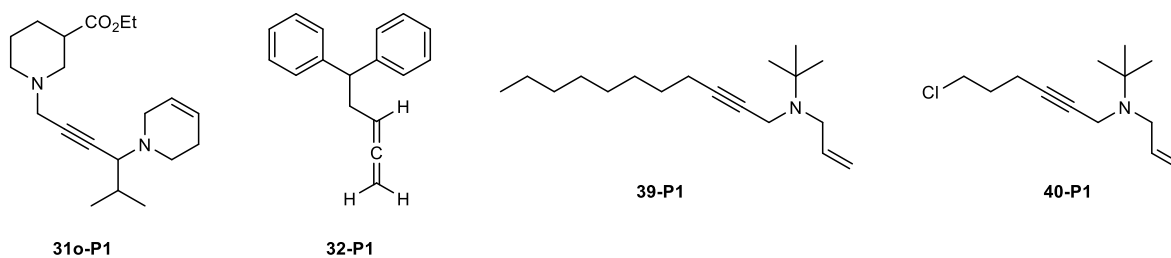
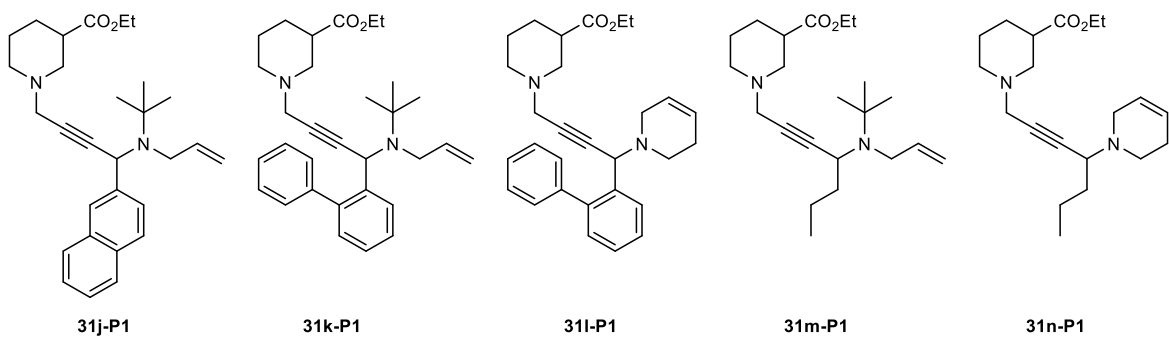
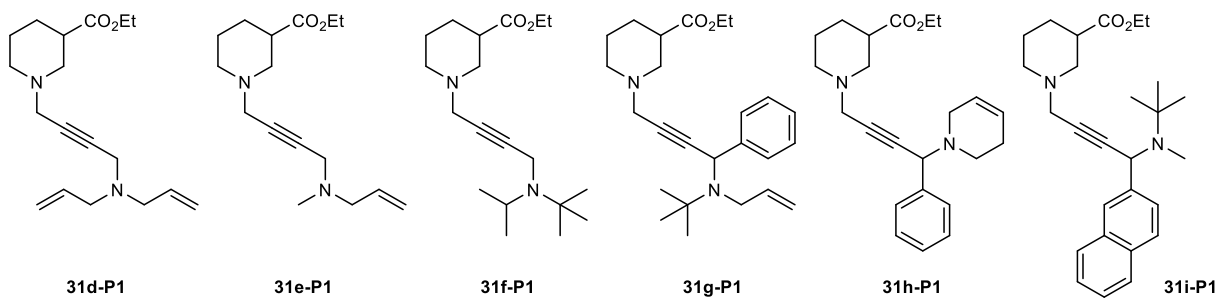
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*Journal of Organic Chemistry* **2017**, 82, 8371-8388.

