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

Total Synthesis of Loline Alkaloids and Studies toward Naphthomycin K

vorgelegt von
Mesut Çakmak
aus München, Deutschland

2012

Erklärung:

Diese Dissertation wurde im Sinne von § 7 der Promotionsordnung vom 28. November 2011 von Herrn Prof. Dr. Dirk Trauner betreut.

Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

München, den 11. Juni 2012

(Mesut Çakmak)

Dissertation eingereicht am 11. Juni 2012

1. Gutachter: Prof. Dr. Dirk Trauner
2. Gutachter: Prof. Dr. Konstantin Karaghiosoff

Mündliche Prüfung am 11. Juli 2012

Alles Gescheite ist schon gedacht worden, man muss nur versuchen, es noch einmal zu denken.

Johann Wolfgang von Goethe

Acknowledgement

I would like to first and foremost thank my advisor and mentor, Prof. Dr. Dirk Trauner. Joining the group as his first PhD student at the LMU München was truly a special experience. His enthusiasm for and encyclopedic knowledge of both chemistry and general science has been a constant source of motivation and crucial for the success of my projects. I especially appreciated his trust in my work and the freedom he granted me to explore new ideas and solve problems at hand.

Thanks to Prof. Dr. Karaghiosoff for appraising my dissertation.

And thanks to Prof. Dr. Hoffmann-Röder, Prof. Dr. Bracher, Prof. Dr. Langhals and Prof. Dr. Heuschmann for being available as examiners in my defense.

I would like to thank my wife Aylin, who is “solid as rock” in my life. She constantly supported and motivated me since I met her for the very first time. Such a performance would have been not possible without her wonderful character, her patience and her immense understanding. You have given this work and my life great meaning. I love you!

I owe my family so much that I don’t even know where to start. Their support during my whole education is the reason why I made it this far. My parents believed in providing me with the best possible education no matter the sacrifice. I cannot thank them enough for their unconditional love.

I’d like to thank my uncle Mümtaz for his guidance in educational questions.

Upon spending most of my time in the laboratory, I quickly learned the true value of my labmate and close friend Christian A. (A like awesome) Kuttruff. He truly had a big impact on my dissertation. His help in computational issues, discussions about chemistry and private life, exchange of ideas, squash games, going on vacation (Huttanz!) and his good taste in music made my PhD very enjoyable.

Special thanks go to all my labmates from the Trauner group, namely Jennifer Lachs, Ingrid Chen, T. J. Kimbrough, Anastasia Hager, Christian A. Kuttruff and Elena Herrero-Gómez, for being good colleagues and creating a nice and peaceful lab atmosphere. Further, I would like to acknowledge, Eddie Myers, Robert Webster, David Woodmansee, Julien Lefranc and Christian A. Kuttruff for their help proof-reading applications, publication manuscripts and this dissertation.

Thanks also to Arunas Damijonaitis and Julien Lefranc for taking over my projects.

I also like to thank all the other members of the Trauner group, Laura Salonen, Laura Laprell, Tatsuya Urushima, Katie Abole, Dmitry Mazunin, Boris Gasper, Maria Matveenko for handing me over the oil pump group job, Martin Olbricht for his delicious wedding cake, Irina Albrecht inviting me to her wedding, Vilius Franckevicius for super Denksport explanations, Giulio Volpin for making fun of others, Timm Fehrentz for having a good time in our last Praktikum, Robert Webster for teaching me squash, Simon Geiger for his support in the naphthomycin project, Sebastian Strych for discussions about chemistry, Matthias Schönberger for joining adventure activities, Johannes Broichhagen for his continuous visits of lab exile, Florian Löbermann for his dinner invitation, Anastasia Hager for borrowing her pc for pymol videos, Albert Schröckeneder for showing me how to tinker an alu-rose, Eddie Myers for exotic Denksports, Michael Kienzler for having Döner-sessions before going to the gym, Vladimir Sofiyev for being vladcore, Holger Moroder for his introduction about self-assembly, Jan Schwarz for having workouts at 7 am, Julian Egger for playing Bushido all day long, Michael Pangerl for demonstration of big-scale reactions, T. J. Kimbrough for teaching me how to do pipette columns, David Woodmansee for giving awesome talks, Desiree Stichnoth for joining our soccer games, Jennifer Lachs for her funny sneezing, Ingrid Chen for talking about long-distance relationships, Elena Herrero-Gómez for giving me hints for the ICIQ summerschool, Marco Stein for helping me to matriculate, Pascal Ellerbrock for taking over my groupjob, Alwin Reiter for our chats about scuba diving, Dominik Hager for showing me the ozon generator, Daniel Hog for organizing soccer games, Florian Huber for chatting about bodybuilding, Philipp Stawski for his help in making my poster, Harald Janovjak for chatting about boxing and all together for creating such a professional, educational and enjoyable work environment.

I’d like to express my gratitude to the people who made my dissertation possible:
Staff from the Trauner Group: Tobias Kauer, Petra Böhrer, Carrie Louis, Dr. Martin Sumser and especially Heike Traub for being supportive in all kind of bureaucratic issues;
Staff from the LMU Analytic department: Dr. Spahl and Frau Kosak for mass spectroscopic data, Dr. Stevenson and Fr. Dubler for NMR data and especially Dr. Mayer for his patience and efforts in finding suitable crystals for x-ray analysis.
I am also grateful to many teachers that fostered my interest in organic chemistry. These people include Frau Engelberger, Frau Geisler, Dr. Dimitrios Mihalios, Dr. Sebastian Brandes, Dr. Birte Basler, Dr. Roger Norcross, Prof. Thorsten Bach and Dr. Herbert Schuster.
I’d like to thank Bastian Sauerer for having funny pizza dinners with progress reports.
During my PhD studies I had the joy to supervise a number of very motivated undergraduate co-workers, who spend a lot of time with me in the lab and were all very hard-working: Sebastian Götte, Christine Sturm, Ufuk Borucu, Caroline Pflüger, Christine Hieke, Ebru Zeynep Serdar, Andreas Ahlers, Hiroki Nakatsu, Johannes Feierfeil and Klaus Speck. Thank you all for being so supportive.
Last but not least, special thanks go to my close friends Ömer Özcan (Bergtürke), Akram Barkia (Camel) and Zoran Pranjic (RedNinja), who have been as supportive as friends can possibly be and challenged me in go-cart races, wakeboarding and rafting.

This dissertation is dedicated to my father.

Parts of this dissertation have been published or will be published soon:

1. M. Cakmak, P. Mayer, D. Trauner, *Nat. Chem.* **2011**, *3*, 543–545.
   An Efficient Synthesis of Loline Alkaloids

2. C. A. Kuttruff, S. Geiger, M. Cakmak, P. Mayer, D. Trauner, *Org. Lett.* **2012**, *14*, 1070–1073.
   An Approach to Aminonaphthoquinone Ansamycins Using a Modified Danishefsky Diene

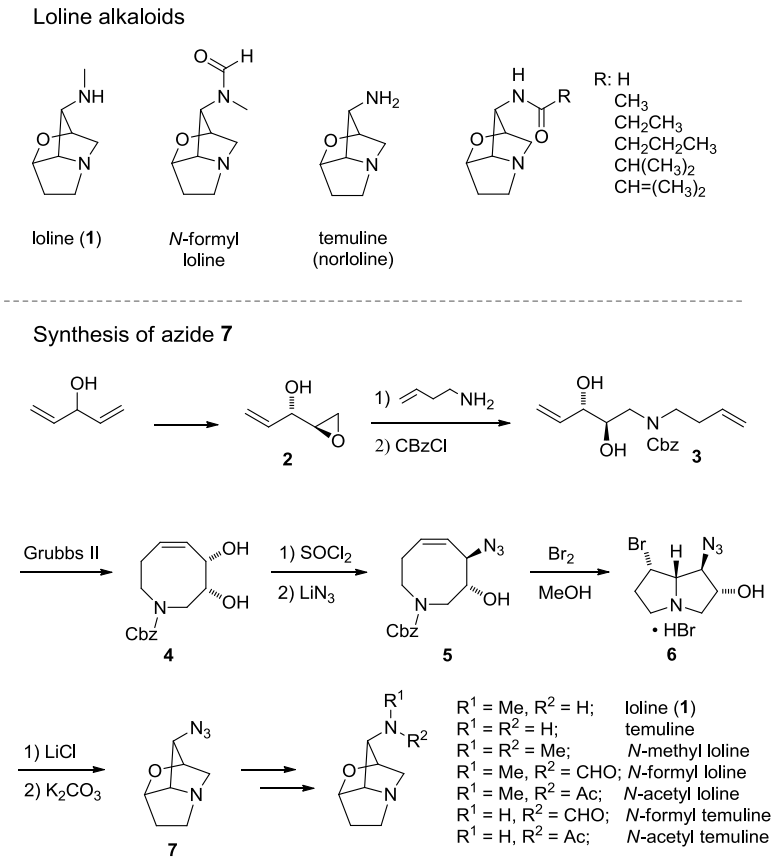
3. M. Cakmak, P. Mayer, R. Paton, D. Trauner, *in preparation*
   Loline Alkaloids: Evolution of a Strategy

Table of Contents

Summary

I. Total Synthesis of Loline Alkaloids

Loline (**1**) is the eponymous member of an alkaloid family, originally isolated in 1892 from tall fescue grasses, but later found in many other plant families (Scheme 1).[1] They are produced by endophytic fungi and are as toxic to insects as nicotine, thereby protecting the host plant from herbivores, but many aspects of their chemical ecology are not yet understood.



Scheme 1: Loline alkaloids and their synthesis *via* key azide **7**.

Despite its long history and intriguing biological activity, there has been only one successful asymmetric synthesis of loline to date, which required 20 steps.[2] This may be due to its strained, heterotricyclic molecular skeleton, that incorporates polar functionalities in close proximity, thus rendering the loline alkaloids more challenging targets than they may appear at first sight.

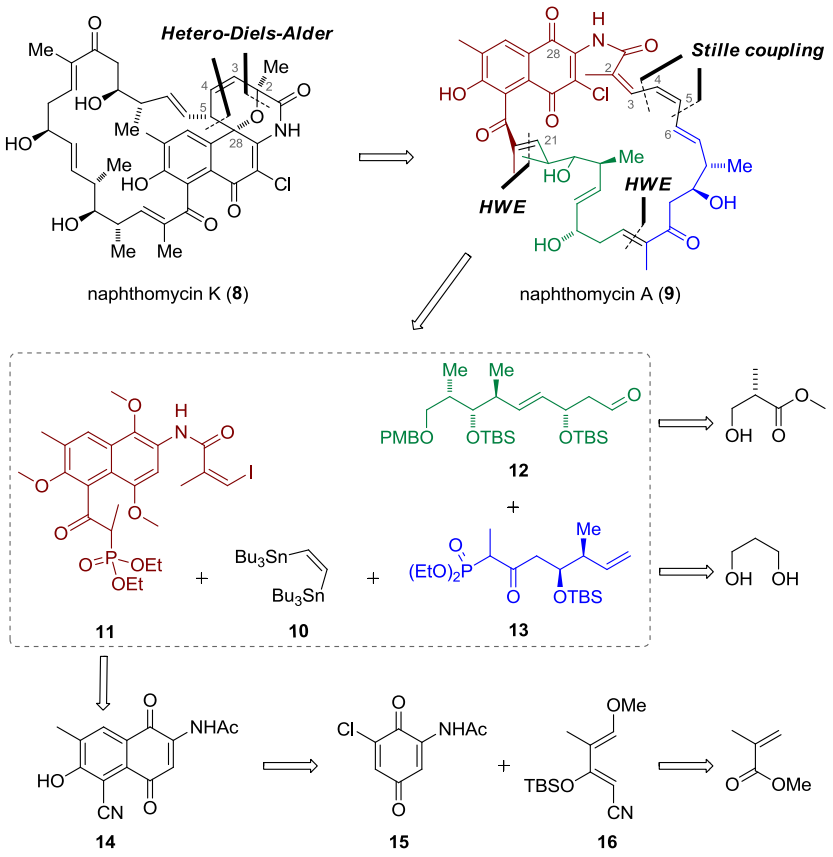
This dissertation deals with different approaches for the synthesis of loline alkaloids and reports interesting outcomes. The synthesis, which finally led to success, started with an achiral alcohol that can be easily desymmetrized to give epoxide **2**. Nucleophilic epoxide opening with butenylamine and *in situ* protection yielded diene **3**. A ring-closing metathesis converted this compound into the eight-membered heterocycle **4**, which was activated as a cyclic sulfite and selectively substituted in the allylic position to yield azidoalcohol **5**. In the key step, compound **5** was treated with bromine in methanol to give the bicyclic pyrrolizidine **6**. After a Finkelstein like reaction and subsequent Williamson ether formation, the heterotricyclic core of the loline alkaloids was established. Azide **7** serves as a branching point for the total synthesis of various loline alkaloids.

In summary, we have developed a highly efficient, asymmetric total synthesis of (+)-loline (**1**) that requires only 10 steps.[3] Our synthesis is scalable, diversifiable, gives access to all loline alkaloids and has served to provide several research groups sufficient material to investigate the interesting chemical ecology of these alkaloids.

II. Studies toward Naphthomycin K

The naphthomycins are a class of ansamycin antibiotics that contain a macrocycle of polyketide origin with an amide linkage to a naphthalenic moiety. To date, 11 different naphthomycins (naphthomycin A–K) have been isolated and structurally elucidated. In spite of their unique structure and broad spectrum of biological activities, none of the naphthomycins have been synthesized to date.

Recently, a novel member of the naphthomycin family, naphthomycin K (**8**) depicted in Scheme 2, was isolated from the commercial strain *Streptomyces sp.* of the medicinal plant *Maytenus hookeri*.[4] Naphthomycin K shares a number of unique structural features, including an unprecedented heterocyclic ring system, a highly modified naphthoquinone core and nine stereogenic centers. In view of its interesting biological properties and unique molecular architecture, we engaged in the total synthesis of naphthomycin K.



Scheme 2: Retrosynthetic analysis of naphthomycin K.

Scheme 2 presents, in retrosynthetic format, the devised synthetic strategy for the total synthesis of naphthomycin K. Thus, the oxa-azabicyclo[3.3.1]-nonenone is expected to be formed via intramolecular hetero-Diels-Alder reaction between the quinone-carbonyl and the diene of the ansa chain of naphthomycin A (**9**). We envisioned that a double Stille-coupling employing bis-stannane **10** would facilitate late-stage macrocyclization and allow us to both control the geometry of the C4–C5 double bond and to construct the challenging triene. Compound **9** could be further dissected to arrive at naphthalene **11**, aldehyde **12** and phosphonate **13**.

This dissertation includes the syntheses of aldehyde **12** and phosphonate **13** from inexpensive commercially available starting materials in 9 steps each and their coupling in a Horner-Wadsworth-Emmons reaction (HWE) and further transformation to give the C6–C23 fragment of naphthomycin A (**9**). In addition, naphthoquinone precursor **14** has been synthesized starting from literature known quinone **15** and cyanide **16**. The synthesis of the novel Danishefsky-type diene **16** and its reactivity in Diels-Alder reactions is reported.[5]

---

[1] Schardl, C.L., Grossman, R.B., Nagabhyru, P., Faulkner, J.R., Mallik, U.P. *Phytochemistry* **2007**, *68*, 980.

[2] Blakemore, P.R., Kim, S.-K., Schulze, V.K., White, J.D. *J. Chem. Soc*., *Perkin Trans. 1*, **2001**, 1831.

[3] Cakmak, M., Mayer, P., Trauner, D. *Nat. Chem*. **2011**, *3*, 543.

[4] Lu, C., Shen, Y. *J. Antibiot.* **2007**, *60*, 649.

[5] Kuttruff, C. A., Geiger, S., Cakmak, M., Mayer, P., Trauner, D. *Org. Lett.* **2012**, *14*, 1070–1073.

I Total Synthesis of Loline Alkaloids

1. Introduction to Lolines

1.1 History of Loline

Fescue, belonging to the family of *poaceae*, is extensively used as a pasture grass. Originally native to Europe and the Mediterranean, it is now spread throughout the world.[1] Reports construe that livestock poisonings can be caused by tall fescue. Cows grazing on this grass have been known to show signs of a lameness called “fescue foot”.[2] However, it is widely used due to the fact that it grows well on marginal soil, is inured to drought and affords good yield of dry matter per acre.[3] Therefore, much effort has been put into the isolation of the toxic compounds causing the illness. This led to the identification of several alkaloids, amongst others a number of pyrrolizidine alkaloids with a unique ether linkage bridging C2 and C7 (Figure 1).

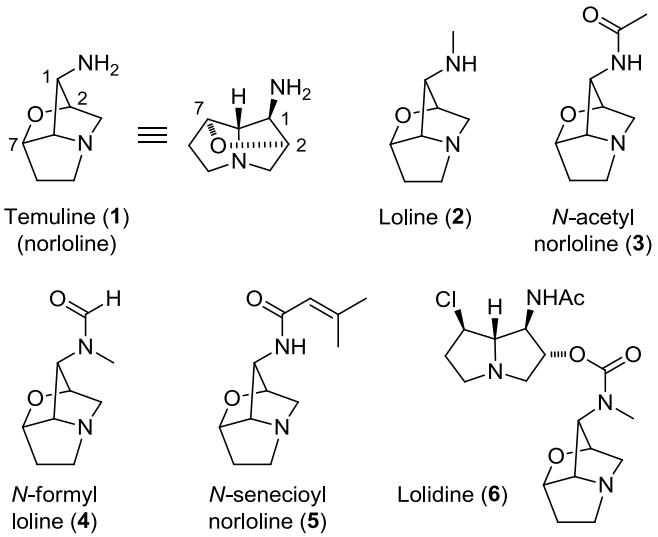


Figure 1: Members of the loline alkaloids with a common heterocyclic core. The distinguishing feature is the different substitution pattern of the nitrogen at C1.

The first report of an alkaloid isolated from tall fescue dates back to the 1890´s. Hofmeister isolated and identified a compound from *Lolium temulentum* with the elemental formula $C_7H_{12}N_2O$ and named it temuline (**1**) (Figure 1), which was later renamed norloline.[4-5] In 1955, loline (**2**) was first mentioned by Yanusov and Akramov after extraction of the alkaloid from darnel seeds together with related alkaloids, such as *N*-acetyl norloline (**3**) and *N*-formyl loline (**4**). Another loline derivative, *N*-senecioyl norloline (**5**), which is an apparent metabolite, could be

extracted from horse urine.[6] The most unusual loline alkaloid, lolidine (**6**), consists of a loline linked to another pyrrolizidine, that instead of an ether bridge bears a chlorine at C-7 and a hydroxyl group at C-2. The structure of lolidine (**6**) was proposed based on mass-spectrometric data, but due to lack of material it could not be further elucidated.[7] If this structure could be confirmed, a biosynthetic pathway for the ether bridge formation could be suggested.

After initial misassignment of the loline structure, the absolute configuration was finally established by X-ray crystallographic analysis of loline dihydrochloride.[8] Degradation studies of loline (**1**) showed that upon treatment with concentrated hydrochloric acid, the ether bridge gets nucleophilicly opened by chlorine to form chlorinated pyrrolizidine **7**. Further degradation led to a mixture of *N*-methylpyrrolizidine, methylamine and pyrrolizidine (Figure 2).[9]

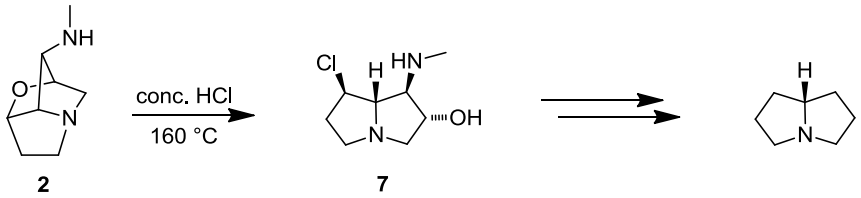


Figure 2: Degradation of loline (**2**).

Until 1993, isolations and identifications had been done without knowing that a fungal endophyte was the producer of these alkaloids in the plant tissue.[10] In the 1890´s, first studies of *Lolium temulentum* mentioned a novel symbiotic fungus as well as a novel group of metabolites, nowadays known as loline alkaloids.[4, 11] Despite the early discovery it took more than 70 years until the endophytes and lolines were explicitly linked in literature.[10] The symbiotic fungus is now known as *Neotyphodium occultans* (family Clavicipitaceae) and lolines have since been found constantly with congeners of *N. occultans*.[12] Final evidence for the hypothesis that clavicipitaceous endophytes are capable of *de novo* synthesis of lolines was provided through results showing that *Neotyphodium uncinatum* is able to produce lolines in defined-medium fermentation cultures. It was demonstrated that this endophyte is capable of the full biosynthesis if provided with sugars and either organic or inorganic nitrogen sources.[13] Many of these symbiotic fungi protect their plant hosts from herbivory by producing these alkaloids.

Eventually, the toxicity of ryegrasses, always tied to lolines, could be traced to ergot alkaloids (necines).[1] Neither lolines nor *N. occultans* could be connected to mammal toxicity. Instead, lolines rather exhibit potent activity against a wide range of insect herbivores, which is a highly desirable feature for pasture grass.[14-15]

1.2 Biological Activity of Loline Alkaloids

Antiinsect activities of lolines have been reported consistently. A first survey of tall fescue plants infected with an endophytic fungus demonstrated a correlation between feeding deterrence of the bird-cherry oat aphid (*Rhopalosiphum padi*) and the greenbug (*Schizaphis graminum*) to the presence of loline alkaloids in the plant tissue.[16] In order to identify the compounds causing the deterring feeding, tissue extracts from the endophyte infected plants were prepared. Unfortunately all of the extracts contained a mixture of alkaloids. The loline containing fractions always included a known insect feeding deterrent, peramine. In contrast to the greenbug, which effectively deters feeding, peramine seemed to have no effect on the bird-cherry oat aphid. However it is still possible that lolines and peramines might act synergetically. Therefore the effect of loline could not be confirmed.[16]

First tests in which alkaloid-containing extracts from seeds of *N. coenophialum*-symbiotic tall fescue were fed to the large milkweed bug showed that fractions enriched with *N*-formyl loline (**4**) were highly toxic to the insect larvae.[14] Later surveys investigating the effects of loline derivatives on the fall armyworm (*Spodoptera frugiperda*) and the European corn borer (*Ostrinia nubilalis*) utilized a variety of naturally occurring lolines, such as loline (**2**), *N*-acetyl loline (**3**) or *N*-formyl loline (**4**) as well as synthetic loline derivatives with longer acyl groups. These studies demonstrated that the presence of *N*-acyl loline derivatives in the diet of these bugs modified their feeding behavior. For instance *N*-acetyl loline (**3**) significantly reduced larval weight gain in both test subjects. However, the specific effect of a derivative was dependent upon the species of larvae tested, suggesting that different insect species respond differently to loline derivatives.[15] The authors stated that the reason for the reduced weight gain could simply result from decreased ingestion of diet rather than toxicity. For further investigation of the toxicity against insects, solutions of loline derivatives were sprayed on plants infested with adult greenbugs. The LC_{50} values measured were very close to the levels of the potent insecticide nicotine sulfate.[15]

These observations suggest a protective role for lolines. Due to the fact that all of the previous tests varied in the combination of fungus and plant the toxicity assays were necessarily artificial.[17] Therefore a Mendelian genetic analysis to determine the antiinsect activity of lolines was conducted. *Epichloaë fustucae*, which is the fungal symbiont of *lolium* grasses, is a close sexual relative of the asexual *Neotyphodium* species.[18] Two sexually compatible *E. festucae* parents, differing in loline expression, were crossed and their progenyies were segregated into loline expression (Lol^+) and nonexpression (Lol^-) phenotypes. Linkage to DNA polymorphisms was consistent to the anti-aphid activity with expression of lolines. Only the symbionts expressing loline exhibited activity against populations of *S. graminum* and *R. padi*. (Figure 3).

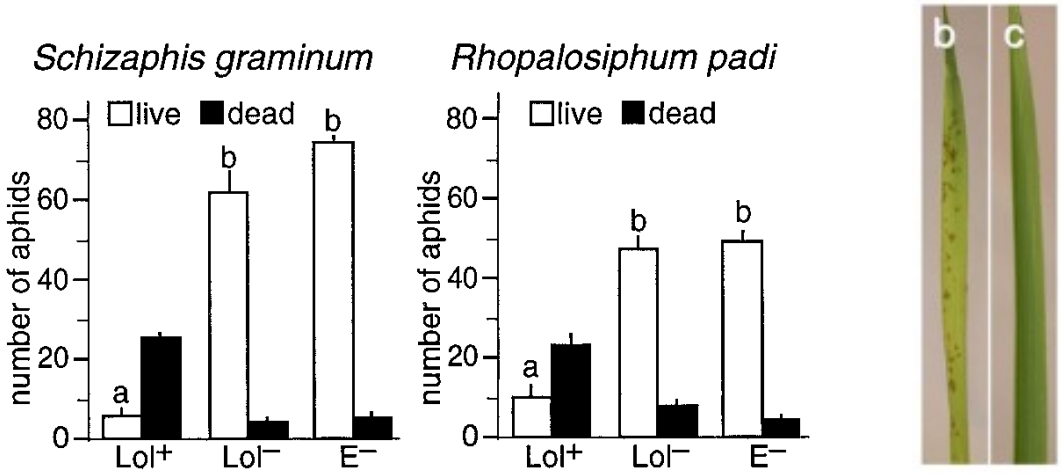


Figure 3: (a) Antiinsect activity of lolines against the aphids *S. gramium* (left) and *R. padi* (right). Meadow fescue plants containing no endophyte (E-) and the progenies segregated for their loline production (Lol^+) or nonproduction (Lol^-). Picture (b) and (c) show leaves of the tall fescue without (b) or with (c) the loline producing endophyte *N. coenophialum*. In contrast to leave (b) there is no infestation of *P. padi* aphids on the leave shown in panel (c).[1, 17]

Given the results that lolines provide significant protection to their host plants, which is a prime example for a symbiotic mutualism, it is even more remarkably that wounding of plants induces high levels of lolines (Figure 4). Hence it can be concluded that lolines, although they are produced by fungi, are plant defenses against chewing insects. It is of crucial importance for the plants to reduce parasites in order to retain their capability of photosynthesis. The rise of loline alkaloids, due to mock herbivory (clipping), could be observed in tall fescue with *N. coenophialum* and

in meadow fescue with *N. unicatum*.[10, 19-20] The most dramatic induction, with a rise from 0.1 % to 1.9 % of plant dry mass could be observed in meadow fescue with *N. siegelii* within eleven days after clipping.[20] Consequently induction of loline production implies communication between host and symbiont, but the mechanism is unknown and still a point for further investigations. It is imaginable that a specific signal from the wounded plant could be detected by the endophyte, which then could affect its metabolism.

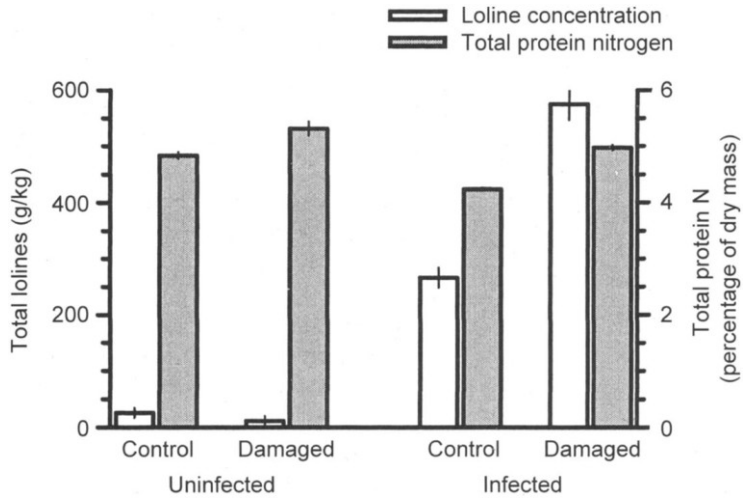


Figure 4: Loline levels from tall fescue uninfected and infected with *N. coenophialum* 14 days after clipping and from unclipped control plants. White bars indicate concentration of *N*-acetyl loline (**3**) and *N*-formyl loline (**4**). Grey bars indicate the percentage of total nitrogen of dry mass of plants (error bars represent ± 1 SE).[19]

Arising from the studies, which employed crude or partially purified extractions from tall fescue, the wrong impression that lolines might be the cause for fescue foot and summer syndrome in cattle was generated.[14] Although the extracts most certainly contained significant amounts of ergot alkaloids, which are known for their toxicity to livestock, the lolines were related to the problem as well.[21] This misassignment could to some extent be attributed to the abundance of lolines in tall fescue symbionts and the fact that they are more easily assayed than ergot alkaloids. All of this led to the wrong hypothesis that lolines are toxic to livestock. However, no evidence for mammal toxicity could be found.[1]

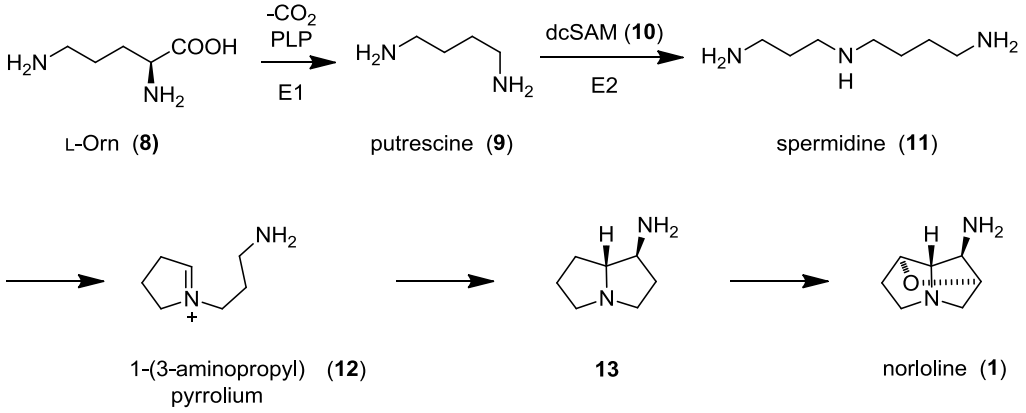
Nevertheless very small physiological effects, even at extremely high doses, on mammalian herbivores have been reported. Studies show that lolines are capable of

reducing the release of prolactin by rat pituitary cells.[22] Furthermore, *N*-Acyl lolines show modest antitumor activity. In brine shrimp assays and human breast, lung and colon cancer cell lines, *N*-acyl derivatives with a chain length of 12 to 18 showed significant cytotoxicity.[23] However, the *in vivo* antitumor effects remain to be determined.

1.3 Biosynthesis

1.3.1 First Proposed Biosynthesis

Due to the structural similarity of the loline alkaloids to the plant-produced pyrrolizidines (necines), the assumption that lolines and necines might share similar biosynthetic pathways, deriving from polyamines, was widely established.[10] This hypothesis was particular attractive when it was believed that lolines were plant metabolites (Scheme 1).



E1: ornithine decarboxylase; E2: spermidine synthase

Scheme 1: First proposed biosynthesis on the hypothesis that lolines are plant metabolites.[10, 24]

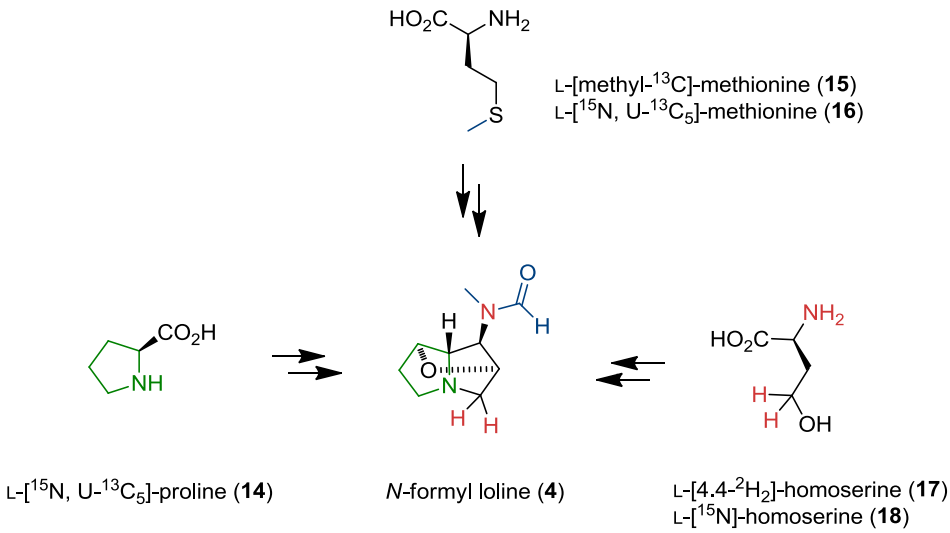
A pyridoxal-phosphate (PLP) dependent decarboxylation of L-ornithine (**8**) gives putrescine (**9**). The aminopropyl group is transferred from a decarboxylated *S*-adenosyl methionine (dcSAM, **10**) giving spermidine (**11**). Ring closure would give amino pyrrolizidine **13** and linkage in position 2 and 7 through an oxygen bridge would yield norloline (**1**).[10]

The hypothesis shown in Scheme 1 has been tested and rejected by precursor feeding experiments.[25] These studies utilized the endophyte of meadow fescue *N. unicatum*, which is capable of producing lolines, especially *N*-formyl loline (**4**), in

defined-medium fermentation cultures. The obtained results demonstrated that loline alkaloid biosynthesis differs from the pyrrolizidine biosynthesis of necines.[25]

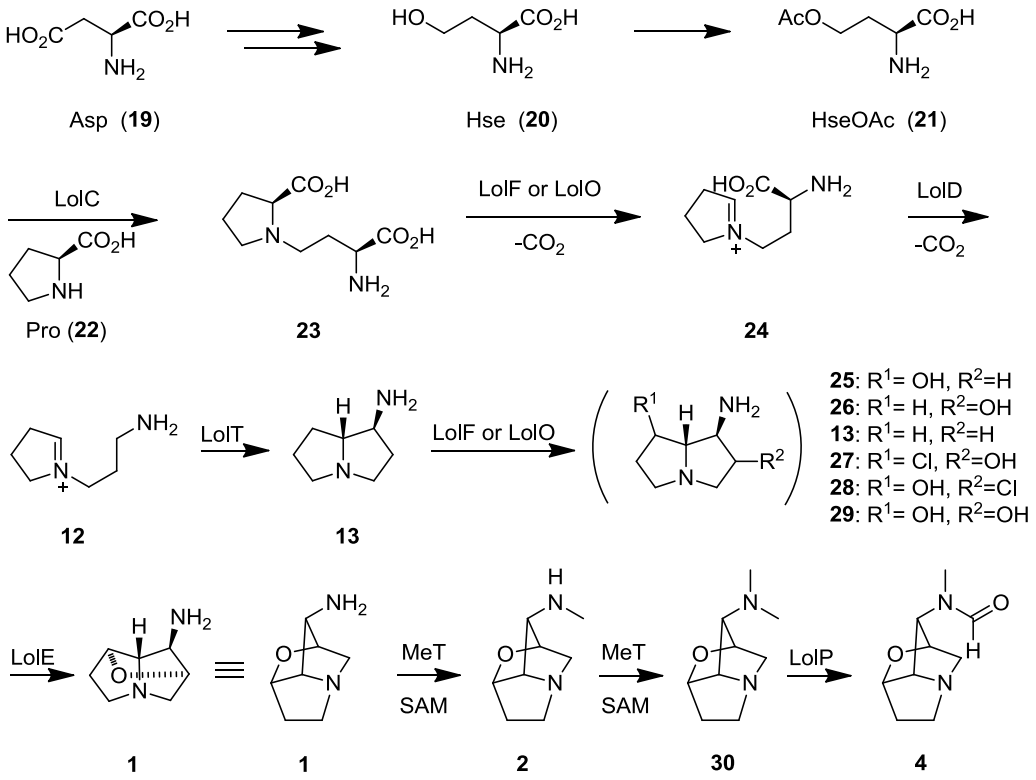
1.3.2 Revised Biosynthesis

The use of radiolabeled precursors allowed the determination of the origin of the pyrrolizidine moieties. Proline (Pro, **14**) contributes N-4 and C-5 till C-8, labeled L-methionine (L-Met, **15**, **16**) contributes the *N*-methyl and *N*-formyl groups and homoserine (Hse, **17**, **18**) the 1-amino group and C-1 till C-3 (Scheme 2).[26]



Scheme 2: Incorporation of labeled precursors into *N*-formyl loline.[26]

The established biosynthetic pathway commences with aspartate (Asp **19**), which is converted to homoserine (Hse **20**). The proposed first determinant step is a γ-substitution of the 3-amino-3-carboxypropyl moiety from *O*-acetylhomoserine (HseOAc **21**) to the N of L-proline (**22**) giving the first committed intermediate **23** (Scheme 3). This unusual C-N bond formation, which seems to be unprecedented in biosynthetic pathways, might be catalyzed by a γ-type pyridoxal phosphate (PLP)-containing enzyme, most likely the product of the *LolC* gene. Subsequently two oxidative decarboxylations of pyrrolidine **23** take place to form the imminium ion **12**. One decarboxylation could be catalyzed by a PLP-containing enzyme, probably *LolD*. The intermediate **12** can also be found in the biosynthetic pathway of polyamines, raising the question whether endophytes might incorporate both plant and endophyte metabolized 1-(3-aminopropyl) pyrrolium (**12**). Another PLP containing enzyme, encoded by *LolT*, probably closes the ring. The next step in the biosynthesis appears to be the incorporation of an O atom bridging C-2 and C-7.[1]



Scheme 3: Biosynthesis of loline alkaloids.[1]

There are four plausible options how the enzyme *LolE* could form the biosynthetically unique ether bridge (Scheme 3). It is possible that either C-2 (**25**) or C-7 (**26**) could be hydroxylated followed by a subsequent oxidative ring closure. Another option might be the insertion of a single oxygen atom into **13** yielding norloline (**1**). The third possible option is that C-2 and C-7 could be hydroxylated and halogenated to form haloalcohols **27** or **28**, respectively. The last option would be dihydroxylation to yield diol **29**. Haloalcohols **27** and **28** and diol **29** could undergo a Williamson-type reaction. Therefore, if the structure of lolidine (**6**) could be confirmed, a plausible pathway for the loline biosynthesis, including an unusual C-7 chlorinated intermediate **27**, could be postulated.[26]

Methylation carried out by *S*-adenosylmethionine (SAM) gives loline (**2**) and *N*-methyl loline (**30**). The sequence of *LolP* indicates that it encodes a cytochrome P450 monooxydase responsible for an NADPH+H^+ dependent two step oxidation of a *N*-methyl group to form a *N*-formyl group yielding *N*-formyl loline (**4**).[27]

Gene	Predicted function
LolC	γ-Type PLP enzyme
LolE	Epoxidase/hydroxylase
LolD	α-Type PLP enzyme/group IV decarboxylase
LolT	α-Type PLP enzyme
LolF	FAD-monooxygenase
LolO	Oxidoreductase/dioxygenase
MeT	Methyltransferase
LolP	Cytochrome P450 monooxygenase

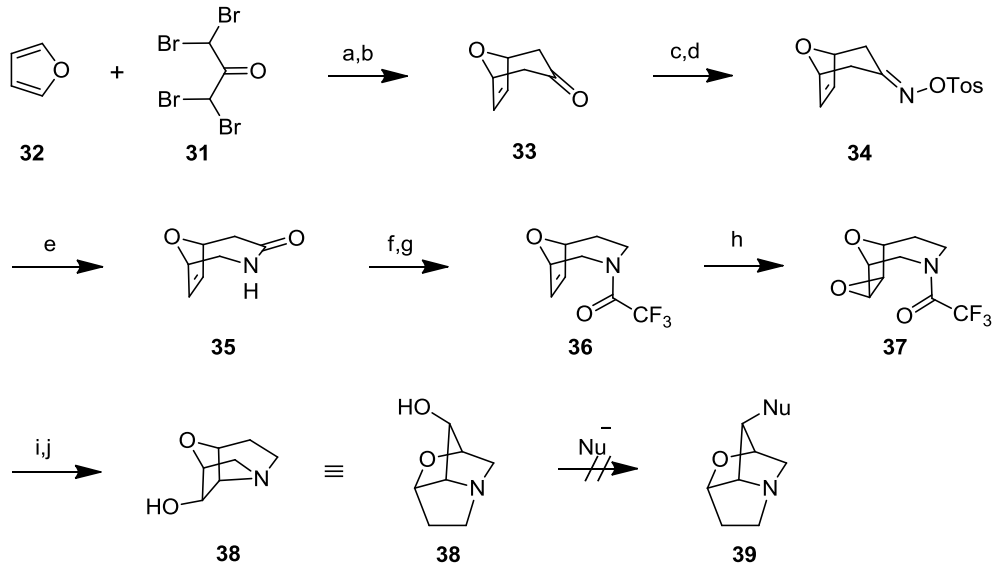
Table 1: Functions of the predicted products of the *LOL1* gene cluster of *N. unicatum*.[1]

1.4 Semisyntheses and Total Syntheses of Lolines

1.4.1 Interconversions and Semisyntheses of Lolines

Because there was no practical synthesis providing sufficient material, loline alkaloids were accessed through extraction and purification from darnel seeds. Subsequent interconversions between lolines with methyl, formyl or acyl substituents at the C-1 amine can be easily achieved by using standard reaction conditions.[28-29] For instance, temuline (**1**) can be prepared by treatment of loline (**2**) with $KMnO_4$ in cold 20% H_2SO_4. Refluxing of **1** in an equimolar mixture of formaldehyde and formic acid yields *N*-methyl loline (**30**). A variety of *N*-acyl derivatives can be obtained by reaction of **2** with the appropriate acyl chlorides.

The first attempt towards the total synthesis of loline was carried out by Glass and coworkers in 1978 (Scheme 4).[30] Tetrabromoacetone (**31**) in dry furan (**32**) was treated with $Fe_2(CO)_9$, followed by a Zn-Cu couple reduction, in order to prepare ketone **33**. Oxim formation and subsequent tosylation gave compound **34**, which underwent a Beckmann rearrangement to afford lactam **35**. Upon reduction with lithium aluminum hydride (LAH) and acetylation with trifluoroacetic anhydride (TFAA) compound **36** was epoxidized with *meta*-chloro-peroxybenzoic acid (*m*-CPBA) to yield **37**.

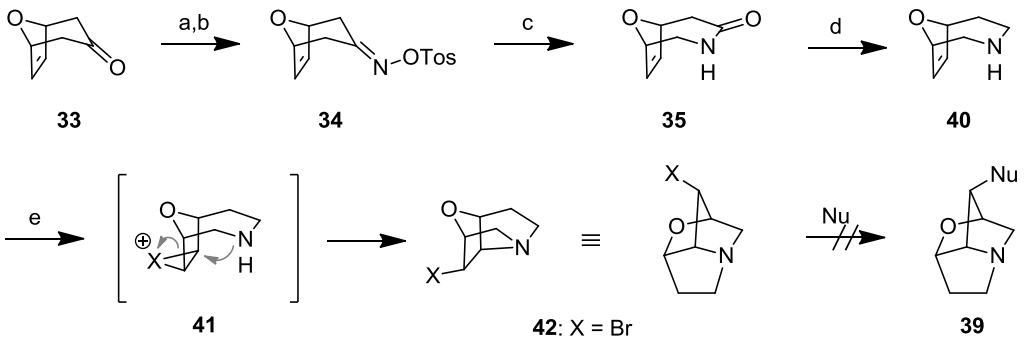


(a) $Fe_2(CO)_9$, THF:benzene (1:5), 80 °C; (b) Zn-Cu, MeOH, 60% (2 steps); (c) Oxim formation, 79%; (d) TsCl, Et_2O, KOH, 68%; (e) Beckmann-rearrangement, 98%; (f) $LiAlH_4$, Et_2O; (g) TFAA, K_2CO_3, 76% (2 steps); (h) *m*-CPBA, CH_2Cl_2, 73%; (i) K_2CO_3, MeOH; (j) EtOH, reflux, 60% (2 steps).

Scheme 4: Studies toward loline by Glass and coworkers.[30]

Cleavage of the trifluoroacetyl group followed by intramolecular cyclization through nucleophilic attack of the resulting amine yielded **38**. Unfortunately a S_N2-type substitution with a nitrogen nucleophile was unsuccessful.

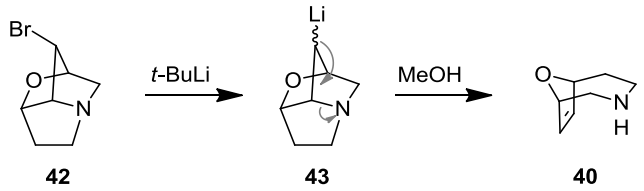
A second approach by Wilson and coworkers exploited a similar concept,[31] in which compound **40** was synthesized in an analogous fashion as performed by Glass (Scheme 5). The main difference between both approaches was the ring closing step. Whereas Glass utilized an epoxide, Wilson used halonium ions (bromine and iodine) as the reactive intermediates to achieve ring closure. However, nucleophilic substitution could not be achieved either. The absence of S_N2-type reactions can be attributed to the small angle between C-8, C-1 and C-2 (88°) and electronic repulsions between the lone pair of the nitrogen and the incoming nucleophile.[31]



(a) HO-NH_2·HCl, $NaHCO_3$, MeOH, reflux, 5 h, 81%; (b) TsCl, pyridine, CH_2Cl_2, -10 °C to rt, overnight, 91%; (c) aq. THF, K_2CO_3, rt, overnight, 85%; (d) $LiAlH_4$, THF:Et_2O (1:6), reflux, 5 h, overnight at rt, 65%; (e) X_2, (X = Br, I), CH_2Cl_2, rt, overnight, 99%.

Scheme 5: Studies towards loline by Wilson and coworkers.[31]

The only reaction observed was a bromine-metal exchange upon treatment with *t*-BuLi affording **43**. This lithiated intermediate subsequently underwent β-elimination upon hydrolysis to give the amine **40** (Scheme 6).