"Synthesis of Allene Substituted Nipecotic Acids by Allenylation of Terminal Alkynes"



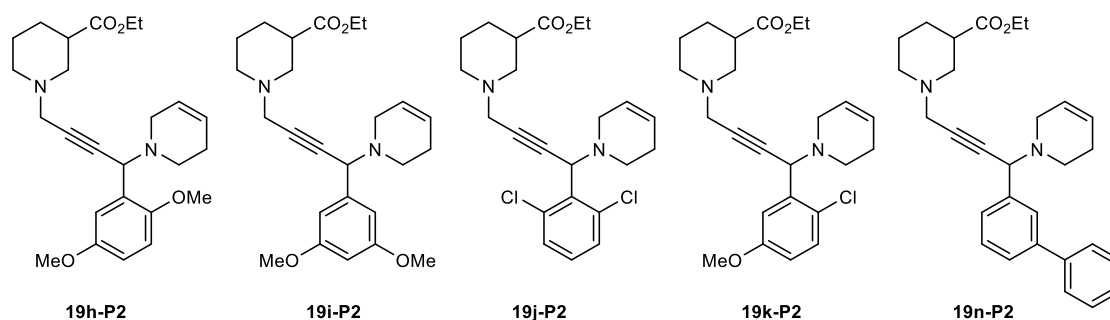
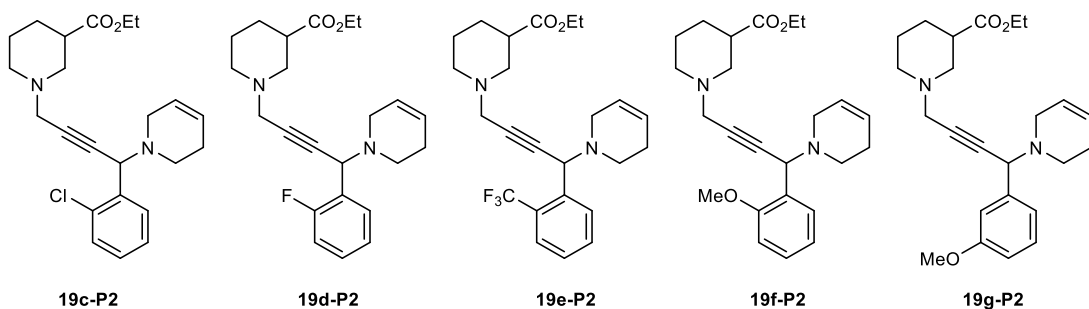
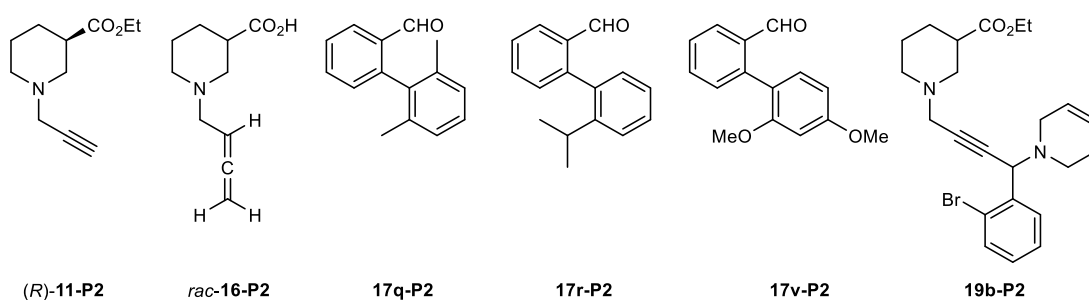