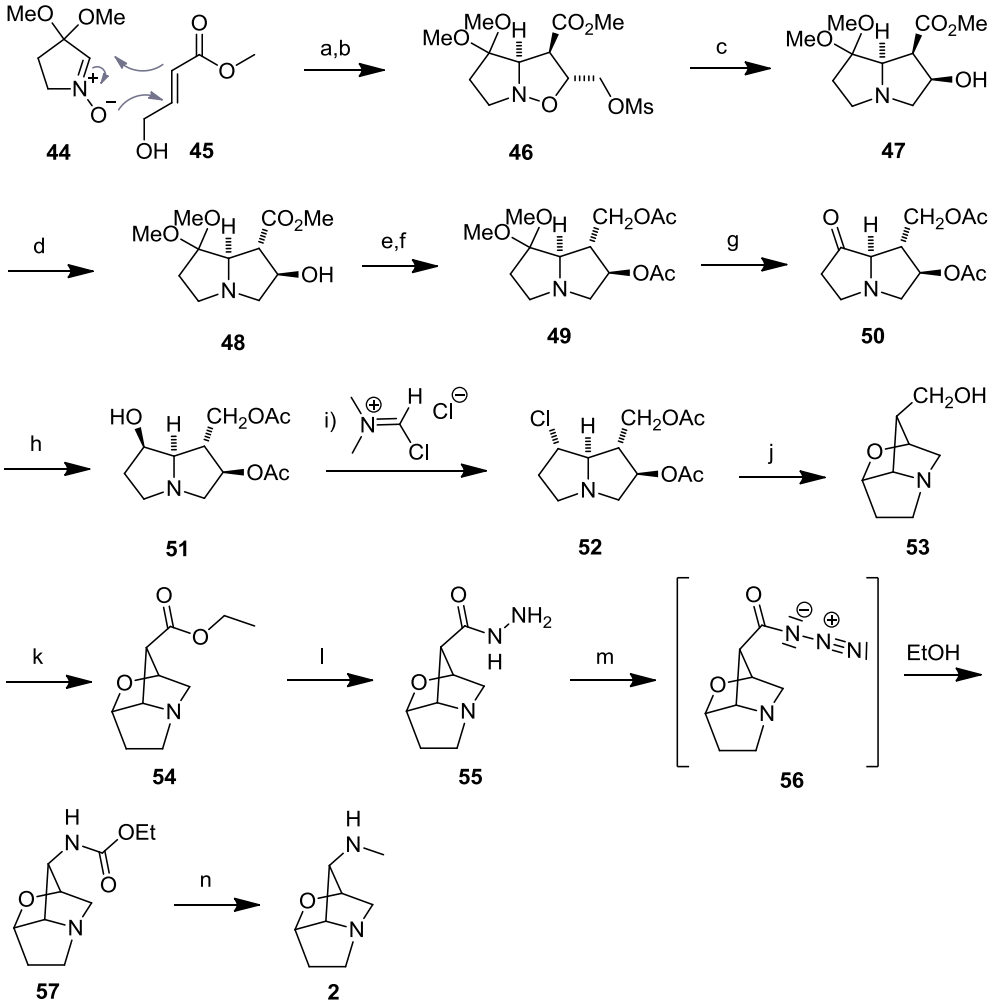
Scheme 6: Bromine-metal exchange and subsequent hydrolysis of compound **43**.

1.4.2 Racemic Synthesis of Loline

The first racemic total synthesis of loline (**2**) was accomplished by Tufariello and coworkers in 1986 (Scheme 7).[32] In this approach a nitrone-based methodology was used, which had been successfully applied in the synthesis of several pyrrolizidine alkaloids.[33-34]

The synthesis started with a 1,3-dipolar cycloaddition of dimethoxynitrone **44** and methyl 4-hydroxycrotonate **45**, followed by mesylation to give isoxazolidine **46**. Hydrogenolysis of the N-O bond afforded pyrollizidine **47** by simultaneous substitution of the mesylate by the newly formed secondary amine.[33] Alteration in the stereochemistry at C-1 was carried out using NaOMe in excellent yield. The driving force for the formation of the diastereomer was the removal of steric compression between the methyl ester and the ketal methoxy groups. Ester **48** was then reduced with LAH to give a diol which was subsequently protected as the

diacetate **49**. Hydrolysis afforded ketone **50**, which was selectively hydrogenated in the presence of Adams catalyst in glacial acetic acid. The hydrogenation occurred selectively from the less hindered convex side to give alcohol **51** in good yield.[32] Introduction of the chloride with inversion of configuration was achieved by using Vilsmeier reagent. Deprotection of the hydroxyl groups and the resulting Williamson-type cycloetherfication gave the lolium alkaloid skeleton present in **53**. The latter was next converted into the corresponding ethyl ester by oxidation with Jones reagent followed by acidic esterification. Treatment of ester **54** with hydrazine afforded hydrazide **55**, which underwent a Curtius rearrangement when exposed to isoamyl nitrite (giving intermediary **56**) and acidic ethanol to yield ethyl carbamate **57**. Finally carbamate **57** was reduced with LAH to complete the synthesis of racemic loline.[32]



(a) $CHCl_3$, 45 °C, 86%; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 99%; (c) Pd/C, H_2, MeOH, 84%; (d) NaOMe, MeOH, quantitative; (e) $LiAlH_4$; (f) acetylation, 85% (2 steps); (g) TFA, rt, then $NaHCO_3$, H_2O, quantitative; (h) PtO_2, AcOH, 95%; (i) $SOCl_2$, DMF, 75%; (j) NaOMe, MeOH, 88%; (k) CrO_3, H_2SO_4, acetone, then EtOH, H_2SO_4 in benzene, 80%; (l) $N_2H_4 \cdot H_2O$, reflux; (m) isoamyl nitrite, HCl_{anh}, EtOH; (n) $LiAlH_4$, THF, reflux, 83% (3 steps).

Scheme 7: Synthesis of racemic loline (**2**) by Tufariello and coworkers.[32-33]

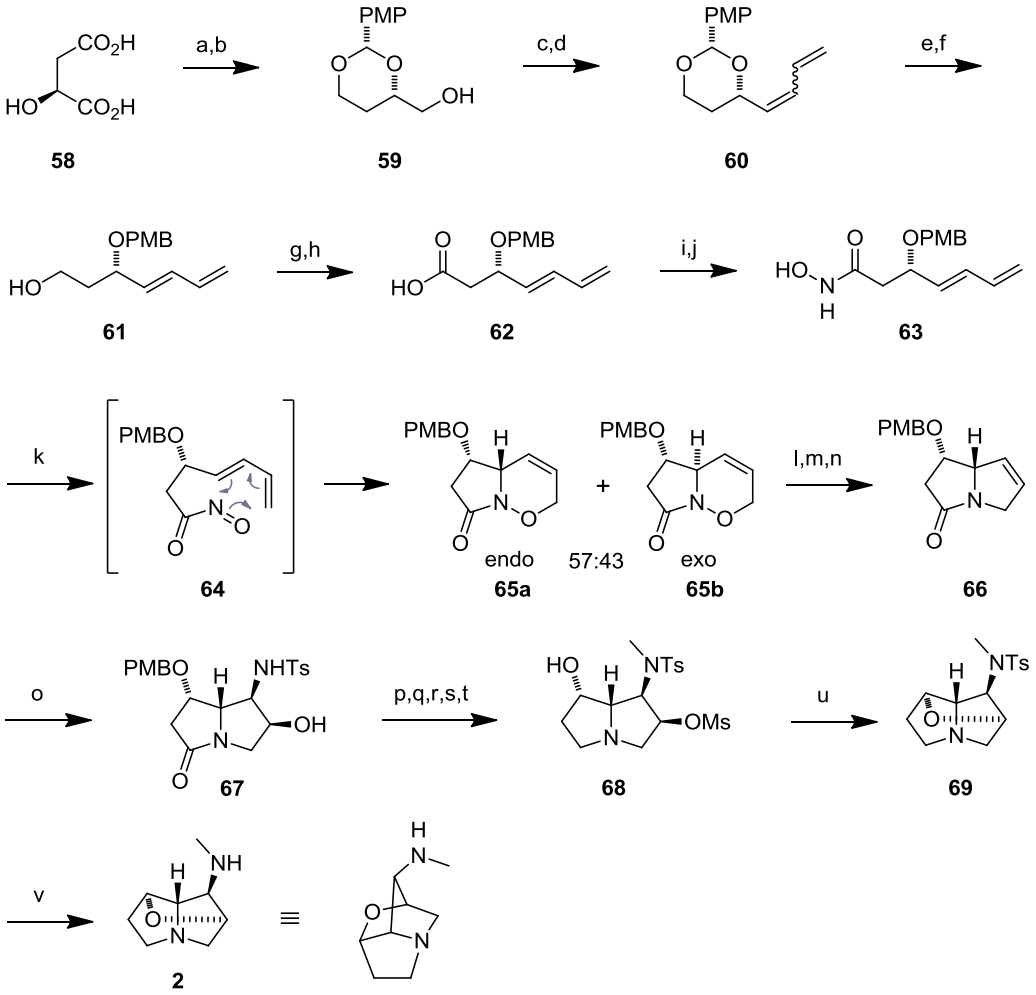
In summary the key steps of this synthesis were the Huisgen-type 1,3-dipolar cycloaddition to generate the pyrrolizidine ring system **47**, the efficient diastereoselective reduction of ketone **50** and the employment of a Curtius rearrangement to introduce the secondary amine **57**, which avoided the substitution problems described by Glass and Wilson.[30-31] Although the introduction of the amine seems a bit tedious, the total synthesis of racemic loline could be accomplished in 12 steps.

1.4.3 First Asymmetric Synthesis of Loline

The first asymmetric synthesis of loline (**2**) was performed in 20 steps and employed an intramolecular hetero-Diels-Alder reaction of a reactive acylnitrosodiene intermediate as a key step (Scheme 8).[35]

The synthesis commenced with malic acid (**58**), which was reduced with borane and converted diastereoselectively into *p*-methoxyphenyl acetal **59**. The aldehyde generated by Swern Oxidation was subjected to a Wittig reaction yielding diene **60** as a 3:7 mixture of *E*- and *Z*-isomers. Reduction and isomerization afforded diene **61** in an *E*:*Z* ratio of ≥95:5. Carboxylic acid **62,** obtained by a two-step oxidation, was reacted with *N*-trifluoroacetoxy-succinimide to give first the corresponding *O*-succinimidyl ester which was then replaced by hydroxylamine to yield hydroxamic acid **63**. Acylnitrosodiene **64** was generated *in situ* by oxidation of compound **63**, which spontaneously underwent an intramolecular hetero-Diels-Alder reaction to yield a mixture of endo **65a** and exo **65b** diastereomers in a ratio of 57:43. Pyrrolizidine **66** was prepared out of diastereomer **65a** within three steps by a sequence of reductive N-O bond cleavage, mesylation and reannealing. Sharpless asymmetric aminohydroxylation in the presence of chiral bischinchona alkaloid ligand [$(DHQD)_2PHAL$] afforded amino alcohol **67** and its regioisomer (not shown in the scheme) in a 3:1 ratio in moderate yield. Subsequent functional group manipulations yielded hydroxyl mesylate **68**, which upon thermal treatment cyclized to yield *N*-tosyl loline (**69**). Reductive cleavage of the *N*-tosyl group yielded loline (**2**).[35]

In consideration of a 20 step synthesis that employs two key steps with moderate diastereo- (hetero-Diels-Alder) and regionselectivity (Sharpeless asymmetric aminohydroxylation) combined with modest yields this approach seems not very efficient. Nevertheless a hetero-Diels-Alder chemistry was established as an effective way for pyrrolizidine synthesis.

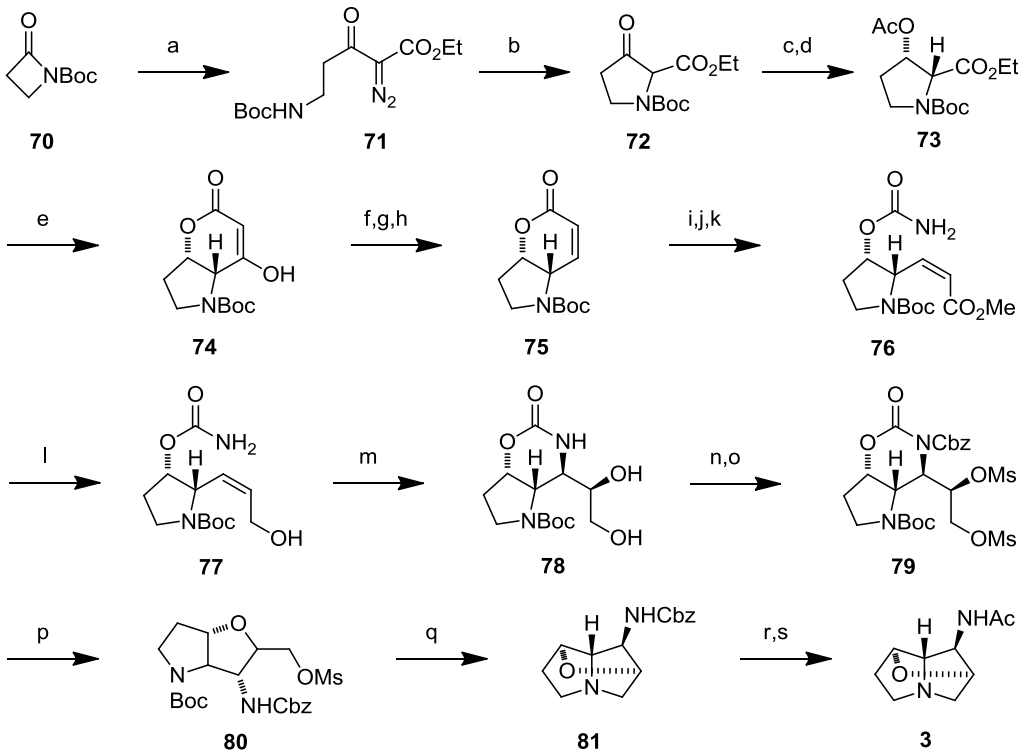


(a) $BH_3{\cdot}SMe_2$, $B(OMe)_3$,THF, 0 °C to rt; (b) $PMPCH(OMe)_2$, PPTS, CH_2Cl_2, reflux, 20 h, 64% (2 steps); (c) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, then NEt_3, -60 °C to rt; (d) allyltriphenylphosphonium bromide, *n*-BuLi, THF, -30 °C to rt, 40% (2 steps); (e) DIBAL- H, CH_2Cl_2, 0 °C to rt; (f) I_2, h*v*, benzene, rt, 1 h, 63% (2 steps); (g) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, then NEt_3, -60 °C to rt; (h) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methylbut-2-ene, *t*-BuOH, H_2O, 0 °C to rt; (i) CF_3CO_2SUC, Py, THF, rt, 20 h; (j), $HONH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, 0 °C, 75% (4 steps); (k) Bu_4NIO_4, $CHCl_3$, rt, 2.5 h, 87%; (l) Na(Hg), Na_2HPO_4, EtOH, 0 °C, 91%; (m) MsCl, Et_3N, CH_2Cl_2, 0 °C; (n) LDA, THF, -78 °C to 0 °C, 88% (2 steps); (o) Chloramine-T·$2H_2O$, $(DHQD)_2PHAL$, $K_4OsO_4(OH)_4$, *t*-BuOH:H_2O (1:1), rt, 72 h, 52%; (p) CH_3I, *t*-BuOK, *t*-BuOH, 50 °C,16 h, 76%; (q) MsCl, Et_3N, CH_2Cl_2, 0 °C, 15 min, 99%; (r) $BH_3{\cdot}SMe_2$, THF, rt, 5 h; (s) $Pd(OH)_2$/C, MeOH, rt, 14 h, 73% (2 steps); (t) DDQ, CH_2Cl_2/H_2O (20:1), rt, 48 h, 70%; (u) *o*-$Cl_2C_6H_4$, 180 °C, 22 h, 75%; (v) Sodium naphthalenide, DME, -60 °C, 20 min, 48%.

Scheme 8: Synthesis of (+)-loline by White and coworkers.[35]

1.4.4 Racemic Synthesis of *N*-Acetyl Norloline

In 2011, a new racemic synthesis of *N*-acetyl norloline (**3**) by Scheerer and coworkers was reported using a tethered aminohydroxylation (Scheme 9).[36]



(a) Ethyl diazoacetate, LiHMDS, -78 °C, 80%; (b) $Rh_2(OAc)_4$, toluene, 90 °C, 99%; (c) $NaBH_4$, MeOH; (d) Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt, 16 h, 93% (2 steps); (e) LiHMDS, THF, -78 °C, 1 h, to -20 °C, 2 h, 69%; (f) *t*-$BuNH_2 \cdot BH_3$, MeOH, 0 °C, 1.5 h; (g) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C to rt, overnight; (h) DBU, CH_2Cl_2, rt, 2 h, 68% (3 steps); (i) LiOH, THF, H_2O, 5 h, rt; (j) K_2CO_3, MeI, DMF, 2 h, rt; (k) $Cl_3CON{=}C{=}O$, CH_2Cl_2, 0 °C, 10 min, then $NaHCO_3$, MeOH 0 °C to rt, overnight, 65 % (3 steps); (l) DIBAL-H, CH_2Cl_2, -78 °C, 1.5 h, 73%; (m) *t*-BuOCl, NaOH, K_2OsO_4, H_2O, *n*-PrOH, rt, 20 h, 68%; (n) MsCl, pyridine, rt, overnight; (o) CbzCl, NEt_3, DMAP, THF, rt, 6 h , 94% (2 steps); (p) $CsCO_3$, MeOH, rt, 3 h, 34%; (q) TFA, NEt_3, CH_2Cl_2, 0 °C, 1 h, 99%; (r) H_2, Pd/C, MeOH/EtOAc 1:1, rt, 1 h; (s) Ac_2O, $CHCl_3$, rt, 1 h, 71% (2 steps).

Scheme 9: Total synthesis of racemic N-acetyl norloline (**3**) by Scheerer and coworkers.[36]

The synthesis starts with a Claisen condensation of β-lactam **70** and ethyl diazoacetate to yield the condensation product **71**, which was subjected to rhodium catalyzed N-H insertion to afford β-ketoester **72**. Reduction and subsequent acetylation of **72** afforded the racemic ester **73** which upon treatment with LiHMDS underwent Dieckmann condensation to yield enol lactone **74** in good yield. To convert enol lactone **74** into the α,β -unsaturated lactone **75,** a sequence of reduction-elimination steps was performed. Hydrolysis of lactone **75**, esterification and conversion of the hydroxyl group into the primary carbamate with trichloroacetyl isocyanate afforded ester **76**. Reduction of ester **76** yielded allylic alcohol **77**, which was subjected to OsO_4 catalyzed intramolecular aminohydroxylation to yield diol **78**. In order to form the pyrrolizidine core and the ether bridge subsequent modification of

the functional groups were performed to provide carbamate **79**. The strained ether bridge of compound **80** was formed upon methanolysis of carbamate **79** in very moderate yield. Deprotection of the Boc protecting group led to subsequent intramolecular alkylation, forming the *N*-Cbz norloline (**81**). By simple hydrogenation and acetylation it was demonstrated that Cbz-protected amine **81** can be transformed into *N*-acetyl norloline in good yield.

Scheerer and coworkers demonstrated that a tethered aminohydroxylation is a powerful tool to functionalize alkenes. He circumvented the regioselectivity issues of the aminohydroxylation used by White and coworkers and synthesized racemic *N*-acetyl norloline (**3**) in 17 steps.

References

[1] C. L. Schardl, R. B. Grossman, P. Nagabhyru, J. R. Faulkner, U. P. Mallik, *Phytochemistry* **2007**, *68*, 980–996.

[2] J. R. Cowan, *Advances in Agronomy,* (Ed.: A. G. Norman), Academic Press, **1956**, pp. 283–320.

[3] S. G. Yates, H. L. Tookey, J. J. Ellis, W. H. Tallent, I. A. Wolff, *J. Agr. Food Chem.* **1969**, *17*, 437–442.

[4] F. Hofmeister, *N-S Arch. Pharmacol.* **1892**, *30*, 202–230.

[5] G. Dannhardt, L. Steindl, *Planta Med.* **1985**, 212–214.

[6] A. Takeda, E. Suzuki, K. Kamei, H. Nakata, *Chem. Pharm. Bull. (Tokyo)* **1991**, *39*, 964–968.

[7] É. Batirov, V. Malikov, S. Yunusov, *Chem. Nat. Compd.* **1976**, *12*, 52–54.

[8] R. B. Bates, S. R. Morehead, *Tetrahedron Lett.* **1972**, *17*, 1629–1630.

[9] S. Y. Yunusov, S. T. Akramov, *Zh. Obshch. Khim.* **1960**, *30*, 683–689.

[10] L. P. Bush, F. F. Fannin, M. R. Siegel, D. L. Dahlman, H. R. Burton, *Agric. Ecosyst. Environ.* **1993**, *44*, 81–102.

[11] P. Guérin, *Journal de Botanique* **1898**, *12*, 230–238.

[12] C. D. Moon, B. Scott, C. L. Schardl, M. J. Christensen, *Mycologia* **2000**, *92*, 1103–1118.

[13] J. D. Blankenship, M. J. Spiering, H. H. Wilkinson, F. F. Fannin, L. P. Bush, C. L. Schardl, *Phytochemistry* **2001**, *58*, 395–401.

[14] S. G. Yates, J. C. Fenster, R. J. Bartelt, *J. Agr. Food Chem.* **1989**, *37*, 354–357.

[15] W. E. Riedell, R. E. Kieckhefer, R. J. Petroski, R. G. Powell, *J. Entomol. Sci.* **1991**, *26*, 122–129.

[16] M. R. Siegel, G. C. M. Latch, L. P. Bush, F. F. Fannin, D. D. Rowan, B. A. Tapper, C. W. Bacon, M. C. Johnson, *J. Chem. Ecol.* **1990**, *16*, 3301–3315.

[17] H. H. Wilkinson, M. R. Siegel, J. D. Blankenship, A. C. Mallory, L. P. Bush, C. L. Schardl, *Mol. Plant Microbe In.* **2000**, *13*, 1027–1033.

[18] A. Leuchtmann, C. L. Schardl, M. R. Siegel, *Mycologia* **1994**, *86*, 802–812.

[19] T. L. Bultman, G. Bell, W. D. Martin, *Ecology* **2004**, *85*, 679–685.

[20] K. D. Craven, J. D. Blankenship, A. Leuchtmann, K. Hignight, C. L. Schardl, *Sydowia* **2001**, *53*, 44–73.

[21] J. D. Robbins, S. R. Wilkinson, J. G. Sweeny, D. Burdick, *J. Agr. Food Chem.* **1972**, *20*, 1040–1043.

[22] J. R. Strickland, D. L. Cross, G. P. Birrenkott, L. W. Grimes, *Am. J. Vet. Res.* **1994**, *55*, 716–721.

[23] R. J. Petroski, R. G. Powell, S. Ratnayake, J. L. McLaughlin, *Int. J. Pharm.* **1994**, *32*, 409–412.

[24] P. M. Dewick, *Medicinal natural products : a biosynthetic approach*, 3. ed., Wiley, Chichester, **2009**.

[25] J. D. Blankenship, J. B. Houseknecht, S. Pal, L. P. Bush, R. B. Grossman, C. L. Schardl, *ChemBioChem* **2005**, *6*, 1016–1022.

[26] J. R. Faulkner, S. R. Hussaini, J. D. Blankenship, S. Pal, B. M. Branan, R. B. Grossman, C. L. Schardl, *ChemBioChem* **2006**, *7*, 1078–1088.

[27] M. J. Spiering, J. R. Faulkner, D. X. Zhang, C. Machado, R. B. Grossman, C. L. Schardl, *Fungal Genet. Biol.* **2008**, *45*, 1307–1314.

[28] R. J. Petroski, S. G. Yates, D. Weisleder, R. G. Powell, *J. Nat. Prod.* **1989**, *52*, 810–817.

[29] S. Y. Yunusov, S. T. Akramov, *Zh. Obshch. Khim* **1960**, *30*, 677–682.

[30] R. S. Glass, D. R. Deardorff, L. H. Gains, *Tetrahedron Lett.* **1978**, *19*, 2965–2968.

[31] S. R. Wilson, R. A. Sawicki, J. C. Huffman, *J. Org. Chem.* **1981**, *46*, 3887–3891.

[32] J. J. Tufariello, H. Meckler, K. Winzenberg, *J. Org. Chem.* **1986**, *51*, 3556–3557.

[33] J. J. Tufariello, G. E. Lee, *J. Am. Chem. Soc.* **1980**, *102*, 373–374.

[34] J. J. Tufariello, J. P. Tette, *J. Chem. Soc. D.* **1971**, 469–470.

[35] P. R. Blakemore, S. K. Kim, V. K. Schulze, J. D. White, A. F. T. Yokochi, *J. Chem. Soc. Perk. T. 1* **2001**, 1831–1845.

[36] M. T. Hovey, E. J. Eklund, R. D. Pike, A. A. Mainkar, J. R. Scheerer, *Org. Lett.* **2011**, *13*, 1246–1249.

2. Results

2.1 M. Cakmak, P. Mayer, D. Trauner, *Nat. Chem.* **2011**, *3*, 543–545.

nature chemistry

ARTICLES

PUBLISHED ONLINE: 19 JUNE 2011 | DOI: 10.1038/NCHEM.1072

An efficient synthesis of loline alkaloids

Mesut Cakmak, Peter Mayer and Dirk Trauner*

Loline (1) is a small alkaloid that, in spite of its simple-looking structure, has posed surprising challenges to synthetic chemists. It has been known for more than a century and has been the subject of extensive biological investigations, but only two total syntheses have been achieved to date. Here, we report an asymmetric total synthesis of loline that, with less then ten steps, is remarkably short. Our synthesis incorporates a Sharpless epoxidation, a Grubbs olefin metathesis and an unprecedented transannular aminobromination, which converts an eight-membered cyclic carbamate into a bromopyrrolizidine. The synthesis is marked by a high degree of chemo- and stereoselectivity and gives access to several members of the loline alkaloid family. It delivers sufficient material to support a programme aimed at studying the complex interactions between plants, fungi, insects and bacteria brokered by loline alkaloids.

Efficiency continues to be one of the greatest challenges in total synthesis. It can be addressed at the level of individual steps, for example through high-yielding and atom-economic reactions[1], or at the strategic level, for example through highly step-economic synthetic schemes[2]. These approaches are closely intertwined, because new reactions allow for the redefinition of strategies, and strategic needs often provoke the invention of new reactions. Certain rules have emerged to maximize strategic efficiency. For instance, protecting groups should be circumvented, or should be cleaved in the course of strategic bond-forming operations[3,4]. If unavoidable, they should at least become a part of the molecule after they have fulfilled their defensive role. Oxidation state adjustments that are not directed towards the final oxidation state of the target molecule should also be avoided[5]. Generally, corrective measures should be kept to a minimum. All this requires highly selective (in particular chemo- and stereoselective) reactions, which need to be optimally arranged to make a synthesis as short and practical as possible.

Loline (**1**), a small alkaloid that has been known for decades, represents an interesting target for testing the state of synthetic efficiency (Fig. 1). It is the eponymous member of a family of alkaloids that were initially isolated from tall fescue grasses but were later found in many other plant families. Its congener temuline (**2**) was isolated from *Lolium temulentum* in 1892 and subsequently renamed norloline[6,7]. *N*-Acetyl norloline (**3**) occurs in *Festuca arundinancea*, together with several other loline members[8]. Its biosynthetic derivative *N*-formyl loline (**4**) is the most abundant loline alkaloid. *N*-Senecioyl norloline (**5**) was found in the urine of horses, which enjoy grazing on tall fescue grass[9,10]. The structure of the unusual chlorine-containing alkaloid lolidine (**6**) was proposed based on mass-spectrometric data, but the compound could not be further evaluated due to a scarcity of material[11].

The loline alkaloids play a remarkable range of biological roles, many of which are poorly understood and are still being unravelled. Produced by endophytic fungi, these widely distributed alkaloids appear to provide chemoprotection to their plant hosts, primarily against certain types of insects and aphids. Although most loline alkaloids are as toxic to these animals as nicotine, they seem to have relatively few negative effects on mammalian herbivores, including horses. In fact, the toxic affects occasionally associated with tall fescue have been traced to ergot alkaloids[9]. Emphasizing the interest that lolines have generated among biologists, their biosynthesis has been investigated in detail and the gene cluster accounting for their production has recently been cloned[9].

Despite their long history and intriguing biological activities, few successful syntheses of loline alkaloids have been reported to date. This may be due to their strained, heterotricyclic molecular skeleton, which incorporates polar functionalities in close proximity and makes the lolines more challenging than they appear at first sight. The molecules feature a pyrrolizidine and a morpholine ring system, as well as four stereocentres, only one of which is independent. As such, they are about as complex as oseltamivir (Tamiflu)[12], epibatidine[13] or kainic acid[14], which have received much attention in the synthetic community. Loline itself has also been the subject of several synthetic approaches, two of which were abandoned due to an inability to introduce the secondary amine at C1 via nucleophilic substitution[15,16]. In 1986, Tufariello published a racemic synthesis of the alkaloid that was based on a nitrone cycloaddition[17]. This was followed 14 years later by the first, and thus far only, asymmetric synthesis, which required 20 steps to reach the target molecule and established hetero Diels–Alder chemistry as an effective way to synthesize complex pyrrolizidines[18,19]. Very recently, a racemic synthesis of *N*-acetyl norloline (**3**) has been reported[20].

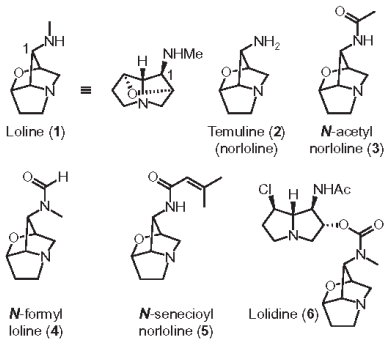


Figure 1 | Loline alkaloids. Members of the loline family of alkaloids have a common heterotricyclic core and are distinguished by the substitution pattern at the nitrogen in position 1.

Department of Chemistry and Pharmacology, Ludwig-Maximilians-Universität, München, and Center for Integrated Protein Science, 81377 Munich, Germany. *e-mail: dirk.trauner@lmu.de

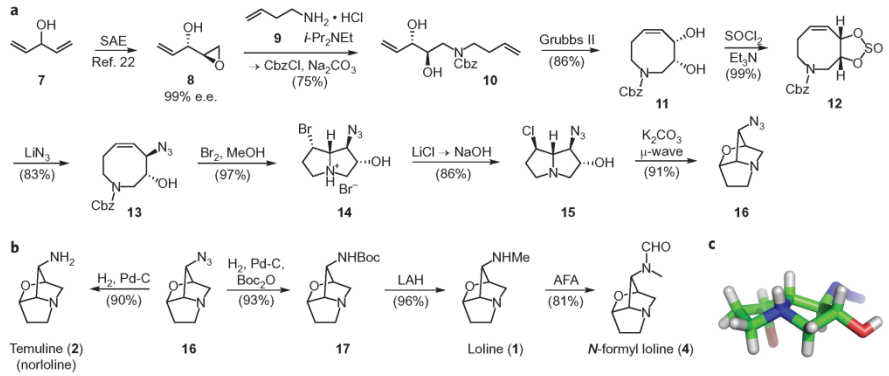


Figure 2 | Short total synthesis of loline alkaloids. a, Synthesis starts with an achiral alcohol **7** that can be easily desymmetrized to give epoxide **8** and then diene **10**. A ring-closing metathesis converts this compound into the eight-membered heterocycle **11**, which is further processed to yield azidoalcohol **13**. In the key step, this compound is transformed into the bicyclic pyrrolizidine **14**. Establishment of the oxygen bridge then yields an azide (**16**), a branching point of the synthesis. **b**, Azide **16** can be converted to temuline **2** by reduction of the azide. Alternatively, reduction of the azide in the presence of di-*tert*-butyldicarbonate gives the *N*-Boc protected compound, which can be further transformed into *N*-methyl compound loline **1** and *N*-formyl loline **4**. **c**, X-ray crystal structure of the key intermediate pyrrolizidine **14**. AFA, acetic formic anhydride.

Results

We now report an asymmetric total synthesis of temuline (**2**), loline (**1**) and *N*-formyl loline (**4**) (Fig. 1). It starts with epoxy alcohol **8**, which is readily available from achiral divinyl carbinol **7** through a highly enantiotopos and diastereoface-selective Sharpless epoxidation[21,22].

Nucleophilic opening of epoxide **8** with 3-butenylamine (**9**), followed by *in situ* protection of the newly formed secondary amine as a benzyl carbamate, yielded diene **10**. This compound underwent smooth ring-closing metathesis in the presence of a Grubbs II catalyst. The resultant diol (**11**) was activated for nucleophilic substitution as cyclic sulfite (**12**). This ring-closing and activation sequence could also be performed as a one-pot procedure (see Supplementary Information). Treatment of sulfite **12** with lithium azide then yielded azido alcohol **13** with excellent regioselectivity and in good yield. No products of S_N2' substitution were observed.

In the key step of our synthesis, we treated a solution of azido alcohol **13** in methanol with 1 equiv. of bromine at 0 °C and obtained an excellent yield of bromopyrrolizidine hydrobromide **14** (ref. 23) (see crystal structure in Fig. 2c). Although transannular nucleophilic substitutions have been used before in the synthesis of pyrrolizidines, the particular combination of electrophile and nucleophile used in this deoxycarbonylative aminobromination is unprecedented, to the best of our knowledge.

Bromopyrrolizidine **14** requires inversion at C7 to form the emblematic ether bridge of the loline alkaloids via a Williamson-type nucleophilic substitution. This inversion was achieved through a Finkelstein reaction, using LiCl in dimethyl formamide (DMF), which gave chloropyrrolizidine **15** in good yield. Notably, **15** corresponds to the chloropyrrolizidine subunit of lolidine (**6**), the most complex and structurally mysterious of the loline alkaloids. Heating a solution of **15** in a microwave apparatus in the presence of potassium carbonate as a base led to the smooth formation of the ether bridge and gave azide **16** in excellent yield. Under these conditions, only 5-*exo*-tet nucleophilic substitution occurred and no elimination products could be observed. The Finkelstein reaction and subsequent Williamson ether synthesis could also be carried out as a one-step procedure, further streamlining our synthesis (see Supplementary Information).

Azide **16** can serve as a branching point for the total synthesis of various loline alkaloids. Simple hydrogenation gave temuline (norloline) (**2**), whereas hydrogenation in the presence of di-*tert*-butyl pyrocarbonate yielded *N*-Boc temuline **17**. This compound could be cleanly reduced with lithium aluminium hydride to finally afford loline itself (**1**). Formylation of loline with acetic-formic anhydride then gave *N*-formyl loline (**4**), which is of considerable biological interest. The spectral data of all synthetic compounds corresponded to those reported in the literature (see Supplementary Information).

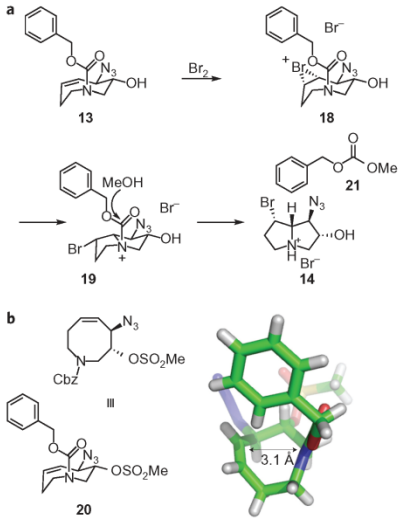


Figure 3 | Mechanism of the key step. a, Electrophilic activation of **13** with bromine affords bromonium ion **18**, which presumably undergoes transannular attack of the carbamate nitrogen to yield *N*-acylammonium ion **19**. Subsequent cleavage by methanol affords a carbonate by-product (**21**) and the pyrrolizidine core of the loline alkaloids (**14**). **b**, X-ray crystal structure of **20**, a sulfonate ester of **13**, which shows that the nitrogen is essentially in van der Waals contact with the carbon with which it eventually forms a bond.

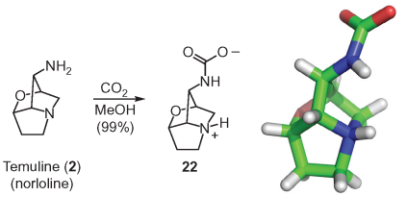


Figure 4 | Synthesis and X-ray structure of temuline carbamate. Exposure of temuline to CO_2 yields a zwitterionic carbamate. Also shown is the X-ray crystal structure, a rare example of a solid-state structure bearing a free carbamate.

Discussion

The key aminobromination of **13** warrants further mechanistic analysis (Fig. 3). Presumably, this reaction is initiated by the formation of a bromonium ion **18**, which is attacked by the nearby nitrogen atom and not, as one might expect, by the nucleophilic carbamate oxygen. Indeed, an X-ray structure of compound **20**, the mesylate of **13**, shows that the nitrogen resides in very close proximity (~3.1 Å) to the carbon atom with which it subsequently forms a bond (Fig. 3; see Supplementary Information for the synthesis of **20**). A similar arrangement has been observed by Wilson, who studied related transannular aminobrominations involving secondary amines in detail[24,25]. This conformational preorganization, in combination with the strain of the cyclic carbonate that would be formed through the more common *O*-attack, determines the course of the reaction. Transannular nucleophilic attack of the nitrogen then presumably yields acyl ammonium ion **19**, which is subsequently cleaved by the solvent, methanol, which cannot attack the bromonium ion directly due to steric hindrance. Supporting this mechanism, benzyl methyl carbonate (**21**) could be identified as a by-product of the reaction in stoichiometric yield.

Owing to their rigidity and polarity, the loline alkaloids exhibit some unusual physicochemical properties and chemical behaviour. For instance, it is well known that temuline (norloline) (**2**) has a strong propensity to absorb CO_2 (ref. 17). To gain more insight into this phenomenon, we deliberately exposed a solution of **2** in methanol to a CO_2 atmosphere (Fig. 4). Slow evaporation of the solvent yielded crystals of the zwitterionic carbamate **22** suitable for X-ray analysis. The X-ray structure of **22** is one of the few examples of a solid-state structure bearing a free carbamate reported in the literature (Fig. 4)[26,27]. Interestingly, there are no intramolecular hydrogen bonds, but strong intermolecular hydrogen bonds are apparent in the supramolecular packing of **22** (see Supplementary Information).

In summary, we have developed a highly efficient, asymmetric total synthesis of (+)-loline (**1**) that requires 10 (or in the streamlined version 8) steps, starting from the easily available achiral divinyl carbinol **7**. It features a Sharpless epoxidation, a Grubbs olefin metathesis and uses an unusual transannular attack of carbamate nitrogen to yield the pyrrolizidine skeleton. The only protecting group used in the synthesis is lost in the course of a strategic bond formation and does not require an additional cleavage step. Our synthesis is scalable, diversifiable and should give ample access to a range of other loline alkaloids, including lolidine (**6**). The synthetic natural products and derivatives thereof will be used to further explore the complex interactions between plants, fungi, insects and bacteria brokered by loline alkaloids.

Received 18 November 2010; accepted 17 May 2011; published online 19 June 2011

References

1. Trost, B. M. The atom economy—a search for synthetic efficiency. *Science* **254,** 1471–1477 (1991).
2. Wender, P. A. & Miller, B. L. Synthesis at the molecular frontier. *Nature* **460,** 197–201 (2009).
3. Young, I. S. & Baran, P. S. Protecting-group-free synthesis as an opportunity for invention. *Nature Chem.* **1,** 193–205 (2009).
4. Baran, P. S., Maimone, T. J. & Richter, J. M. Total synthesis of marine natural products without using protecting groups. *Nature* **446,** 404–408 (2007).
5. Burns, N. Z., Baran, P. S. & Hoffmann, R. W. Redox economy in organic synthesis. *Angew. Chem. Int. Ed.* **48,** 2854–2867 (2009).
6. Hofmeister, F. The active constituents of lolium temulentum. *Arch. Exp. Pathol. Pharmakol.* **30,** 203–230 (1892).
7. Dannhardt, G. & Steindl, L. Alkaloids of *Lolium temulentum*—isolation, identification and pharmacological activity. *Planta Med.* **51,** 212–214 (1985).
8. Robbins, J. D., Sweeny, J. G., Wilkinson, S. R. & Burdick, D. Volatile alkaloids of Kentucky 31 tall fescue seed (*Festuca arundinancea*). *J. Agric. Food Chem.* **20,** 1040–1043 (1972).
9. Schardl, C. L., Grossman, R. B., Nagabhyru, P., Faulkner, J. R. & Mallik, U. P. Loline alkaloids: currencies of mutualism. *Phytochemistry* **68,** 980–996 (2007).
10. Takeda, A., Suzuki, E., Kamei, K. & Nakata, H. Detection and identification of loline and its analogues in horse urine. *Chem. Pharm. Bull.* **39,** 964–968 (1991).
11. Batirov, E. K., Malikov, V. M. & Yunusov, S. Y. Lolidine—a new chlorine-containing alkaloid from the seeds of *Lolium cuneatum*. *Chem. Nat. Prod.* **12,** 52–54 (1977).
12. Magano, J. Synthetic approaches to the neuraminidase inhibitors zanamivir (relenza) and oseltamivir phosphate (Tamiflu) for the treatment of influenza. *Chem. Rev.* **109,** 4398–4438 (2009).
13. Olivo, H. F. & Hemenway, M. S. Recent synthesis of epibatidine. A review. *Org. Prep. Proced. Int.* **34,** 1–25 (2002).
14. Sakaguchi, H., Tokuyama, H. & Fukuyama, T. Stereocontrolled total synthesis of (−)-kainic acid. *Org. Lett.* **9,** 1635–1638 (2007).
15. Glass, R. S., Deardorff, D. R. & Gains, L. H. Pyrrolizidine synthesis by intramolecular cyclization of a substituted azacyclooctane-4,5-oxide. *Tetrahedron Lett.* **19,** 2965–2968 (1978).
16. Wilson, S. R., Sawicki, R. A. & Huffman, J. C. Synthetic and structural studies of the lolium alkaloids. *J. Org. Chem.* **46,** 3887–3891 (1981).
17. Tufariello, J. J., Meckler, H. & Winzenberg, K. Synthesis of the lolium alkaloids. *J. Org. Chem.* **51,** 3556–3557 (1986).
18. Blakemore, P. R., Schulze, V. K. & White, J. D. Asymmetric synthesis of (+)-loline. *Chem. Commun.* 1263–1264 (2000).
19. Blakemore, P. R., Kim, S.-K., Schulze, V. K., White, J. D. & Yokochi, A. F. T. Asymmetric synthesis of (+)-loline, a pyrrolizidine alkaloid from rye grass and tall fescue. *J. Chem. Soc. Perkin Trans. 1* 1831–1845 (2001).
20. Hovey, M. T., Eklund, E. J., Pike, R. D., Mainkar, A. A. & Scheerer, J. R. Synthesis of (±)-acetylnorloline via stereoselective tethered aminohydroxylation. *Org. Lett.* **13,** 1246–1249 (2011).
21. Schreiber, S. L., Schreiber, T. S. & Smith, D. B. Reactions that proceed with a combination of enantiotopic group and diastereotopic face selectivity can deliver products with very high enantiomeric excess: experimental support of a mathematical model. *J. Am. Chem. Soc.* **109,** 1525–1529 (1987).
22. Smith, D. B., Zhaoyin, W. & Schreiber, S. L. The asymmetric epoxidation of divinyl carbinols: theory and applications. *Tetrahedron* **46,** 4793–4808 (1990).
23. Wernerova, M. & Hudlicky, T. On the practical limits of determining isolated product yields and ratios of stereoisomers: reflections, analysis, and redemption. *Synlett.* 2701–2707 (2010).
24. Wilson, S. R. & Sawicki, R. A. Transannular cyclizations of 1-aza-4-cyclooctene. *J. Org. Chem.* **44,** 287–291 (1979).
25. Wilson, S. R. & Sawicki, R. A. The synthesis of hemiloline: 3-aza-9-oxabrendane. *Tetrahedron Lett.* **19,** 2969–2972 (1978).
26. Neda, I., Kaukorat, T. & Fischer, A. K. Unusual stabilization of 1,2-diamino derivatives of quincorine and quincoridine by carbon dioxide: persistent crystalline prim-ammonium-carbamate salts and their reactivity towards isatoic acid anhydride. *Eur. J. Org. Chem.* 3784–3790 (2003).
27. Jo, E. *et al.* Crystal structure and electronic properties of 2-amino-2-methyl-1-propanol (AMP) carbamate. *Chem. Commun.* **46,** 9158–9160 (2010).

Acknowledgements

The authors thank undergraduate participants E. Zeynep Serdar and C. Hieke, and thank E. Lauterwasser, E. Downs-Beaulieu and C.A. Kuttruff for insightful discussions.

Author contributions

M.C. and D.T. conceived the synthetic route and wrote the manuscript. M.C. conducted the experimental work, analysed the results and wrote the Supplementary Information. P.M. solved the crystal structures.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints/. Correspondence and requests for materials should be addressed to D.T.

nature chemistry

SUPPLEMENTARY INFORMATION

DOI: 10.1038/NCHEM.1072

An Efficient Synthesis of Loline Alkaloids

Mesut Cakmak, Peter Mayer and Dirk Trauner*

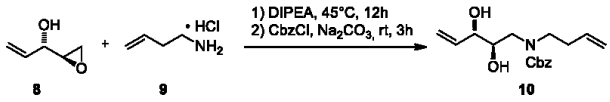
Department of Chemistry and Biochemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5–13, 81377 Munich (Germany)

Index:

General Experimental Details. Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Diisopropylethylamine (DIPEA) and Triethylamine (TEA) were distilled over calcium hydride immediately before use. Reactions were magnetically stirred and monitored by crude NMR or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F_{254} precoated glass plates. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. Flash column chromatography was performed as described by *Still et al.* employing silica gel (60 Å, 40-63 μm, Merck) and a forced flow of eluant at 1.3–1.5 bar pressure.[1] Yields refer to spectroscopically (^{1}H NMR and ^{13}C NMR) pure material.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ 7.26, MeOH: δ 3.31, H_2O: δ 4.79). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, *br* = broad, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.0, MeOH: δ 49.0). Infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System). FTIR Data is reported in frequency of absorption (cm^{-1}). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument. Microwave reactions were performed on a CEM machine (Model: Discovery System, No. 908010).

Synthetic procedures.



Diene 10:

6.97 g (69.7 mmol, 1 eq.) epoxy alcohol **8**[2] was dissolved in methanol (150 mL) and treated with 11.19 g (104.5 mmol, 1.5 eq.) 4-butenylamine hydrochloride (**9**) and 39.0 mL (230.0 mmol, 3.3 eq.) DIPEA. The reaction mixture was stirred at 45 °C for 12 h in a sealed tube. 22.1 g (209.1 mmol, 3 eq.) Na_2CO_3 in water (100 mL) and 23.7 mL (167.3 mmol, 2.4 eq.) benzyl chloroformate were subsequently added at 0 °C and stirred for 3 h at rt. The reaction mixture was subsequently diluted with H_2O (200 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 3:1) to yield 15.9 g (52.3 mmol, 75%) diene **10** as a clear oil (one spot on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.48 (UV, CAM).

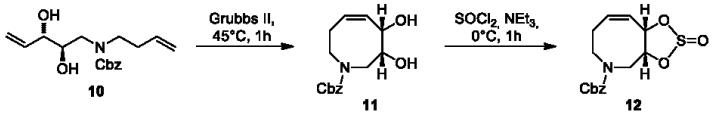
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.35 (m, 5H), 5.93–5.87 (m, 1H), 5.73–5.67 (m, 1H), 5.34 (d, *J*=17.3 Hz, 1H), 5.25 (d, *J*=10.5 Hz, 1H), 5.13 (s, 2H), 5.03–4.98 (dd, *J*=9.9, 16.7 Hz, 2H), 4.06 (s, 1H), 3.70 (s, 1H), 3.62 (dd, *J*=6.2, 14.8 Hz, 1H), 3.43–3.29 (m, 6H), 2.36 – 2.24 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 158.4, 136.7, 136.3, 134.9, 128.5, 128.1, 127.9, 117.2, 117.0, 74.3, 74.0, 67.7, 49.9, 48.6, 32.9.

IR (Diamond-ATR, neat) ν_{max}: 3397, 2978, 2937, 1743, 1671, 1478, 1423, 1221, 1147, 1094, 994, 917, 734, 697 cm^{-1}.

$[\alpha]^{25}_D$ – 9.2° (*c* = 0.46, $CHCl_3$).

HRMS (ESI) calcd for $C_{17}H_{23}NO_4$ $[M+H]^+$: 306.1700; found: 306.1706.