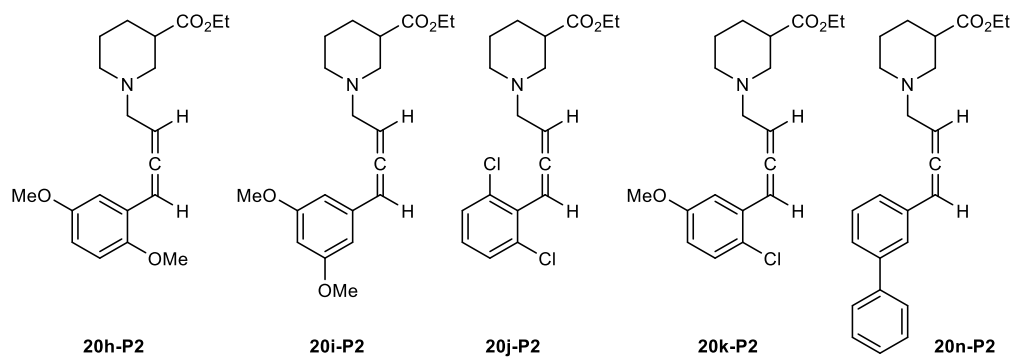
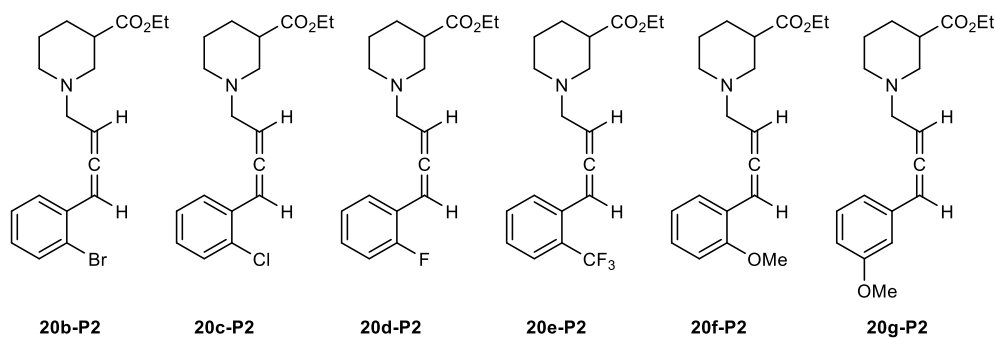
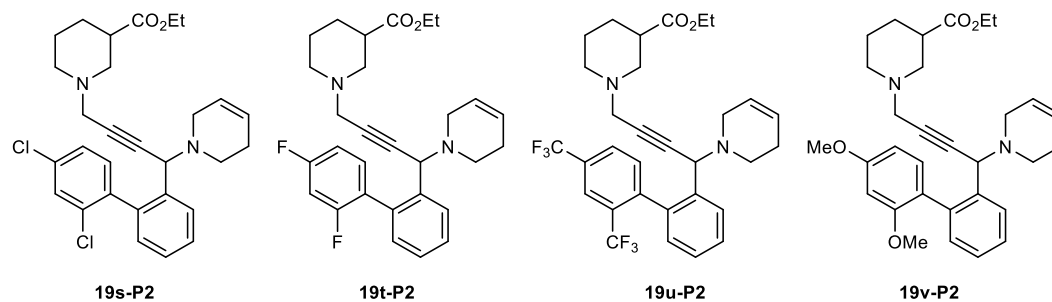
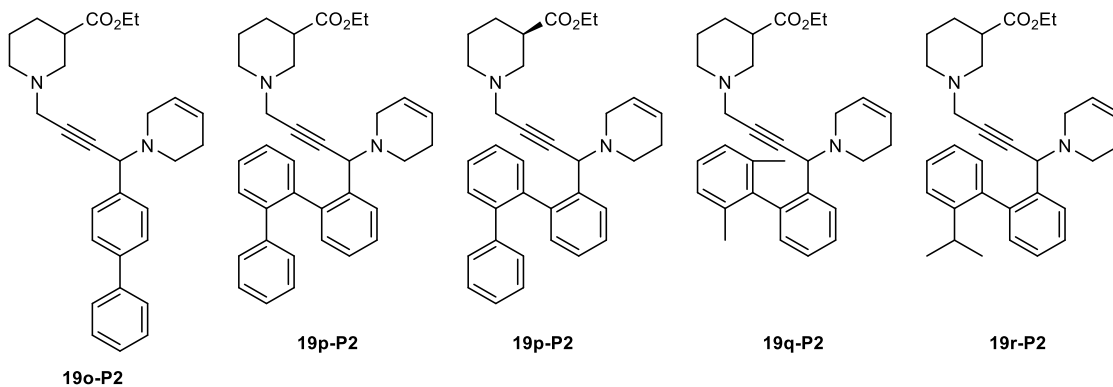
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