Diol 11

A solution of 2.10 g (6.9 mmol, 1.0 eq.) diene **10** in CH_2Cl_2 (3.0 L) was heated to reflux and 292 mg (0.34 mmol, 0.05 eq.) Grubbs 2nd Generation catalyst was added in one portion. The reaction mixture was refluxed for 1 h, then concentrated *in vacuo* to a total volume of ca. 50 mL and in general used for the next reaction without further purification.

The reaction was repeated five times using the same batch of CH_2Cl_2, which was recycled by distillation from the reaction mixture.

For characterization purpose, the reaction mixture was concentrated *in vacuo* and the crude product was purified by flash column chromatography (hexanes:EtOAc = 2:1) to yield 1.64 g (5.9 mmol, 86%) diol **11** as brown oil (one spot on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.15 (UV, CAM).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.37–7.27 (m, 5H), 5.92–5.65 (m, 2H), 5.17–5.06 (m, 2H), 4.46–4.25 (m, 2H), 4.21–3.62 (m, 2H), 3.30 (brs, 1H), 3.18 (brs, 1H), 2.95 (brs, 1H), 2.71–2.56 (m, 1H), 2.30–2.12 (m, 2H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ= 156.9, 156.1, 136.4, 136.3, 133.7, 132.5, 129.2, 128.6, 128.5, 128.3, 128.1, 128.1, 127.9, 127.8, 73.1, 72.7, 69.9, 69.4, 67.5, 67.4, 51.7, 51.3, 50.2, 49.5, 28.3, 28.1.

IR (Diamond-ATR, neat) ν_{max}: 3408, 2936, 1680, 1472, 1419, 1264, 1222, 1107, 1053, 955, 731, 697 cm^{-1}.

$[\alpha]^{25}_D$ + 48.5° (*c* = 0.42, $CHCl_3$).

HRMS (EI) calcd for $C_{15}H_{19}NO_4$: 277.1314; found: 277.1291.

Note: Multiple signals of ^{1}H- and ^{13}C-NMR are due to rotamers and conformers.

Sulfite 12

Crude diol **11** (100% yield assumed from RCM reactions, 34.5 mmol) in CH_2Cl_2 (ca. 250 mL) was cooled to 0 °C. 19.2 mL (138.0 mmol, 4 eq.) NEt_3 was added followed by a dropwise addition of 7.51 mL (103.5 mmol, 3 eq.) $SOCl_2$ and stirred at 0 °C for 1 h. The reaction mixture was diluted with $CHCl_3$ (400 mL), washed with H_2O (3 × 150 mL) and brine (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column

chromatography (hexanes:EtOAc = 3:1) to yield 9.48 g (29.3 mmol, 85% over 2 steps) sulfite **12** as a mixture of diastereomers in ratio of (54:46).

TLC (hexanes:EtOAc = 2:1), R_f = 0.81 (UV, CAM).

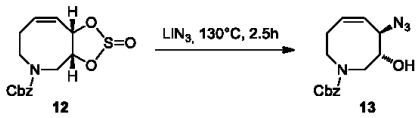
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.36 (brs, 5H), 6.19–5.94 (m, 2H), 5.63–5.43 (m, 1H), 5.39–5.05 (m, 2H), 5.04–4.69 (m, 1H), 4.45–4.12 (m, 2H), 3.31–2.91 (m, 1H), 2.82–2.60 (m, 1H), 2.43–2.21 (m, 1H), 2.19–1.93 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 155.6, 136.2, 136.0, 132.7, 132.1, 131.6, 130.3, 129.7, 129.2, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 84.1, 83.1, 81.7, 81.6, 80.8, 80.5, 78.8, 78.1, 67.9, 67.8, 67.7, 48.1, 47.9, 47.7, 47.7, 47.2, 47.1, 46.3, 29.8, 29.5, 29.2, 29.0.

IR (Diamond-ATR, neat) ν_{max}: 2947, 1695, 1463, 1417, 1211, 963, 740, 698 cm^{-1}.

$[\alpha]^{25}_D$ – 7.2° (*c* = 0.42, $CHCl_3$).

HRMS (EI) calcd for $C_{15}H_{17}NO_5S$: 323.0827; found: 323.0826.



12 **13**

Azido alcohol 13

500 mg (1.55 mmol, 1 eq.) sulfite **12** was dissolved in DMF (37 mL) and treated with 1.14 mL (4.64 mmol, 3 eq., 20% solution in water) LiN_3. The reaction mixture was stirred at 130 °C for 2.5 h, cooled to room temperature and diluted with H_2O (150 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were subsequently washed with H_2O (3 × 100 mL), 10% aq. LiCl (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 3:1) to yield 390 mg (1.29 mmol, 83%) azido alcohol **13** as a clear oil (one spot on TLC).

Note: Reaction scales larger than 1.55 mmol afforded the product in 55-70% yield.

TLC (hexanes:EtOAc = 6:4), R_f = 0.50 (UV, CAM).

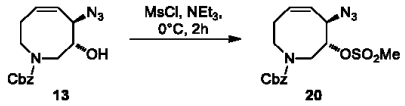
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.45–7.31 (m, 5H), 5.95–5.79 (dd, *J*=8.0, 18.8 Hz, 1H), 5.61–5.47 (m, 1H), 5.29–5.16 (m, 3H), 4.27–4.02 (m, 2H), 3.82–3.69 (m, 1H), 3.15 (dd, *J*=4.2, 15.2 Hz, 1H), 2.75–2.54 (m, 1H), 2.40–2.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 158.8, 136.0, 130.1, 130.0, 129.3, 128.7, 128.5, 128.3, 128.2, 77.0, 68.3, 63.9, 54.3, 49.5, 28.8.

IR (Diamond-ATR, neat) ν_{max}: 3376, 2930, 2099, 1663, 1417, 1258, 1210, 1132, 1066, 987, 733, 696 cm^{-1}.

$[\alpha]^{25}_D$ – 11.6° (*c* = 0.43, $CHCl_3$).

HRMS (ESI) calcd for $C_{15}H_{18}N_4O_3$ $[M+Na]^+$: 325.1277; found: 325.1271.



Azido mesylate 20

To a solution of 90 mg (0.298 mmol, 1 eq.) azido alcohol **13** and 100 μL (0.715 mmol, 2.4 eq.) NEt_3 in CH_2Cl_2 (12 mL) at 0 °C was added dropwise 28 μL (0.358 mmol, 1.2 eq.) MsCl. The reaction mixture was stirred for 2 h at 0 °C and then diluted with sat. aq. NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 96 mg (0.253 mmol, 85%) azido mesylate **20** as a yellow solid (one spot on TLC).

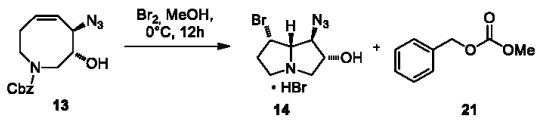
TLC (hexanes:EtOAc = 6:4), R_f = 0.45 (UV, CAM).

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.44–7.32 (m, 5H), 5.92–5.83 (m, 1H), 5.54–5.41 (m, 1H), 5.27–5.09 (m, 2H), 4.74–4.50 (m, 1H), 4.38 (dt, *J*=9.3, 17.7 Hz, 1H), 3.65 (m, 3H), 3.31–3.20 (m, 2H), 2.91 (s, 2H), 2.33 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 156.3, 136.2, 131.7, 131.3, 128.8, 128.5, 128.3, 128.0, 127.4, 80.6, 67.8, 67.6, 61.5, 50.4, 50.4, 47.3, 38.5, 38.0, 28.1, 27.8.

IR (Diamond-ATR, neat) ν_{max}: 2102, 1693, 1467, 1419, 1350, 1255, 1171, 1137, 946, 737 cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{27}N_4O_4S$: 380.1154; found: 380.1156.



Bromo pyrrolizidine hydrobromide 14

To a solution of 2.30 g (7.62 mmol, 1 eq.) azido alcohol **13** in MeOH (1.4 L) at 0 °C was added 390 µL (7.62 mmol, 1 eq.) Br_2. The reaction mixture was stirred under exclusion of light (to avoid radical reactions) for 12 h at 0 °C and concentrated *in vacuo*. The crude product was triturated with Et_2O (200 mL) and the formed precipitate was filtered off to yield 2.40 g (7.40 mmol, 97%) bromo pyrrolizidine hydrobromide **14** as colorless crystals.

The filtrate was concentrated *in vacuo* to yield 1.20 g (7.24 mmol, 95%) carbonate **21**.

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.65 ($KMnO_4$).

^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.86–4.82 (m, 1H), 4.38–4.31 (m, 1H), 4.29 (t, *J*=7.3 Hz, 1H), 4.11 (t, *J*=7.3 Hz, 1H), 3.90 (dd, *J*=6.1, 11.7 Hz, 1H), 3.67 (ddd, *J*=6.5, 7.5, 11.9 Hz, 1H), 3.49 (dt, *J*=6.5, 11.8 Hz, 1H), 3.20 (dd, *J*=9.1, 11.8 Hz, 1H), 2.72–2.56 (m, 2H).

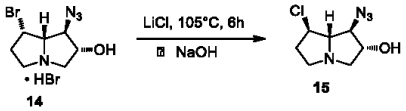
^{13}C NMR (MeOH-d_4, 100 MHz): δ= 74.1, 70.5, 68.6, 57.4, 53.4, 44.4, 34.8.

IR (Diamond-ATR, neat) ν_{max}: 3308, 2528, 2458, 2110, 1471, 1381, 1284, 1129, 1063, 986, 860 669 cm^{-1}.

$[\alpha]^{25}_D$ + 22.0° (*c* = 0.41, MeOH).

HRMS (ESI) calcd for $C_7H_{11}BrN_4O$ $[M+H]^+$: 247.0189; found: 247.0189.

M.p.: 172 °C



Choro pyrrolizidine 15

A solution of 1.71 g (5.26 mmol, 1 eq.) bromo pyrrolizidine hydrobromide **14** and 4.42 g (105.2 mmol, 20 eq.) LiCl in DMF (90 mL) was stirred for 6 h at 105 °C. The reaction mixture was

cooled to rt, diluted with H_2O (700 mL) and 1M aq. HCl (30 mL) and washed with EtOAc (2 × 250 mL). The aqueous layer was adjusted to pH = 10 with 1M aq. NaOH and extracted with EtOAc (5 × 300 mL). The combined organic layers were subsequently washed with H_2O (2 × 500 mL), 10% aq. LiCl (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 913 mg (4.52 mmol, 86%) chloro pyrrolizidine **15** as a brown oil (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.65 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.28 (dd, *J*=5.5, 12.0 Hz, 1H), 4.24 (dd, *J*=5.9, 12.5 Hz, 1H), 3.60 (t, *J*=5.5 Hz, 1H), 3.45 (dd, *J*=4.9, 10.4 Hz, 1H), 3.34 (dd, *J*=5.5, 10.6 Hz, 1H), 3.33–3.28 (m, 1H), 2.87–2.77 (m, 1H), 2.62 (dd, *J*=6.4, 10.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.12–2.04 (m, 1H).

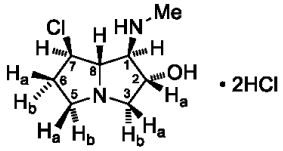
^{13}C NMR ($CDCl_3$, 100 MHz): δ= 76.5, 76.5, 70.1, 60.0, 59.6, 53.6, 35.6.

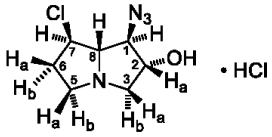
IR (Diamond-ATR, neat) ν_{max}: 2928, 2853, 2096, 1450, 1379, 1251, 1128, 1084, 978, 872, 792, 753, 698, 668 cm^{-1}.

$[\alpha]^{25}_D$ – 68.3° (*c* = 0.38, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{11}ClN_4O$ $[M+H]^+$: 203.0694; found: 203.0694.

Supplementary Table S1. ^{1}H NMR data comparison between reported hydroxychlororololine ·2HCl and chloro pyrrolizidine ·HCl (**15**).



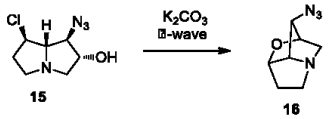


Proton	Literature report[3] (^{1}H, 300 MHz, D_2O)	This report (^{1}H, 400 MHz, D_2O)
H-7	4.80 (ddd, *J*=3.2, 4.6, 4.9 Hz, 1H)	4.68 (ddd, *J*=4.3, 5.0, 5.2Hz, 1H)
H-2	4.66 (dd, *J*=4.9, 5.6 Hz, 1H)	4.33 (dd, *J*=5.0, 5.2 Hz, 1H)
H-8	4.48 (dd, *J*=3.2, 6.1 Hz, 1H)	4.06 (dd, *J*=4.3, 4.8 Hz, 1H)
H-3a	3.92 (dd, *J*=5.6, 13.1 Hz, 1H)	3.76 (dd, *J*=5.2, 12.8 Hz, 1H)
H-5b	3.92 (ddd, *J*=5.3, 6.4, 12.1 Hz, 1H)	3.83 (ddd, *J*=5.8, 6.5, 12.3 Hz, 1H)

H-1	3.77 (dd, *J*=4.9, 6.1 Hz, 1H)	4.14 (dd, *J*=4.6, 5.1 Hz, 1H)
H-5a	3.52 (ddd, *J*=5.0, 7.1, 12.1 Hz, 1H)	3.37 (ddd, *J*=5.9, 6.6,12.5 Hz, 1H)
H-3b	3.37 (dd, *J*=5.6, 13.1 Hz, 1H)	3.18 (dd, *J*=5.0, 12.9 Hz, 1H)
NMe	2.79 (s, 3H)	–
H-6b	2.74 (dddd, *J*=4.9, 5.0, 6.4, 15.0 Hz, 1H)	2.67 (dddd, *J*=5.4, 5.6, 6.8, 14.5 Hz, 1H)
H-6a	2.34 (dddd, *J*=4.6, 5.3, 7.1, 15.0 Hz, 1H)	2.21 (dddd, *J*=5.1, 5.9, 6.6, 14.4 Hz, 1H)

Supplementary Table S2. ^{13}C NMR data comparison between reported hydroxychlororololine ·2HCl and chloro pyrrolizidine ·HCl (**15**).

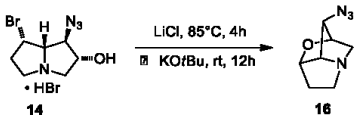
Carbon	Literature report[3] (^{13}C, 75.5 MHz, D_2O)	This report (^{13}C, 100 MHz, D_2O)
C-8	77.5	77.8
C-2	73.6	73.5
C-1	68.2	66.9
C-7	60.8	57.1
C-3	60.4	58.0
C-5	57.6	55.1
C-6	36.1	33.8
NMe	34.8	–



Azide 16

A solution of 580 mg (2.87 mmol, 1 eq.) chloro pyrrolizidine **15** and 990 mg (7.18 mmol, 2.5 eq.) K_2CO_3 in MeOH (30 mL) was stirred in a microwave reactor for 10 min at 150 °C/300 W. 10 g silica was added and the reaction mixture was concentrated *in vacuo*. The crude product

was purified by flash column chromatography ($CHCl_3$:MeOH = 10:1) to yield 429 mg (2.58 mmol, 90%) azide **16** as a yellow oil (one spot on TLC).



14 **16**

One-pot-procedure: azide 16

A solution of 15 mg (0.046 mmol, 1 eq.) bromo pyrrolizidine hydrobromide **14** and 48 mg (1.15 mmol, 25 eq.) LiCl in DMSO (1 mL) was stirred for 4 h at 85 °C. The reaction mixture was cooled to rt, treated with 26 mg (0.230 mmol, 5 eq.) KO*t*Bu and stirred for 12 h at rt. The reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 5 mg (0.030 mmol, 65%) azide **16** as a yellow oil.

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.67 ($KMnO_4$).

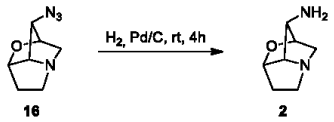
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.47 (dd, *J*=1.8, 4.5 Hz, 1H), 4.15 (s, 1H), 4.06 (s, 1H), 3.49 (d, *J*=11.7 Hz, 1H), 3.31 (s, 1H), 3.14–3.10 (m, 1H), 3.02–2.97 (m, 1H), 2.45 (d, *J*=11.7 Hz, 1H), 2.10–2.05 (m, 1H), 2.02–1.96 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 82.1, 74.4, 69.6, 66.4, 61.2, 54.8, 33.7.

IR (Diamond-ATR, neat) ν_{max}: 2940, 2103, 1354, 1310, 1263, 1097, 1050, 1006, 958, 849, 791, 724 cm^{-1}.

$[\alpha]^{25}_D$ – 49.2° (*c* = 0.44, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{10}N_4O$ $[M+H]^+$: 167.0927; found: 167.0928.



16 **2**

Temuline (2)

A solution of 15 mg (0.090 mmol, 1 eq.) azide **16** and 6 mg (0.006 mmol, 0.06 eq.) 10% Pd/C in MeOH (3 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 4 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to yield 11.4 mg (0.081 mmol, 90%) temuline (**2**) as a yellow oil (one spot on TLC).

*Note: When temuline (**2**) is exposed to air, it readily forms the corresponding carbamate, a crystalline solid.*

TLC ($CHCl_3$:MeOH = 2:1), R_f = 0.16 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.40 (dd, *J*=1.9, 4.5 Hz, 1H), 3.84 (d, *J*=1.7 Hz, 1H), 3.60 (dd, *J*=0.8, 1.7 Hz, 1H), 3.50 (dd, *J*=0.7, 11.7 Hz, 1H), 3.10 (ddd, *J*=3.6, 8.3, 12.7 Hz, 1H), 3.05 (dd, *J*=1.4, 1.5 Hz, 1H), 2.93 (ddd, *J*=7.3, 9.3, 12.8 Hz, 1H), 2.42 (d, *J*=11.8 Hz, 1H), 2.03 (ddd, *J*=7.3, 8.2, 14.3 Hz, 1H), 1.97 (dddd, *J*=3.6, 4.4, 9.4, 14.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 81.7, 76.2, 71.9, 60.8, 60.5, 54.5, 34.1.

IR (Diamond-ATR, neat) ν_{max}: 3366, 3288, 3184, 1606, 1472, 1318, 1250, 1216, 1174, 1087, 1040, 1020, 955, 846, 798, 772, 695, 626 cm^{-1}.

$[\alpha]^{25}_D$ + 27.3° (*c* = 0.37, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{12}N_2O$ $[M+H]^+$: 141.1022; found: 141.1024.

Supplementary Table S3. ^{1}H NMR data comparison between reported natural temuline (**2**) and synthetic temuline (**2**).

Literature report[3] (^{1}H, 300 MHz, $CDCl_3$)[a]	This report (^{1}H, 400 MHz, $CDCl_3$)
4.25 (dd, *J*=1.9, 4.4 Hz, 1H)	4.40 (dd, *J*=1.9, 4.5 Hz, 1H)
3.72 (dd, *J*=1.6, <2 Hz, 1H)	3.84 (d, *J*=1.7 Hz, 1H)
3.48 (dd, *J*=1.8, <2 Hz, 1H)	3.60 (dd, *J*=0.8, 1.7 Hz, 1H)
3.38 (dd, *J*=1.6, 11.7 Hz, 1H)	3.50 (dd, *J*=0.7, 11.7 Hz, 1H)

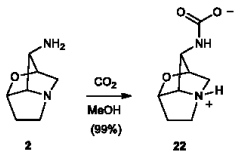
2.98 (ddd, *J*=3.8, 8.3, 12.8 Hz, 1H)	3.10 (ddd, *J*=3.6, 8.3, 12.7 Hz, 1H)
2.92 (dd, *J*=1.8, 1.9 Hz, 1H)	3.05 (dd, *J*=1.4, 1.5 Hz, 1H)
2.80 (ddd, *J*=7.5, 9.3, 12.8 Hz, 1H)	2.93 (ddd, *J*=7.3, 9.3, 12.8 Hz, 1H)
2.29 (d, *J*=11.7 Hz, 1H)	2.42 (d, *J*=11.8 Hz, 1H)
1.94 (ddd, *J*=7.5, 8.3, 14.3 Hz, 1H)	2.03 (ddd, *J*=7.3, 8.2, 14.3 Hz, 1H)
1.84 (dddd, *J*=3.8, 4.4, 9.3, 14.3 Hz, 1H)	1.97 (dddd, *J*=3.6, 4.4, 9.4, 14.2 Hz, 1H)

[a]Chemical shifts are reported relative to TMS with $CDCl_3$ solution.

Note: Slight differences in the ^{1}H-NMR spectrum could be due to concentration effects (c.f. Ref. 4)[4]

Supplementary Table S4. ^{13}C NMR data comparison between reported natural temuline (**2**) and synthetic temuline (**2**).

Literature report[3] (^{13}C, 75.5 MHz, $CDCl_3$)	This report (^{13}C, 100 MHz, $CDCl_3$)
81.7	81.7
76.2	76.2
71.9	71.9
60.8	60.8
60.5	60.5
54.5	54.5
34.1	34.1



2 22

Temuline carbamate (22)

CO_2 was bubbled trough a solution of 14 mg (0.1 mmol) temuline (**2**) in Methanol (5 mL) for 2 min. The reaction mixture was concentrated down to afford 18.2 mg (0.099 mmol, 99%) temuline carbamate (**22**) as a colourless crystalline solid.

TLC ($CHCl_3$:MeOH = 7:3), R_f = 0.27 ($KMnO_4$).*

^{1}H NMR (MeOH-d_4, 600 MHz): δ= 4.61 (dd, *J*=2.2, 5.0 Hz, 1H), 4.33 (s, 1H), 4.27 (s, 1H), 4.18 (d, *J*=12.0 Hz, 1H), 3.95 (d, *J*=2.2 Hz, 1H), 3.67 (ddd, *J*=3.6, 9.0, 12.4 Hz, 1H), 3.59–3.54 (m, 1H), 3.19 (d, *J*=12.0 Hz, 1H), 2.43–2.37 (m, 1H), 2.31–2.26 (m, 1H).

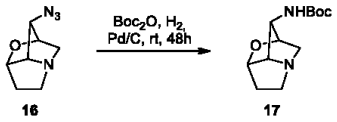
^{13}C NMR (MeOH-d_4, 151 MHz): δ= 79.3, 74.9, 74.0, 61.3, 57.8, 52.5, 29.9.

IR (Diamond-ATR, neat) ν_{max}: 3354, 2921, 2784, 2549, 1653, 1475, 1444, 1375, 1343, 1215, 1181, 1085, 1001, 963, 937, 836, 799, 778cm^{-1}.

$[\alpha]^{25}_D$ – 46.0° (*c* = 0.19, MeOH).

HRMS (EI) calcd for $C_8H_{12}N_2O_3$ [M–CO_2]: 140.0944; found: 140.0936.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



16 **17**

***N*-Boc temuline (17)**

A solution of 10 mg (0.060 mmol, 1 eq.) azide **16**, 26 mg (0.120 mmol, 2 eq.) Boc_2O and 6 mg (0.006 mmol, 0.09 eq.) 10% Pd/C in THF (5 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 48 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 13.4 mg (0.056 mmol, 93%) *N*-Boc temuline (**17**) as a yellow oil (one spot on TLC).

TLC (**$CHCl_3$:MeOH:NH_4OH** = 9:2:0.2), R_f = 0.66 ($KMnO_4$).

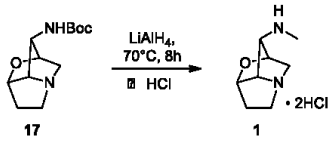
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 5.45 (brs, 1H), 4.46 (dd, *J* =1.6, 4.4 Hz, 1H), 4.23 (d, *J*=5.6 Hz, 1H), 4.14 (s, 1H), 3.36 (d, *J*=11.8 Hz, 1H), 3.12–3.08 (m, 2H), 2.96–2.91 (m, 1H), 2.43 (d, *J*=11.8 Hz, 1H), 2.10–2.04 (m, 1H), 2.02–1.97 (m, 1H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 155.5, 81.0, 79.6, 74.1, 69.7, 61.0, 58.5, 54.6, 33.8, 28.3.

IR (Diamond-ATR, neat) ν_{max}: 2974, 2937, 1697, 1547, 1365, 1289, 1251, 1161, 1152, 999, 961, 850, 794, 749, 665 cm^{-1}.

$[\alpha]^{25}_D$ + 38.7° (*c* = 0.35, $CHCl_3$).

HRMS (ESI) calcd for $C_{12}H_{20}N_2O_3$ $[M+H]^+$: 241.1547; found: 241.1545.



Loline ·2HCl (1)

A solution of 11 mg (0.046 mmol, 1 eq.) *N*-Boc temuline (**17**) in THF (5 mL) was degassed with N_2 in a sonicator for 5 minutes, then treated with 275 µL (0.275 mmol, 6 eq., 1M solution in THF) $LiAlH_4$ and refluxed for 8 h. The reaction mixture was quenched with 1M aq. NaOH (0.3 mL) and 0.5 g silica was added and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH:NH_4OH = 10:4:1) and the resulting free base was treated with 3M HCl in methanol (2 mL) and concentrated *in vacuo* to yield 10 mg (0.044 mmol, 96%) loline ·2HCl (**1**) as a yellow oil (one spot on TLC).

*Note: When loline (**1**) (as a free base) is exposed to air, it readily forms the corresponding carbamate, a crystalline solid.*

TLC ($CHCl_3$:MeOH:NH_4OH = 9:3:0.5), R_f = 0.12 ($KMnO_4$).

^{1}H NMR (D_2O, 400 MHz): δ= 4.82 (s, 1H), 4.80 (s, 1H), 4.75 (dd, *J*=2.3, 4.8 Hz, 1H), 4.26 (s, 1H), 4.15 (d, J=13.9 Hz, 1H), 3.82–3.76 (m, 1H), 3.76–3.70 (m, 1H), 3.60 (d, *J*=13.9 Hz, 1H), 2.83 (d, *J*=0.9 Hz, 3H), 2.42 (ddd, *J*=7.6, 10.0, 15.0 Hz, 1H), 2.31 (ddd, *J*=5.0, 8.4, 15.0 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 83.4, 74.0, 72.2, 66.0, 64.2, 58.2, 36.4, 36.1

$[\alpha]^{25}_D$ + 5.4° (*c* = 0.31, H_2O).

HRMS (ESI) calcd for $C_8H_{14}N_2O$ $[M+H]^+$: 155.1179; found: 155.1176.

Supplementary Table S5. ^{1}H NMR data comparison between reported natural loline ·2HCl (**1**) and synthetic loline ·2HCl (**1**).

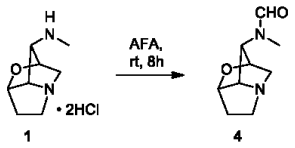
Literature report[3] (^{1}H, 300 MHz, D_2O)	This report (^{1}H, 400 MHz, D_2O)
4.79 (dd, *J*=1.0, <2 Hz, 1H)	4.82 (s, 1H)
4.79 (dd, *J*=1.9, 2.2 Hz, 1H)	4.80 (s, 1H)
4.76 (bm, 1H)	-
4.72 (dd, *J*=2.2, 4.8 Hz, 1H)	4.75 (dd, *J*=2.3, 4.8 Hz, 1H)
4.23 (dd, *J*=1.0, <2 Hz, 1H)	4.26 (s, 1H)
4.15 (dd, *J*=1.0, 13.9 Hz, 1H)	4.15 (d, *J*=13.9 Hz, 1H)
3.73 (ddd, *J*=7.7, 8.2, 12.8 Hz, 1H)	3.78 (ddd, *J*=7.6, 8.7, 12.8 Hz, 1H)
3.73 (ddd, *J*=5.0, 9.6, 12.8 Hz, 1H)	3.73 (ddd, *J*=4.9, 9.8, 12.7 Hz, 1H)
3.55 (d, *J*=13.9 Hz, 1H)	3.60 (d, *J*=13.9 Hz, 1H)
2.79 (s, 3H)	2.83 (d, *J*=0.9 Hz, 3H)
2.37 (ddd, *J*=7.7, 9.6, 14.6 Hz, 1H)	2.42 (ddd, *J*=7.6, 10.0, 15.0 Hz, 1H)
2.28 (dddd, *J*=4.8, 5.0, 8.2, 14.6 Hz, 1H)	2.31 (ddd, *J*=5.0, 8.4, 15.0 Hz, 1H)

Note: Slight differences in the ^{1}H-NMR spectrum could be due to concentration effects. (c.f. Ref. 4)[4]. The doublet at 2.83 ppm is due to coupling of the N-methyl group to the N-H.

Supplementary Table S6. ^{13}C NMR data comparison between reported natural loline ·2HCl (**1**) and synthetic loline ·2HCl (**1**).

Literature report[3] (^{13}C, 75.5 MHz, D_2O)	This report (^{13}C, 100 MHz, D_2O)
83.2	83.4
73.9	74.0
72.2	72.2
65.9	66.0

64.2	64.2
58.1	58.2
36.5	36.4
31.6	31.6



1 4

***N*-Formylloline (4)**

Formic acid (0.1 mL) and Acetic anhydride (0.2 mL) was stirred for 2 h at 55 °C and then added to 10 mg (0.044 mmol) loline ·2HCl (**1**). The reaction mixture was stirred at rt for 8 h before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 6.5 mg (0.036 mmol, 81%) *N*-formylloline (**4**) as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 3:1), R_f = 0.5 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 8.44 (s), 8.07 (s), 4.71 (d, *J*=2.1 Hz), 4.52 (dd, *J*=1.8, 4.4 Hz), 4.45 (dd, *J*=1.8, 4.4 Hz), 4.21 (d, *J*=1.6 Hz), 4.06–4.04 (m), 3.85 (d, *J*=1.3 Hz), 3.42 (s), 3.37 (s), 3.27 (d, *J*=11.9 Hz), 3.23 (d, *J*=11.6 Hz), 3.13 (s), 3.12–3.08 (m), 3.05–2.98 (m), 2.95 (d, *J*=0.5 Hz), 2.51 (d, *J*=12.0 Hz), 2.44 (d, *J*=11.8 Hz), 2.09 (ddd, *J*=7.1, 7.4, 14.4 Hz), 1.98 (dddd, *J*=4.3, 4.3, 9.4, 14.4 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 163.5, 163.2, 82.0, 80.3, 74.0, 73.1, 67.9, 67.5, 65.4, 62.4, 61.0, 60.5, 54.8, 54.6, 33.4, 33.1, 32.8, 29.9.

IR (Diamond-ATR, neat) ν_{max}: 3488, 2934, 2880, 1665, 1388, 1355, 1254, 1085, 1049, 1024, 962, 811, 751 cm^{-1}.

$[\alpha]^{25}_D$ + 4.3° (*c* = 0.22, $CHCl_3$).

HRMS (ESI) calcd for $C_9H_{14}N_2O_2$ $[M+H]^+$: 183.1128; found: 183.1126.

Supplementary Table S7. ^{1}H NMR data comparison between reported natural *N*-formylloline (**4**) and synthetic *N*-formylloline (**4**).

Literature report[3] (^{1}H, 300 MHz, $CDCl_3$)[a]	This report (^{1}H, 400 MHz, $CDCl_3$) [a]
8.23 (s)	8.44 (s)
7.25 (s)	8.07 (s)
4.56 (dd, *J*=1.4, <2 Hz)	4.71 (d, *J*=2.1 Hz)
4.34 (dd, *J*=1.8, 4.3 Hz)	4.52 (dd, *J*=1.8, 4.4 Hz)
4.27 (dd, *J*=1.8, 4.3 Hz)	4.45 (dd, *J*=1.8, 4.4 Hz)
4.05 (dd, *J*=1.5, <2 Hz)	4.21 (d, *J*=1.6 Hz)
3.82 (dd, *J*=1.4, 2.0 Hz)	4.05 (d, *J*=1.5 Hz)
3.68 (dd, *J*=1.5, 2.0 Hz)	3.85 (d, *J*=1.3 Hz)
3.34 (dd, *J*=1.8, 2.0 Hz)	3.42 (s)
3.30 (dd, *J*=1.8, 2.0 Hz)	3.37 (s)
3.10 (dd, *J*=<2, 11.8 Hz)	3.27 (d, *J*=11.9 Hz)
3.09 (dd, *J*=<2, 11.9 Hz)	3.23 (d, *J*=11.6 Hz)
2.94 (s)	3.13 (s)
2.91 (ddd, *J*=4.4, 7.8, 13.1 Hz)	3.10 (ddd, *J*=4.2, 7.9, 13.1 Hz)
2.83 (ddd, *J*=7.1, 9.3, 13.1 Hz)	3.05–2.98 (ddd, *J*=7.0, 9.4, 13.1 Hz)
2.76 (s)	2.95 (d, *J*=0.5 Hz)
2.33 (d, *J*=11.9 Hz)	2.51 (d, *J*=12.0 Hz)
2.29 (d, *J*=11.8 Hz)	2.44 (d, *J*=11.8 Hz)
1.94 (ddd, *J*=7.1, 7.8, 14.3 Hz)	2.09 (ddd, *J*=7.1, 7.4, 14.4 Hz)
1.80 (dddd, *J*=4.3, 4.4, 9.3, 14.3 Hz)	1.98 (dddd, *J*=4.3, 4.3, 9.4, 14.4 Hz)

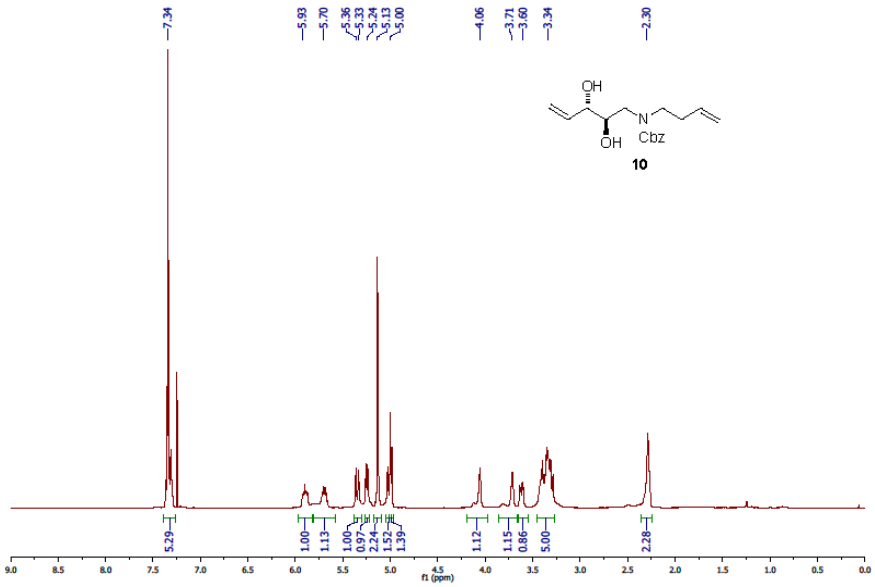
[a]Integrals are not given due to rotamers.

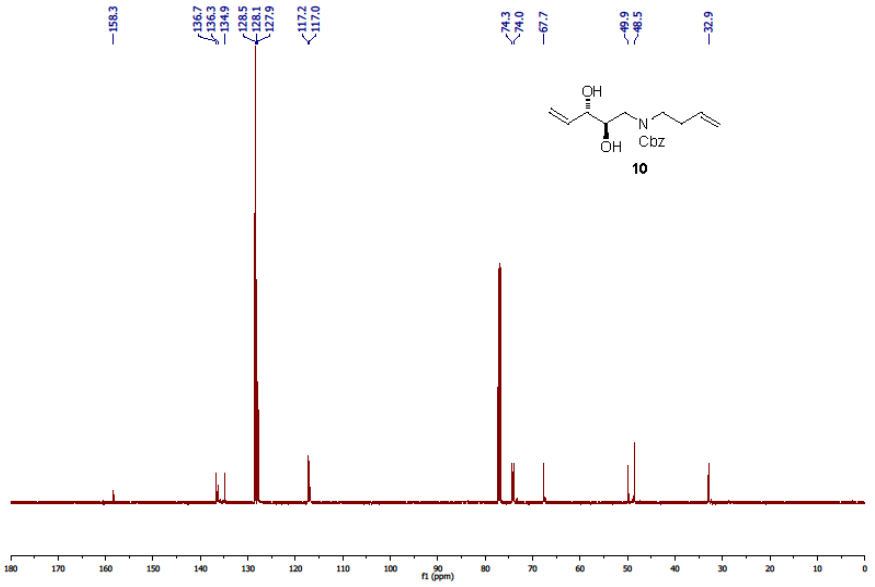
Note: Slight differences in the ^{1}H-NMR spectrum could be due to concentration effects(c.f. Ref. 4)[4].

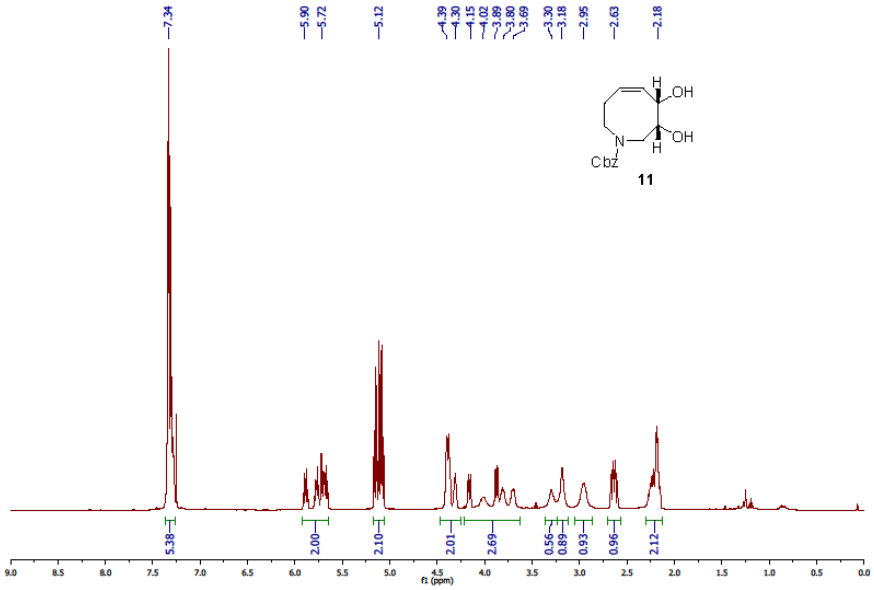
Supplementary Table S8. ^{13}C NMR data comparison between reported natural *N*-formylloline (**4**) and synthetic *N*-formylloline (**4**).

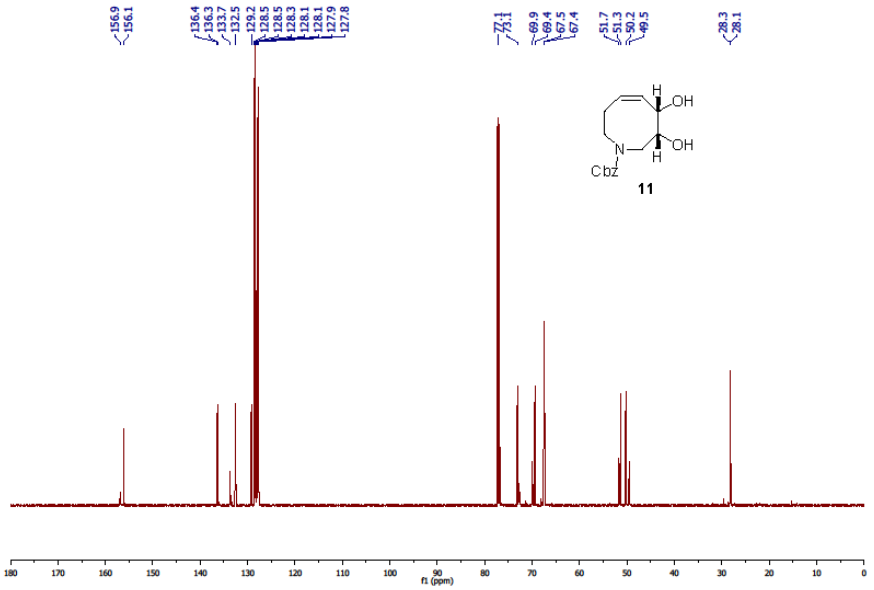
Literature report[3] (^{13}C, 75.5 MHz, $CDCl_3$)	This report (^{13}C, 100 MHz, $CDCl_3$)
163.5	163.5
162.1	162.3
81.8	82.0
80.0	80.3
73.9	74.0
73.0	73.1
67.8	67.9
67.4	67.5
65.3	65.4
62.4	62.4
60.8	61.0
60.4	60.5
54.4	54.8
54.4	54.6
33.4	33.4
32.8	33.1
32.6	32.8
29.8	29.9

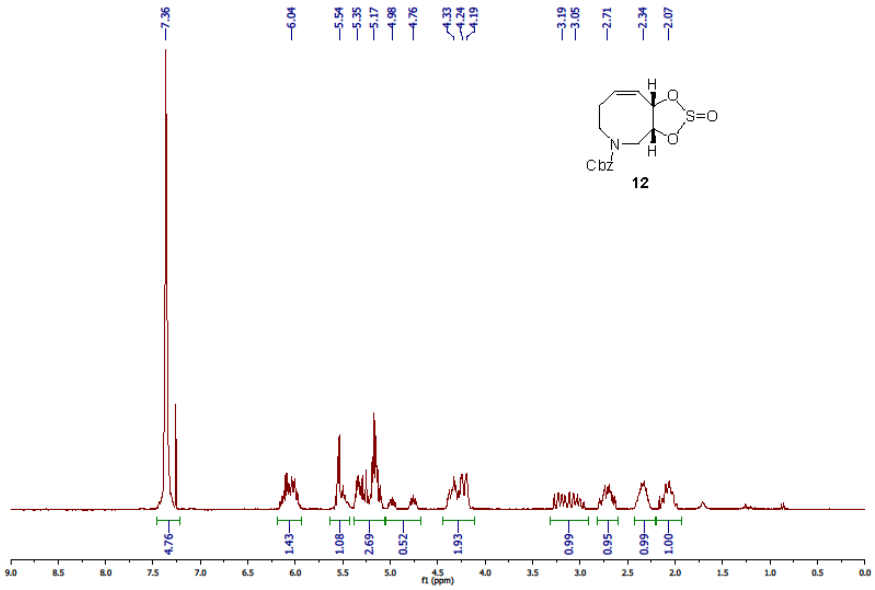
NMR spectra.