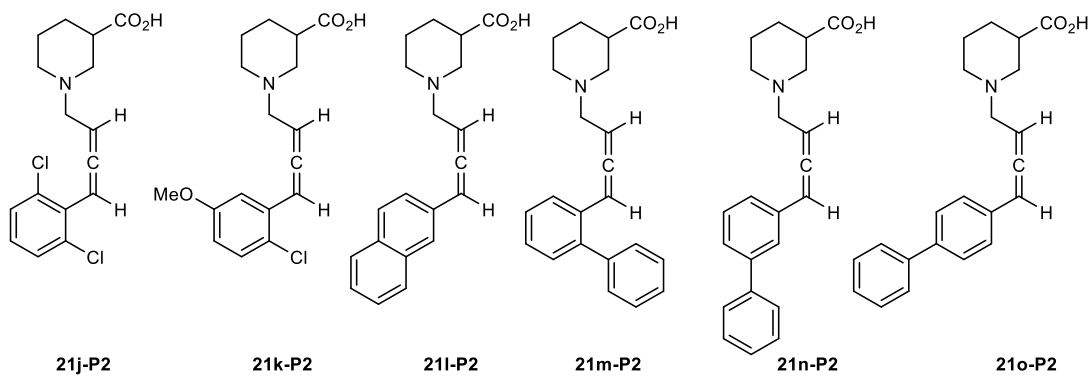
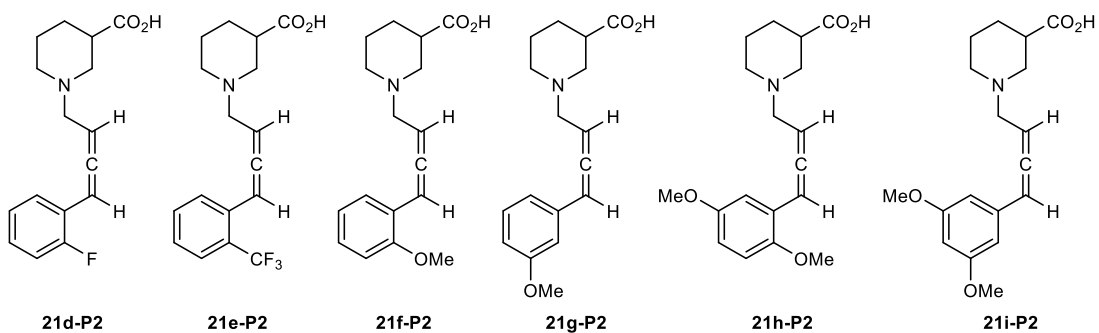
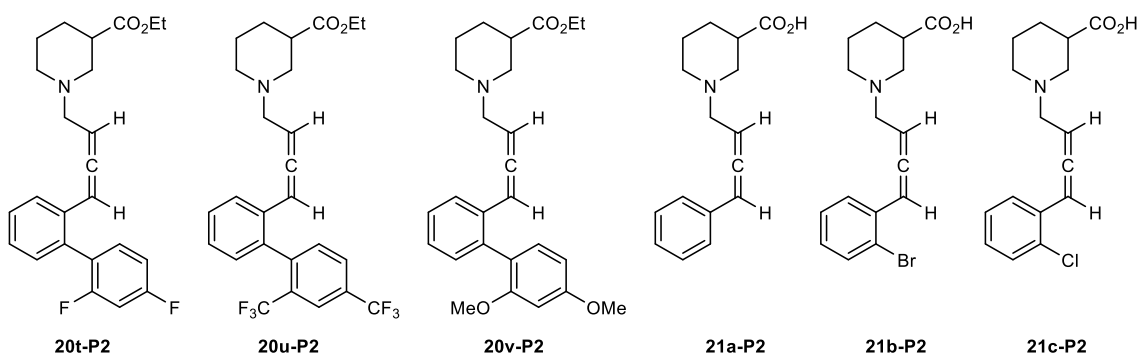
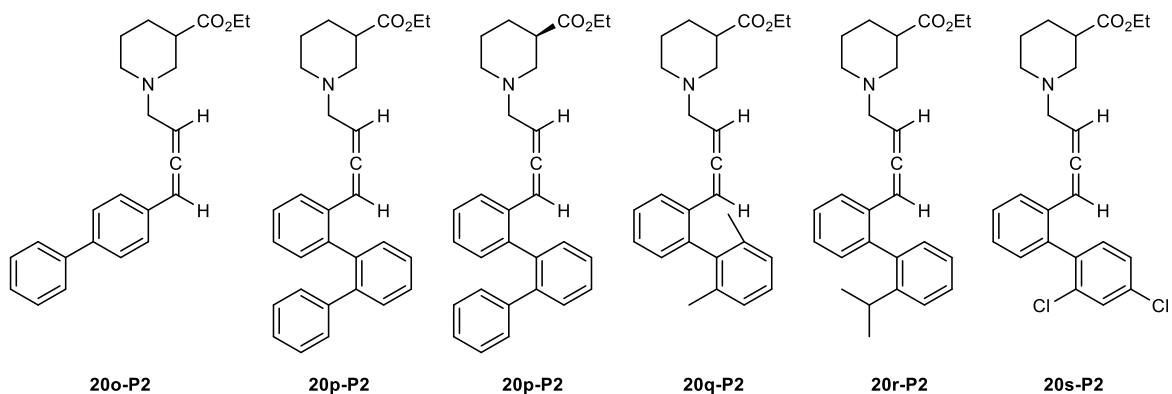
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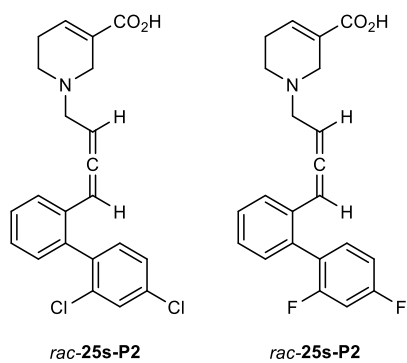
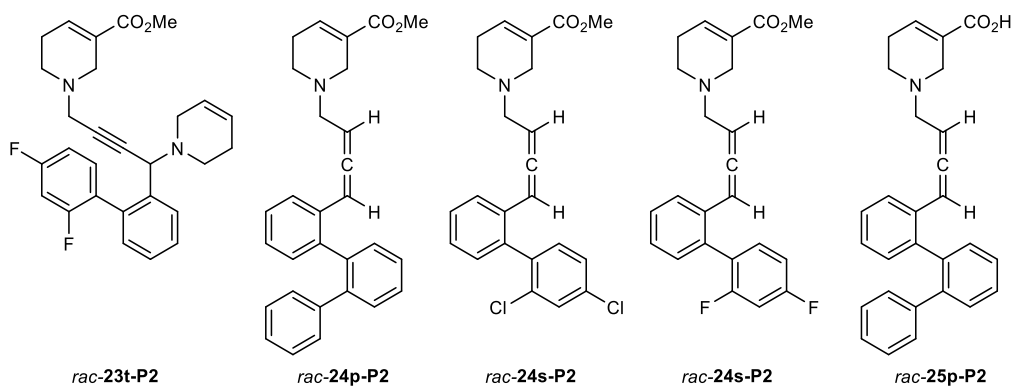
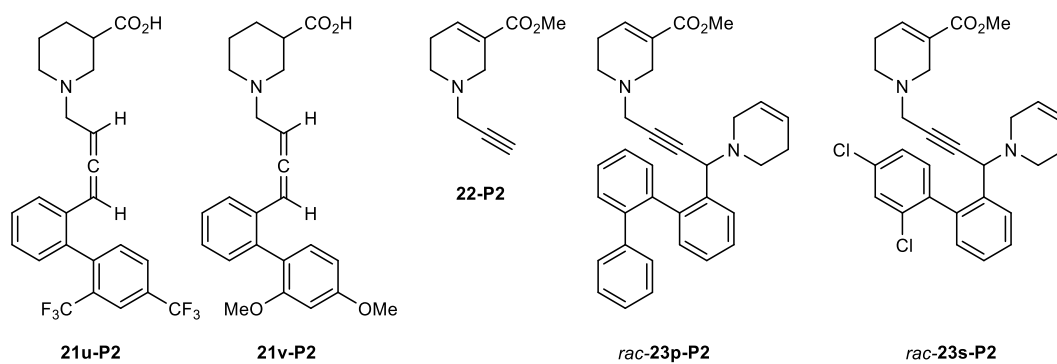
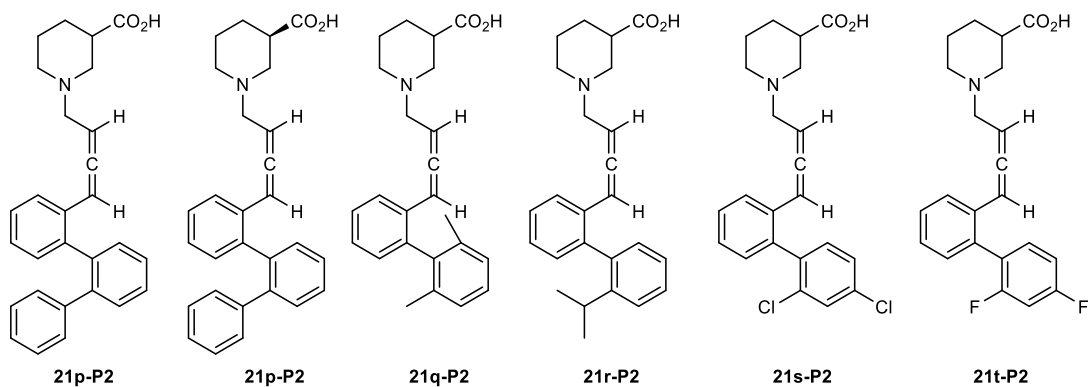
*ChemMedChem* **2019**, accepted article.