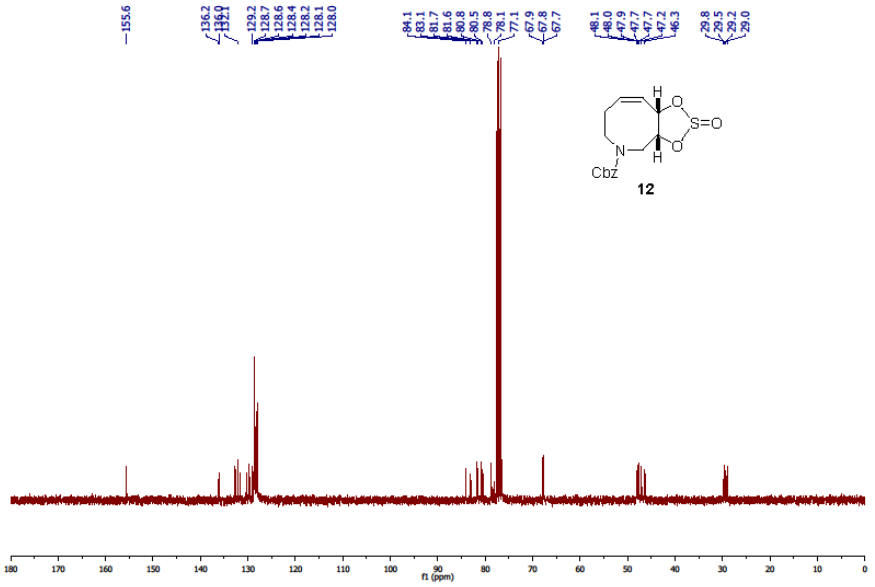


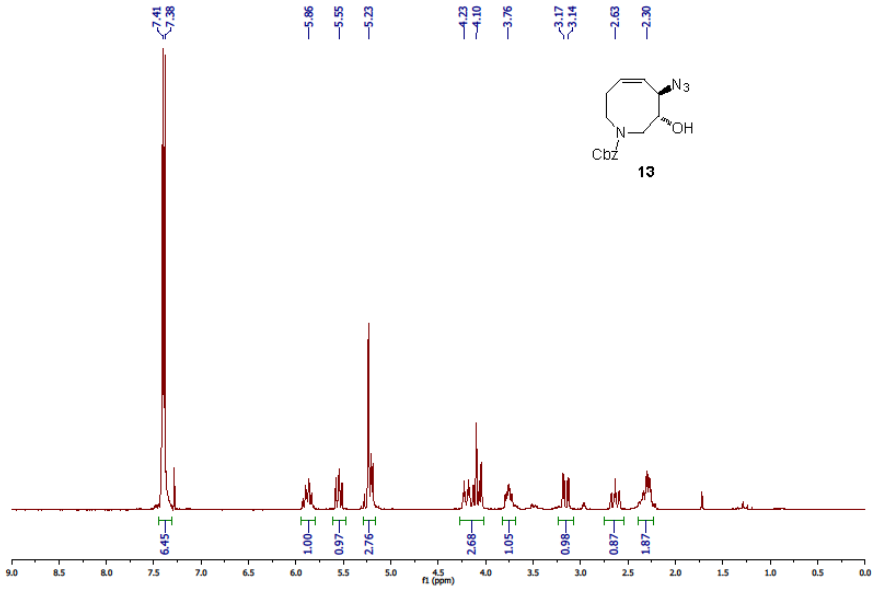


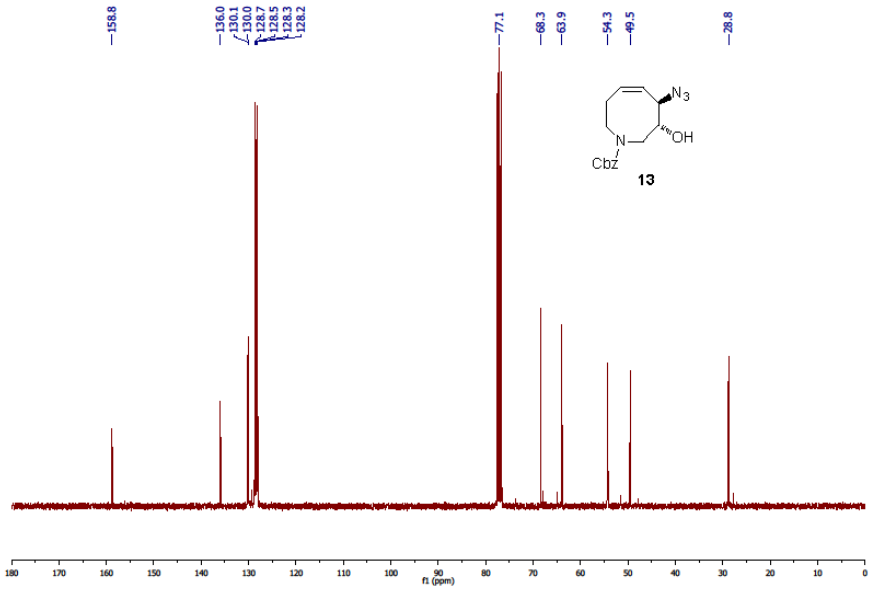


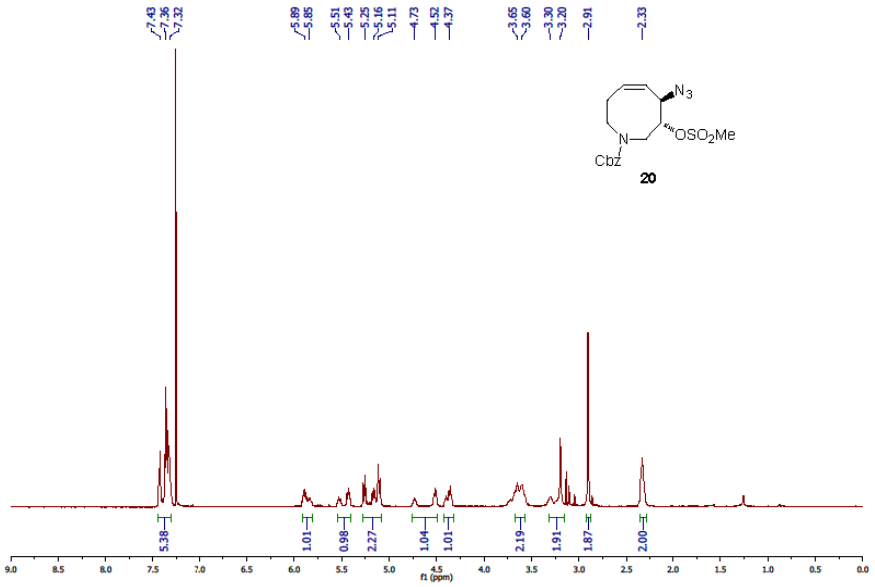


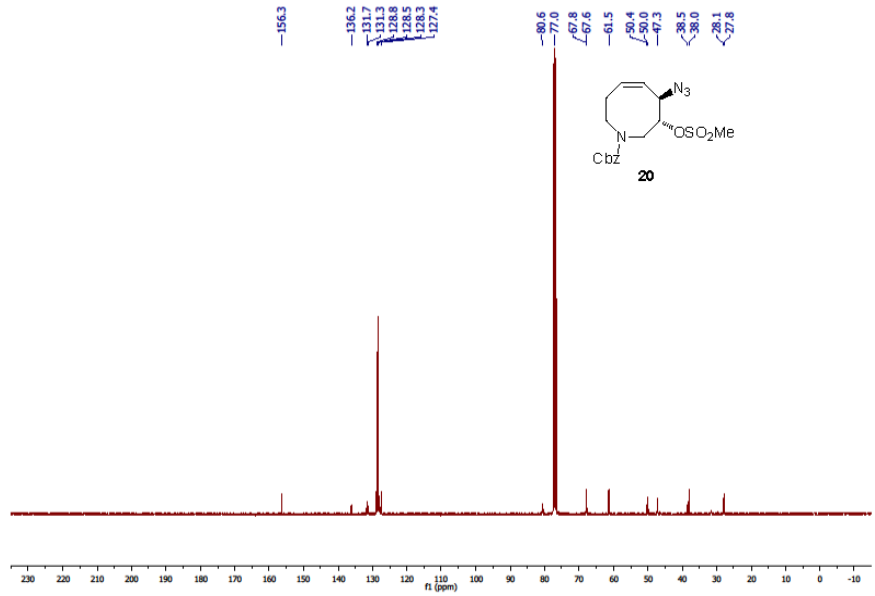


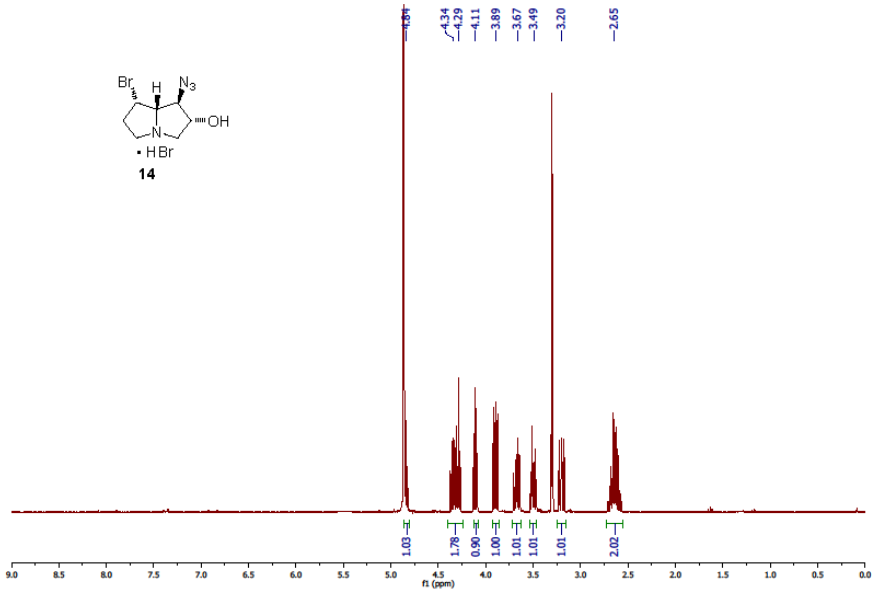


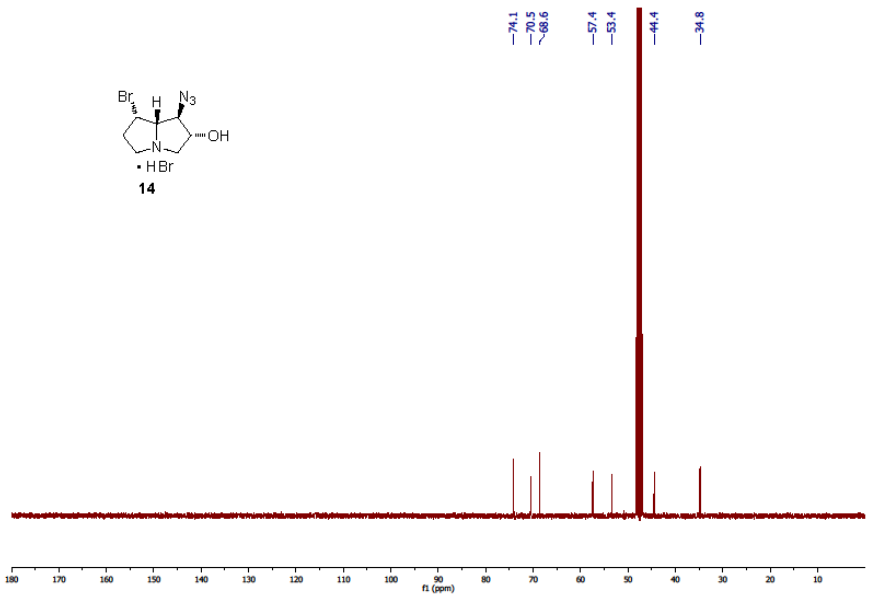


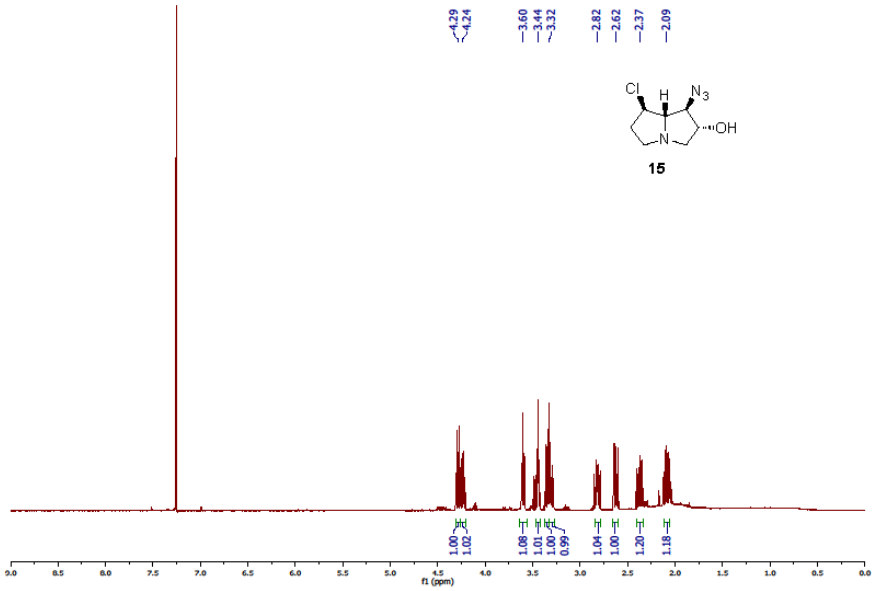


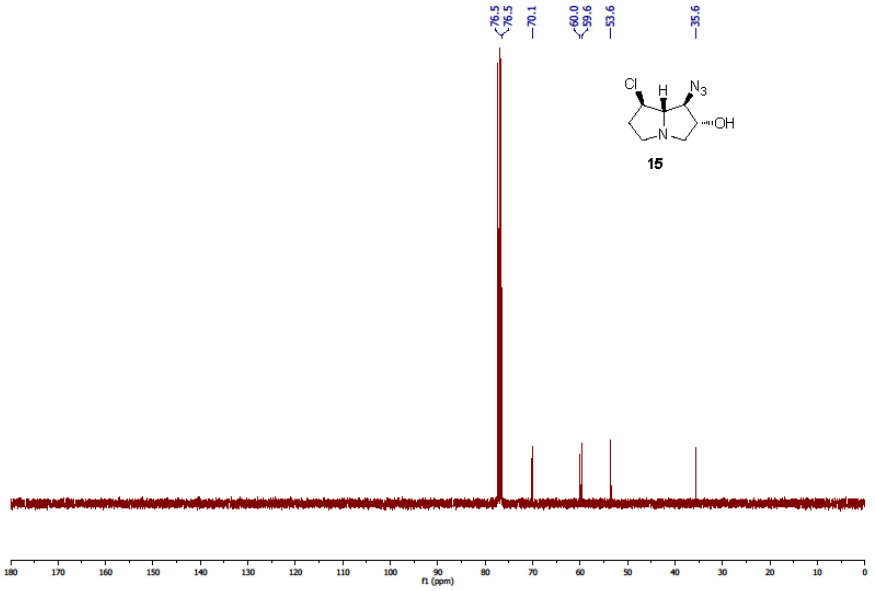


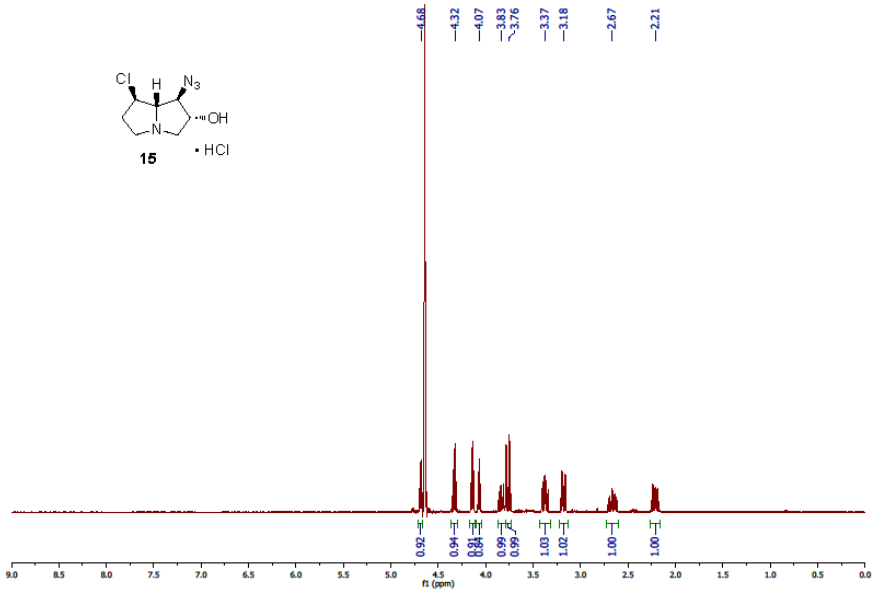


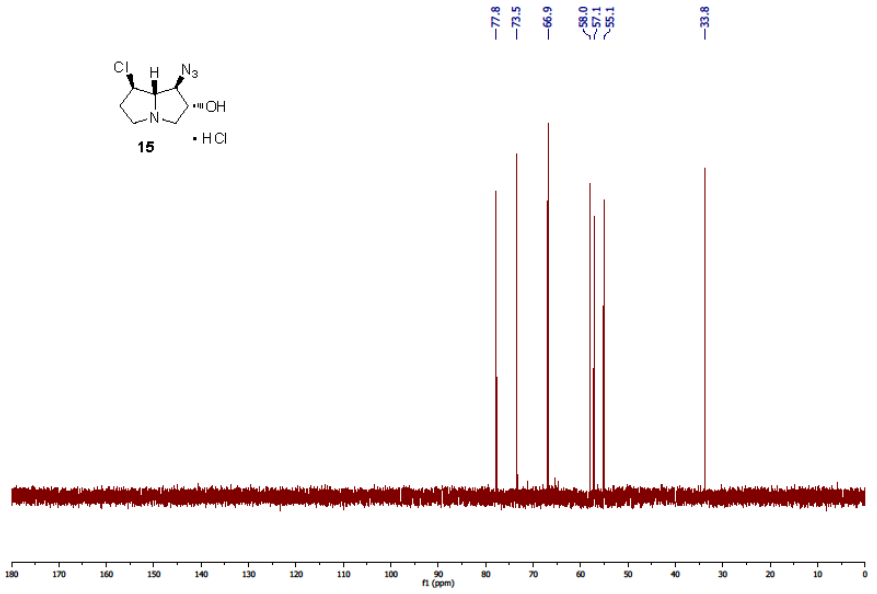


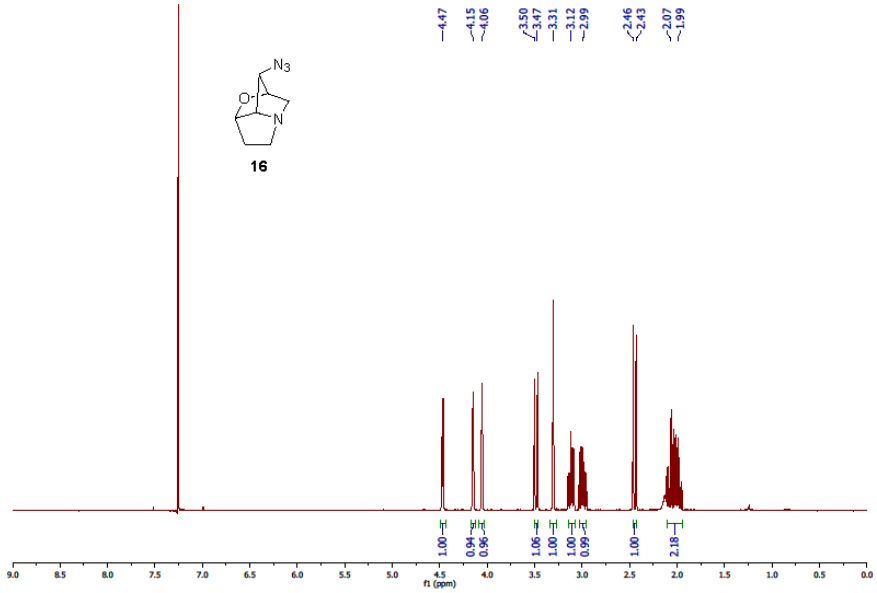


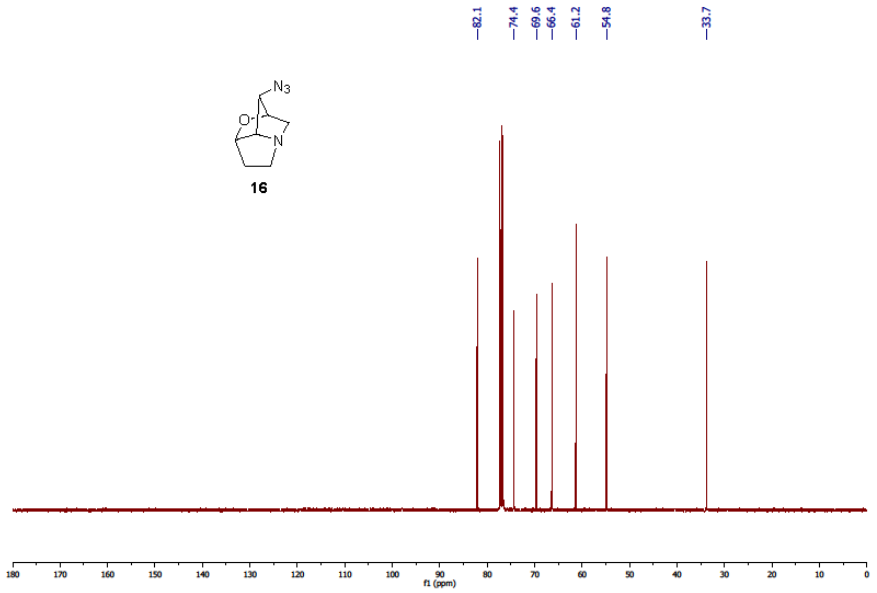


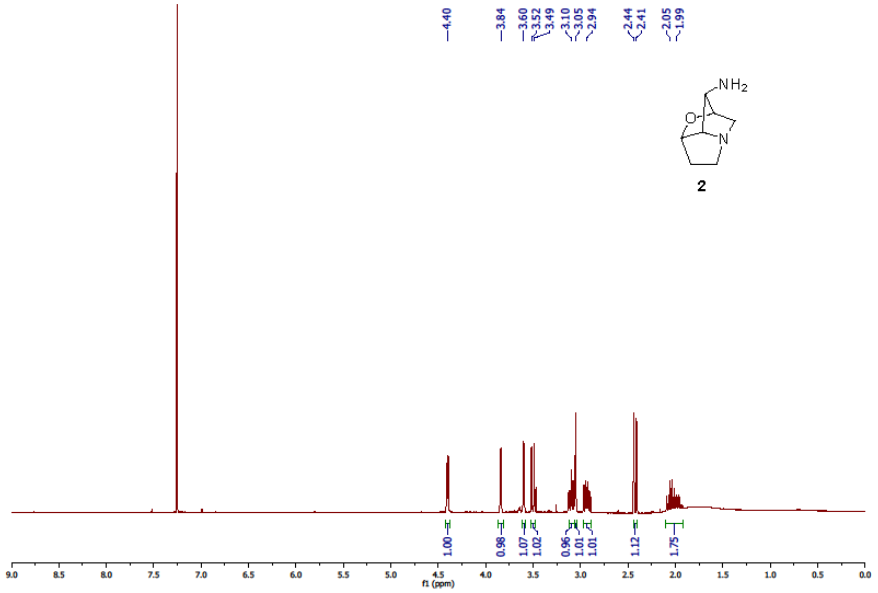


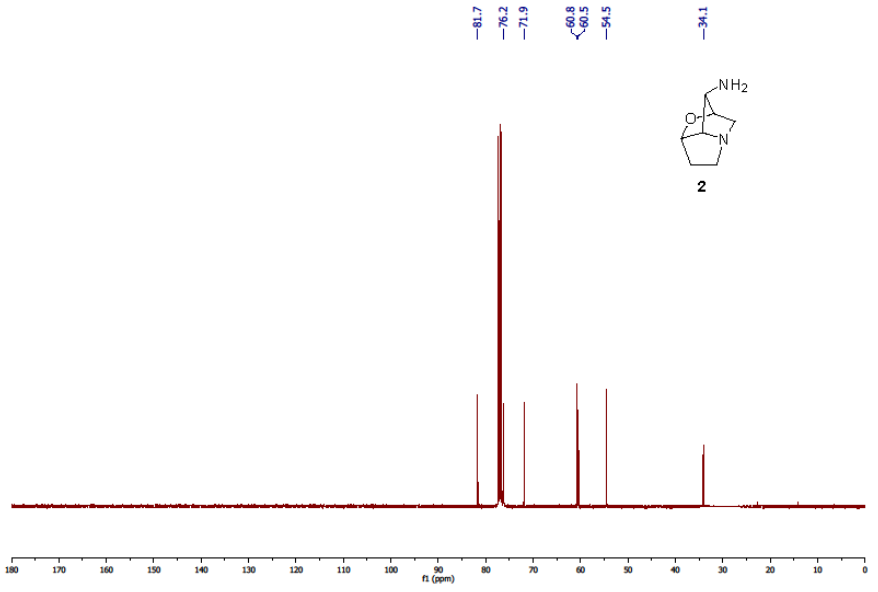


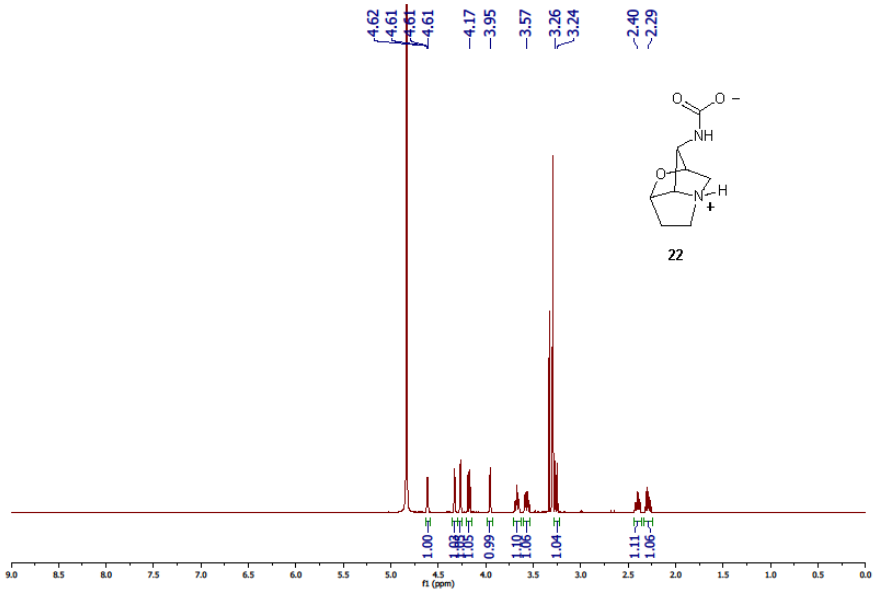




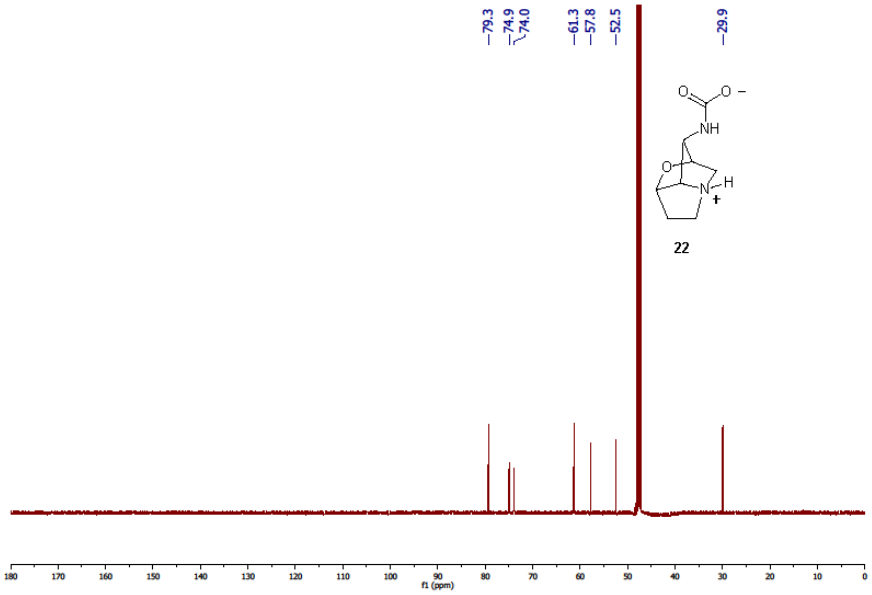




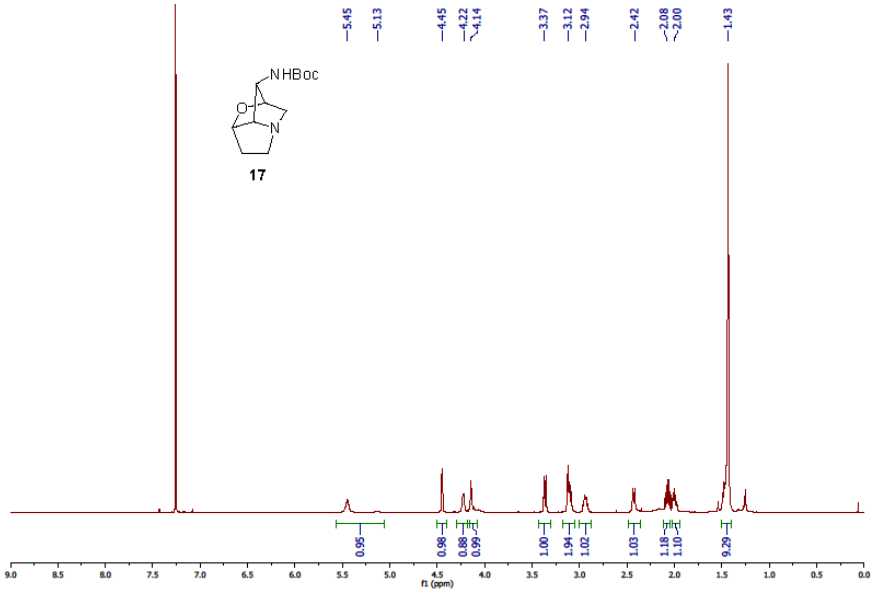


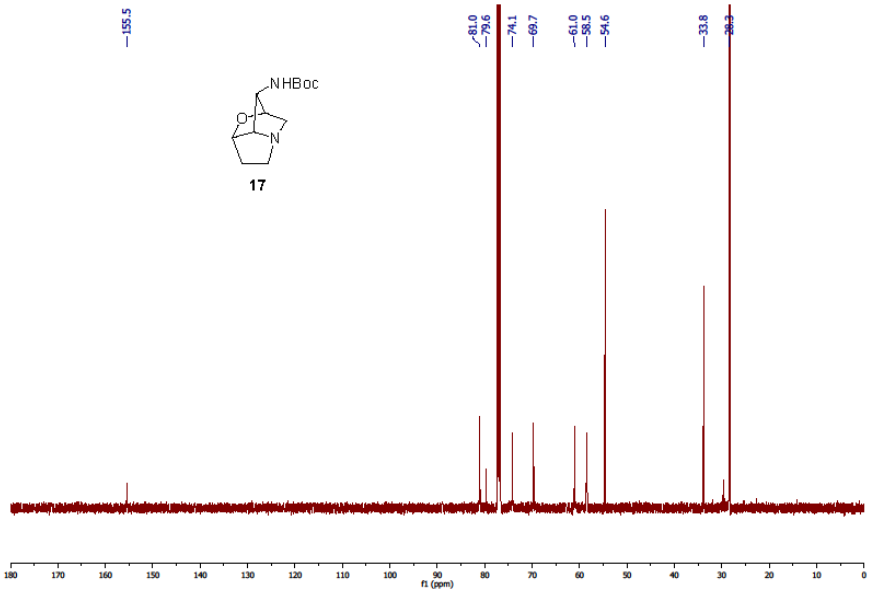


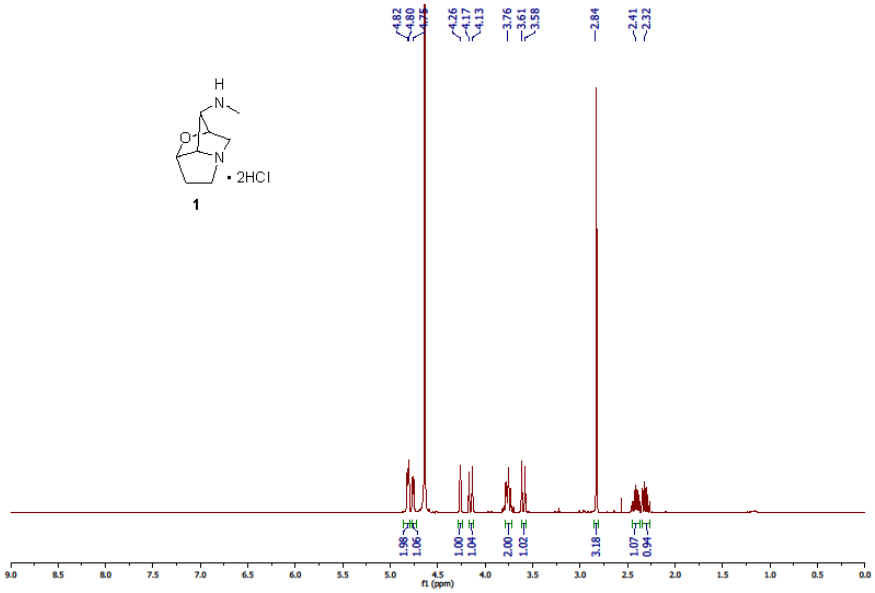
22

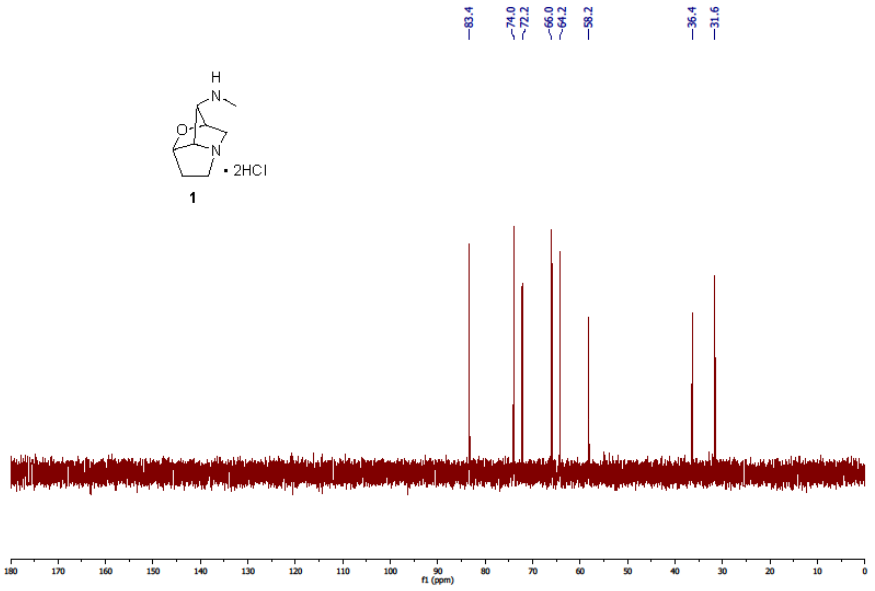


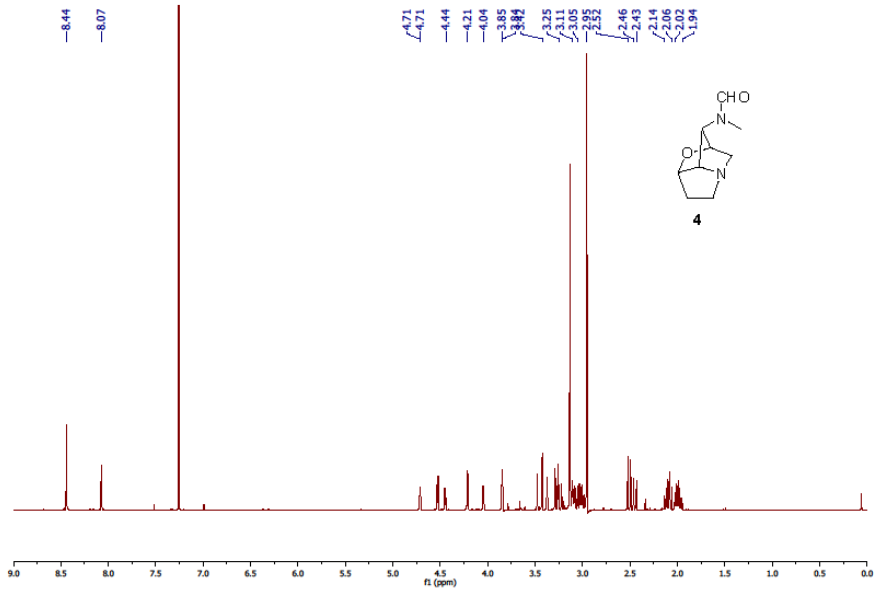
22

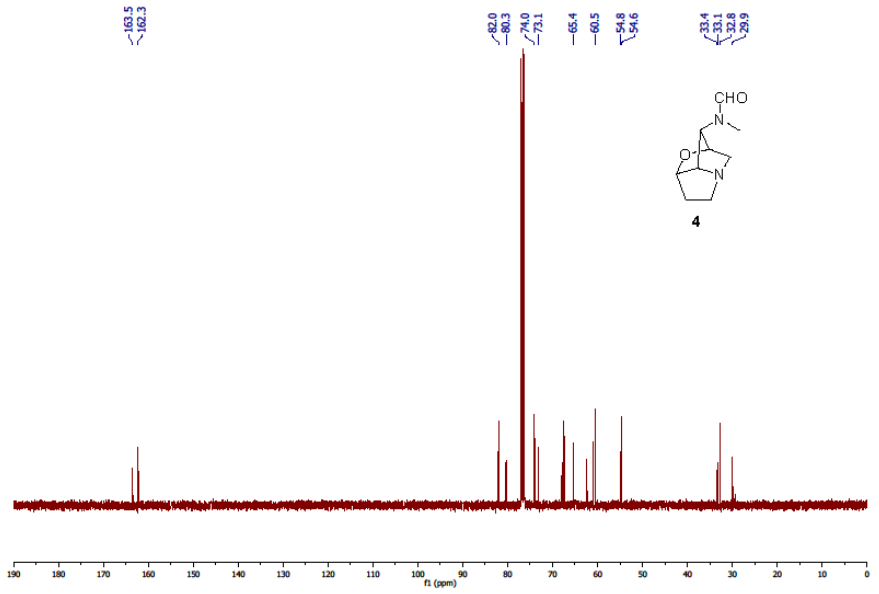






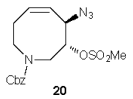




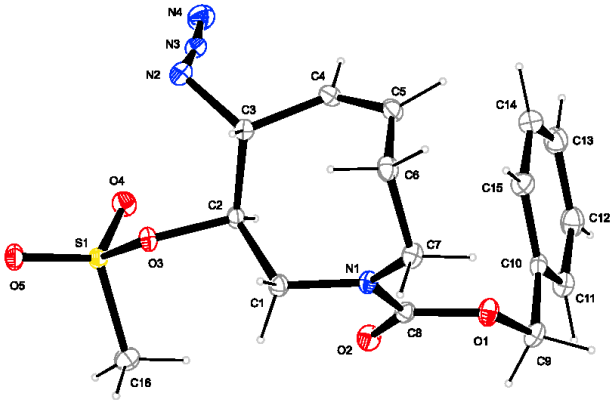


Crystal structures

a) Crystal structure of **20**

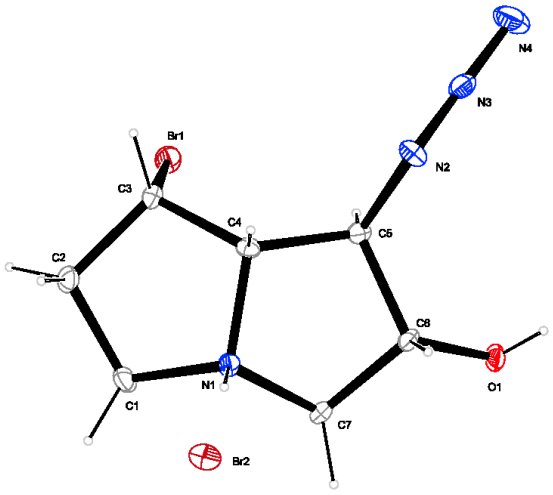


20

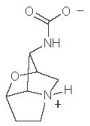


b) Crystal structure of **14**

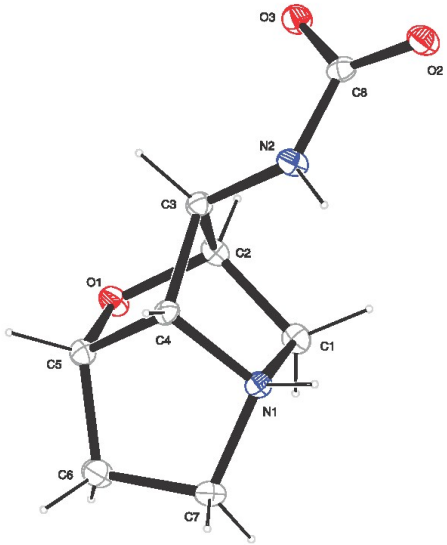
14



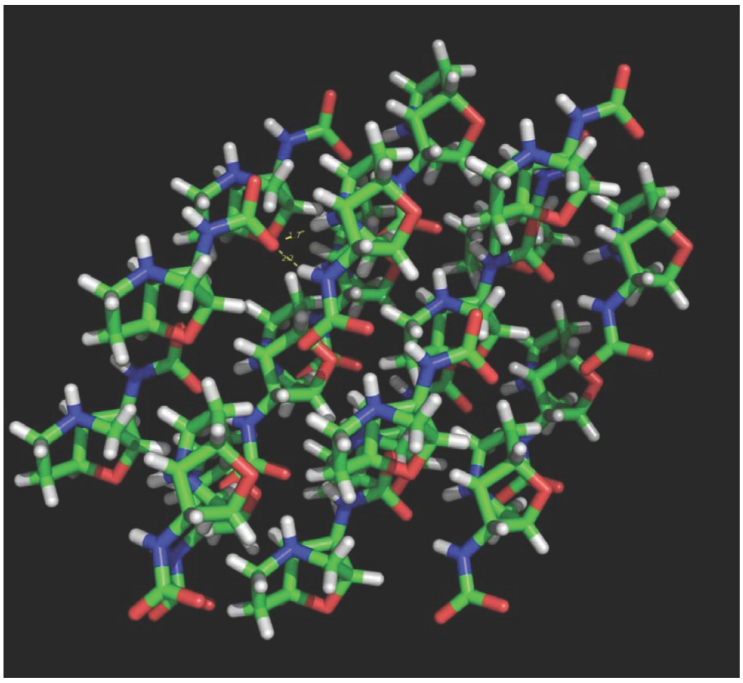
c) Crystal structure of **22**



22



d) Supramolecular structure of **22**



CCDC 801055, 801056 and 822472 (for compounds **20**, **14** and **22**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

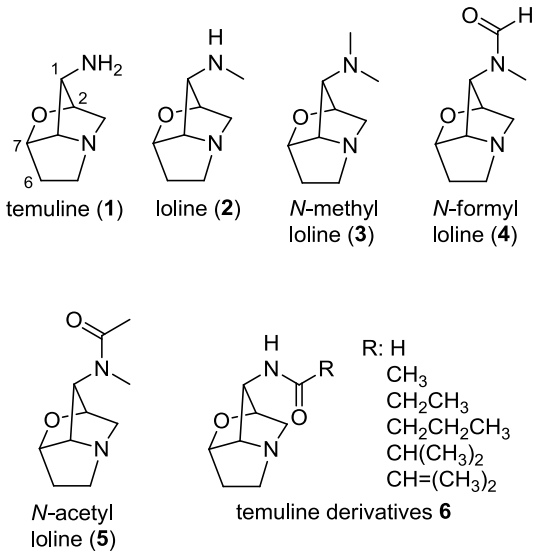
1. Still, W.C., Kahn, M. & Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **43**, 2923-2925 (1978).
2. Smith, D.B., Zhaoyin, W. & Schreiber, S.L. The asymmetric epoxidation of divinyl carbinols: theory and applications. *Tetrahedron* **46**, 4793-4808 (1990).
3. Petroski, R.J., Yates, S.G., Weisleder, D. & Powell, R.G. Isolation, Semi-Synthesis, and NMR Spectral Studies of Loline Alkaloids. *J. Nat. Prod.* **52**, 810-817 (1989).
4. Blakemore, P.R., Kim, S.-K., Schulze, V.K., White, J.D. & Yokochi, A.F.T. Asymmetric synthesis of (+)-loline, a pyrrolizidine alkaloid from rye grass and tall fescue. *J. Chem. Soc., Perkin Trans. 1*, 1831-1845 (2001).

2.2 Loline Alkaloids: Evolution of a Strategy

The first loline alkaloid, temuline (**1**) was isolated in 1892 from *Lolium temulentum*.[1] Six years later there was the report of a novel fungus from the same plant, currently known as *Neotyphodium occultans*.[2] It took almost a century to reveal that these fungal symbionts produce loline alkaloids. The plant profits from the antifeedant and insecticidal activities of loline alkaloids.[3] Furthermore, wounding of plants induces high levels of loline production which suggests communication between plant and fungi.[4]

Lolines are pyrrolizidine alkaloids bearing unique bridgehead ether connecting C2 and C7. Members of the loline alkaloids basically differ only in the substitution pattern of the amine in position 1 (loline nomenclature). The eponymous member is loline (**2**), of which methylated (**3**), formylated (**4**) and acetylated (**5**) family members exist. Besides these, there are six other temuline derivatives (**6**) with different alkyl chains.

Figure 1: Members of the Loline Alkaloid Family

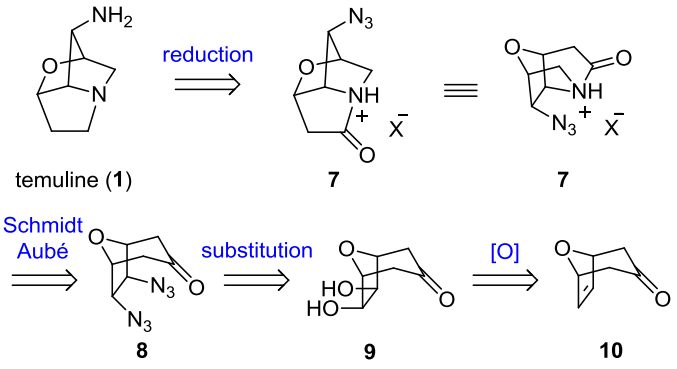


Although loline alkaloids have been known for more than a century, there has been no practical synthesis providing sufficient quantities to allow detailed studies of the biology and ecology of these natural products. This may not only be due to the strained ether linkage, but also to the density of polar heteroatoms. With the exception at C6, every other carbon is attached to a heteroatom, which makes the synthesis more challenging than it appears at first sight.

Indeed, loline (**2**) has been the target of several synthetic groups, including our own research group.[5] Glass and Wilson independently built up the loline skeleton but were not able to introduce the amine at C1 via nucleophilic substitution.[6,7] In 1986 Tufariello published a racemic synthesis of the alkaloid based on a nitrone-cycloaddition.[8] The first asymmetric synthesis of loline was reported 14 years later by White. His synthesis required 20 steps and incorporated an intramolecular hetero-Diels-Alder reaction and an aminohydroxylation to reach the target molecule.[9,10] In 2011 Scheerer overcame the regioselectivity issues of the aminohydroxylation used by White by using an efficient tethered aminohydroxylation (TA) and synthesized (±)-Acetlynorloline.[11]

The investigations of the fascinating ecological relationships between plants, fungi, insects and bacteria could greatly benefit from a reliable synthetic source of loline and its derivatives. This prompted us to revisit the loline alkaloids as synthetic targets and develop a new strategy for their synthesis. Initially, we hoped to synthesize temuline (**2**) by means of a Schmidt-Aubé rearrangement followed by reduction of the highly reactive amide **7** (Scheme 1). That these kinds of bridgehead amides can be formed was demonstrated by Stoltz in his synthesis of 2-quinuclidonium tetraflouroborate.[12] Precursor **8** could be traced back to diol **9**, which was envisioned to be formed from bicyclic ketone **10**, the same compound used by Wilson and Glass.

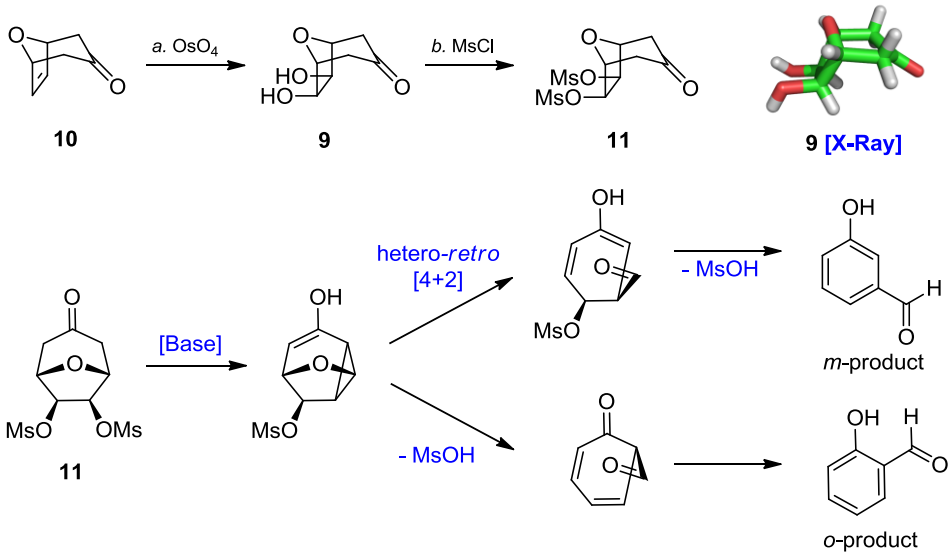
Scheme 1: First Retrosynthetic Analysis



Our synthesis commenced with literature known bicycle **10**, which can be prepaired in multigram quantities.[13-16] An Upjohn Dihydroxylation at 50 °C yielded diol **9**, the structure of which was proven unambiguously by X-ray crystallographic analysis. Exhaustive conditions have been tried to convert diol **9** to bisazide **8**, but none of them were successful. Reaction with two equivalents of MsCl gave bismesylate **11**.

This compound showed sensitivity towards all commercially available azides. Instead of the desired substitution an aromatization occurred to give hydroxybenzaldehydes. This aromatization is caused most likely by the basicity of the azide reagents, for instance sodium acetate, which has a similar pKa as sodium azide, also led to the formation of hydroxybenzaldehydes. Besides the reported formation of *m*-hydroxybenzaldehyde from 8-Oxabicyclocyclo[3.2.1]octan-3-one systems[17,18], we also observed *o*-hydroxybenzaldehyde formation, but always in favor of the *m*-product. In the first step a weak base is sufficient to generate the enolate which substitutes the mesylate to form a three membered ring. When forming a second enolate, the molecule can undergo a hetero-*retro*-Diels–Alder/elimination cascade resulting in *m*-hydroxybenzaldehyde. However, the *o*-hydroxybenzaldehyde arises from a direct elimination of the mesylate leaving group without undergoing a *retro*-[4+2]-reaction (Scheme 2). These rearrangements could not be avoided when forcing the system towards substitution.