“Synthesis and Biological Evaluation of Nipecotic Acid and Guvacine Derived 1,3-Disubstituted Allenes as Inhibitors of Murine GABA Transporter mGAT1”









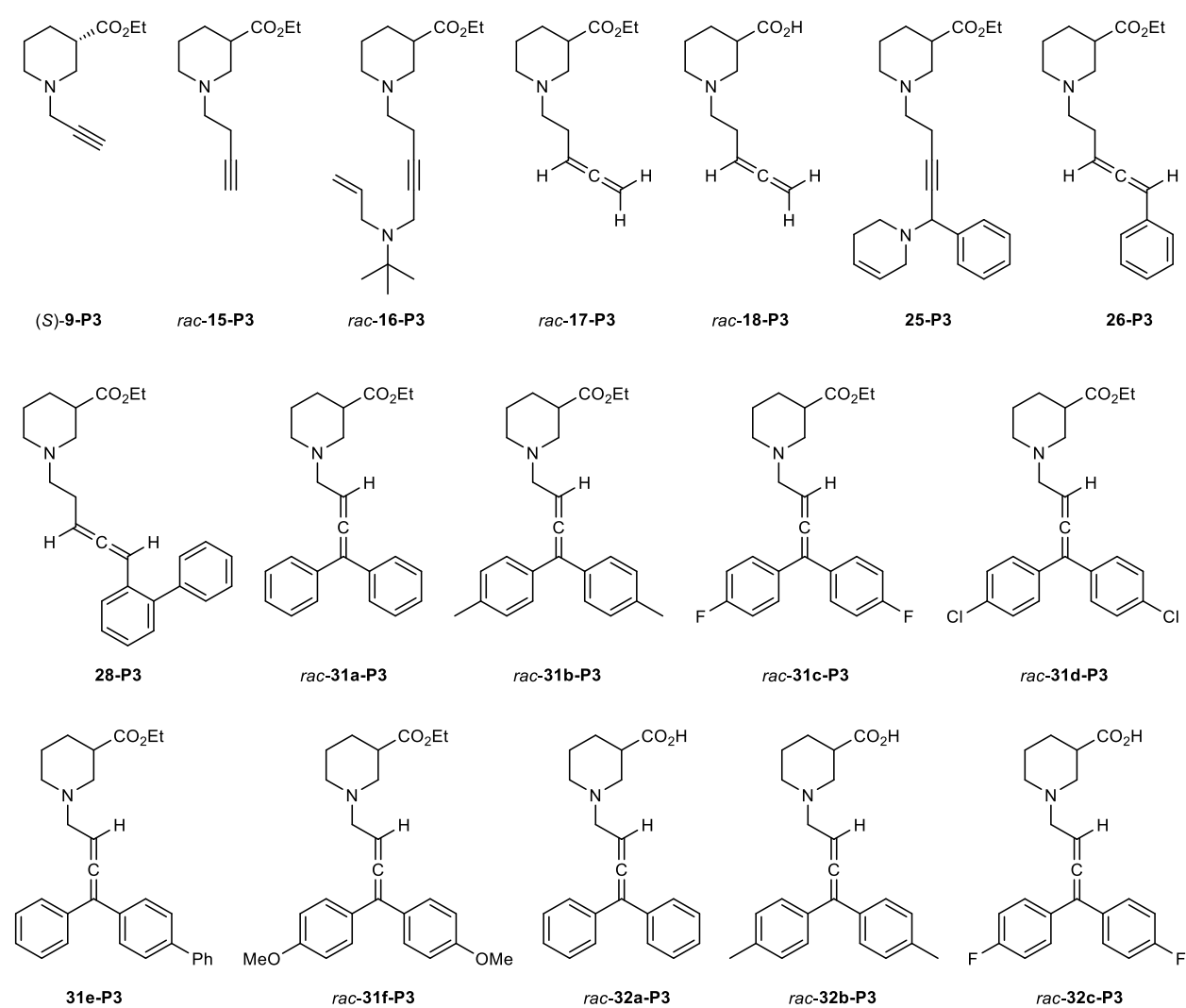