Scheme 2: Preparation of Compound **11** and its Rearrangements[a]

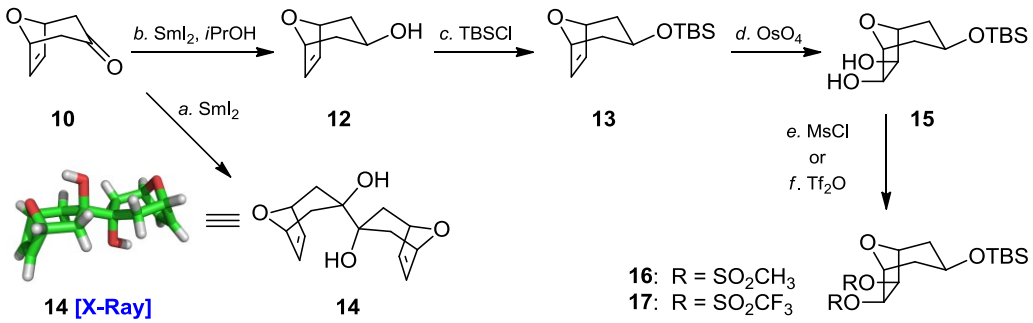


[a]Reagents and Conditions: (a) $K_2OsO_4 \cdot 2\ H_2O$ (0.02 eq.), NMO (2 eq.), acetone/H_2O, 50 °C, 2 h, 69%; (b) MsCl (2.4 eq.), NEt_3 (3.0 eq.), CH_2Cl_2, 0 °C, 2 h, 96%. NMO = *N*-methylmorpholine-*N*-oxide, MsCl = methanesulfonyl chloride, MsOH = methanesulfonic acid.

In order to reduce the sensitivity towards bases we decided to reduce the carbonyl group and protect it. The equatorial alcohol was preferred in order to avoid steric clash with the incoming nucleophile in the concave site. Thus, reduction of ketone **10** using SmI_2 and *i*PrOH gave the desired alcohol **12**[13], which was subsequently

protected as the TBS-ether **13**. A side product of the reduction was the formation of dimer **14**, a compound isolated in good yield when *i*PrOH was not added. The structure was confirmed by X-ray crystallographic analysis. Upjohn Dihydroxylation provided access to diol **15**, which was transformed into the corresponding mesylate **16** or triflate **17**, respectively. Compound **16** turned out to be surprisingly unreactive towards substitution while triflate **17** tended to decompose rather than react with azide anions.

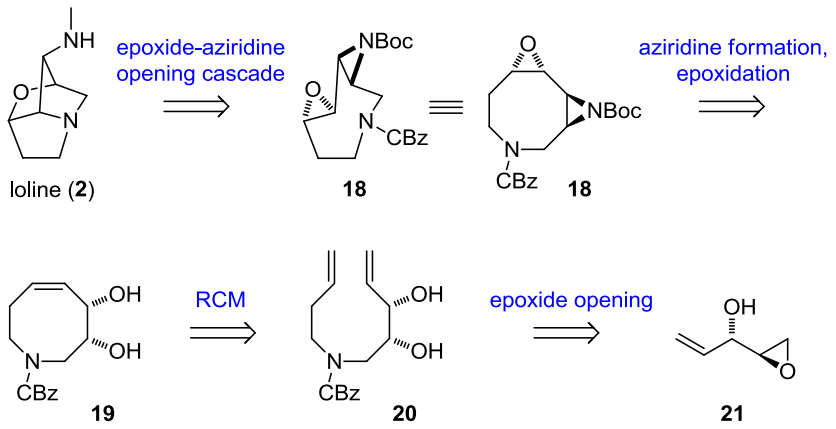
Scheme 3: Synthesis of Reduced Bicycles **16** and **17**[a]



[a]Reagents and Conditions: (a) Sm (2.5 eq.), I_2 (2.0 eq.), THF, 70 °C, 3 h, 72%; (b) Sm (2.5 eq.), I_2 (2.0 eq.), *i*PrOH (1.0 eq.), THF, 70 °C, 3 h; (c) TBSCl (1.2 eq.), im (2.5 eq.), CH_2Cl_2, rt, 12 h, 56% for two steps; (d) $K_2OsO_4 \cdot 2\ H_2O$ (0.02 eq.), NMO (2 eq.), acetone/H_2O, 50 °C, 2 h, 73%; (e) MsCl (2.4 eq.), NEt_3 (3.0 eq.), CH_2Cl_2, 0 °C, 2 h, 99%; (f) Tf_2O (2.2 eq.), py (6.0 eq.), CH_2Cl_2, -10 °C, 45 min. THF = tetrahydrofuran, TBSCl = *tert*-butyldimethylsilyl chloride, im = imidazol, Tf_2O = triflic anhydride, py = pyridine.

A new strategy was envisioned to assemble the heterotricylic core of loline (**2**), which is outlined in Scheme 4. This requires epoxy aziridine **18** for the key step. A critical feature of the plan is the final ether formation, which is a 5-*endo*-tet cyclisation. Although disfavored by the Baldwin rules[19], exceptions have been reported, especially in nitrogen containing systems.[20,21] Boc was chosen as a protecting group of the aziridine because it is directly convertible into a methyl group. Epoxy aziridine **18** can be traced back to cyclic diol **19** and the route to this molecule was projected employing metathesis of diene **20**. Literature known epoxide **21** is the starting point of the synthesis.

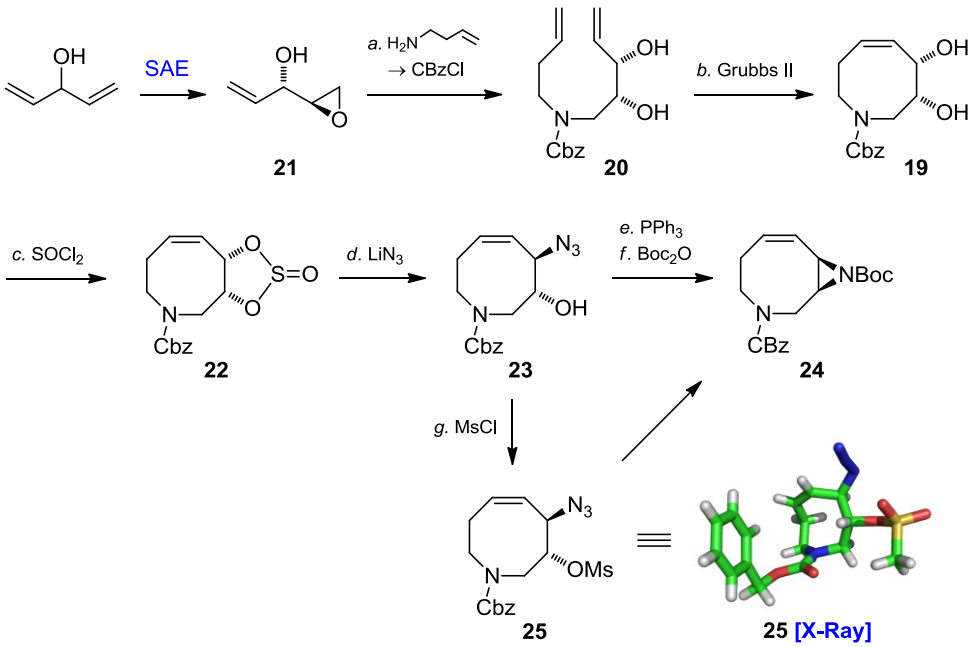
Scheme 4: Second Retrosynthetic Analysis[a]



[a] RCM = ring-closing-metathesis.

The synthesis commenced with the desymmetrisation of divinyl carbinol (Scheme 5). A highly enantioselective Sharpless epoxidation set the first two stereocenters through a racemic resolution.[22,23] Epoxide **21** was next opened with commercially available 4-butenylamine hydrochloride and the resulting secondary amine was subsequently protected as a benzyl carbamate in a one-pot procedure to yield diene **20**. This compound was treated with Grubbs II catalyst to form the 8-membered ring. Various attempts to convert the diol **19** into an aziridine failed. However, exposure of cyclic diol **19** to thionyl chloride afforded the cyclic sulfite **22** which could then be substituted with lithium azide. The reaction occurred selectively in allylic position to give azido alcohol **23** in good yield. Heating of azido alcohol **23** with triphenyl phosphine in toluene cleanly formed the aziridine, which was subsequently protected as *tert*-butoxy carbamate **24**. This compound could alternatively synthesized via azido-mesylate **25**, reduction of the azide followed by cyclisation and protection.

Scheme 5: Synthesis of Aziridine **24**[a]



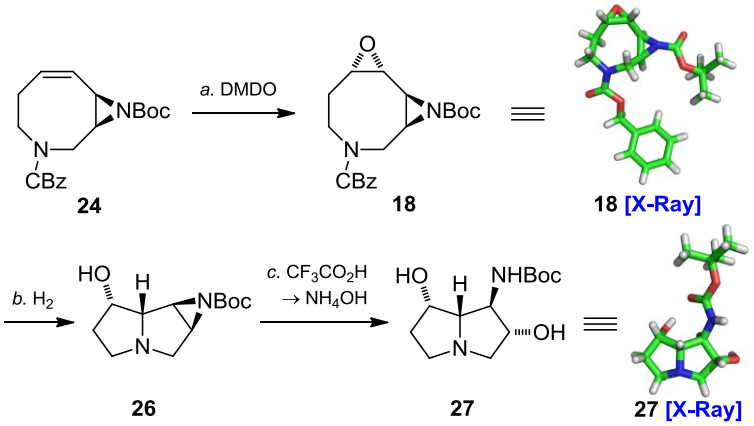
[a]Reagents and Conditions: (a) 4-butenylamine hydrochloride (1.5 eq.), DIPEA (3.3 eq.), MeOH, 45 °C, 12 h then Na_2CO_3 (3.0 eq.), CbzCl (2.4 eq.), H_2O/MeOH, rt, 3 h, 75%; (b) Grubbs 2nd Generation catalyst (0.05 eq.), CH_2Cl_2, 45 °C, 1 h; (c) $SOCl_2$ (3.0 eq.), NEt_3 (4.0 eq.), CH_2Cl_2, 0 °C, 1 h, 85% for two steps; (d) LiN_3 (3.0 eq.), DMF, 130°C, 2.5 h, 83%; (e) PPh_3 (1.2 eq.), tolunene, 130 °C, 12 h; (f) Boc_2O (3.0 eq.), DMAP (0.3 eq.), CH_2Cl_2, rt, 3 h, 98% for two steps; (g) MsCl (1.2 eq.), NEt_3 (2.4 eq.), CH_2Cl_2, 0 °C, 2 h, 85%. SAE = Sharpless asymmetric epoxidation, DIPEA = *N*,*N*-diisopropylethylamin, CBzCl = benzyl chloroformate, DMF = *N*,*N*-dimethylformamide, Boc_2O = di-*tert*-butyl dicarbonate, DMAP = 4-(dimethylamino)-pyridine.

The epoxidation of **24** using DMDO proceeded with excellent diastereoselectivity to afford epoxy aziridine **18** as the only observed isomer in quantitative yield (Scheme 6). The relative stereochemistry of **18** was confirmed by X-ray crystallographic analysis. Hydrogenolysis of **18** generated a secondary amine, which underwent transanular epoxide opening at 60 °C to afford pyrrolizidino-aziridine **26**. We have not been able to open this aziridine by way of a (formal) 5-*endo*-tet cyclization. Treatment of **26** under a variety of thermal, basic, Brønsted-acidic or Lewis-acidic conditions failed to give the loline skeleton but has sometimes yielded surprising results.

Exposure of **26** to three equivalents of trifluoroacetic acid, which presumably protonates both the pyrrolizidine and the pyramidalized aziridine nitrogen, only yielded aminopyrrolizidine diol **27** in excellent yield. This compound is presumably formed from the protonated aziridine by nucleophilic attack of the trifluoroacetic acid anion, rather than intramolecular opening by the hydroxyl group. The corresponding

trifluoro acetate is not stable and gets cleaved upon quenching with aqueous ammonia (Scheme 6). The use of acids with less nucleophilic corresponding anions, such as methanesulfonic acid or trifluoromethanesulfonic acid also resulted in the undesired intermolecular attack.

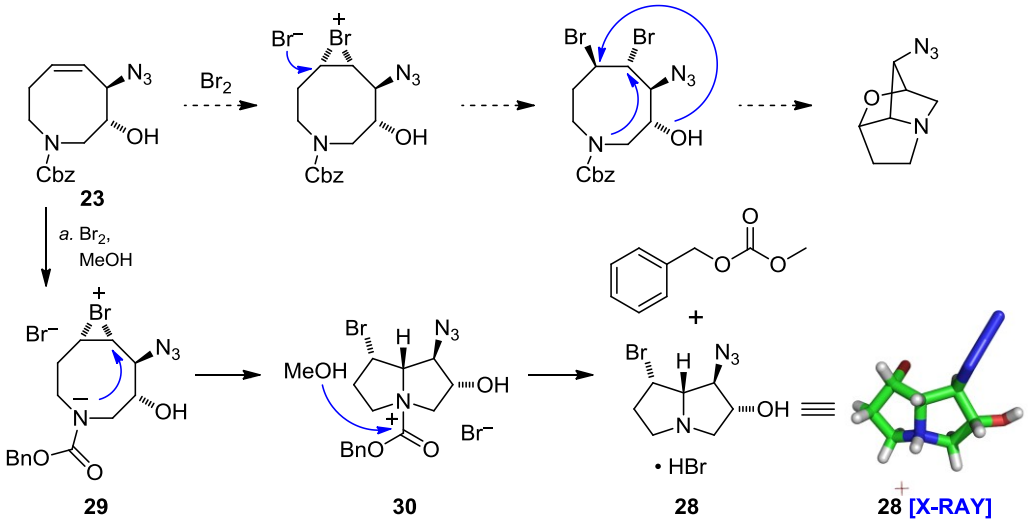
Scheme 6: Synthesis of Aziridine **26** and its Unexpected Behavior[a]



[a]Reagents and Conditions: (a) DMDO (2.5 eq.), CH_2Cl_2/acetone, -10 °C, 10 h, 99%; (b) H_2 atmosphere, Pd/C (0.10 eq.), EtOH, rt, 16 h then 60 °C, 72%; (c) CF_3CO_2H (3.0 eq.), $CHCl_3$, 0 °C → rt, 10 h then NH_4OH (excess), 99%. DMDO = dimethyldioxirane,

While **27** does not represent a "dead end", attempts to streamline it further to loline or find better conditions for the intramolecular aziridine ring opening were not pursued due to a more interesting outcome during the bromination of azido alcohol **23**. This compound has the correct stereochemistry in position 1 and 2. Due to steric hindrance we assumed a backside attack of bromide from the less hindered side.[24,25] Substitution of the two bromines with deprotected amine and alcohol would give the loline skeleton. To our surprise, treatment of **23** with bromine in methanol led to the formation of bromopyrrolizidine **28** in very good yield. This reaction is probably initiated by the formation of bromonium ion **29**. Instead of an attack from the bromide, the bromonium ion is trapped by the carbamate nitrogen, which resides in Van-der-Waals distance (ca. 3.1 Å) to C8 according to crystal structure **25**. An O-attack of the carbamate would lead to a strained cyclic carbonate and would therefore be unfavored. Transannular nucleophilic attack would initially yield acyl ammonium ion **30**, which would be subsequently cleaved by the solvent methanol. Our proposed mechanism is supported by the fact that benzyl methyl carbonate was identified as a byproduct in stoichiometric amounts.

Scheme 7: Bromination of Azidoalcohol **23**, expected reactivity and experimental outcome[a]

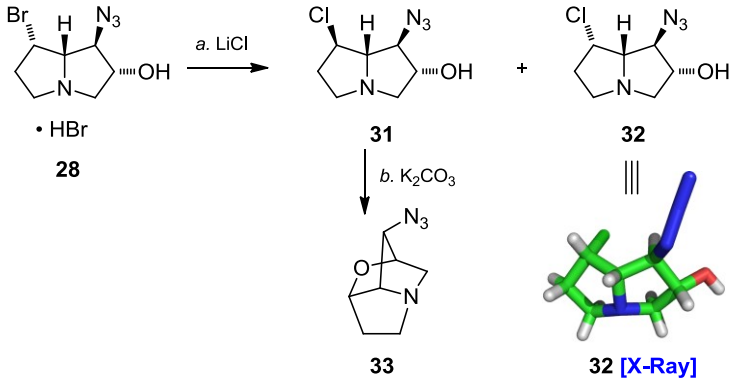


[a]Reagents and Conditions: (a) Br_2 (1.0 eq.), MeOH, 0 °C → rt, 10 h, 97%.

In order to form the quintessential ether bridge of the loline alkaloids bromopyrrolizidine **28** requires inversion at C7. Thus, bromide was substituted with chloride in a Finkelstein type reaction, using LiCl in DMF. This reaction yielded two chloropyrrolizidines **31** and **32** in a ratio of 19:1 in favor of the desired chloropyrrolizidine **31** in 86% yield. When using bromopyrrolizidine as a free base, the yield decreased to 24% with a ratio of 9:1. This interesting result raises questions about the mechanism of this substitution reaction, weather it partially occurs via S_N1. The structure of chloropyrrolizidine **32** was confirmed by X-Ray crystallographic analysis (Scheme 8).

With sufficient amounts of chloropyrrolizidine **31** in hand, the synthesis of various loline alkaloids was straightforward. Heating a solution of **31** in a microwave apparatus with potassium carbonate as a base led to formation of the ether bridge and gave azide **33** in very good yield. Under these conditions, no elimination products could be observed. In order to streamline our synthesis, the Finkelstein reaction and Williamson ether synthesis could be carried out as a one-pot procedure.

Scheme 8: Synthesis of Azide **32**.

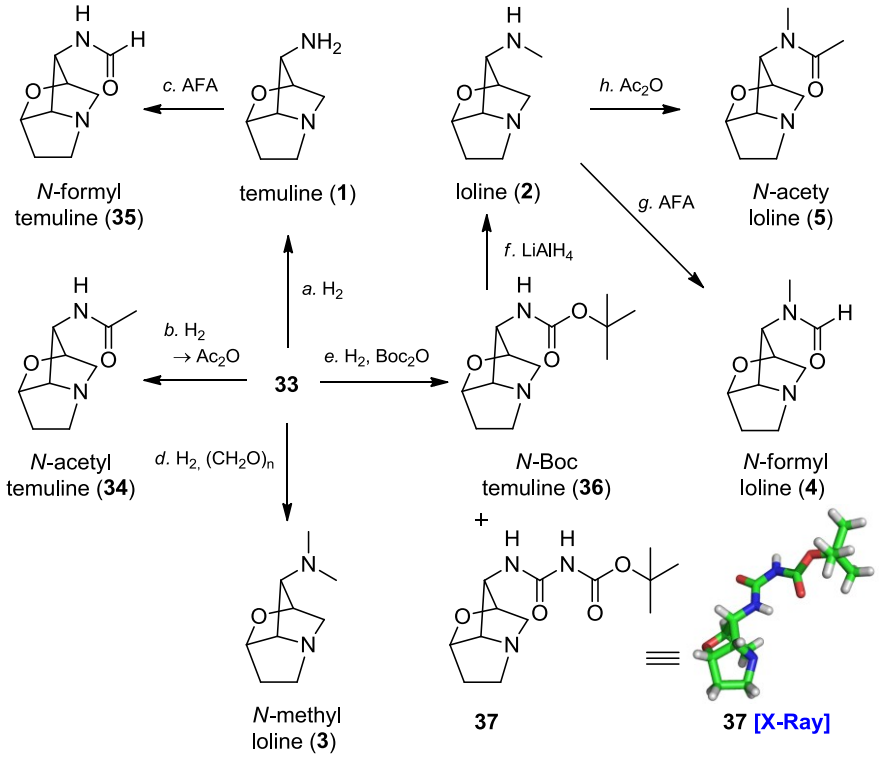


[a]Reagents and Conditions: (a) LiCl (20 eq.), DMF, 105 °C, 6 h then workup NaOH, 86%; (b) K_2CO_3 (2.5 eq.), MeOH, μ-wave, 150 °C, 300 W, 10 min, 90%.

The key azide **33** serves as a branching point for the total synthesis of various loline alkaloids (Scheme 9). Hydrogenation afforded temuline (norloline) (**2**), whereas hydrogenation followed by addition of acetic anhydride gave *N*-acetyl temuline (**34**). Formylation of temuline with acetic-formic anhydride yielded in *N*-formyl temuline (**35**). Hydrogenation in the presence of *para*-formaldehyde gave *N*-methyl loline (**3**). To make loline itself, azide **33** was hydrogenated in the presence of Boc_2O to yield *N*-Boc temuline (**36**) in very good yield. The Boc group was reduced with lithium aluminum hydride to the corresponding methyl group. Treatment of loline (**2**) with acetic-formic anhydride or acetic anhydride gave *N*-formyl loline (**4**) and *N*-acetyl loline (**5**), respectively.

Interestingly, *N*-Boc urea **37** was identified as an unexpected side product when azide **33** was hydrogenated in the presence of Boc_2O. Although these conditions are well represented in literature[26-28], to the best of our knowledge no Boc protected urea of this type has been reported as a side product. The structure was unambiguously confirmed by X-Ray crystallographic analysis (Scheme 9).

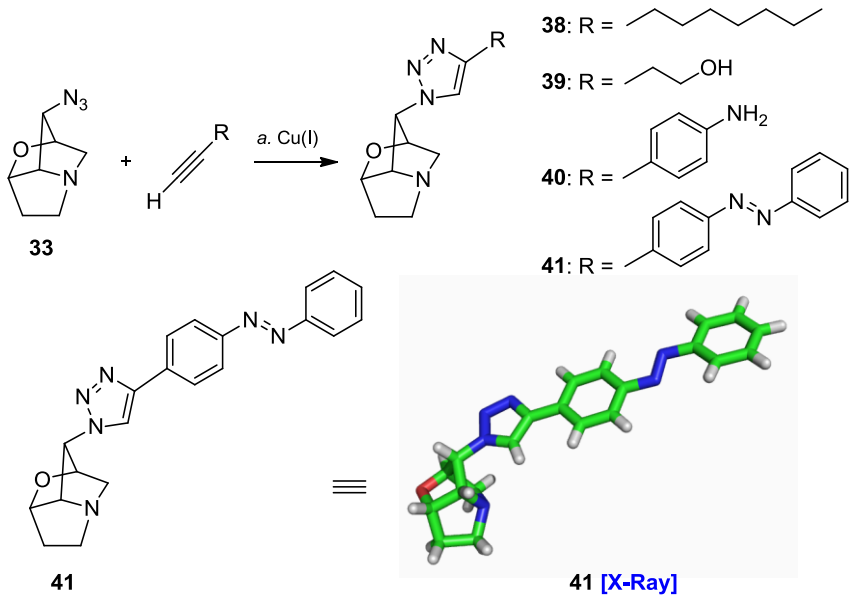
Scheme 9: Azide **33** as a Branching Point for the Synthesis of Several Loline Alkaloids[a]



[a]Reagents and Conditions: (a) H_2 atmosphere, Pd/C (0.06 eq.), MeOH, rt, 4 h, 90%; (b) H_2 atmosphere, Pd/C (0.05 eq.), THF, rt, 3 h then Ac_2O (1.2 eq.), rt, 16 h, 98%; (c) AFA, rt, 8 h, 99%; (d) H_2 atmosphere, Pd/C (3.7 eq.), $(CH_2O)_n$ (excess), MeOH, rt, 8 h, 99%; (e) H_2 atmosphere, Pd/C (0.05 eq.), Boc_2O (2.0 eq.), THF, rt, 48 h, 93% of **36**, 5% of **37**; (f) $LiAlH_4$ (6.0 eq), THF, 70 °C, 8 h, 96%; (g) AFA, rt, 8 h, 81%. AFA = acetic formic anhydride.

It soon came to our attention that azide **33** is a substrate which could be easily derivatized with click chemistry. This is a powerful reaction to build up libraries under very mild conditions.[29] The azide at C1 is fairly hindered and requires higher temperatures for the cycloaddition. While this type of cycloaddition usually proceeds at room temperature, in our case elevated temperature was needed to make the reaction occur. In an example of the rapid diversification that is possible with this approach four alkynes were exposed to the optimized 1–3 dipolar cycloaddition condition with azide **33** yielding triazols **38**–**41**. The crystal structure of compound **41** is depicted in Scheme 10.

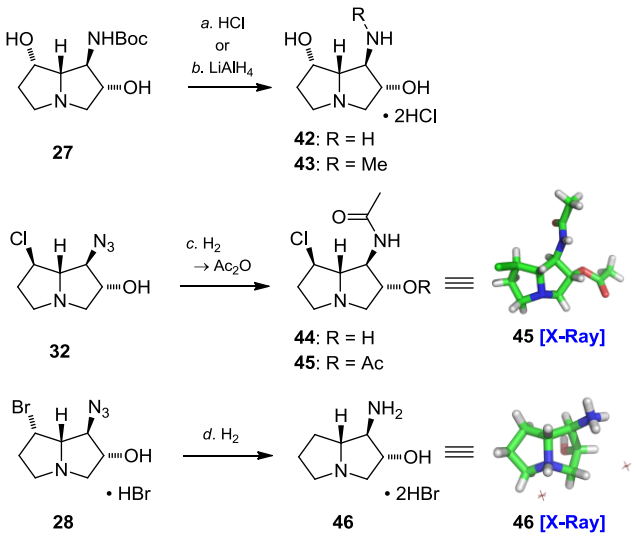
Scheme 10: Click Chemistry with Azide **33**



[a]Reagents and Conditions: (a) alkyne (0.9 eq.), $CuSO_4 \cdot 5H_2O$ (0.08 eq.), sodium ascorbate (0.11 eq.), $MeOH/H_2O$, 45 °C, 12 h, 82-98%.

Our collaborators were interested in pyrrolizidine derivatives, which could be potential metabolites of lolines consumed by insects. For this purpose, we aimed for derivatives that bear a hydroxyl, chlorine or hydrogen at C7 instead of the ether oxygen (Scheme 11). The *N*-Boc protecting group of substrate **27** can be cleaved or reduced to a methyl group to give diols **42** and **43**, respectively. Chloropyrrolizidine **32** already possesses a chlorine at C7 and simple reduction followed by acetylation gave amides **44** and **45**. Bromopyrrolizidine **28** can be fully reduced with PtO_2 to yield amino alcohol **46**. The crystal structures of pyrrolizidines **45** and **46** are depicted in Scheme 11.

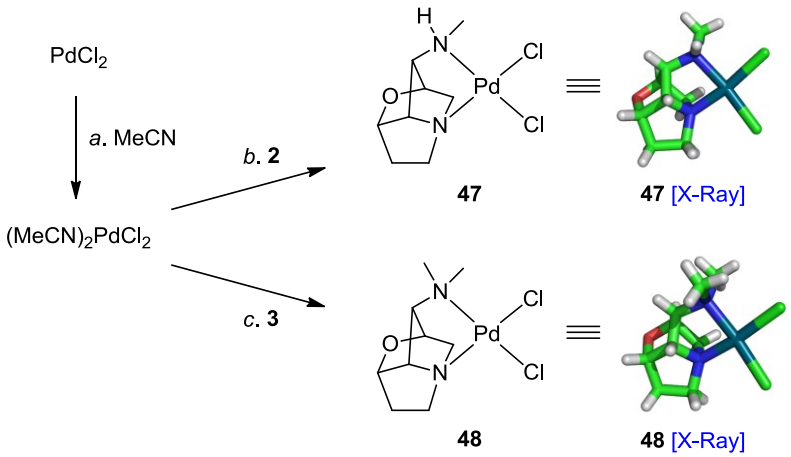
Scheme 11: Pyrrolizidine Derivatives made for Biological Investigations[a]



[a]Reagents and Conditions: (a) HCl (g), MeOH, rt, 10 min., 99%; (b) $LiAlH_4$ (6.0 eq.), THF, 70 °C, 8 h then HCl (g), 96%; (c) H_2 atmosphere, Pd/C (0.05 eq.), THF, rt, 3 h then Ac_2O (2.0 eq.), rt, 16 h, 78% of **45**, 15% of **46**; (d) H_2 atmosphere, PtO_2 (0.1 eq.), H_2O, rt, 30 min., 75%.

The ethylenediamine unit of the loline alkaloids could be a suitable ligand for transition metal complexes. Natural product complexes, such as the sparteine-palladium complex, have been synthesized and successfully used for organic reactions.[30] In a similar fashion, $PdCl_2$ was refluxed in acetonitrile and the resulting acetonitrile complex was treated with loline (**2**) or *N*-methyl loline (**3**) to give complexes **47** and **48**, respectively. The syntheses and the crystal structures of complexes **47** and **48** are depicted in Scheme 12.

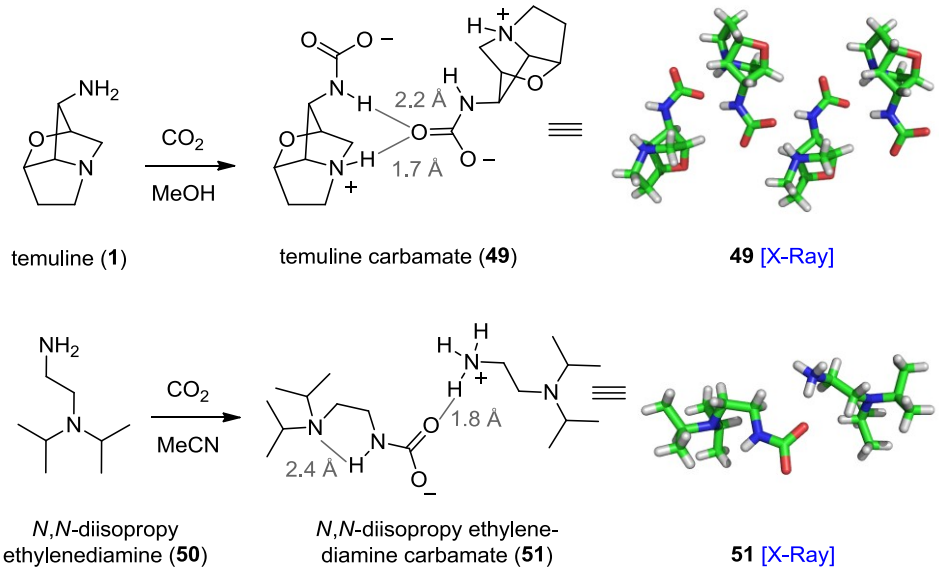
Scheme 12: Synthesis and X-Ray Structures of Pd Complexes **47** and **48**[a]



[a]Reagents and Conditions: (a) MeCN, 90 °C, 2 h; (b) **2** (1.0 eq.), MeCN, rt, 12 h, 79%; (c) **3** (1.0 eq.), MeCN, rt, 12 h, 85%;

An unusual chemical characteristic of temuline (**1**) is that it binds CO_2 when exposed to air and forms a crystalline solid.[8] Only a few examples of free carbamate crystal structures have been reported.[31,32] Thus, in order to understand this affinity, we exposed a methanolic solution of temuline (**1**) to CO_2, that upon slow evaporation yielded suitable crystals of temuline carbamate (**49**) for X-ray analysis (Scheme 13). The structure revealed no intramolecular hydrogen bonds but rather strong intermolecular hydrogen bonds were apparent, leading to form a zig-zag motive. This unexpected result sparked our interest in free carbamates, prompting us to investigate if this type of CO_2 binding is a general motive for ethylenediamines. Therefore, a diisopropylamine **50** solution in acetonitrile was saturated with CO_2 to give carbamate **51**, which shows different and weaker interactions than carbamate **49**. Instead of forming a zitterionic compound, the primary amine of a second molecule is protonated, leading to both intermolecular and intramolecular hydrogen bonds. Further efforts to crystallize and understand interactions of other ethylenediamine carbamates are continuing in our laboratories.

Scheme 13: Synthesis and X-Ray Structure of Free Carbamates **49** and **51**



In summary, we have shown an unprecedented rearrangement of 8-oxabicyclocyclo[3.2.1]octan-3-one systems. We have seen confirmation of the validity of the Baldwin rules, due to an unexpected aziridine opening. In the end, we have developed a highly efficient, asymmetric total synthesis of loline that proceeds in 10 steps from divinyl carbinol and successfully synthesized 7 different loline alkaloids. Our synthesis features a Sharpless epoxidation, a Grubbs olefin metathesis and incorporates an unusual transannular attack of a carbamate nitrogen to yield the pyrrolizidine skeleton. The only protecting group used is lost in the course of a strategic bond formation and does not require an additional cleavage step. Our synthesis is scalable, diversifiable and gives ample access to all loline alkaloids. These synthetic natural products and the derivatives have been used to explore the complex interactions between fungi, insects and bacteria in fescue grass. In addition click chemistry has been performed with azide **33** and the affinity of lolines to Pd and CO_2 has been investigated.

References

(1) Hofmeister, F. *Arch. Exp. Pathol. Pharmakol.* **1892**, *30*, 203–230.

(2) Guérin, P. *J. Botanique* **1898**, *12*, 230–238.

(3) Riedell, W. E.; Kieckhefer, R. E.; Petroski, R. J.; Powell, R. G. *J. Entomol. Sci.* **1991**, *26*, 122–129.

(4) Bultman, T. L.; Borowicz, K. L.; Schneble, R. M.; Coudron, T. A.; Bush, L. P. *Ecology* **1997**, *85*, 679–685.

(5) Cakmak, M.; Mayer, P.; Trauner, D. *Nat. Chem.* **2011**, *3*, 543–545.

(6) Glass, R. S.; Deardorff, D. R.; Gains, L. H. *Tetrahedron Lett.* **1978**, *19*, 2965–2968.

(7) Wilson, S. R.; Sawicki, R. A.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 3887–3891.

(8) Tufariello, J. J.; Meckler, H.; Winzenberg, K. *J. Org. Chem.* **1986**, *51*, 3556–3557.

(9) Blakemore, P. R.; Schulze, V. K.; White, J. D. *Chem. Commun.* **2000**, 1263–1264.

(10) Blakemore, P. R.; Kim, S.-K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1831–1845.

(11) Hovey, M. T.; Eklund, E. J.; Pike, R. D.; Mainkar, A. A.; Scheerer, J. R. *Org. Lett.* **2011**, *13*, 1246–1249.

(12) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731–734.

(13) Treu, J.; Hoffmann, H. M. R. *J. Org. Chem.* **1997**, *62*, 4650–4652.

(14) Noyori, R.; Hayakawa, Y. *Tetrahedron* **1985**, *41*, 5879–5886.

(15) Kim, H.; Hoffmann, H. Â MartinÂ R. *Eur. J. Org. Chem.* **2000**, *2000*, 2195–2201.

(16) Mann, J.; Barbosa, L.-C. d. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 787–790.

(17) Gaoni, Y. *Tetrahedron* **1972**, *28*, 5533–5541.

(18) Föhlisch, B.; Herrscher, O. *Tetrahedron* **1985**, *41*, 1979–1983.

(19) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.

(20) Blagoev, B.; Novkova, S. *Tetrahedron* **1982**, *38*, 1609–1613.

(21) Van Brabandt, W.; Dejaegher, Y.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1101–1104.

(22) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525−1529.

(23) Smith, D. B.; Zhaoyin, W.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793−4808.

(24) Wilson, S. R.; Sawicki, R. A. *Tetrahedron Lett.* **1978**, *19*, 2969−2972.

(25) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287−291.

(26) Nakajima, T.; Yamashita, D.; Suzuki, K.; Nakazaki, A.; Suzuki, T.; Kobayashi, S. *Org. Lett.*, *13*, 2980−2983.

(27) Pronin, S. V.; Kozmin, S. A. *J. Am. Chem. Soc.* **2010**, *132*, 14394−14396.

(28) Jiang, Z.-X.; Qin, Y.-Y.; Qing, F.-L. *J. Org. Chem.* **2003**, *68*, 7544−7547.

(29) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599.

(30) Nielsen, R. J.; Keith, J. M.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2004**, *126*, 7967-7974.

(31) Neda, I.; Kaukorat, T.; Fischer, AxelÂ K. *Eur. J. Org. Chem.* **2003**, 3784-3790.

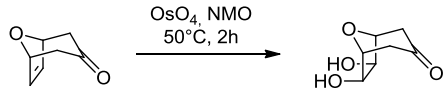
(32) Jo, E.; Jhon, Y. H.; Choi, S. B.; Shim, J.-G.; Kim, J.-H.; Lee, J. H.; Lee, I.-Y.; Jang, K.-R.; Kim, J. *Chem. Comm.* **2010**, *46*, 9158-9158.

2.2.1 Supplementary Information

General Experimental Details. Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Diisopropylethylamine (DIPEA) and Triethylamine (TEA) were distilled over calcium hydride immediately before use. Reactions were magnetically stirred and monitored by crude NMR or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F_{254} precoated glass plates. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. Flash column chromatography was performed as described by *Still et al.* employing silica gel (60 Å, 40-63 μm, Merck) and a forced flow of eluant at 1.3–1.5 bar pressure.[1] Yields refer to spectroscopically (^{1}H NMR and ^{13}C NMR) pure material.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ 7.26, MeOH: δ 3.31, H_2O: δ 4.79). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, *br* = broad, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.0, MeOH: δ 49.0). Infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System). FTIR Data is reported in frequency of absorption (cm^{-1}). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument. Microwave reactions were performed on a CEM machine (Model: Discovery System, No. 908010).

Synthetic procedures.



10 9

Bicyclodiol 9

100 mg (0.81 mmol, 1 eq.) alkene **10** was dissolved in 30 mL acetone/H_2O (1/1) and 6 mg (16 µmol, 0.02 eq.) $K_2OsO_4 \cdot 2H_2O$ was added at rt followed by addition of 189 mg (1.62 mmol, 2 eq.) NMO. The mixture was stirred at 50 °C for 2 h, quenched with 450 mg (2.85 mmol, 3.5 eq.) solid $Na_2S_2O_3$, filtered and concentrated *in vacuo* to afford 110 mg of a brown oil. The crude product was purified by flash column chromatography (EtOAc) to yield 88.0 mg (0.56 mmol, 69%) of the desired product **9** as colorless crystals (one spot on TLC).

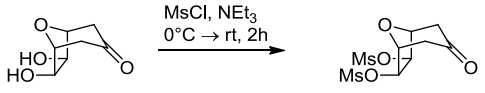
TLC (EtOAc), R_f = 0.30 ($KMnO_4$).

^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.42–4.40 (m, 2H), 4.01 (s, 2H), 2.69 (dd, *J*=6.1, 16.7 Hz, 2H), 2.36–2.31 (m, 2H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ= 207.8, 83.7, 75.9, 47.3.

IR (Diamond-ATR, neat) ν_{max}: 3320, 2907, 1707, 1419, 1341, 1295, 1194, 1101, 1032, 968, 840, 799, 679 cm^{-1}.

HRMS (ESI) calcd for $C_7H_{10}O_4$ $[M]^+$: 158.0579; found: 158.0561.



9 11

Bismesylate 11

158 mg (1.0 mmol, 1 eq.) diol **9** was dissolved in CH_2Cl_2 (30 mL) and 418 µL (3.0 mmol, 3 eq.) NEt_3 was added. The reaction mixture was cooled to 0 °C and 186 µL (2.4 mmol, 2.4 eq.) MsCl was added dropwise. The reaction mixture was stirred for 2 h at 0 °C and 1 h at rt. The reaction mixture was diluted with EtOAc (50 mL) and 1N HCl (30 mL). The water layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 240 mg of a yellow solid. The crude product was purified by flash column chromatography (EtOAc/hexane = 1/1) to yield 301 mg (0.96 mmol, 96%) of the desired product **11** as a colorless solid (one spot on TLC).

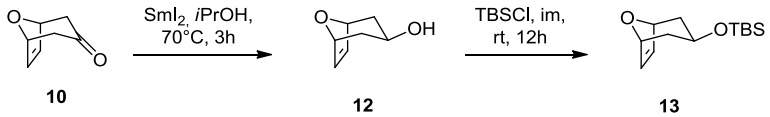
TLC (EtOAc), R_f = 0.53 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 5.00 (s, 2H), 4.87–4.86 (m, 2H), 3.14 (s, 6H), 2.80 (dd, *J*=6.3, 17.1 Hz, 2H), 2.56–2.53 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 202.3, 80.3, 79.7, 45.8, 38.6.

IR (Diamond-ATR, neat) ν_{max}: 3026, 2940, 1724, 1338, 1169, 984, 866, 841, 811, 757 cm^{-1}.

HRMS (ESI) calcd for $C_9H_{14}O_4S_2$ $[M+Na]^+$: 337.0028; found: 337.0024.



Alcohol 12

182 mg (1.21 mmol, 2.5 eq.) Samarium was suspended in THF (12 mL), 245 mg (0.967 mmol, 2 eq.) I_2 was added and the mixture was stirred for 2h at rt in the dark (deep blue solution). After heating to reflux, 60 mg (0.483 mmol, 1 eq.) ketone **10** and 37 μL (0.483 mmol, 1 eq.) *i*PrOH in THF (3 mL) were added dropwise. The reaction mixture was refluxed for 3h, then cooled to rt, quenched by addition of ice, 1N HCl (7 mL) and sat. aq. $Na_2S_2O_3$ (8 mL). The reaction mixture was diluted with EtOAc (30 mL), layers were separated and the water layer was extracted with EtOAc (3 × 25 mL). Combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 35 mg of crude alcohol **12**.

TLC (EtOAc), R_f = 0.12 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 6.09 (s, 2H), 4.79–4.77 (m, 2H), 3.93–3.77 (m, 1H), 2.08 (brs, 1H), 1.96–1.86 (m, 2H), 1.65–1.52 (m, 2H).

TBS-ether 13

35 mg (0.277 mmol, 1 eq.) crude alcohol **12** and 47 mg (0.694 mmol, 2.5 eq.) imidazol was dissolved in CH_2Cl_2 (2 mL). 50 mg (0.333 mmol, 1.2 eq.) TBSCl was added and the reaction mixture was stirred at rt for 12h. The reaction mixture was diluted with CH_2Cl_2 (15 mL), filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc/hexane = 1/1) to afford a 65 mg (0.271 mmol, 56% over two steps) of the protected alcohol **13** as a colorless oil.

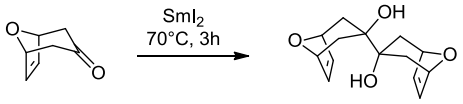
TLC (EtOAc), R_f = 0.86 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 6.10 (d, *J*=0.8 Hz, 2H), 4.76–4.74 (m, 2H), 3.88 (tt, *J*=6.5, 9.3 Hz 1H), 1.80–1.62 (m, 4H), 0.85 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ= 130.9, 78.1, 64.6, 35.8, 25.8, 18.0, -4.6.

IR (Diamond-ATR, neat) ν_{max}: 2949, 2854, 1471, 1251, 1110, 1086, 1045, 961, 871, 835, 774, 702, 668 cm^{-1}.

HRMS (EI) calcd for $C_{12}H_{21}O_2Si$ [M-CH_3]: 225.1311; found: 225.1302.



10 **14**

Dimer 14

137 mg (0.915 mmol, 2.5 eq.) Samarium was suspended in THF (10 mL), 186 mg (0.732 mmol, 2 eq.) I_2 was added and stirred for 2h at rt in the dark (deep blue solution). After heating to 70 °C, 45 mg (0.366 mmol, 1 eq.) ketone **10** in THF (3 mL) was added dropwise. The reaction mixture turned green after 3h. After cooling to rt, the reaction mixture was quenched by addition of ice, 1N HCl (5 mL) and sat. aq. $Na_2S_2O_3$ (6 mL). The reaction mixture was diluted with EtOAc (20 mL), layers were separated and the water layer was extracted with EtOAc (3 × 20 mL). Combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 75 mg of a yellow solid. The crude product was purified by flash column chromatography (EtOAc) to yield 33 mg (0.132 mmol, 72%) of dimer **14** as a colorless solid (one spot on TLC).

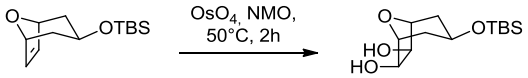
TLC (EtOAc), R_f = 0.16 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 6.40 (s, 2H), 6.26 (m, 2H), 4.85 (d, *J*=8.6 Hz, 2H), 4.50 (d, *J*=4.5 Hz, 2H), 2.31 (d, *J*=11.9 Hz, 2H), 1.91 (dd, *J*=9.0, 14.3 Hz, 2H), 1.73 (d, *J*=13.4 Hz, 2H), 1.36 (d, *J*=14.3 Hz, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 135.2, 134.5, 78.4, 77.3, 76.1, 74.0, 34.3, 32.0.

IR (Diamond-ATR, neat) ν_{max}: 3496, 2949, 2924, 1345, 1276, 1216, 1058, 1048, 1021, 954, 859, 825, 752, 706 cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{17}O_4$ $[M-H]^-$: 249.1127; found: 249.1138.



13 15

Diol 15

65 mg (0.271 mmol, 1 eq.) alkene **13** was dissolved in 20 mL acetone/H_2O (1/1) and 2 mg (6 µmol, 0.02 eq.) $K_2OsO_4 \cdot 2H_2O$ was added at rt followed by addition of 65 mg (0.554 mmol, 2 eq.) NMO. The mixture was stirred at 50 °C for 2 h, quenched with 150 mg (0.970 mmol, 3.5 eq.) solid $Na_2S_2O_3$, filtered and concentrated *in vacuo* to afford 94 mg of a brown oil. The crude product was purified by flash column chromatography (EtOAc) to yield 54 mg (0.197 mmol, 73%) of the desired product **15** as colorless oil (one spot on TLC).

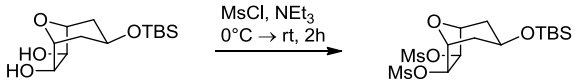
TLC (EtOAc), R_f = 0.26 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 4.20 (brs, 2H), 4.09 (s, 2H), 3.58–3.52 (m, 1H), 1.87–1.83 (m, 2H), 1.66–1.61 (m, 2H), 0.85 (s, 9H), 0.02 (s, 6H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 82.6, 74.6, 63.6, 38.7, 25.7, 18.0, -4.6.

IR (Diamond-ATR, neat) ν_{max}: 3296, 2950, 2926, 2855, 1469, 1256, 1242, 1101, 1081, 1027, 1033, 997, 986, 869, 834, 776, 668, 619 cm^{-1}.

HRMS (ESI) calcd for $C_{13}H_{26}O_4Si$ $[M-H]^-$: 273.1522; found: 273.1537.



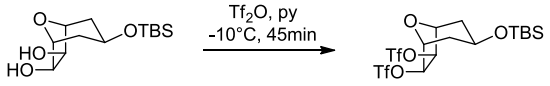
15 16

Bismesylate 16

25 mg (0.091 mmol, 1.0 eq.) diol **15** was dissolved in CH_2Cl_2 (3 mL) and 38 µL (0.273 mmol, 3.0 eq.) NEt_3 was added. The reaction mixture was cooled to 0 °C and 17 µL (0.219 mmol, 2.4 eq.) MsCl was added dropwise. The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with EtOAc (10 mL) and 1N HCl (3 mL). The water layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 42 mg of a yellow solid. The crude product was purified by flash column chromatography (EtOAc/hexane = 1/1) to yield 39 mg (0.090 mmol, 99%) of the desired product **16** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.24 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 5.01 (s, 2H), 4.52 (s, 2H), 3.61–3.55 (m, 1H), 3.12 (s, 6H), 1.94 (ddd, *J*=1.6, 5.8, 14.7 Hz, 2H), 1.74–1.69 (m, 2H), 0.85 (s, 9H), 0.04 (s, 6H).
^{13}C NMR ($CDCl_3$, 150 MHz): δ= 80.4, 79.3, 62.9, 38.7, 38.0, 25.6, 17.9, -4.5.
HRMS (ESI) calcd for $C_{15}H_{31}O_8S_2Si$ $[M+H]^+$: 431.1230; found: 431.1253.