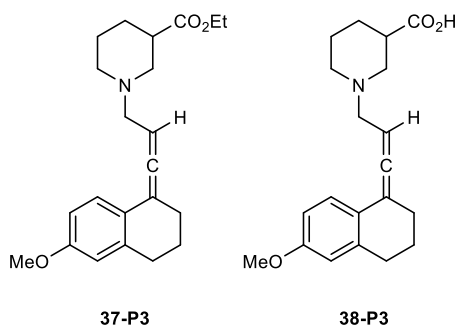
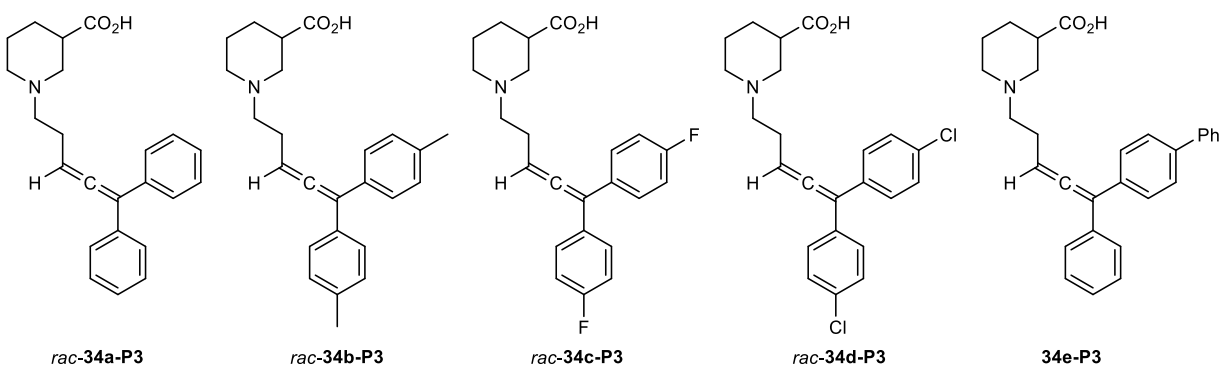
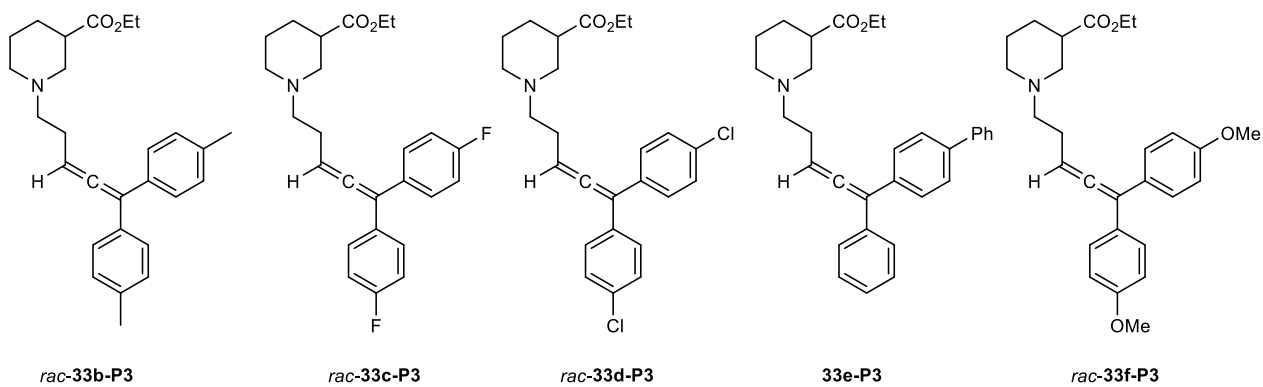
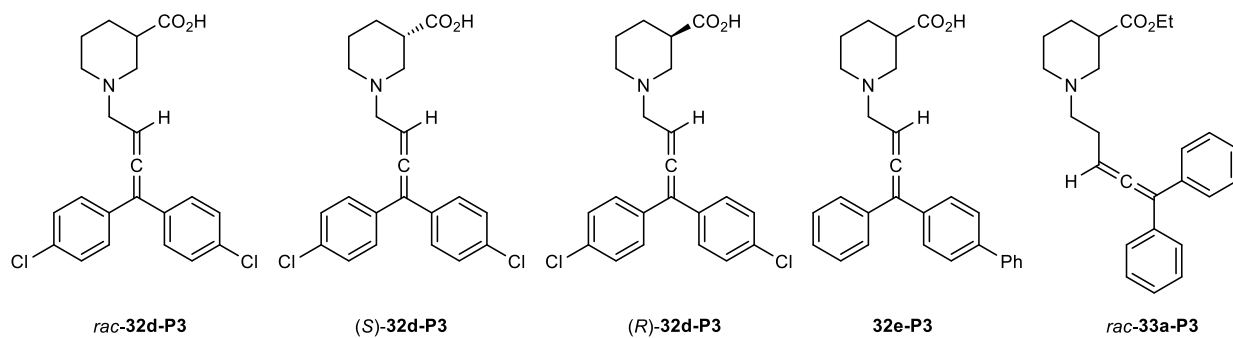
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Manuscript to be submitted.

“Synthesis and Biological Evaluation of Nipecotic Acid Derivatives as GABA Uptake Inhibitors with Terminally Double-Substituted Allenic Spacers”





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