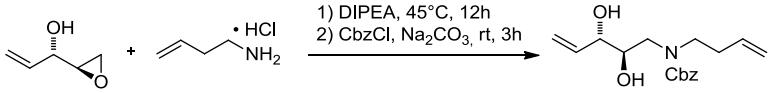


15 **17**

Bistriflate 17

20 mg (0.073 mmol, 1.0 eq.) diol **15** was dissolved in CH_2Cl_2 (5 mL) and 35 µL (0.437 mmol, 6.0 eq.) py was added. The reaction mixture was cooled to –10 °C and 27 µL (0.160 mmol, 2.2 eq.) Tf_2O was added dropwise. The reaction mixture was stirred for 45 min at –10 °C before it was concentrated *in vacuo*. The reaction mixture was triturated with Et_2O (2 × 10 mL) and filtered to afford 37 mg (0.069 mmol, 94%) of the desired product **17** as a colorless solid.

TLC (hexanes:EtOAc = 1:1), R_f = 0.20 ($KMnO_4$).
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 5.17 (s, 2H), 4.60 (s, 2H), 3.58–3.52 (m, 1H), 1.95 (dd, *J*= 5.8, 13.1 Hz, 2H), 1.83–1.78 (m, 2H), 087 (s, 9H), 0.07 (s, 6H).
^{13}C NMR ($CDCl_3$, 150 MHz): δ= 119.4, 84.7, 80.2, 62.5, 37.7, 25.5, 17.8, -4.5.
HRMS (ESI) calcd for $C_{15}H_{25}F_6O_8S_2Si$ $[M+H]^+$: 539.0664; found: 539.0649.



21 **20**

Diene 20:

6.97 g (69.7 mmol, 1 eq.) epoxy alcohol **21**[2] was dissolved in methanol (150 mL) and treated with 11.19 g (104.5 mmol, 1.5 eq.) 4-butenylamine hydrochloride and 39.0 mL (230.0 mmol, 3.3 eq.) DIPEA. The reaction mixture was stirred at 45 °C for 12 h in a sealed tube. 22.1 g (209.1 mmol, 3 eq.) Na_2CO_3 in water (100 mL) and 23.7 mL (167.3 mmol, 2.4 eq.) benzyl chloroformate were subsequently added at 0 °C and stirred for 3 h at rt. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated

in vacuo. The crude product was purified by flash column chromatography (hexanes:EtOAc = 3:1) to yield 15.9 g (52.3 mmol, 75%) diene **20** as a clear oil (one spot on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.48 (UV, CAM).

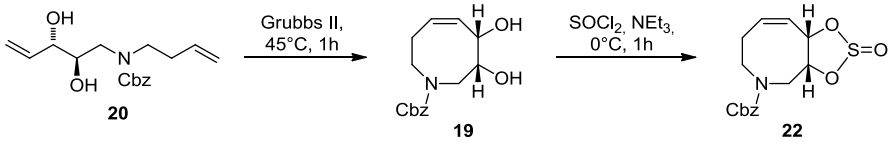
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.35 (m, 5H), 5.93–5.87 (m, 1H), 5.73–5.67 (m, 1H), 5.34 (d, *J*=17.3 Hz, 1H), 5.25 (d, *J*=10.5 Hz, 1H), 5.13 (s, 2H), 5.03–4.98 (dd, *J*=9.9, 16.7 Hz, 2H), 4.06 (s, 1H), 3.70 (s, 1H), 3.62 (dd, *J*=6.2, 14.8 Hz, 1H), 3.43–3.29 (m, 6H), 2.36 – 2.24 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 158.4, 136.7, 136.3, 134.9, 128.5, 128.1, 127.9, 117.2, 117.0, 74.3, 74.0, 67.7, 49.9, 48.6, 32.9.

IR (Diamond-ATR, neat) ν_{max}: 3397, 2978, 2937, 1743, 1671, 1478, 1423, 1221, 1147, 1094, 994, 917, 734, 697 cm^{-1}.

$[\alpha]^{25}_D$ = – 9.2° (*c* = 0.46, $CHCl_3$).

HRMS (ESI) calcd for $C_{17}H_{23}NO_4$ $[M+H]^+$: 306.1700; found: 306.1706.



Diol 19

A solution of 2.10 g (6.9 mmol, 1.0 eq.) diene **20** in CH_2Cl_2 (3.0 L) was heated to 45 °C and 292 mg (0.34 mmol, 0.05 eq.) Grubbs 2nd Generation catalyst was added in one portion. The reaction mixture was refluxed for 1 h, then concentrated *in vacuo* to a total volume of ca. 50 mL and in general used for the next reaction without further purification.

The reaction was repeated five times using the same batch of CH_2Cl_2, which was recycled by distillation from the reaction mixture.

For characterization purpose, the reaction mixture was concentrated *in vacuo* and the crude product was purified by flash column chromatography (hexanes:EtOAc = 2:1) to yield 1.64 g (5.9 mmol, 86%) diol **19** as brown oil (one spot on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.15 (UV, CAM).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.37–7.27 (m, 5H), 5.92–5.65 (m, 2H), 5.17–5.06 (m, 2H), 4.46–4.25 (m, 2H), 4.21–3.62 (m, 2H), 3.30 (brs, 1H), 3.18 (brs, 1H), 2.95 (brs, 1H), 2.71–2.56 (m, 1H), 2.30–2.12 (m, 2H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ= 156.9, 156.1, 136.4, 136.3, 133.7, 132.5, 129.2, 128.6, 128.5, 128.3, 128.1, 128.1, 127.9, 127.8, 73.1, 72.7, 69.9, 69.4, 67.5, 67.4, 51.7, 51.3, 50.2, 49.5, 28.3, 28.1.

IR (Diamond-ATR, neat) ν_{max}: 3408, 2936, 1680, 1472, 1419, 1264, 1222, 1107, 1053, 955, 731, 697 cm^{-1}.

$[\alpha]^{25}_D$ = + 48.5° (*c* = 0.42, $CHCl_3$).

HRMS (EI) calcd for $C_{15}H_{19}NO_4$: 277.1314; found: 277.1291.

Note: Multiple signals of ^{1}H- and ^{13}C-NMR are due to rotamers and conformers.

Sulfite 22

Crude diol **19** (100% yield assumed from RCM reactions, 34.5 mmol) in CH_2Cl_2 (ca. 250 mL) was cooled to 0 °C. 19.2 mL (138.0 mmol, 4 eq.) NEt_3 was added followed by a dropwise addition of 7.51 mL (103.5 mmol, 3 eq.) $SOCl_2$ and stirred at 0 °C for 1 h. The reaction mixture was diluted with $CHCl_3$ (400 mL), washed with H_2O (3 × 150 mL) and brine (400 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 3:1) to yield 9.48 g (29.3 mmol, 85% over 2 steps) sulfite **22** as a mixture of diastereomers in ratio of (54:46).

TLC (hexanes:EtOAc = 2:1), R_f = 0.81 (UV, CAM).

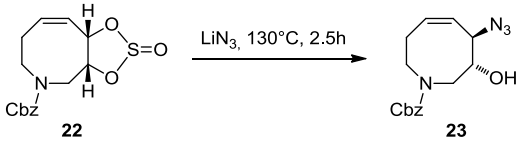
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.36 (brs, 5H), 6.19–5.94 (m, 2H), 5.63–5.43 (m, 1H), 5.39–5.05 (m, 2H), 5.04–4.69 (m, 1H), 4.45–4.12 (m, 2H), 3.31–2.91 (m, 1H), 2.82–2.60 (m, 1H), 2.43–2.21 (m, 1H), 2.19–1.93 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 155.6, 136.2, 136.0, 132.7, 132.1, 131.6, 130.3, 129.7, 129.2, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 84.1, 83.1, 81.7, 81.6, 80.8, 80.5, 78.8, 78.1, 67.9, 67.8, 67.7, 48.1, 47.9, 47.7, 47.7, 47.2, 47.1, 46.3, 29.8, 29.5, 29.2, 29.0.

IR (Diamond-ATR, neat) ν_{max}: 2947, 1695, 1463, 1417, 1211, 963, 740, 698 cm^{-1}.

$[\alpha]^{25}_D$ = – 7.2° (*c* = 0.42, $CHCl_3$).

HRMS (EI) calcd for $C_{15}H_{17}NO_5S$: 323.0827; found: 323.0826.



22 **23**

Azido alcohol 23

500 mg (1.55 mmol, 1.0 eq.) sulfite **22** was dissolved in DMF (37 mL) and treated with 1.14 mL (4.64 mmol, 3.0 eq., 20% solution in water) LiN_3. The reaction mixture was stirred at 130 °C for 2.5 h, cooled to room temperature and diluted with H_2O (150 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers were subsequently washed with H_2O (3 × 100 mL), 10% aq. LiCl (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 3:1) to yield 390 mg (1.29 mmol, 83%) azido alcohol **23** as a clear oil (one spot on TLC).

Note: Reaction scales larger than 1.55 mmol afforded the product in 55-70% yield.

TLC (hexanes:EtOAc = 6:4), R_f = 0.50 (UV, CAM).

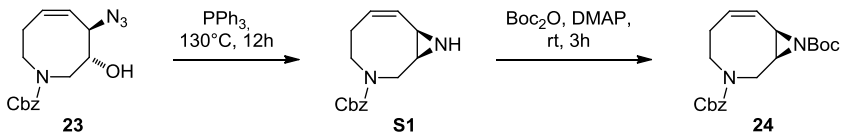
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.45–7.31 (m, 5H), 5.95–5.79 (dd, *J*=8.0, 18.8 Hz, 1H), 5.61–5.47 (m, 1H), 5.29–5.16 (m, 3H), 4.27–4.02 (m, 2H), 3.82–3.69 (m, 1H), 3.15 (dd, *J*=4.2, 15.2 Hz, 1H), 2.75–2.54 (m, 1H), 2.40–2.22 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 158.8, 136.0, 130.1, 130.0, 129.3, 128.7, 128.5, 128.3, 128.2, 77.0, 68.3, 63.9, 54.3, 49.5, 28.8.

IR (Diamond-ATR, neat) ν_{max}: 3376, 2930, 2099, 1663, 1417, 1258, 1210, 1132, 1066, 987, 733, 696 cm^{-1}.

$[\alpha]^{25}_D$ = – 11.6° (*c* = 0.43, $CHCl_3$).

HRMS (ESI) calcd for $C_{15}H_{18}N_4O_3$ $[M+Na]^+$: 325.1277; found: 325.1271.



Aziridine S1

240 mg (0.795 mmol, 1.0 eq.) azidol **23** and 360 mg (0.954 mmol, 1.2 eq.) of triphenylphosphine was dissolved in 10 mL of anhydrous toluene and heated to 130 °C for 12h (evolution of N_2). After cooling to room temperature, the reaction mixture was diluted with toluene (30 mL) and extracted with 20% sat. aq. $NaHSO_3$ (3 × 25 mL). The combined aqueous layers were cooled to 0 °C and adjusted to pH > 10 with K_2CO_3. The aqueous layer was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 204 mg aziridine **S1** as colorless oil (one spot on TLC).

TLC (CH_2Cl_2:MeOH = 9:1), R_f = 0.52 (CAM).

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.39–7.31 (m, 5H), 5.81–5.67 (m, 2H), 5.19–5.11 (m, 2H), 4.24–4.09 (m, 2H), 2.91–2.81 (m, 1H), 2.62 (brs, 2H), 2.48–2.41 (m, 2H), 2.26–2.17 (m, 1H).

HRMS (ESI) calcd for $C_{15}H_{18}N_2O_2$ $[M+H]^+$: 258.1368; found: 258.1376.

***N*-Boc aziridine 24**

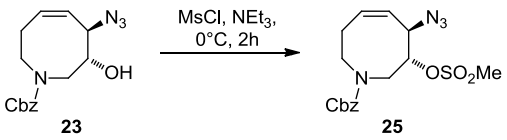
204 mg (0.791 mmol, 1.0 eq.) aziridine **S1**, 544 µL (2.37 mmol, 3.0 eq.) di-*tert*-butyl dicarbonate and 22 mg (0.237 mmol, 0.3 eq.) 4-dimethylaminopyridine were dissolved in CH_2Cl_2 (8 mL) and stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 5:1) to yield 280 mg (0.782 mmol, 98% over two steps) *N*-Boc aziridine **24** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 6:4), R_f = 0.59 (CAM).

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.41–7.30 (m, 5H), 5.86–5.70 (m, 2H), 5.22–5.10 (m, 2H), 4.45–4.10 (m, 2H), 3.04–2.94 (m, 1H), 2.86–2.76 (m, 2H), 2.69–2.50 (m, 1H), 2.40–2.21 (m, 2H), 1.45–1.42 (m, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 162.1, 155.5, 136.6, 132.4, 132.1, 128.5, 128.0, 127.8, 125.8, 125.5, 81.4, 67.3, 47.0, 46.5, 46.3, 41.8, 41.6, 38.9, 38.4, 29.6, 29.3, 27.8.

HRMS (ESI) calcd for $C_{20}H_{26}N_2O_4$ $[M+H]^+$: 358.1893; found: 358.1904.



23 **25**

Azido mesylate 25

To a solution of 90 mg (0.298 mmol, 1 eq.) azido alcohol **23** and 100 µL (0.715 mmol, 2.4 eq.) NEt_3 in CH_2Cl_2 (12 mL) at 0 °C was added dropwise 28 µL (0.358 mmol, 1.2 eq.) MsCl. The reaction mixture was stirred for 2 h at 0 °C and then diluted with sat. aq. NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 96 mg (0.253 mmol, 85%) azido mesylate **25** as a yellow solid (one spot on TLC).

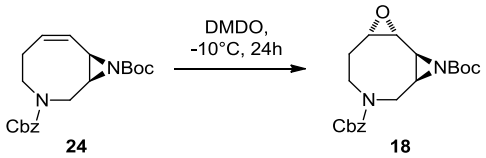
TLC (hexanes:EtOAc = 6:4), R_f = 0.45 (UV, CAM).

^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.44–7.32 (m, 5H), 5.92–5.83 (m, 1H), 5.54–5.41 (m, 1H), 5.27–5.09 (m, 2H), 4.74–4.50 (m, 1H), 4.38 (dt, *J*=9.3, 17.7 Hz, 1H), 3.65 (m, 3H), 3.31–3.20 (m, 2H), 2.91 (s, 2H), 2.33 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 156.3, 136.2, 131.7, 131.3, 128.8, 128.5, 128.3, 128.0, 127.4, 80.6, 67.8, 67.6, 61.5, 50.4, 50.4, 47.3, 38.5, 38.0, 28.1, 27.8.

IR (Diamond-ATR, neat) ν_{max}: 2102, 1693, 1467, 1419, 1350, 1255, 1171, 1137, 946, 737 cm^{-1}.

HRMS (EI) calcd for $C_{16}H_{27}N_4O_4S$: 380.1154; found: 380.1156.



Epoxyaziridine 18

210 mg (0.586 mmol, 1.0 eq.) alkene **24** was dissolved in CH_2Cl_2 (5 mL) and cooled to –10 °C. 14.7 mL (1.47 mmol, 2.5 eq., 1M solution in acetone) freshly prepared DMDO was added dropwise and the reaction mixture was stirred at –10 °C for 30 h. The reaction mixture was concentrated *in vacuo* to yield 219 mg (0.585 mmol, 99%) of the desired epoxide **18** as a colorless solid (one spot on TLC).

TLC (hexanes:EtOAc = 6:4), R_f = 0.44 (CAM).

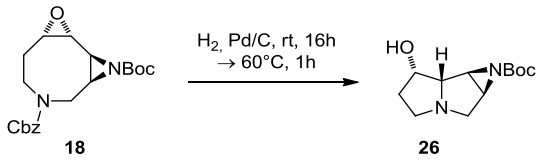
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.47–7.30 (m, 5H), 5.24–5.08 (m, 2H), 4.60–4.36 (m, 1H), 4.34–4.19 (m, 1H), 3.18 (d, *J*=3.1 Hz, 1H), 3.09–2.95 (m, 1H), 2.86 (dd, *J*=10.5, 14.8 Hz, 1H), 2.75–2.64 (m, 2H), 2.62–2.49 (m, 1H), 2.46–2.25 (m, 1H), 1.47–1.44 (m, 9H), 1.28–1.12 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 162.2, 155.5, 136.4, 128.6, 128.1, 127.9, 81.9, 67.5, 55.6, 52.9, 52.8, 48.1, 47.2, 42.8, 42.7, 40.1, 40.0, 39.9, 37.6, 37.2, 31.4, 31.1, 27.8.

IR (Diamond-ATR, neat) ν_{max}: 2977, 1697, 1449, 1420, 1367, 1285, 1232, 1152, 1076, 970, 900, 851, 827, 766, 752, 732, 697 cm^{-1}.

$[\alpha]^{25}_D$ = – 33.6° (*c* = 0.44, $CHCl_3$).

HRMS (ESI) calcd for $C_{20}H_{26}N_2O_5$ $[M+H]^+$: 375.1914; found: 375.1914.



Hydroxyaziridine 26

A solution of 260 mg (0.693 mmol, 1.0 eq.) epoxide **18** and 74 mg (69.3 µmol, 0.10 eq.) 10% Pd/C in ethanol (20 mL) was flushed with H_2 (3 ×) and stirred for 16 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was heated to 60 °C for 1 h before concentrating *in vacuo* to yield 120 mg (0.499 mmol, 72%) of the desired product **26** (one spot on TLC).

TLC (CH_2Cl_2:MeOH:NH_4OH = 8:8:0.2), R_f = 0.34 ($KMnO_4$).

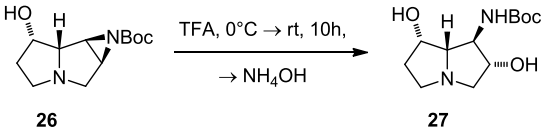
^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.31 (q, *J*=3.3 Hz, 1H), 3.44 (d, *J*=3.5 Hz, 1H), 3.39 (d, *J*=10.4 Hz, 1H), 3.25 (dd, *J*=2.5, 4.6 Hz, 1H), 3.23 (d, *J*=4.6 Hz, 1H), 3.08 (dt, *J*=6.2, 10.9 Hz, 1H), 2.83–2.74 (m, 1H), 2.00–1.96 (m, 2H), 1.43 (s, 9H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ= 162.6, 82.3, 73.4, 71.4, 57.8, 53.4, 44.9, 42.8, 37.7, 28.2.

IR (Diamond-ATR, neat) ν_{max}: 3357, 2922, 2852, 1714, 1575, 1367,1319, 1293, 1256, 1154, 1020, 795 cm^{-1}.

$[\alpha]^{25}_D$ = – 6. 8° (*c* = 0.64, $CHCl_3$).

HRMS (ESI) calcd for $C_{12}H_{20}N_2O_3$ $[M+H]^+$: 240.1474; found: 240.1460.



Dihydroxy pyrrolizidine 27

72 mg (0.30 mmol, 1.0 eq.) aziridin **26** was dissolved in $CHCl_3$ (9 mL) and cooled to 0 °C. 69 µL (0.90 mmol, 3.0 eq.) trifluoroacetic acid was added dropwise and the reaction mixture was allowed to warm to rt while stirring for 10 h. The reaction mixture was treated with NH_4OH (0.5 mL) dropwise and concentrated *in vacuo*. The crude product was purified by flash column chromatography (CH_2Cl_2:hexanes:MeOH:NH_4OH = 8:10:3:0.2) to yield 77 mg (0.29 mmol, 99%) of the desired product **27** as a colorless solid (one spot on TLC).

TLC (CH_2Cl_2:hexanes:MeOH:NH_4OH = 8:10:3:0.2), R_f = 0.21 ($KMnO_4$).

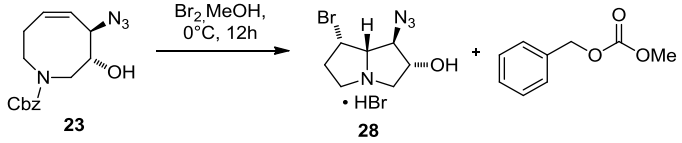
^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.26–4.19 (m, 2H), 3.97 (t, *J*=7.5 Hz, 1H), 3.28 (dd, *J*=6.0, 9.4 Hz, 1H), 3.18 (dd, *J*=4.2, 7.3 Hz, 1H), 3.11 (t, *J*=7.8 Hz, 1H), 2.78 (ddd, *J*=5.8, 9.3, 12.1 Hz, 1H), 2.56 (t, *J*=9.1 Hz, 1H), 2.03 (dd, *J*=5.7, 13.2 Hz, 1H), 1.96–1.86 (m, 1H), 1.45 (s, 9H).

^{13}C NMR (MeOH-d_4, 100 MHz): δ= 159.0, 80.6, 77.5, 74.6, 71.0, 61.0, 56.6, 53.9, 36.8, 28.7.

IR (Diamond-ATR, neat) ν_{max}: 3407, 3325, 2973, 2952, 2828, 1663, 1554, 1368, 1313, 1158, 1147, 1064, 1002, 855, 746, 686 cm^{-1}.

$[\alpha]^{25}_D$ = – 22.1° (*c* = 0.22, $CHCl_3$).

HRMS (ESI) calcd for $C_{12}H_{22}N_2O_4$ $[M+H]^+$: 258.1580; found: 258.1571.



Bromo pyrrolizidine hydrobromide 28

To a solution of 2.30 g (7.62 mmol, 1 eq.) azido alcohol **23** in MeOH (1.4 L) at 0 °C was added 390 µL (7.62 mmol, 1 eq.) Br_2. The reaction mixture was stirred under exclusion of light (to avoid radical reactions) for 12 h at 0 °C and concentrated *in vacuo*. The crude product was triturated with Et_2O (200 mL) and the formed precipitate was filtered off to yield 2.40 g (7.40 mmol, 97%) bromo pyrrolizidine hydrobromide **28** as colorless crystals.

The filtrate was concentrated *in vacuo* to yield 1.20 g (7.24 mmol, 95%) benzyl methy carbonate.

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.65 ($KMnO_4$).

^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.86–4.82 (m, 1H), 4.38–4.31 (m, 1H), 4.29 (t, *J*=7.3 Hz, 1H), 4.11 (t, *J*=7.3 Hz, 1H), 3.90 (dd, *J*=6.1, 11.7 Hz, 1H), 3.67 (ddd, *J*=6.5, 7.5, 11.9 Hz, 1H), 3.49 (dt, *J*=6.5, 11.8 Hz, 1H), 3.20 (dd, *J*=9.1, 11.8 Hz, 1H), 2.72–2.56 (m, 2H).

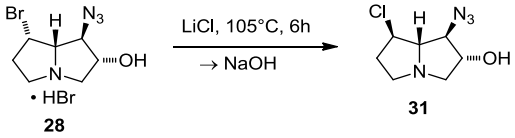
^{13}C NMR (MeOH-d_4, 100 MHz): δ= 74.1, 70.5, 68.6, 57.4, 53.4, 44.4, 34.8.

IR (Diamond-ATR, neat) ν_{max}: 3308, 2528, 2458, 2110, 1471, 1381, 1284, 1129, 1063, 986, 860 669 cm^{-1}.

$[\alpha]^{25}_D$ = + 22.0° (*c* = 0.41, MeOH).

HRMS (ESI) calcd for $C_7H_{11}BrN_4O$ $[M+H]^+$: 247.0189; found: 247.0189.

M.p.: 172 °C



Choro pyrrolizidine 31

A solution of 1.71 g (5.26 mmol, 1 eq.) bromo pyrrolizidine hydrobromide **28** and 4.42 g (105.2 mmol, 20 eq.) LiCl in DMF (90 mL) was stirred for 6 h at 105 °C. The reaction mixture was cooled to rt, diluted with H_2O (700 mL) and 1M aq. HCl (30 mL) and washed with EtOAc (2 × 250 mL). The aqueous layer was adjusted to pH = 10 with 1M aq. NaOH and extracted with EtOAc (5 × 300 mL). The combined organic layers were subsequently washed with H_2O (2 × 500 mL), 10% aq. LiCl (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 913 mg (4.52 mmol, 86%) chloro pyrrolizidine **31** as a brown oil (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.65 ($KMnO_4$).

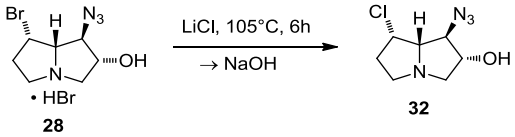
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.28 (dd, *J*=5.5, 12.0 Hz, 1H), 4.24 (dd, *J*=5.9, 12.5 Hz, 1H), 3.60 (t, *J*=5.5 Hz, 1H), 3.45 (dd, *J*=4.9, 10.4 Hz, 1H), 3.34 (dd, *J*=5.5, 10.6 Hz, 1H), 3.33–3.28 (m, 1H), 2.87–2.77 (m, 1H), 2.62 (dd, *J*=6.4, 10.6 Hz, 1H), 2.42–2.34 (m, 1H), 2.12–2.04 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 76.5, 76.5, 70.1, 60.0, 59.6, 53.6, 35.6.

IR (Diamond-ATR, neat) ν_{max}: 2928, 2853, 2096, 1450, 1379, 1251, 1128, 1084, 978, 872, 792, 753, 698, 668 cm^{-1}.

$[\alpha]^{25}_D$ = – 68.3° (*c* = 0.38, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{11}ClN_4O$ $[M+H]^+$: 203.0694; found: 203.0694.



Iso-Choro pyrrolizidine 32

A solution of 1.71 g (5.26 mmol, 1 eq.) bromo pyrrolizidine hydrobromide **28** and 4.42 g (105.2 mmol, 20 eq.) LiCl in DMF (90 mL) was stirred for 6 h at 105 °C. The reaction mixture was cooled to rt, diluted with H_2O (700 mL) and 1M aq. HCl (30 mL) and washed with EtOAc (2 × 250 mL). The aqueous layer was adjusted to pH = 10 with 1M aq. NaOH and extracted with EtOAc (5 × 300 mL). The combined organic layers were subsequently

washed with H_2O (2 × 500 mL), 10% aq. LiCl (500 mL) and brine (500 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 45 mg (0.226 mmol, 4%) chloro pyrrolizidine **32** as a yellowish solid (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.65 ($KMnO_4$).

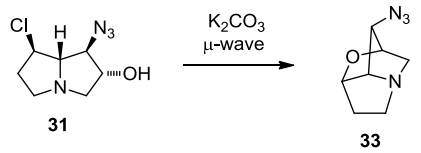
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.52 (dd, *J*=4.2, 7.2 Hz, 1H), 4.47 (ddd, *J*=6.4, 8.2, 9.7 Hz, 1H), 4.13 (t, *J*=7.9 Hz, 1H), 3.54 (dd, *J*=4.7, 7.6 Hz, 1H), 3.39 (dd, *J*=6.4, 8.6 Hz, 1H), 3.18 (ddd, *J*=3.3, 6.0, 9.4 Hz, 1H), 2.87 (ddd, *J*=6.7, 8.0, 9.7 Hz, 1H), 2.63 (dd, *J*=8.7, 9.7 Hz, 1H), 2.35–2.32 (m, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 78.0, 71.0, 67.9, 60.4, 59.6, 51.7, 38.0.

IR (Diamond-ATR, neat) ν_{max}: 3061, 2920, 2856, 2114, 1377, 1303, 1281, 1108, 1094, 1060, 972 cm^{-1}.

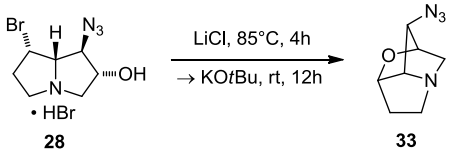
$[\alpha]^{25}_D$ = –8.6° (*c* = 0.18, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{11}ClN_4O$ $[M+H]^+$: 203.0700; found: 203.0696.



Azide 33

A solution of 580 mg (2.87 mmol, 1 eq.) chloro pyrrolizidine **31** and 990 mg (7.18 mmol, 2.5 eq.) K_2CO_3 in MeOH (30 mL) was stirred in a microwave reactor for 10 min at 150 °C/300 W. 10 g silica was added and the reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 10:1) to yield 429 mg (2.58 mmol, 90%) azide **33** as a yellow oil (one spot on TLC).



One-pot-procedure: azide 33

A solution of 15 mg (0.046 mmol, 1 eq.) bromo pyrrolizidine hydrobromide **28** and 48 mg (1.15 mmol, 25 eq.) LiCl in DMSO (1 mL) was stirred for 4 h at 85 °C. The reaction mixture

was cooled to rt, treated with 26 mg (0.230 mmol, 5 eq.) KO*t*Bu and stirred for 12 h at rt. The reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (5 × 5 mL). The combined organic layers were washed with H_2O (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 5 mg (0.030 mmol, 65%) azide **33** as a yellow oil.

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.2), R_f = 0.67 ($KMnO_4$).

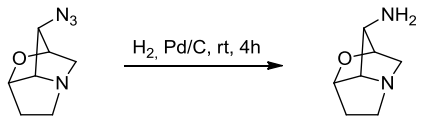
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.47 (dd, *J*=1.8, 4.5 Hz, 1H), 4.15 (s, 1H), 4.06 (s, 1H), 3.49 (d, *J*=11.7 Hz, 1H), 3.31 (s, 1H), 3.14–3.10 (m, 1H), 3.02–2.97 (m, 1H), 2.45 (d, *J*=11.7 Hz, 1H), 2.10–2.05 (m, 1H), 2.02–1.96 (m, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 82.1, 74.4, 69.6, 66.4, 61.2, 54.8, 33.7.

IR (Diamond-ATR, neat) ν_{max}: 2940, 2103, 1354, 1310, 1263, 1097, 1050, 1006, 958, 849, 791, 724 cm^{-1}.

$[\alpha]^{25}_D$ = – 49.2° (*c* = 0.44, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{10}N_4O$ $[M+H]^+$: 167.0927; found: 167.0928.



33 **1**

Temuline (1)

A solution of 15 mg (0.090 mmol, 1 eq.) azide **33** and 6 mg (0.006 mmol, 0.06 eq.) 10% Pd/C in MeOH (3 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 4 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to yield 11.4 mg (0.081 mmol, 90%) temuline (**1**) as a yellow oil (one spot on TLC).

*Note: When temuline (**1**) is exposed to air, it readily forms the corresponding carbamate, a crystalline solid.*

TLC ($CHCl_3$:MeOH = 2:1), R_f = 0.16 ($KMnO_4$).

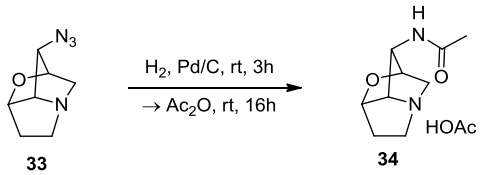
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 4.40 (dd, *J*=1.9, 4.5 Hz, 1H), 3.84 (d, *J*=1.7 Hz, 1H), 3.60 (dd, *J*=0.8, 1.7 Hz, 1H), 3.50 (dd, *J*=0.7, 11.7 Hz, 1H), 3.10 (ddd, *J*=3.6, 8.3, 12.7 Hz, 1H), 3.05 (dd, *J*=1.4, 1.5 Hz, 1H), 2.93 (ddd, *J*=7.3, 9.3, 12.8 Hz, 1H), 2.42 (d, *J*=11.8 Hz, 1H), 2.03 (ddd, *J*=7.3, 8.2, 14.3 Hz, 1H), 1.97 (dddd, *J*=3.6, 4.4, 9.4, 14.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 81.7, 76.2, 71.9, 60.8, 60.5, 54.5, 34.1.

IR (Diamond-ATR, neat) ν_{max}: 3366, 3288, 3184, 1606, 1472, 1318, 1250, 1216, 1174, 1087, 1040, 1020, 955, 846, 798, 772, 695, 626 cm^{-1}.

$[\alpha]^{25}_D$ = + 27.3° (*c* = 0.37, $CHCl_3$).

HRMS (ESI) calcd for $C_7H_{12}N_2O$ $[M+H]^+$: 141.1022; found: 141.1024.



33 **34**

***N*-Acetyl temuline acetate (34)**

A solution of 30 mg (0.181 mmol, 1 eq.) azide **33** and 9.6 mg (0.009 mmol, 0.05 eq.) 10% Pd/C in THF (9 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 3 h at rt under H_2 atmosphere (balloon). The atmosphere was exchanged for N_2 and 22 mg (0.217 mmol, 1.2 eq.) Ac_2O was added. The reaction mixture was stirred for 16 h, filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to afford 43 mg (0.178 mmol, 98%) *N*-Acetyl temuline acetate **(34)** as a yellowish solid (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.28 ($KMnO_4$).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.67 (brs, 1H), 4.52 (brs, 2H), 4.35 (s, 1H), 3.63 (d, *J*=11.9 Hz, 1H), 3.53 (s, 1H), 3.19 (t, *J*=7.6 Hz, 1H), 2.62 (d, *J*=11.9 Hz, 1H), 2.22–2.08 (m, 2H), 1.99–1.96 (m, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 177.9, 171.4, 80.2, 73.8, 69.3, 60.8, 57.0, 53.6, 31.7, 22.6, 22.3.

IR (Diamond-ATR, neat) ν_{max}: 3252, 2922, 1660, 1558, 1407, 1377, 1296, 1092, 1012, 962, 933, 841 cm^{-1}.

$[\alpha]^{25}_D$ = – 28.0° (*c* = 0.84, MeOH).

HRMS (ESI) calcd for $C_9H_{14}N_2O_2$ $[M+H]^+$: 183.1134; found: 183.1129.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*

1 35

***N*-Formyl temuline (35)**

A mixture of formic acid (1 mL) and acetic anhydride (2 mL) was stirred for 2 h at 55 °C and then added to 40 mg (0.189 mmol) temuline ·2HCl (**1**). The reaction mixture was stirred at rt for 8 h and then treated carefully with MeOH (5 mL) before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH:NH_4OH = 9:1:0.5) to yield 32 mg (0.189 mmol, 99%) *N*-formyltemuline (**35**) as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:1:0.5), R_f = 0.39 ($KMnO_4$).

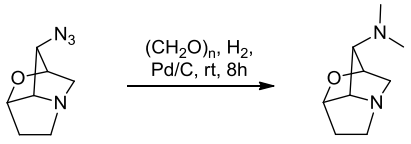
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.73 (brs, 1H), 8.24 (s, 1H), 4.73–4.61 (m, 3H), 4.48 (s, 1H), 4.14 (d, *J*=12.0 Hz, 1H), 3.89–3.79 (m, 1H), 3.59 (ddd, *J*=4.3, 8.5, 12.8 Hz, 1H), 3.09 (d, *J*=12.2 Hz, 1H), 2.48–2.33 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 161.7, 78.4, 73.6, 71.3, 61.9, 55.7, 53.2, 30.3.

IR (Diamond-ATR, neat) ν_{max}: 3260, 2942, 2878, 2360, 1662, 1533, 1472, 1387, 1315, 1295, 1226, 1107, 1047, 1021, 1004, 980, 961, 886, 848, 793, 746 cm^{-1}.

$[\alpha]^{25}_D$ = + 32.1° (*c* = 0.47, $CHCl_3$).

HRMS (ESI) calcd for $C_8H_{12}N_2O_2$ $[M+H]^+$: 169.0977; found: 169.0972.



33 3

***N*-Methyl loline (3)**

A solution of 21 mg (0.126 mmol, 1 eq.) azide **33**, 50 mg (0.472 mmol, 3.7 eq.) 10% Pd/C and 0.1 ml (37 wt% in H_2O) formaldehyde solution in MeOH (2 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 8 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH:NH_4OH = 140:10:0.5) to afford 21 mg (0.125 mmol, 99%) *N*-methyl loline **(3)** as a yellowish oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 6:1), R_f = 0.41 ($KMnO_4$).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ= 4.41 (dd, *J*=1.8, 4.4 Hz, 1H), 3.99 (s, 1H), 3.54 (d, *J*=10.9 Hz, 1H), 3.18 (s, 1H), 3.10–2.90 (m, 2H), 2.69 (d, *J*=1.8 Hz, 1H), 2.35 (d, *J*=10.9 Hz, 1H), 2.28 (s, 6H), 2.08–1.86 (m, 2H).

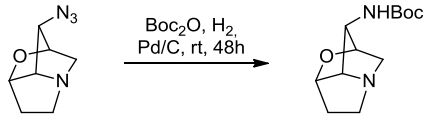
^{13}C NMR ($CDCl_3$, 75 MHz): δ= 82.4, 74.7, 74.5, 69.7, 61.6, 54.7, 44.7, 33.8.

IR (Diamond-ATR, neat) ν_{max}: 3392, 2943, 2822, 2772, 1651, 1466, 1368, 1271, 1182, 1094, 1041, 1022, 961, 888, 854, 814, 793 cm^{-1}.

$[\alpha]^{25}_D$ = + 8.0° (*c* = 0.58, MeOH).

HRMS (ESI) calcd for $C_9H_{16}N_2O$ $[M+H]^+$: 169.1341; found: 169.1336.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



33 **36**

***N*-Boc temuline (36)**

A solution of 10 mg (0.060 mmol, 1 eq.) azide **33**, 26 mg (0.120 mmol, 2 eq.) Boc_2O and 6 mg (0.006 mmol, 0.09 eq.) 10% Pd/C in THF (5 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 48 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 13.4 mg (0.056 mmol, 93%) *N*-Boc temuline (**36**) as a yellow oil (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:2:0.2), R_f = 0.66 ($KMnO_4$).

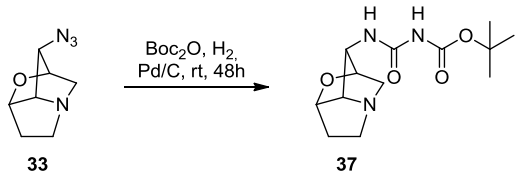
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 5.45 (brs, 1H), 4.46 (dd, *J* =1.6, 4.4 Hz, 1H), 4.23 (d, *J*=5.6 Hz, 1H), 4.14 (s, 1H), 3.36 (d, *J*=11.8 Hz, 1H), 3.12–3.08 (m, 2H), 2.96–2.91 (m, 1H), 2.43 (d, *J*=11.8 Hz, 1H), 2.10–2.04 (m, 1H), 2.02–1.97 (m, 1H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 155.5, 81.0, 79.6, 74.1, 69.7, 61.0, 58.5, 54.6, 33.8, 28.3.

IR (Diamond-ATR, neat) ν_{max}: 2974, 2937, 1697, 1547, 1365, 1289, 1251, 1161, 1152, 999, 961, 850, 794, 749, 665 cm^{-1}.

$[\alpha]^{25}_D$ = + 38.7° (*c* = 0.35, $CHCl_3$).

HRMS (ESI) calcd for $C_{12}H_{20}N_2O_3$ $[M+H]^+$: 241.1547; found: 241.1545.



33 37

***N*-Boc urea (37)**

A solution of 350 mg (2.11 mmol, 1 eq.) azide **33**, 920 mg (4.217 mmol, 2 eq.) Boc_2O and 110 mg (0.105 mmol, 0.05 eq.) 10% Pd/C in THF (60 mL) was degassed with N_2 in a sonicator for 15 minutes, then flushed with H_2 (3 ×) and stirred for 48 h at rt under H_2 atmosphere (balloon). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 31 mg (0.109 mmol, 5%) *N*-Boc urea **37** as a yellowish solid (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:2:0.2), R_f = 0.75 ($KMnO_4$).

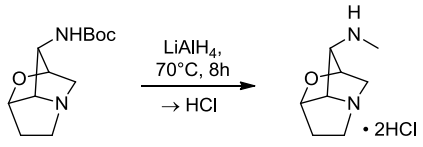
^{1}H NMR ($CDCl_3$, 300 MHz): δ= 8.23 (d, *J*=6.7 Hz, 1H), 7.60 (s, 1H), 4.47 (dd, *J* =1.8, 4.2 Hz, 1H), 4.38 (d, *J*=6.3 Hz, 1H), 4.17 (s, 1H), 3.42 (d, *J*=11.6 Hz, 1H), 3.27 (s, 1H), 3.12 (ddd, *J*=3.7, 8.1, 12.2 Hz, 1H), 3.03–2.93 (m, 1H), 2.45 (d, *J*=12.0 Hz, 1H), 2.13–1.95 (m, 2H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 153.3, 153.0, 82.8, 81.3, 74.0, 69.7, 61.0, 57.7, 54.8, 33.8, 28.0.

IR (Diamond-ATR, neat) ν_{max}: 3318, 3214, 3120, 2973, 2942, 1714, 1691,1552, 1480, 1268, 1247, 1152, 959, 791, 768, 661 cm^{-1}.

$[\alpha]^{25}_D$ = + 9.3° (*c* = 1.32, $CHCl_3$).

HRMS (ESI) calcd for $C_{13}H_{22}N_3O_4$ $[M+H]^+$: 284.1610; found: 284.1608.



36 2

Loline ·2HCl (2)

A solution of 11 mg (0.046 mmol, 1 eq.) *N*-Boc temuline (**36**) in THF (5 mL) was degassed with N_2 in a sonicator for 5 minutes, then treated with 275 μL (0.275 mmol, 6 eq., 1M solution in THF) $LiAlH_4$ and refluxed for 8 h. The reaction mixture was quenched with 1M aq. NaOH (0.3 mL) and 0.5 g silica was added and concentrated *in vacuo*. The crude product

was purified by flash column chromatography ($CHCl_3$:MeOH:NH_4OH = 10:4:1) and the resulting free base was treated with 3M HCl in methanol (2 mL) and concentrated *in vacuo* to yield 10 mg (0.044 mmol, 96%) loline ·2HCl (**2**) as a yellow oil (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 9:3:0.5), R_f = 0.12 ($KMnO_4$).

^{1}H NMR (D_2O, 400 MHz): δ= 4.82 (s, 1H), 4.80 (s, 1H), 4.75 (dd, *J*=2.3, 4.8 Hz, 1H), 4.26 (s, 1H), 4.15 (d, J=13.9 Hz, 1H), 3.82–3.76 (m, 1H), 3.76–3.70 (m, 1H), 3.60 (d, *J*=13.9 Hz, 1H), 2.83 (d, *J*=0.9 Hz, 3H), 2.42 (ddd, *J*=7.6, 10.0, 15.0 Hz, 1H), 2.31 (ddd, *J*=5.0, 8.4, 15.0 Hz, 1H).

^{13}C NMR (D_2O, 100 MHz): δ= 83.4, 74.0, 72.2, 66.0, 64.2, 58.2, 36.4, 36.1.

IR (Diamond-ATR, neat) ν_{max}: 2920, 2692, 2555, 1553, 1462, 1349, 1216, 1160, 1074, 1056, 1002, 958, 832, 793 cm^{-1}.

$[\alpha]^{25}_D$ = + 5.4° (*c* = 0.31, H_2O).

HRMS (ESI) calcd for $C_8H_{14}N_2O$ $[M+H]^+$: 155.1179; found: 155.1176.

2 **4**

***N*-Formylloline (4)**

A mixture of formic acid (0.1 mL) and acetic anhydride (0.2 mL) was stirred for 2 h at 55 °C and then added to 10 mg (0.044 mmol) loline ·2HCl (**2**). The reaction mixture was stirred at rt for 8 h before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 6.5 mg (0.036 mmol, 81%) *N*-formylloline (**4**) as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 3:1), R_f = 0.50 ($KMnO_4$).

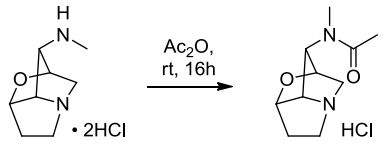
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 8.44 (s), 8.07 (s), 4.71 (d, *J*=2.1 Hz), 4.52 (dd, *J*=1.8, 4.4 Hz), 4.45 (dd, *J*=1.8, 4.4 Hz), 4.21 (d, *J*=1.6 Hz), 4.06–4.04 (m), 3.85 (d, *J*=1.3 Hz), 3.42 (s), 3.37 (s), 3.27 (d, *J*=11.9 Hz), 3.23 (d, *J*=11.6 Hz), 3.13 (s), 3.12–3.08 (m), 3.05–2.98 (m), 2.95 (d, *J*=0.5 Hz), 2.51 (d, *J*=12.0 Hz), 2.44 (d, *J*=11.8 Hz), 2.09 (ddd, *J*=7.1, 7.4, 14.4 Hz), 1.98 (dddd, *J*=4.3, 4.3, 9.4, 14.4 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 163.5, 163.2, 82.0, 80.3, 74.0, 73.1, 67.9, 67.5, 65.4, 62.4, 61.0, 60.5, 54.8, 54.6, 33.4, 33.1, 32.8, 29.9.

IR (Diamond-ATR, neat) ν_{max}: 3488, 2934, 2880, 1665, 1388, 1355, 1254, 1085, 1049, 1024, 962, 811, 751 cm^{-1}.

$[\alpha]^{25}_D$ = + 4.3° (*c* = 0.22, $CHCl_3$).

HRMS (ESI) calcd for $C_9H_{14}N_2O_2$ $[M+H]^+$: 183.1128; found: 183.1126.



2 **5**

***N*-Acetylloline HCl (5)**

18 mg (79.6 µmol, 1 eq.) loline ·2HCl (**5**) was dissolved in Ac_2O (1 mL) and the reaction mixture was stirred at rt for 16 h and then treated carefully with MeOH (3 mL) before concentrating *in vacuo*. The crude product was coevaporated with toluene (4 × 3 ml) to afford 18 mg (77.3 mmol, 97%) *N*-acetylloline HCl (**5**) as a viscous oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.38 ($KMnO_4$). *

^{1}H NMR (MeOH-d_4, 400 MHz): δ= 5.02 (d, *J*=2.0 Hz, 1H), 4.92 (s, 1H), 4.66 (dd, *J*=2.2, 4.7 Hz, 1H), 4.15 (s, 1H), 3.88 (d, *J*=12.5 Hz, 1H), 3.73 (t, *J*=7.8 Hz, 2H), 3.39 (d, *J*=12.5 Hz, 1H), 3.10 (d, *J*=0.8 Hz, 3H), 2.49–2.40 (m, 1H), 2.37–2.29 (m, 1H), 2.15 (s, 3H).

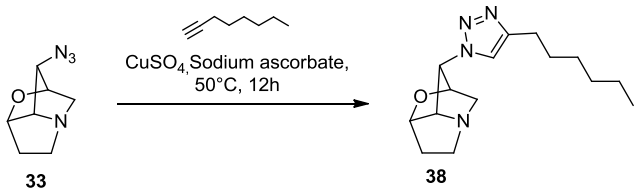
^{13}C NMR (MeOH-d_4, 150 MHz): δ= 175.8, 80.2, 74.9, 73.0, 66.6, 63.3, 54.8, 37.0, 30.9, 23.1.

IR (Diamond-ATR, neat) ν_{max}: 3388, 2927, 2538, 1751, 1638, 1474, 1399, 1347, 1311, 1215, 1144, 1090, 1036, 1015, 1001, 959, 911, 858, 844, 803, 747, 661 cm^{-1}.

$[\alpha]^{25}_D$ = + 42.8° (*c* = 0.51, $CHCl_3$).

HRMS (ESI) calcd for $C_{10}H_{16}N_2O_2$ $[M+H]^+$: 197.1290; found: 197.1285.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



33 **38**

Triazol 38

20 mg (0.120 mmol, 1.1 eq.) azide **33**, 12 mg (0.109 mmol, 1 eq.) 1-octyne, 2.4 mg (8.76 µmol, 0.08 eq.) $CuSO_4$ ·$5H_2O$ and 2.6 mg (13.2 µmol, 0.11 eq.) sodium ascorbate were

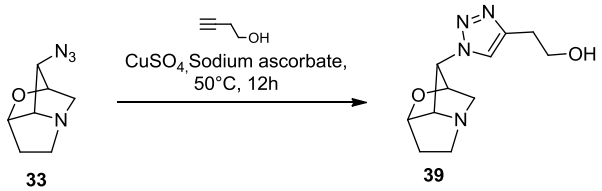
dissolved in 2.5 mL MeOH/H_2O (4/1) and the reaction mixture was stirred at 45 °C for 12 h in a sealed tube before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 98:2) to yield 24.5 mg (0.089 mmol, 82%) of the desired product **38** as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.65 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.74 (s, 1H), 5.11 (d, *J* =2.0 Hz, 1H), 4.66 (dd, *J* =1.8, 4.5 Hz, 1H), 4.53 (d, *J*=2.5 Hz, 1H), 3.60 (m, 1H), 3.16 (ddd, *J*=3.4, 8.7, 12.5 Hz, 1H), 3.07 (d, *J*=11.0 Hz, 1H), 3.09–3.04 (m, 1H), 2.69 (td, *J*=4.3, 7.5 Hz, 1H), 2.51 (d, *J*=12.2 Hz, 1H), 2.18–2.13 (m, 1H), 2.09–2.04 (m, 1H), 1.68–1.63 (m, 1H), 1.37–1.32 (m, 2H), 1.29–1.27 (m, 5H), 1.24 (s, 1H), 0.87 (t, *J*=7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 148.1, 120.9, 82.1, 75.0, 69.4, 65.7, 60.8, 55.1, 33.3, 31.6, 29.4, 29.0, 25.7, 22.6, 14.1.

HRMS (ESI) calcd for $C_{15}H_{24}N_4O$ $[M+H]^+$: 277.2028; found: 277.2026.



33 **39**

Triazol 39

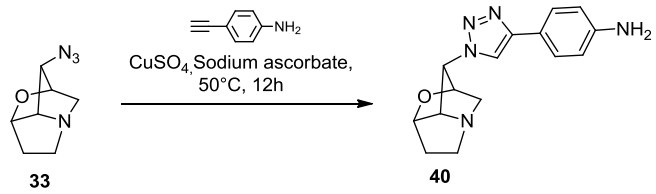
20 mg (0.120 mmol, 1.1 eq.) azide **33**, 12 mg (0.109 mmol, 1 eq.) 3-butyne-1-ol, 2.4 mg (8.76 µmol, 0.08 eq.) $CuSO_4 \cdot 5H_2O$ and 2.6 mg (13.2 µmol, 0.11 eq.) Sodium ascorbate were dissolved in 2.5 mL MeOH/H_2O (4/1) and the reaction mixture was stirred at 45 °C for 12 h in a sealed tube before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 95:5) to yield 22 mg (0.094 mmol, 85%) of the desired product **39** as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.27 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.86 (s, 1H), 5.11 (d, *J* =2.0 Hz, 1H), 4.66 (dd, *J* =1.9, 4.5 Hz, 1H), 4.58 (d, *J*=2.5 Hz, 1H), 3.96–3.90 (m, 2H), 3.64 (m, 1H), 3.17 (ddd, *J*=3.4, 8.6, 12.4 Hz, 1H), 3.08 (d, *J*=11.1 Hz, 1H), 3.07–3.04 (m, 1H), 2.94 (t, *J*=5.8 Hz, 1H), 2.53 (d, *J*=12.3 Hz, 1H), 2.28 (brs, 1H), 2.20–2.15 (m, 1H), 2.12–2.07 (m, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 145.2, 122.0, 82.0, 75.0, 69.5, 65.7, 61.6, 60.7, 55.1, 33.3, 28.7.

HRMS (ESI) calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$: 237.1352; found: 237.1344.



Triazol 40

20 mg (0.120 mmol, 1.1 eq.) azide **33**, 13 mg (0.109 mmol, 1 eq.) 4-ethynyl-aniline, 2.4 mg (8.76 µmol, 0.08 eq.) $CuSO_4 \cdot 5H_2O$ and 2.6 mg (13.2 µmol, 0.11 eq.) Sodium ascorbate were dissolved in 2.5 mL MeOH/H_2O (4/1) and the reaction mixture was stirred at 45 °C for 12 h in a sealed tube before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 27 mg (0.097 mmol, 89%) of the desired product **40** as a clear oil (one spot on TLC).

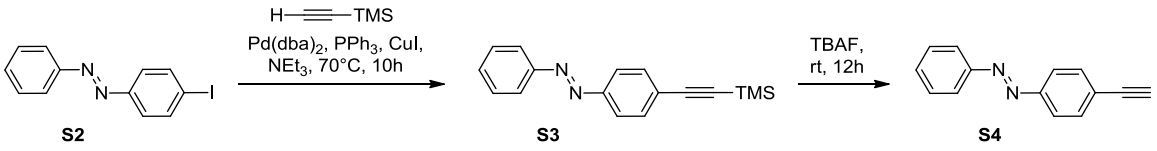
TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.45 ($KMnO_4$).*

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 8.16 (s, 1H), 7.66–7.64 (m, 2H), 6.74–6.71 (m, 2H), 5.19 (d, *J* =2.2 Hz, 1H), 4.67 (dd, *J* =1.8, 4.5 Hz, 1H), 4.56 (d, *J*=2.5 Hz, 1H), 3.74 (brs, 2H), 3.63 (s, 1H), 3.19 (ddd, *J*=3.4, 8.6, 12.4 Hz, 1H), 3.15 (d, *J*=12.4 Hz, 1H), 3.09 (ddd, *J*=7.2, 9.4, 13.0 Hz, 1H), 2.55 (d, *J*=12.3 Hz, 1H), 2.21–2.16 (m, 1H), 2.12–2.07 (m, 1H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 147.8, 145.4, 127.0, 121.1, 118.8, 115.2, 82.1, 75.0, 69.4, 65.8, 60.7, 55.2, 33.4.

HRMS (ESI) calcd for $C_{15}H_{17}N_5O$ $[M+H]^+$: 284.1511; found: 284.1503.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



Alkin S4

100 mg (0.325 mmol, 1 eq.) azobenzene **S2**, 185 µL (1.299 mmol, 4 eq.) trimethyl-silylacetylene, 2.5 mg (12.99 µmol, 0.04 eq.) CuI, 17 mg (64.9 µmol, 0.2 eq.) PPh_3, and 12 mg (12.99 µmol, 0.04 eq.) $Pd(dba)_2$ was dissolved in NEt_3 (2 mL). The reaction mixture was freeze-pump-thaw degassed three times and then heated to 70°C for 10 h. The reaction

mixture was diluted with EtOAc (10 mL) and filtered through a plug af silica. The silica pad was washed with EtOAc (20 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 86 mg of the crude product **S3** as an orange solid, which was used without further purification.

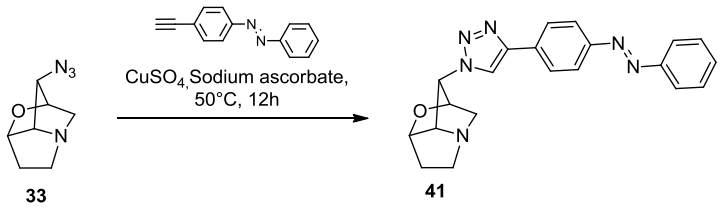
86 mg (0.309 mmol, 1 eq) of crude TMS-alkin **S3** was dissolved in 6 mL THF/H_2O (5/1) and treated with 340 µL (0.340 mmol, 1.1 eq., 1M solution in THF) TBAF. The reaction mixture was stirred at rt for 12 h before concentrating *in vacuo*. The crude product was dissolved in EtOAc (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:CH_2Cl_2 = 4:1) to yield 57 mg (0.277 mmol, 85% over two steps) of the desired product **S4** as an orange solid (one spot on TLC).

TLC ((hexanes:EtOAc = 9:1), R_f = 0.67 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.93–7.88 (m, 4H), 7.64–7.63 (m, 2H), 7.54–7.43 (m, 3H), 3.23 (s, 1H).

IR (Diamond-ATR, neat) ν_{max}: 3278, 1584, 1493, 1481, 1462, 1440, 1395, 1299, 1242, 1216, 1155, 1106, 1016, 1006, 853, 771, 725, 683 cm^{-1}.

HRMS (EI) calcd for $C_{14}H_{10}N_2$ $[M]^+$: 206.0844; found: 206.0828.



33 41

Triazol 41

10 mg (0.060 mmol, 1.1 eq.) azide **33**, 11.3 mg (0.055 mmol, 1 eq.) alkin **S4**, 1.2 mg (4.82 µmol, 0.08 eq.) $CuSO_4 \cdot 5H_2O$ and 1.2 mg (6.02 µmol, 0.10 eq.) sodium ascorbate were dissolved in 1.25 mL MeOH/H_2O (4/1) and the reaction mixture was stirred at 45 °C for 12 h in a sealed tube before concentrating *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 95:5) to yield 20 mg (0.054 mmol, 98%) of the desired product **41** as a orange solid (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.44 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 8.43 (s, 1H), 8.04–8.02 (m, 2H), 8.00–7.98 (m, 2H), 7.94–7.92 (m, 2H), 7.54–7.51 (m, 2H), 7.49–7.46 (m, 1H), 5.25 (d, *J* =2.3 Hz, 1H), 4.70 (dd, *J*

=1.8, 4.5 Hz, 1H), 4.60 (d, *J*=2.5 Hz, 1H), 3.70 (m, 1H), 3.23 (ddd, *J* =3.4, 8.6, 12.4 Hz, 1H), 3.18 (d, *J*=12.4 Hz 1H), 3.16–3.07 (m, 1H), 2.60 (d, *J*=12.5 Hz, 1H), 2.24–2.19 (m, 1H), 2.15–2.10 (m, 1H).*

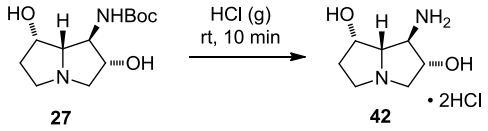
^{13}C NMR ($CDCl_3$, 150 MHz): δ= 152.7, 152.2, 146.7, 133.0, 131.0, 129.1, 128.8, 126.4, 126.0, 123.5, 122.9, 121.3, 120.8, 120.4, 82.1, 82.1, 75.0, 75.0, 69.4, 69.4, 65.9, 65.9, 60.7, 60.7, 55.2, 55.2, 33.3, 33.2.

IR (Diamond-ATR, neat) ν_{max}: 2931, 1606, 1444, 1434, 1217, 1054, 1024, 962, 854, 835, 810, 770, 743, 687 cm^{-1}.

$[\alpha]^{25}_D$ = + 13.0° (*c* = 0.37, $CHCl_3$).

HRMS (ESI) calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$: 373.1777; found: 373.1776.

* Signals only of the major *trans*-isomer are reported.



27 42

Aminodiol 42

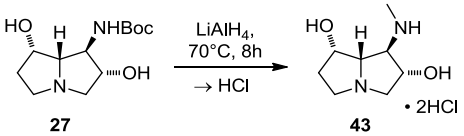
Through a solution of 13 mg (50.3 µmol, 1 eq.) N-Boc diol **27** in EtOAc (5 mL) and MeOH (0.2 mL) was bubbled HCl for 10 min at rt and the resulting colorless solid was filtered to yield 11.5 mg (49.7µmol, 99%) of the desired amine **42** (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 10:8:1), R_f = 0.16 ($KMnO_4$).

^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.62–4.56 (m, 2H), 4.20 (dd, *J*=4.4, 7.3 Hz, 1H), 4.02 (t, *J*=7.8 Hz, 1H), 3.94 (dd, *J*=6.4, 11.2 Hz, 1H), 3.83–3.77 (m, 1H), 3.40 (td, *J*=6.4, 11.5 Hz, 1H), 3.06 (t, *J*=10.5 Hz, 1H), 2.33–2.18 (m, 2H).

^{13}C NMR (MeOH-d_4, 151 MHz): δ= 74.6, 71.9, 69.4, 59.2, 54.4, 54.0, 36.5.

HRMS (EI) calcd for $C_7H_{14}N_2O_2$ [M]: 158.1055; found: 158.1022.



27 43

***N*-Me-amine 43**

A solution of 11 mg (42.6 µmol, 1 eq.) *N*-Boc diol **27** in THF (6 mL) was treated with 256 µL (0.256 mmol, 6 eq., 1M solution in THF) $LiAlH_4$ and heated to 70 °C for 8 h. The reaction

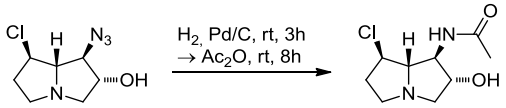
mixture was quenched with 1M aq. NaOH (0.3 mL) and 0.5 g silica was added and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH:NH_4OH = 10:5:1) and the resulting free base was treated with 3M HCl in methanol (2 mL) and concentrated *in vacuo* to yield 10 mg (41.0 μmol, 96%) of the desired *N*-Me-amine **43** as a colorless solid (one spot on TLC).

TLC ($CHCl_3$:MeOH:NH_4OH = 10:5:1), R_f = 0.20 ($KMnO_4$).

^{1}H NMR (D_2O, 300 MHz): δ= 4.89–4.83 (m, 1H), 4.78–4.73 (m, 1H), 4.47 (t, *J*=5.7 Hz, 1H), 4.16–4.11 (m, 2H), 3.96 (ddd, *J*=2.7, 7.9, 10.7 Hz 1H), 3.31 (td, *J*=7.0, 11.6 Hz, 1H), 3.27 (dd, *J*=10.0, 11.5 Hz, 1H), 2.96 (s, 3H), 2.46–2.30 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ= 72.3, 69.9, 68.8, 60.0, 57.8, 53.6, 34.7, 32.1.

HRMS (ESI) calcd for $C_8H_{16}N_2O_2$ $[M+H]^+$: 173.1285; found: 173.1285.



32 **44**

***N*-Acetyl chloro pyrrolizidine (44)**

A solution of 30 mg (0.148 mmol, 1.0 eq.) azide **44** and 7.9 mg (7.42 μmol, 0.05 eq.) 10% Pd/C in THF (9 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 3 h at rt under H_2 atmosphere (balloon). The atmosphere was exchanged for N_2 and 18 mg (0.178 mmol, 1.2 eq.) Ac_2O was added. The reaction mixture was stirred for 8 h, filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 6:1) to yield 22 mg (0.102 mmol, 69%) of the desired product **44** as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 4:1), R_f = 0.19 ($KMnO_4$).

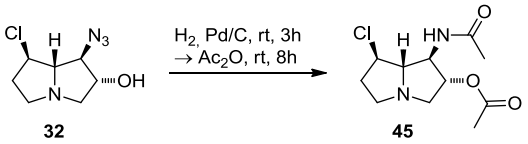
^{1}H NMR ($CDCl_3$, 400 MHz): δ= 6.83 (d, *J*=4.8 Hz, 1H), 4.38 (dd, *J*=6.0, 11.3 Hz, 1H), 4.17 (dd, *J*=5.5, 11.6 Hz, 1H), 3.97 (q, *J*=5.6 Hz, 1H), 3.52 (t, *J*=5.4 Hz, 1H), 3.39 (dd, *J*=5.5, 10.7 Hz, 1H), 3.32 (dt, *J*=6.5, 11.1 Hz, 1H), 2.90 (dt, *J*=6.5, 11.0 Hz, 1H), 2.67 (dd, *J*=6.3, 10.7 Hz, 1H), 2.51–2.43 (m, 1H), 2.10–2.01 (m, 1H), 2.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 172.0, 77.3, 61.9, 60.8, 59.9, 53.3, 35.4, 29.7, 23.1.

IR (Diamond-ATR, neat) ν_{max}: 3290, 2923, 2853, 1649, 1538, 1371, 1312, 1260, 1127, 1082, 1034, 727, 703 cm^{-1}.

$[\alpha]^{25}_D$ = – 9.2° (*c* = 0.45, $CHCl_3$).

HRMS (ESI) calcd for $C_9H_{15}ClN_2O_2$ $[M+H]^+$: 219.0900; found: 219.0893.



32 **45**

***N,O*-diacetyl chloro pyrrolizidine (45)**

A solution of 30 mg (0.148 mmol, 1.0 eq.) azide **33** and 7.9 mg (7.42 µmol, 0.05 eq.) 10% Pd/C in THF (9 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 3 h at rt under H_2 atmosphere (balloon). The atmosphere was exchanged for N_2 and 18 mg (0.296 mmol, 2.0 eq.) Ac_2O was added. The reaction mixture was stirred for 8 h, filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 9:1) to yield 10 mg (0.038 mmol, 26%) of the desired product **45** as a colorless solid (one spot on TLC).

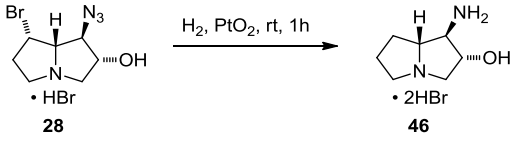
TLC ($CHCl_3$:MeOH = 4:1), R_f = 0.51 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 6.08 (d, *J*=6.6 Hz, 1H), 5.15 (dd, *J*=7.2, 13.4 Hz, 1H), 4.58–4.56 (m, 1H), 4.11 (q, *J*=7.2 Hz, 1H), 3.45 (dd, *J*=6.1, 10.5 Hz, 1H), 3.37 (dd, *J*=3.1, 7.1 Hz, 1H), 3.30 (ddd, *J*=5.9, 8.6, 11.2 Hz, 1H), 2.80 (ddd, *J*=4.2, 6.8, 11.1 Hz, 1H), 2.69 (dd, *J*=7.3, 10.5 Hz, 1H), 2.39–2.33 (m, 1H), 2.04 (s, 3H), 2.03–2.00 (m, 1H), 1.99 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ= 170.8, 170.5, 78.4, 76.2, 61.3, 58.3, 56.8, 53.2, 34.4, 23.2, 20.9.

IR (Diamond-ATR, neat) ν_{max}: 3178, 2924, 2917, 1713, 1649, 1446, 1368, 1292, 1243, 1110, 1032, 1029, 786, 757, 723 cm^{-1}.

HRMS (ESI) calcd for $C_{11}H_{17}ClN_2O_2$ $[M+H]^+$: 261.1006; found: 261.0999.



28 **46**

Pyrrolizidine (47)

A solution of 45 mg (0.138 mmol, 1.0 eq.) azide **15** and 3 mg (13.8 µmol, 0.1 eq.) PtO_2 in H_2O (3 mL) was degassed with N_2 in a sonicator for 5 minutes, then flushed with H_2 (3 ×) and stirred for 1 h at rt under H_2 atmosphere (balloon) until a black precipitation was formed. The

reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to yield 36 mg (0.120 mmol, 87%) of the desired product **46** as a colorless solid (one spot on TLC).

TLC ($CHCl_3$:MeOH = 2:1), R_f = 0.10 ($KMnO_4$).*

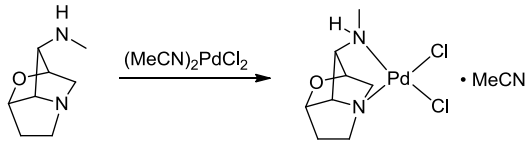
^{1}H NMR (MeOH-d_4, 400 MHz): δ= 4.07 (q, *J*=5.3 Hz, 1H), 3.65 (m, 2H), 3.43–3.38 (m, 1H), 3.16–3.10 (m, 2H), 2.95 (ddd, *J*=2.4, 5.5, 11.6 Hz, 1H), 2.25–2.01 (m, 2H), 1.93–1.84 (m, 1H).

^{13}C NMR (MeOH-d_4, 75 MHz): δ= 78.2, 73.4, 63.7, 59.7, 57.5, 31.1, 26.1.

IR (Diamond-ATR, neat) ν_{max}: 3228, 2910, 2597, 1572, 1480, 1406, 1338, 1127, 1038, 869 cm^{-1}.

HRMS (ESI) calcd for $C_7H_{14}N_2O$ $[M+H]^+$: 143.1184; found: 143.1181.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



2 **47**

Palladium complex 47

17 mg (96.0 µmol, 1.0 eq.) $PdCl_2$ was suspended in MeCN (3mL) and heated to 90 °C for 2 h until the formation of $(MeCN)_2PdCl_2$ was indicated by the color change from yellow to orange. The reaction mixture was cooled down to rt and 15 mg (97.0 µmol, 1.0 eq.) loline (**2**) in MeCN (1 mL) was added. The reaction mixture was stirred at rt for 12 h before concentrating *in vacuo*. The resulting solid was triturated with Et_2O (10 mL) and filtered off to afford 28 mg (75.7 µmol, 79%) Palladium complex **47** as an orange solid.

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.53 ($KMnO_4$).

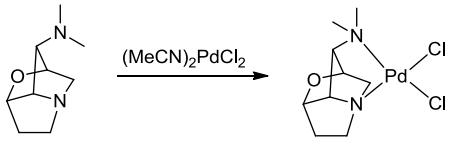
^{1}H NMR ($CDCl_3$, 600 MHz): δ= 6.07 (s, 1H), 5.44 (s, 1H), 5.15 (dd, *J*=1.9, 13.1 Hz, 1H), 4.57 (dd, *J*=2.7, 5.9 Hz, 1H), 4.32 (s, 1H), 3.29 (ddd, *J*=1.5, 7.9, 12.1 Hz, 1H), 3.22 (s, 1H), 3.10 (dt, *J*=8.9, 12.4 Hz, 1H), 2.96 (d, *J*=13.1 Hz, 3H) 2.53 (d, *J*=6.3 Hz, 3H), 2.24 (dddd, *J*=1.9, 6.2, 9.1, 15.3 Hz, 1H), 2.13 (dt, *J*=5.1, 8.3 Hz, 1H), 2.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ= 116.3, 79.6, 78.1, 72.5, 65.3, 64.2, 54.8, 37.0, 31.8, 1.9.

IR (Diamond-ATR, neat) ν_{max}: 3367, 2919, 2687, 1627, 1469, 1342, 1283, 1213, 1164, 1048, 1002, 957, 833, 795 cm^{-1}.

$[\alpha]^{25}_{D}$ = + 21.6° (*c* = 0.31, $CDCl_3$).

HRMS (ESI) calcd for $C_{10}H_{16}ClN_3OPd$ $[M+H]^+$: 336.0095 and 338.0095; found: 336.0096 and 338.0093.



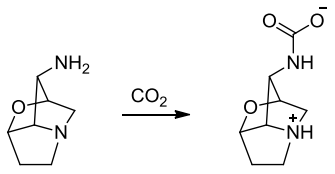
3 48

Palladium complex 48

17 mg (96.0 μmol, 1.0 eq.) $PdCl_2$ was suspended in MeCN (3mL) and heat to 90 °C for 2 h until the formation of $(MeCN)_2PdCl_2$ was indicated by the color change from yellow to orange. The reaction mixture was cooled down to rt and 16 mg (95.0 μmol, 1 eq.) *N*-methyl loline (**3**) in MeCN (1 mL) was added. The reaction mixture was stirred at rt for 12 h before concentrating *in vacuo*. The resulting solid was triturated with Et_2O (10 mL) and filtered off to afford 28 mg (81.1 μmol, 85%) Palladium complex **48** as an orange solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ= 5.00 (dd, *J*=2.0, 13.6 Hz, 1H), 4.48 (dd, *J*=2.7, 5.2 Hz, 1H), 4.43 (s, 1H), 4.38 (s, 1H), 3.19–3.11 (m, 1H), 3.06–3.00 (m, 2H), 2.93 (s, 3H), 2.63–2.58 (m, 1H), 2.50 (s, 3H), 2.14–2.02 (m, 2H).

^{13}C NMR (DMSO-d_6, 100 MHz): δ= 78.2, 77.3, 73.9, 72.4, 63.1, 54.2, 51.3. 46.9, 31.2.



1 49

Temuline carbamate (49)

CO_2 was bubbled trough a solution of 14 mg (0.1 mmol) temuline (**1**) in methanol (5 mL) for 2 min. The reaction mixture was concentrated down to afford 18.2 mg (0.099 mmol, 99%) temuline carbamate (**49**) as a colourless crystalline solid.

TLC ($CHCl_3$:MeOH = 7:3), R_f = 0.27 ($KMnO_4$).*

^{1}H NMR (MeOH-d_4, 600 MHz): δ= 4.61 (dd, *J*=2.2, 5.0 Hz, 1H), 4.33 (s, 1H), 4.27 (s, 1H), 4.18 (d, *J*=12.0 Hz, 1H), 3.95 (d, *J*=2.2 Hz, 1H), 3.67 (ddd, *J*=3.6, 9.0, 12.4 Hz, 1H), 3.59–3.54 (m, 1H), 3.19 (d, *J*=12.0 Hz, 1H), 2.43–2.37 (m, 1H), 2.31–2.26 (m, 1H).

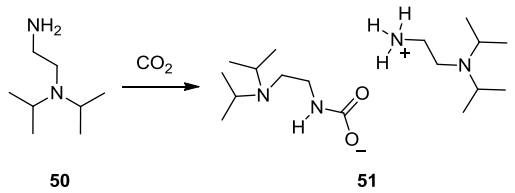
^{13}C NMR (MeOH-d_4, 151 MHz): δ= 79.3, 74.9, 74.0, 61.3, 57.8, 52.5, 29.9.

IR (Diamond-ATR, neat) ν_{max}: 3354, 2921, 2784, 2549, 1653, 1475, 1444, 1375, 1343, 1215, 1181, 1085, 1001, 963, 937, 836, 799, 778cm^{-1}.

$[\alpha]^{25}_D$ = – 46.0° (*c* = 0.19, MeOH).

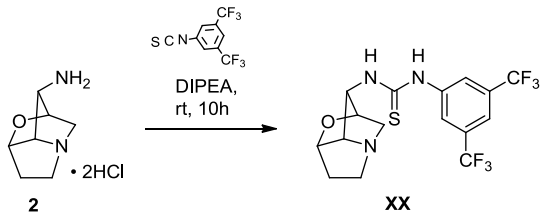
HRMS (EI) calcd for $C_8H_{12}N_2O_3$ [M–CO_2]: 140.0944; found: 140.0936.

** Note: TLC was saturated with NH_3 before running in the solvent mixture.*



Carbamate (51)

CO_2 was bubbled trough a solution of 100 mg (0.69 mmol) amine (**50**) in acetonitrile (15 mL) for 10 min. Slow evaporation of the solvent gave X-ray suitable crystals of carbamate (**51**).



Thiourea **XX**

5 mg (23.58 μmol; 1 eq.) temuline ·2HCl (**2**), 7.5 μl (49.52 μmol, 2.1 eq.) DIPEA and 6.1 mg (22.41 μmol, 0.95 eq.) Isothiocyanate was dissolved in CH_2Cl_2 (1 mL) and stirred at rt for 10 h. The reaction mixture was concentrating *in vacuo* and the crude product was purified by flash column chromatography ($CHCl_3$:MeOH = 95:5) to yield 9 mg (21.73 mmol, 98%) of the desired product **XX** as a clear oil (one spot on TLC).

TLC ($CHCl_3$:MeOH = 9:1), R_f = 0.34 ($KMnO_4$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ= 7.90 (s, 2H), 7.69 (s, 1H), 4.83 (s, 1H), 4.53 (dd, *J*=1.9, 4.6 Hz, 1H), 4.46 (s, 1H), 3.64 (m, 1H), 3.33 (d, *J*=12.0 Hz, 1H), 3.31 (s, 1H), 3.07–3.03 (m,

1H), 2.92–2.87 (m, 1H), 2.50 (d, *J*=12.0 Hz, 1H), 2.26 (brs, 2H), 2.16–2.11 (m, 1H), 2.08–2.03 (m, 1H).

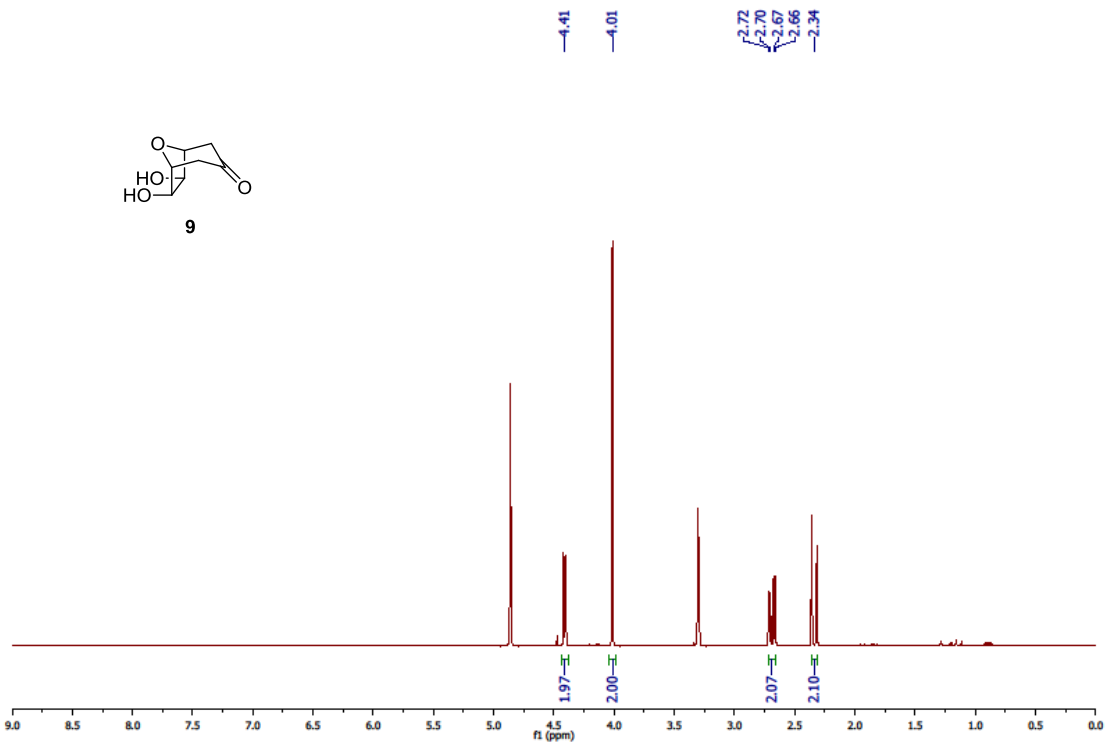
^{13}C NMR ($CDCl_3$, 150 MHz): δ= 181.2, 139.5, 132.6, 123.7, 121.9, 120.1, 119.2, 80.7, 73.7, 69.4, 60.9. 54.6, 33.6.

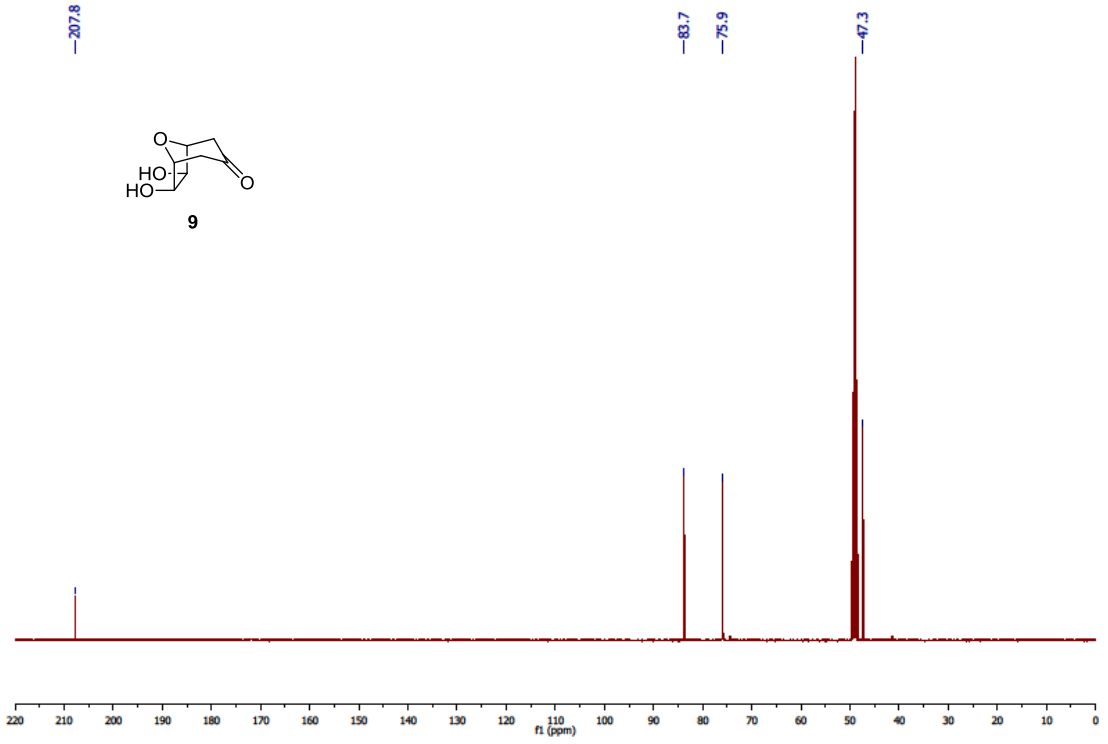
IR (Diamond-ATR, neat) ν_{max}: 2948, 1538, 1472, 1383, 1275, 1173, 1129, 955, 884, 847, 792, 759, 700, 682 cm^{-1}.

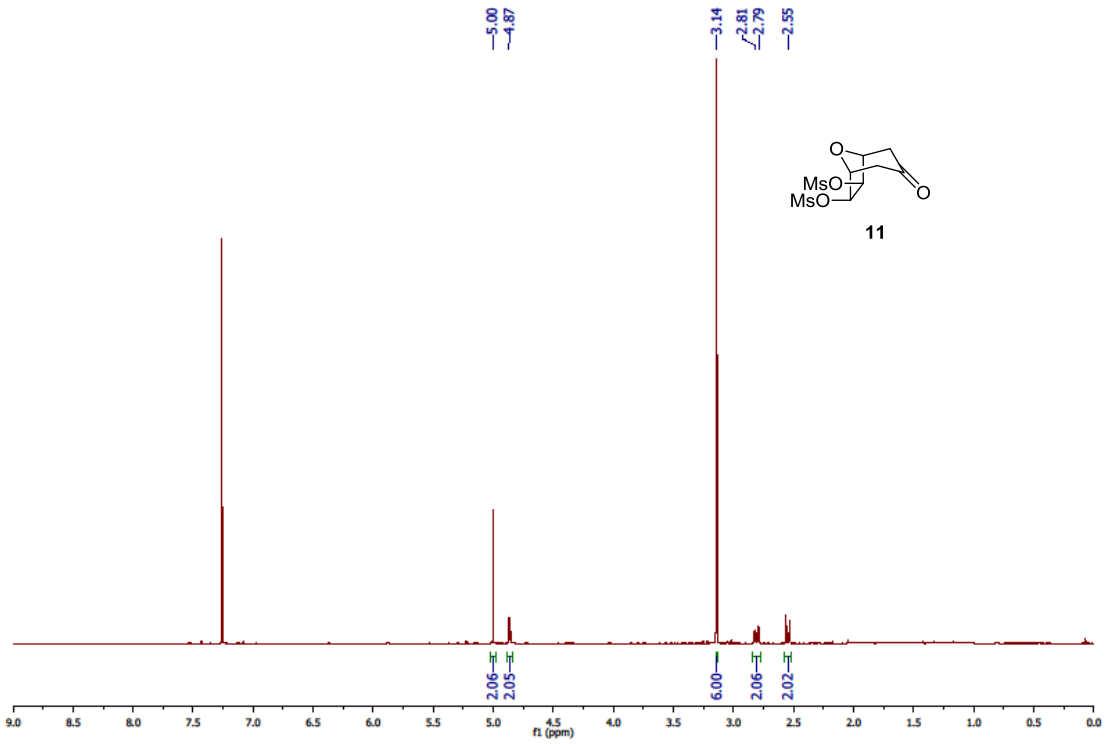
$[\alpha]^{25}_{D}$ = + 11.4° (*c* = 0.19, $CHCl_3$).

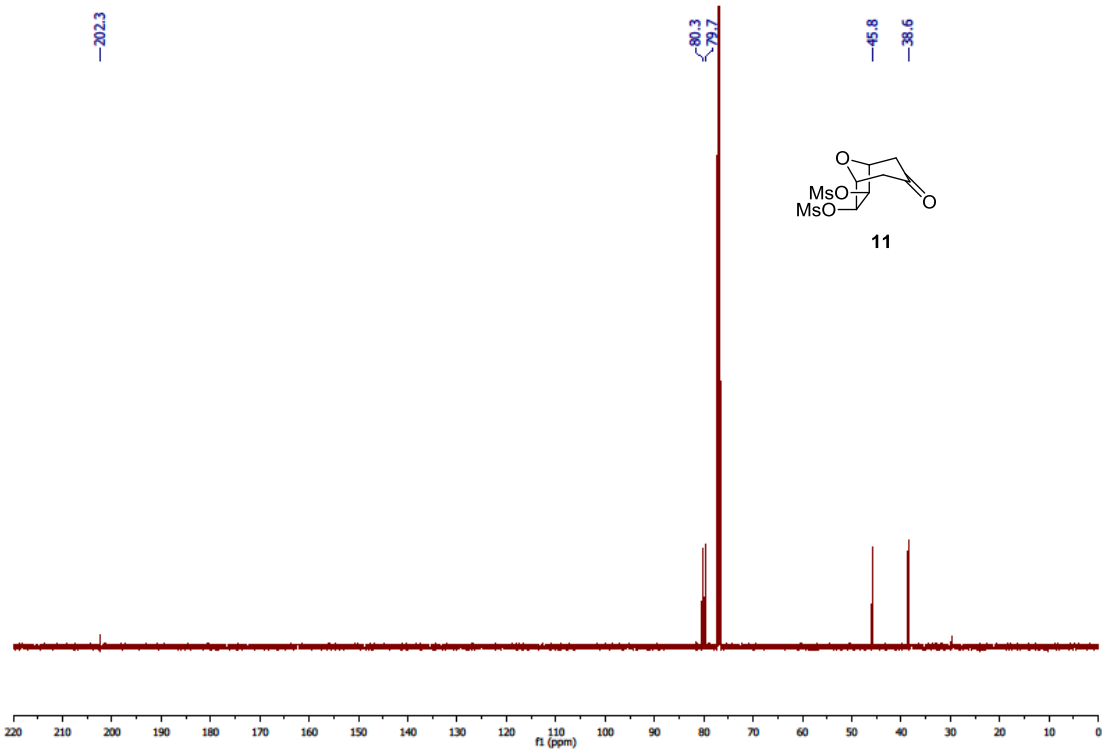
HRMS (ESI) calcd for $C_{16}H_{15}ON_3F_6S$ $[M+H]^+$: 412.0918; found: 412.0914.

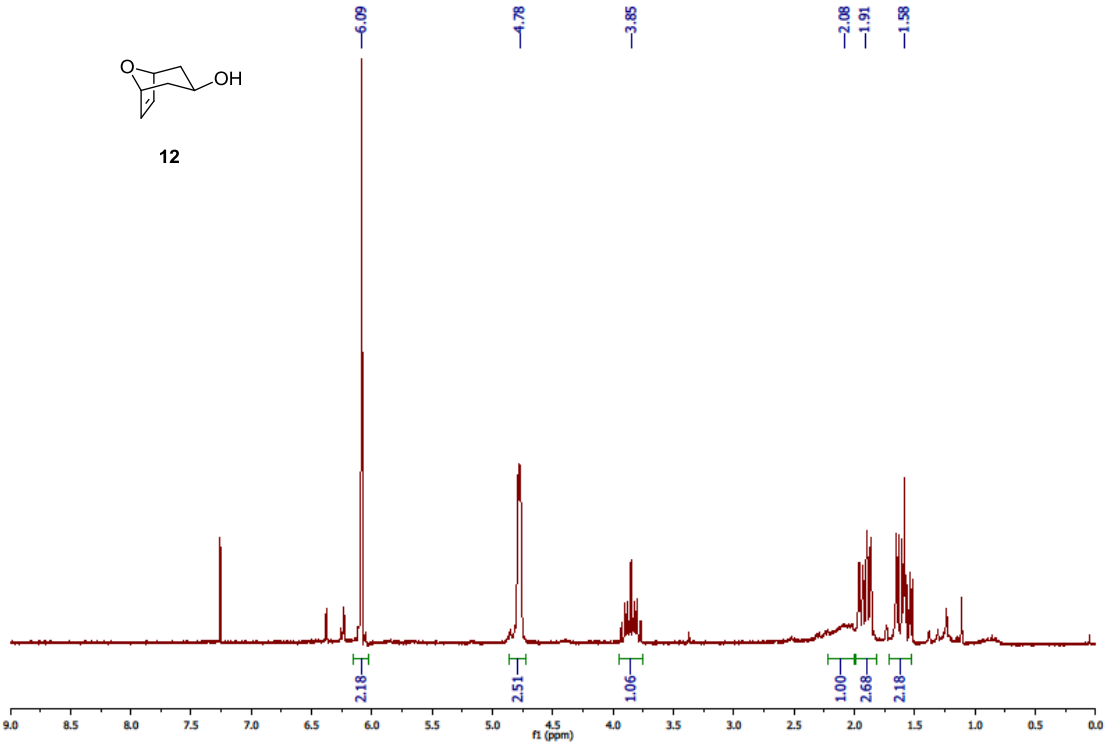
NMR spectra.


4.41
4.01
2.72
2.70
2.67
2.66
2.34
HO
HO
O
O
9
1.97
2.00
2.07
2.10
f1 (ppm)

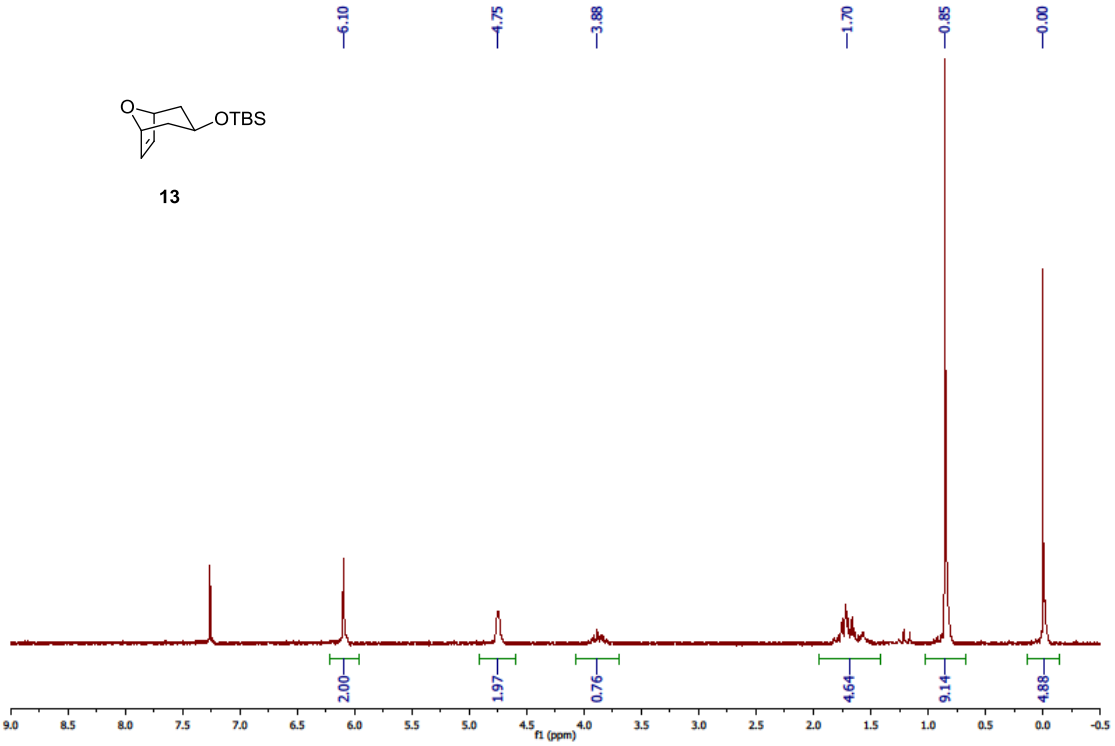

207.8
83.7
75.9
47.3
HO
HO
O
O
9
f1 (ppm)


5.00
4.87
3.14
2.81
2.79
2.55
MsO
MsO
O
O
11
2.06
2.05
6.00
2.06
2.02
f1 (ppm)

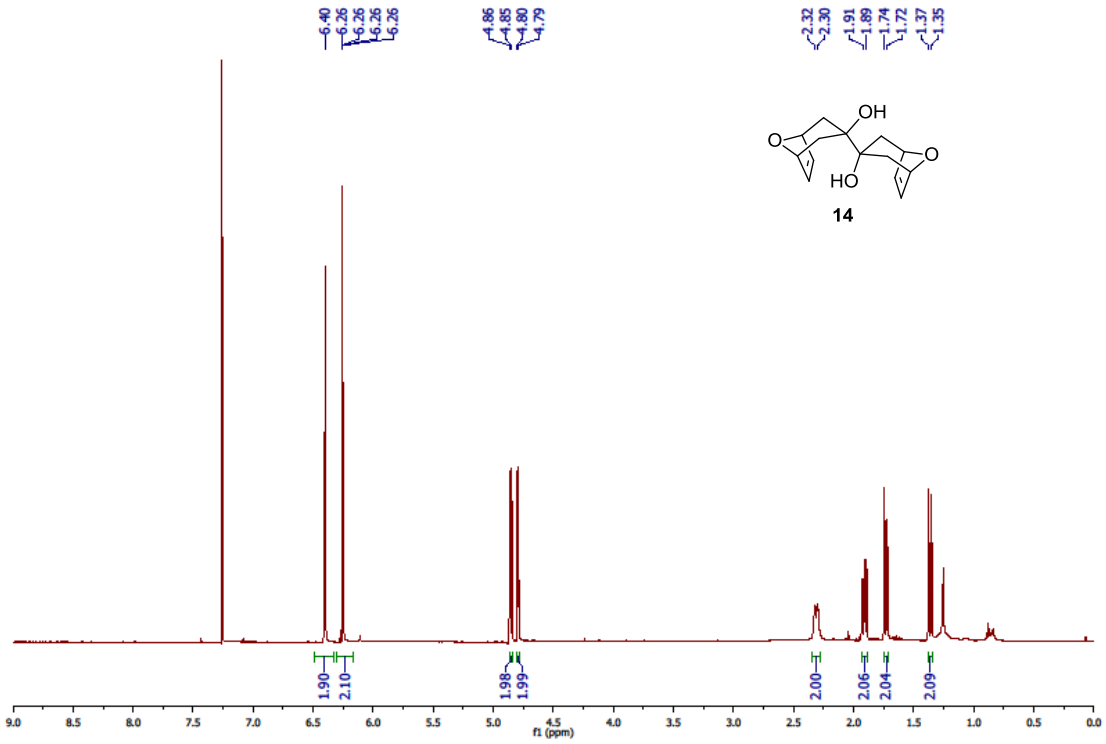

202.3
80.3
79.7
45.8
38.6
MsO
MsO
O
O
11
f1 (ppm)

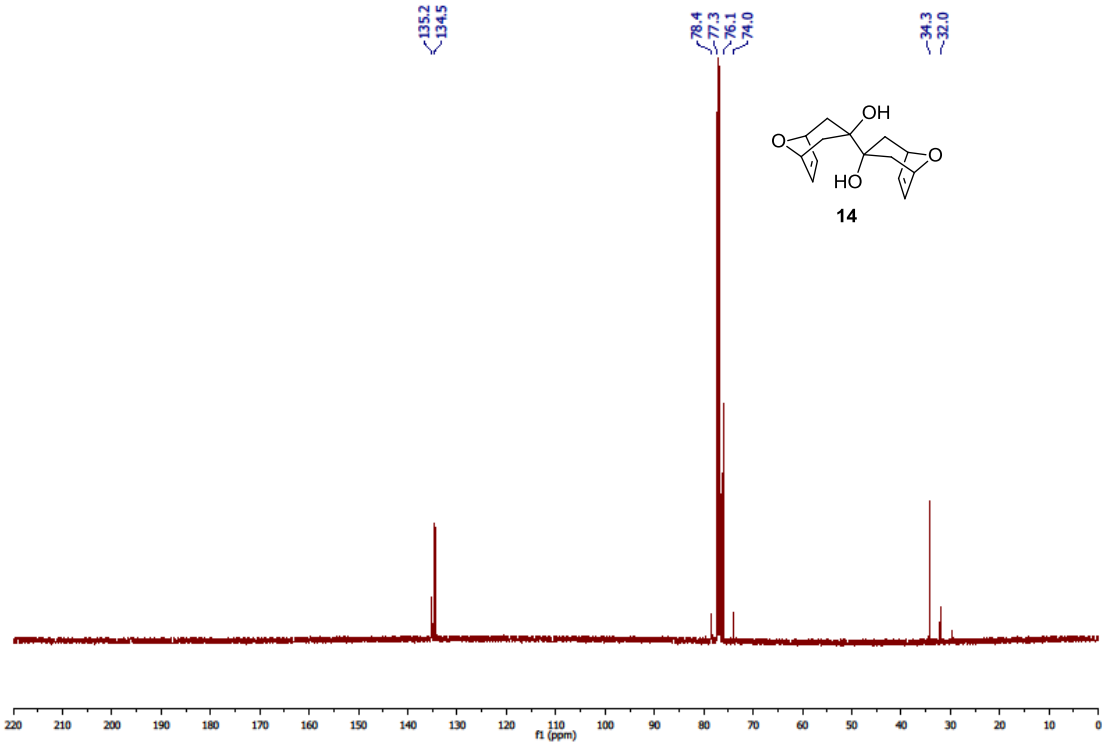

OH
6.09
4.78
3.85
2.08
1.91
1.58
2.18
2.51
1.06
1.00
2.68
2.18
f1 (ppm)

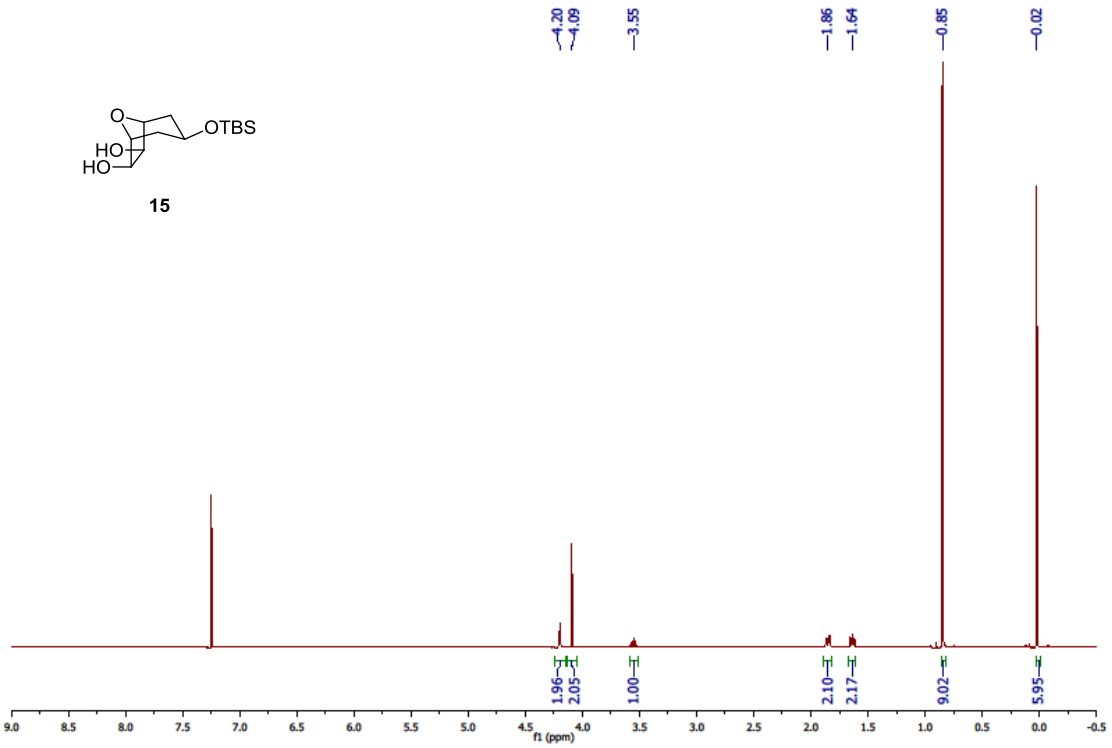
12


OTBS
6.10
4.75
3.88
1.70
0.85
0.00
2.00
1.97
0.76
4.64
9.14
4.88
f1 (ppm)

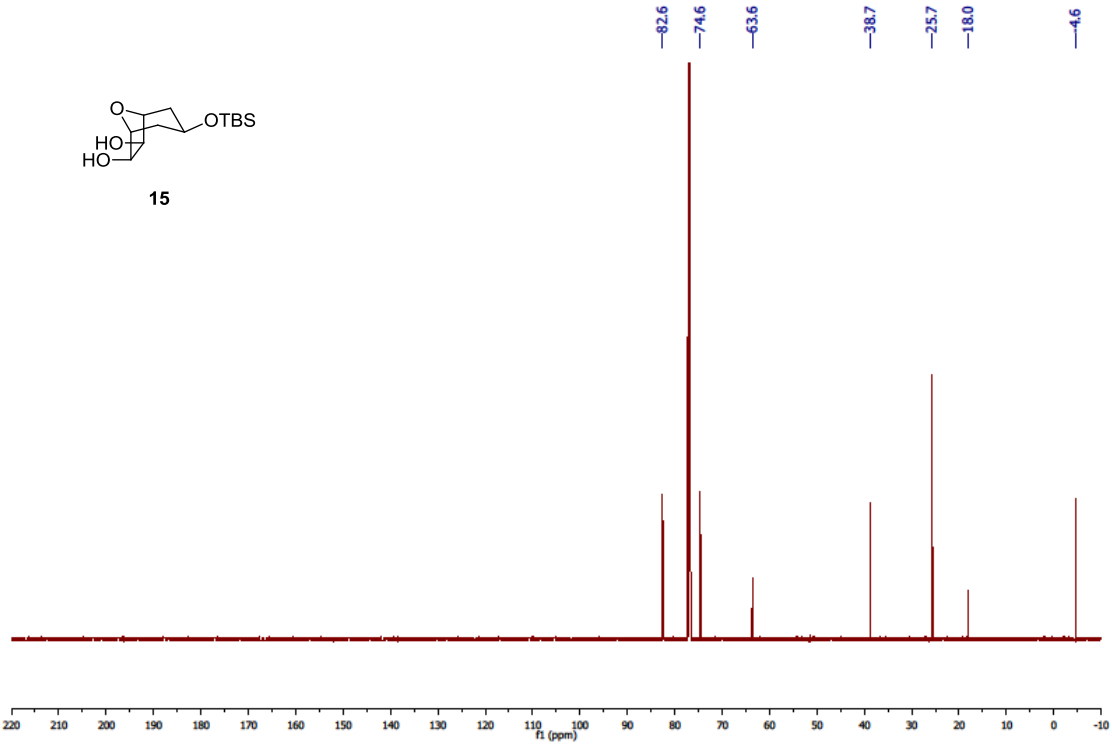
13


6.40
6.26
6.26
6.26
6.26
4.86
4.85
4.80
4.79
2.32
2.30
1.91
1.89
1.74
1.72
1.37
1.35
OH
O
O
HO
14
1.90
2.10
1.98
1.99
2.00
2.06
2.04
2.09
f1 (ppm)

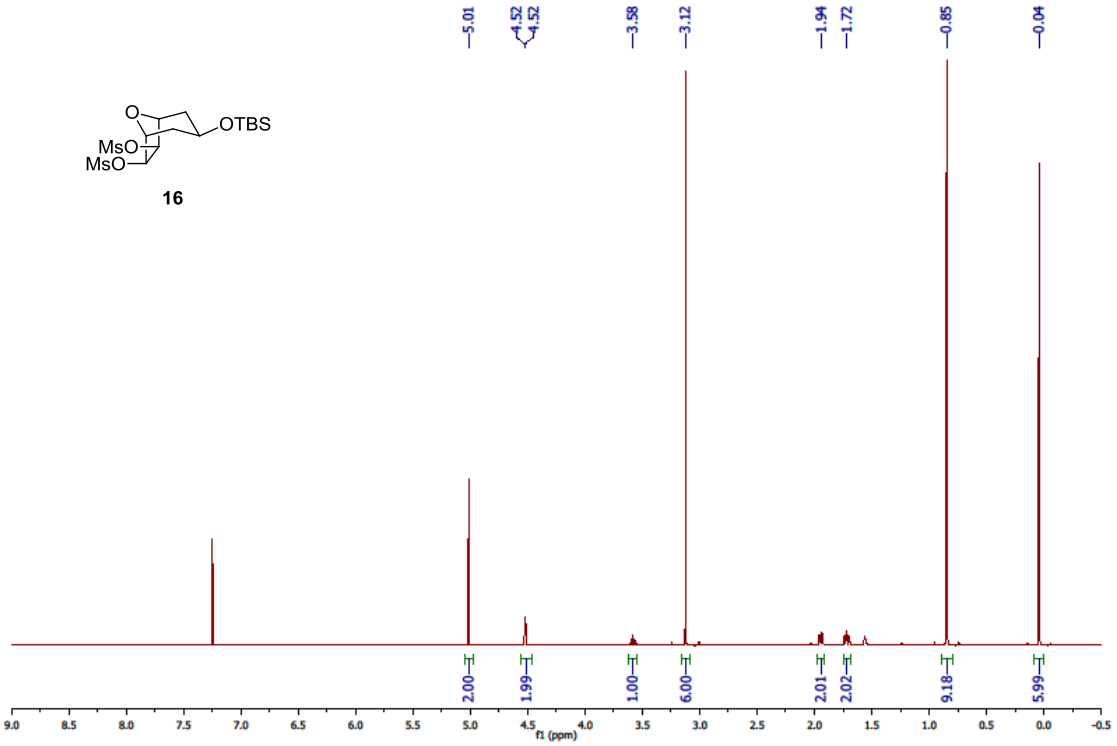

135.2
134.5
78.4
77.3
76.1
74.0
34.3
32.0
OH
O
O
HO
14
f1 (ppm)

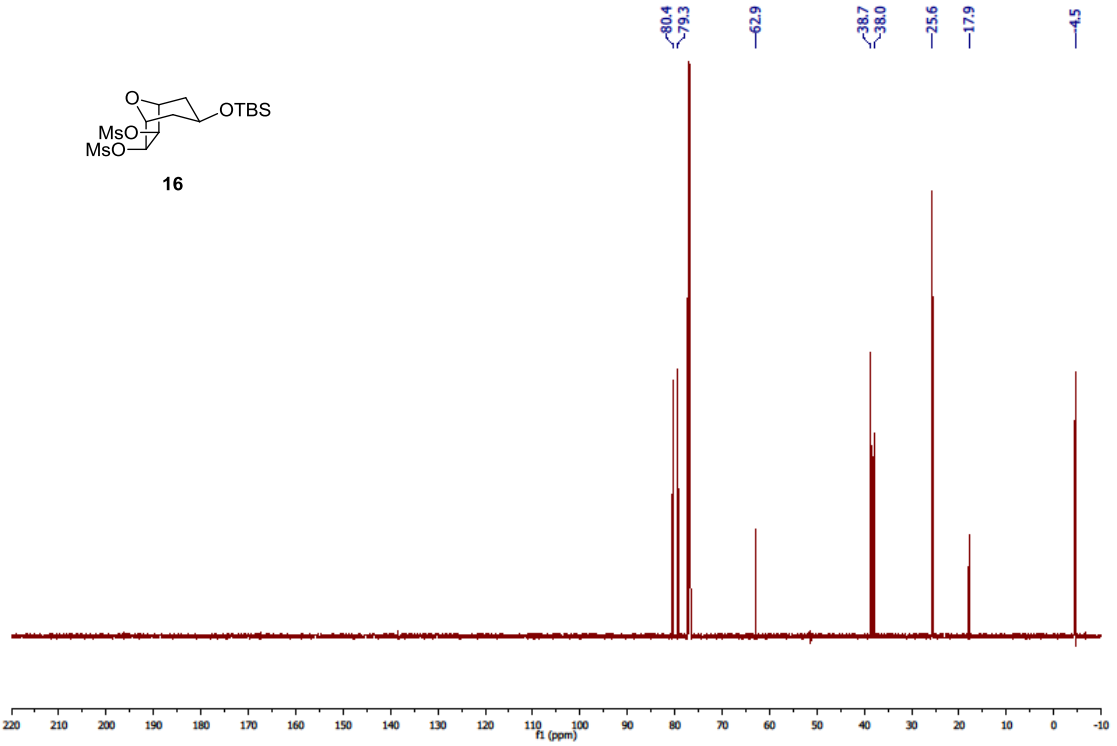

4.20
4.09
3.55
1.86
1.64
0.85
0.02
OTBS
HO
HO
1.96
2.05
1.00
2.10
2.17
9.02
5.95
f1 (ppm)

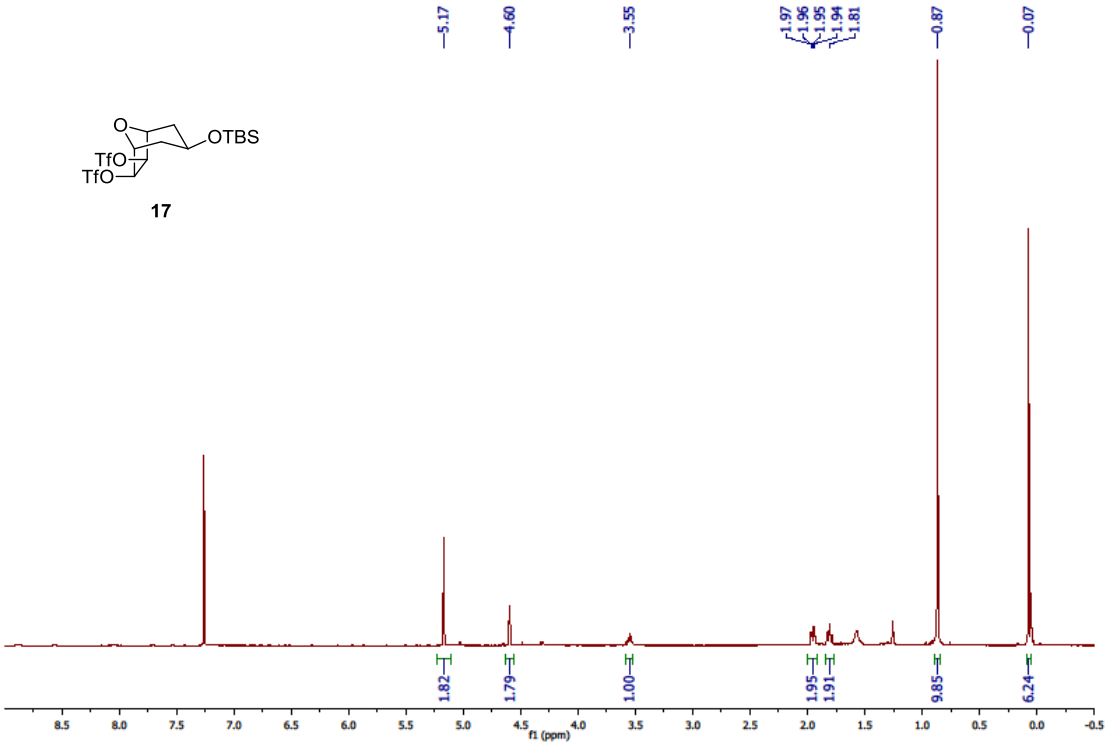
15


82.6
74.6
63.6
38.7
25.7
18.0
4.6
OTBS
HO
HO
f1 (ppm)

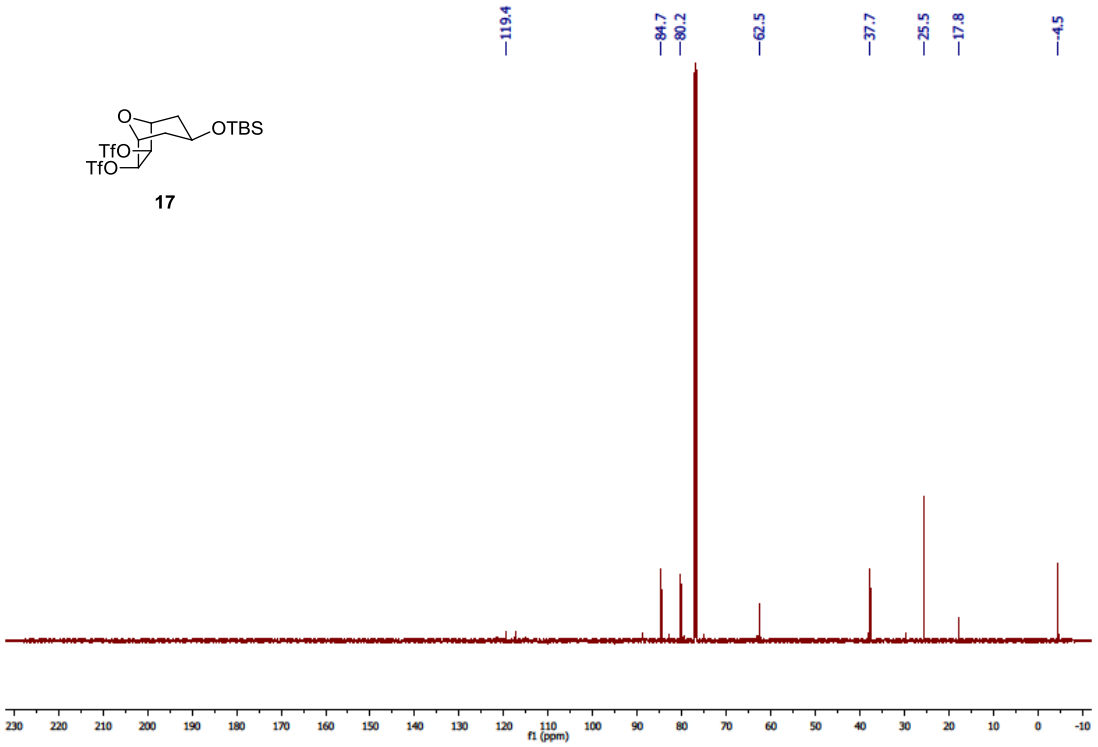
15


OTBS
MsO
MsO
16
5.01
4.52
4.52
3.58
3.12
1.94
1.72
0.85
0.04
2.00
1.99
1.00
6.00
2.01
2.02
9.18
5.99
f1 (ppm)

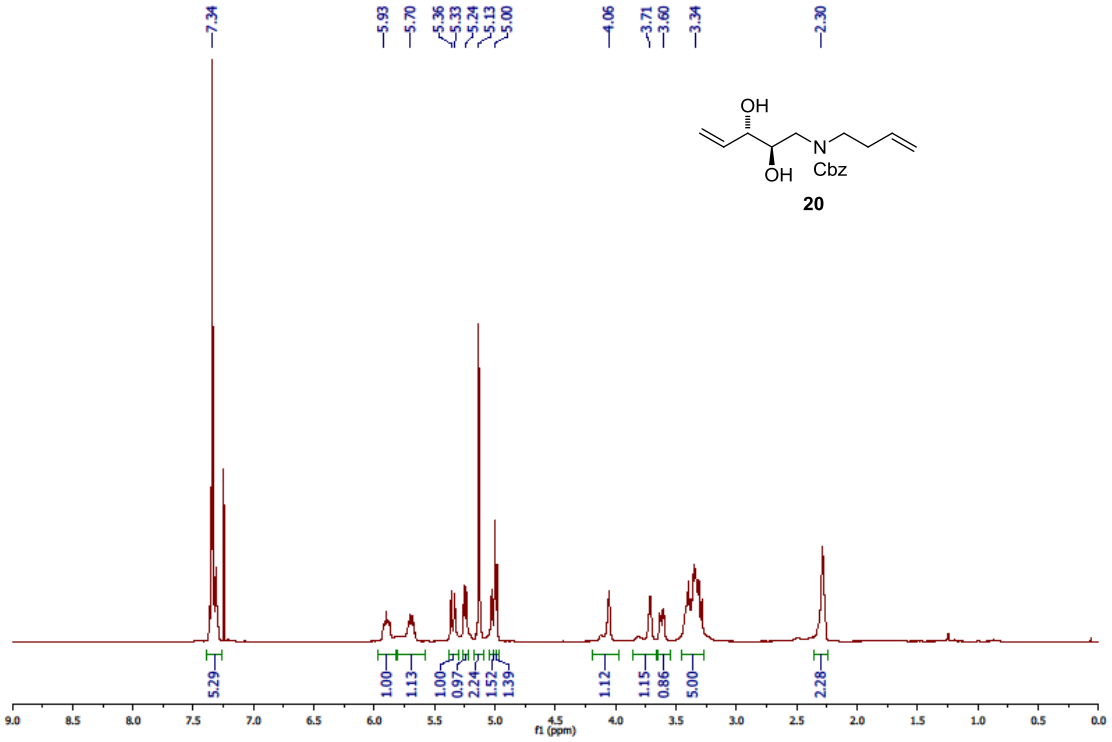

OTBS
MsO
MsO
16
80.4
79.3
62.9
38.7
38.0
25.6
17.9
-4.5
f1 (ppm)


5.17
4.60
3.55
1.97
1.96
1.95
1.94
1.81
0.87
0.07
OTBS
TfO
TfO
1.82
1.79
1.00
1.95
1.91
9.85
6.24
f1 (ppm)

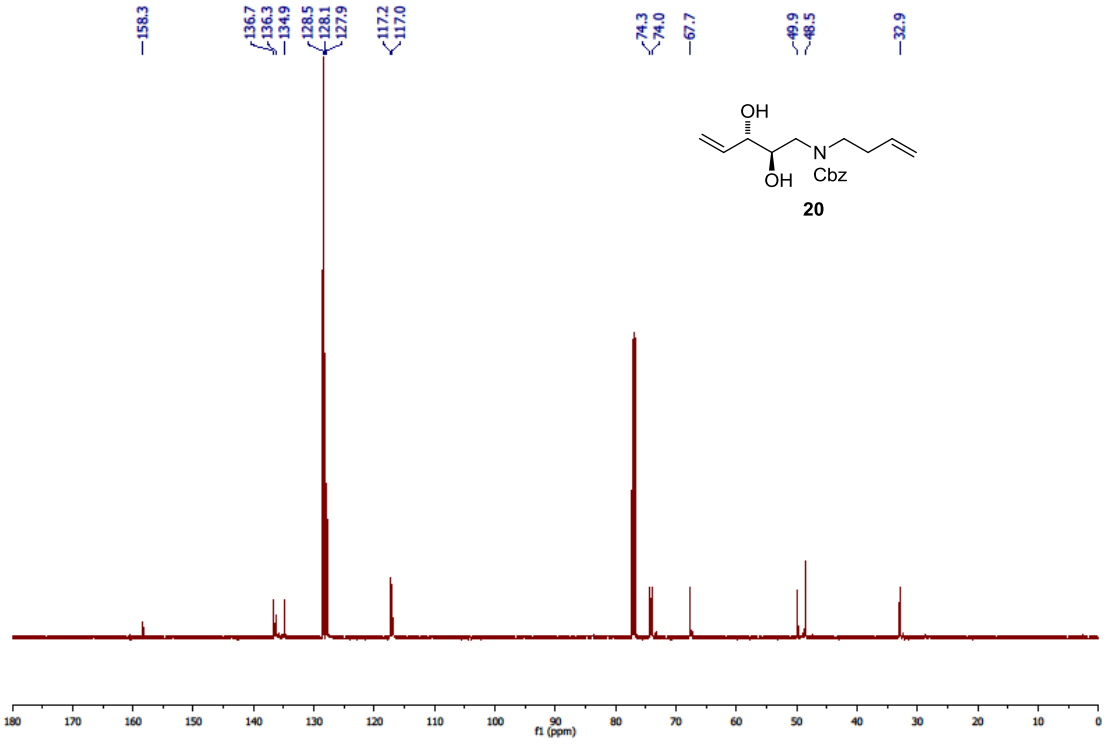
17


119.4
84.7
80.2
62.5
37.7
25.5
17.8
-4.5
OTBS
TfO
TfO
f1 (ppm)

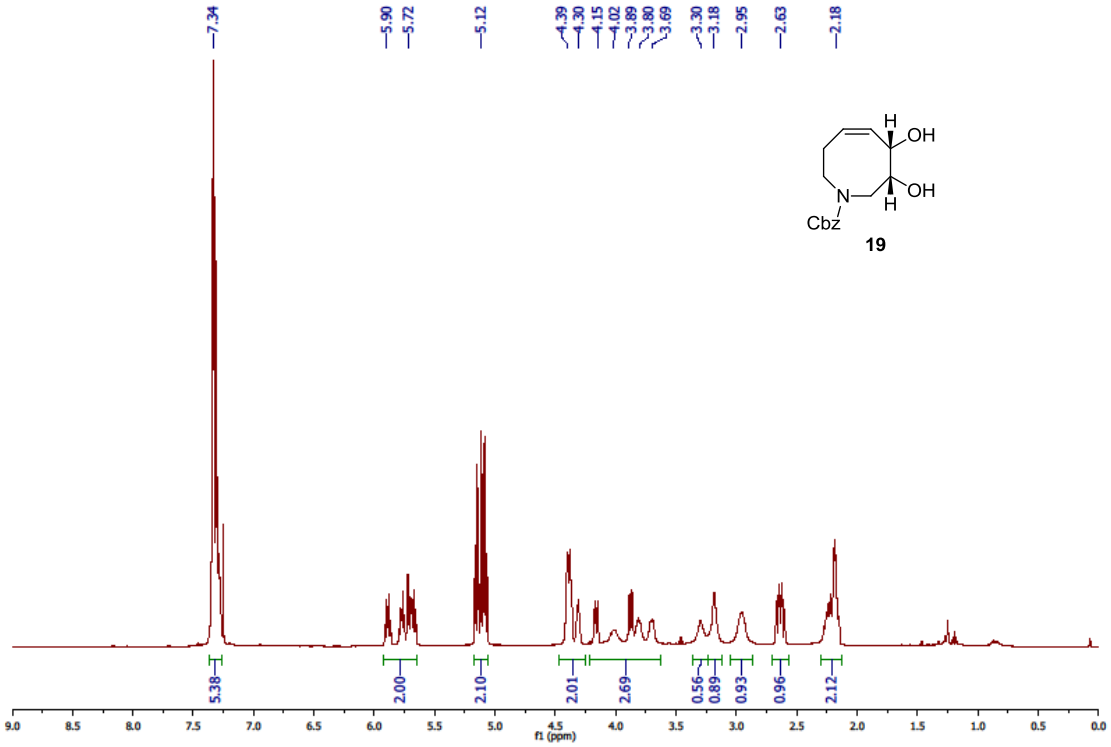
17

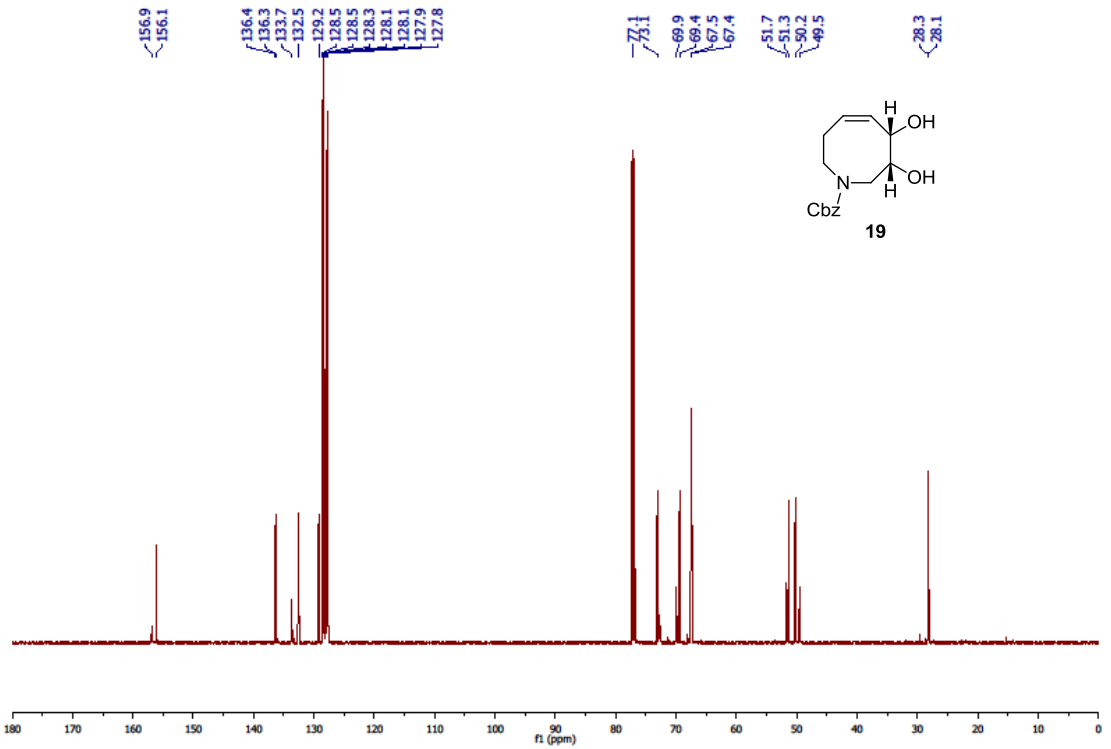

7.34
5.93
5.70
5.36
5.33
5.24
5.13
5.00
4.06
3.71
3.60
3.34
2.30
OH
N
OH
Cbz
5.29
1.00
1.13
1.00
0.97
2.24
1.52
1.39
1.12
1.15
0.86
5.00
2.28
f1 (ppm)

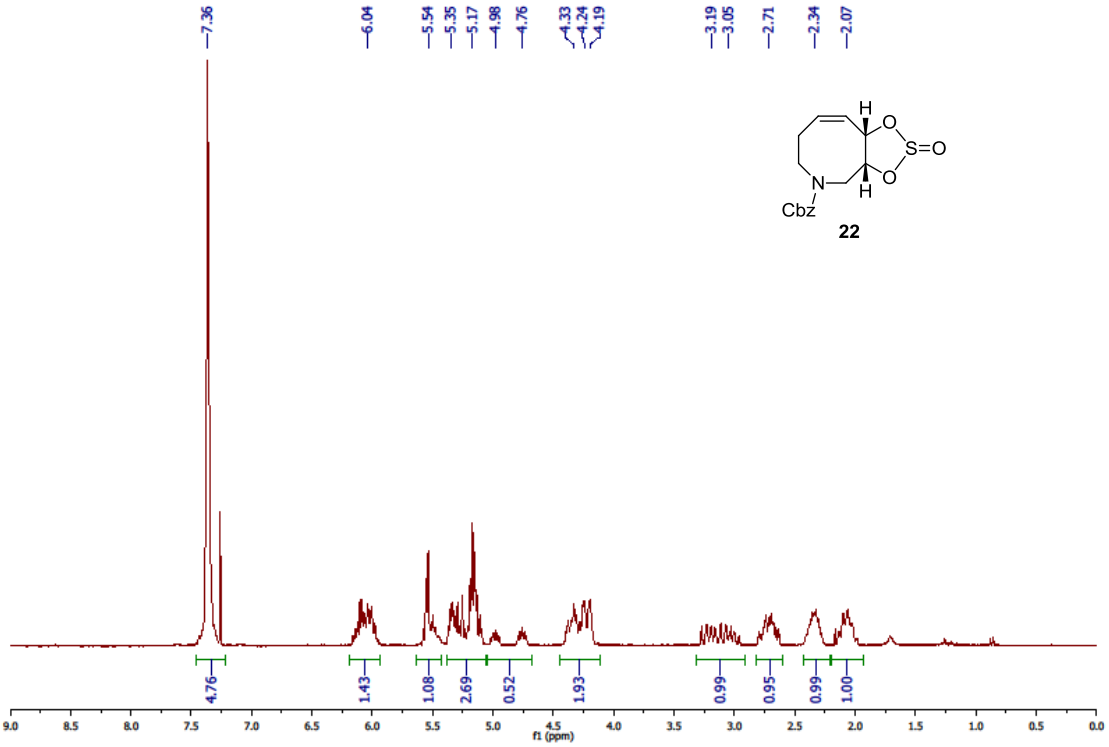
20

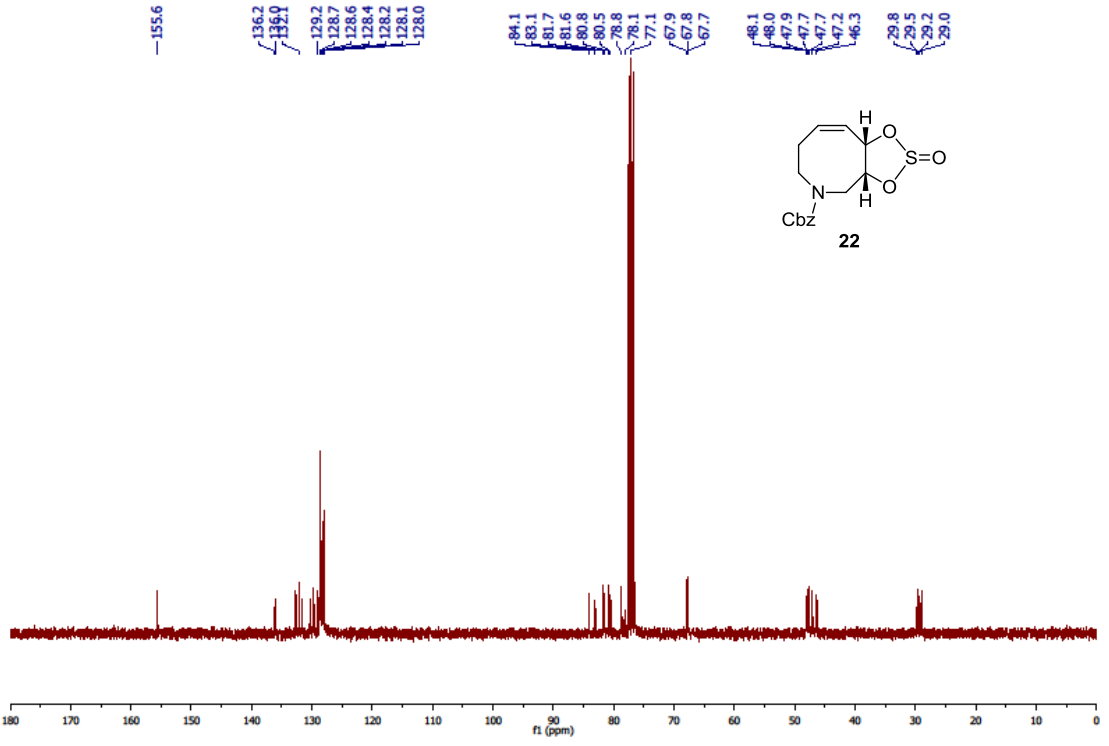

158.3
136.7
136.3
134.9
128.5
128.1
127.9
117.2
117.0
74.3
74.0
67.7
49.9
48.5
32.9
OH
N
OH
Cbz
f1 (ppm)

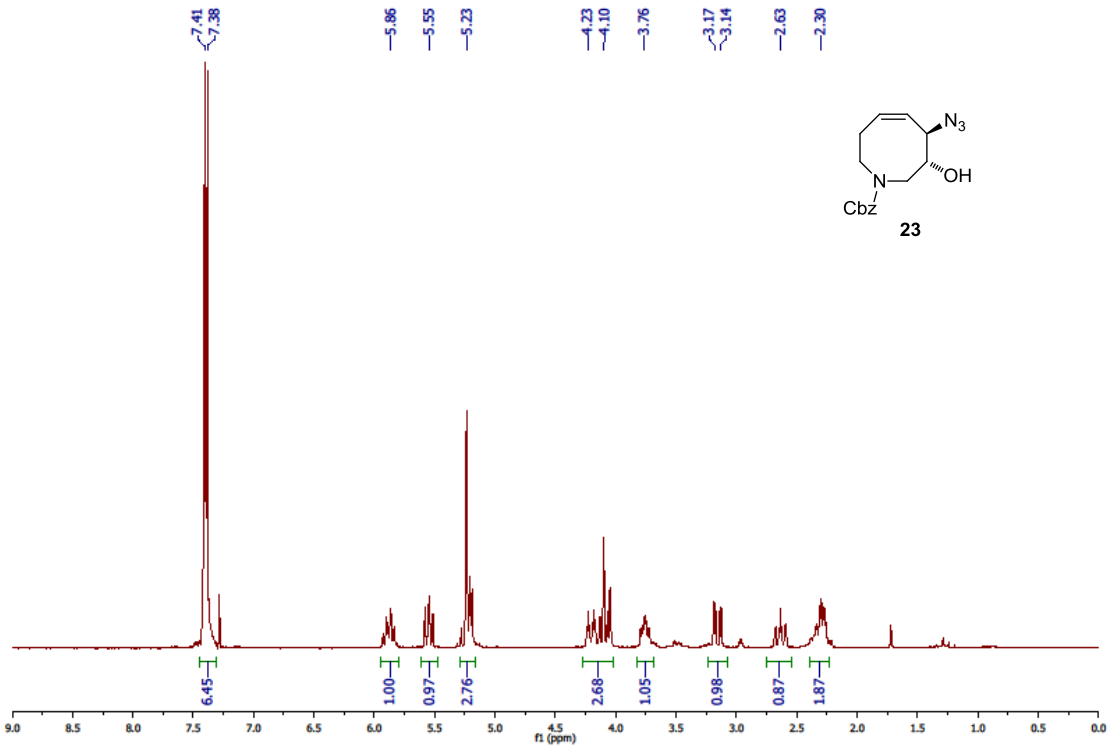
20

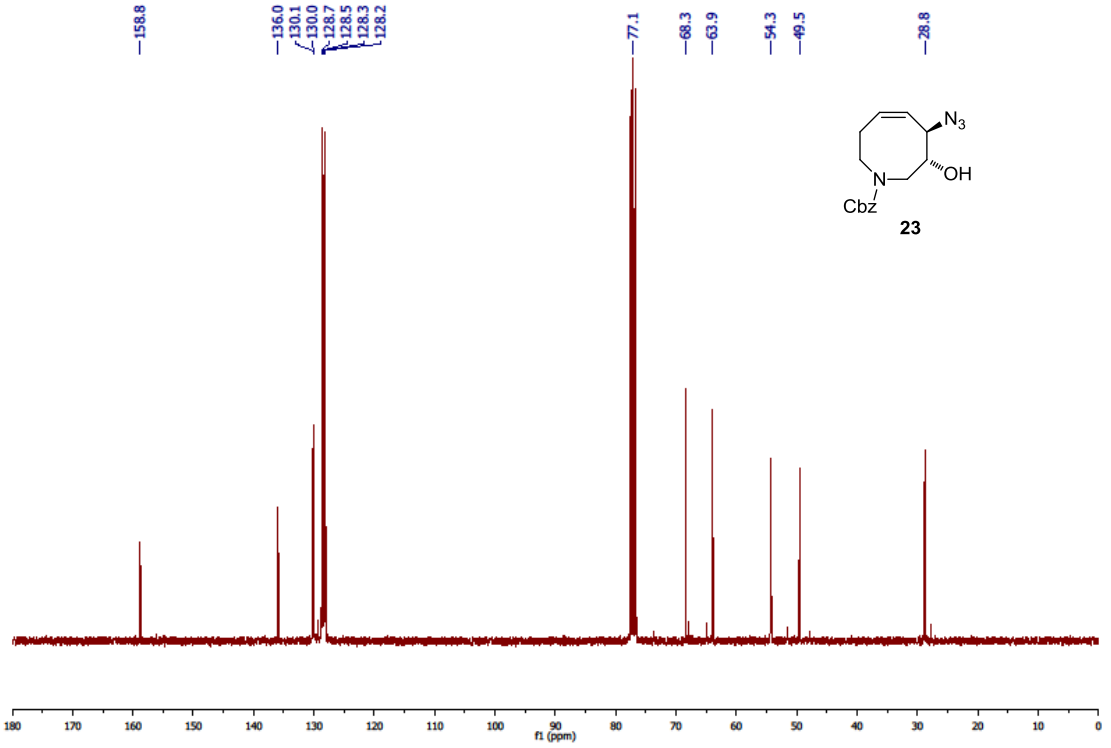

7.34
5.90
5.72
5.12
4.39
4.30
4.15
4.02
3.89
3.80
3.69
3.30
3.18
2.95
2.63
2.18
5.38
2.00
2.10
2.01
2.69
0.56
0.89
0.93
0.96
2.12
f1 (ppm)
H
OH
OH
H
N
Cbz
19

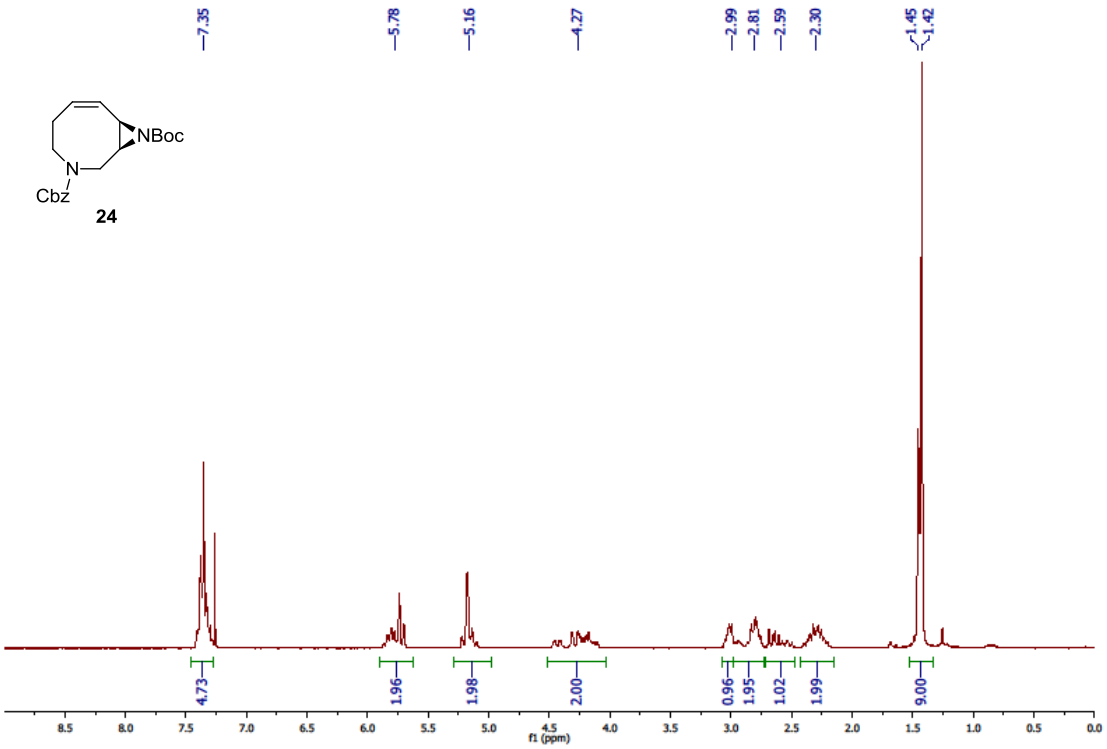

156.9
156.1
136.4
136.3
133.7
132.5
129.2
128.5
128.5
128.3
128.1
128.1
127.9
127.8
77.1
73.1
69.9
69.4
67.5
67.4
51.7
51.3
50.2
49.5
28.3
28.1
f1 (ppm)
H
OH
OH
H
N
Cbz
19

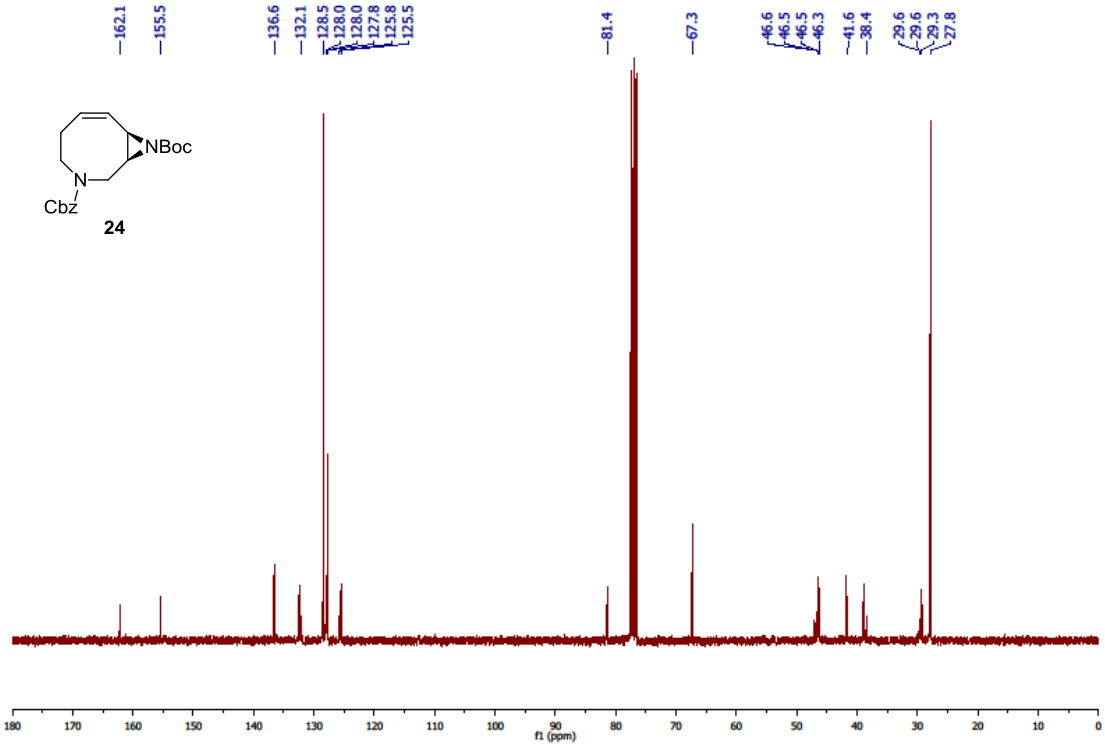

7.36
6.04
5.54
5.35
5.17
4.98
4.76
4.33
4.24
4.19
3.19
3.05
2.71
2.34
2.07
4.76
1.43
1.08
2.69
0.52
1.93
0.99
0.95
0.99
1.00
f1 (ppm)
H
O
S=O
O
N
H
Cbz
22

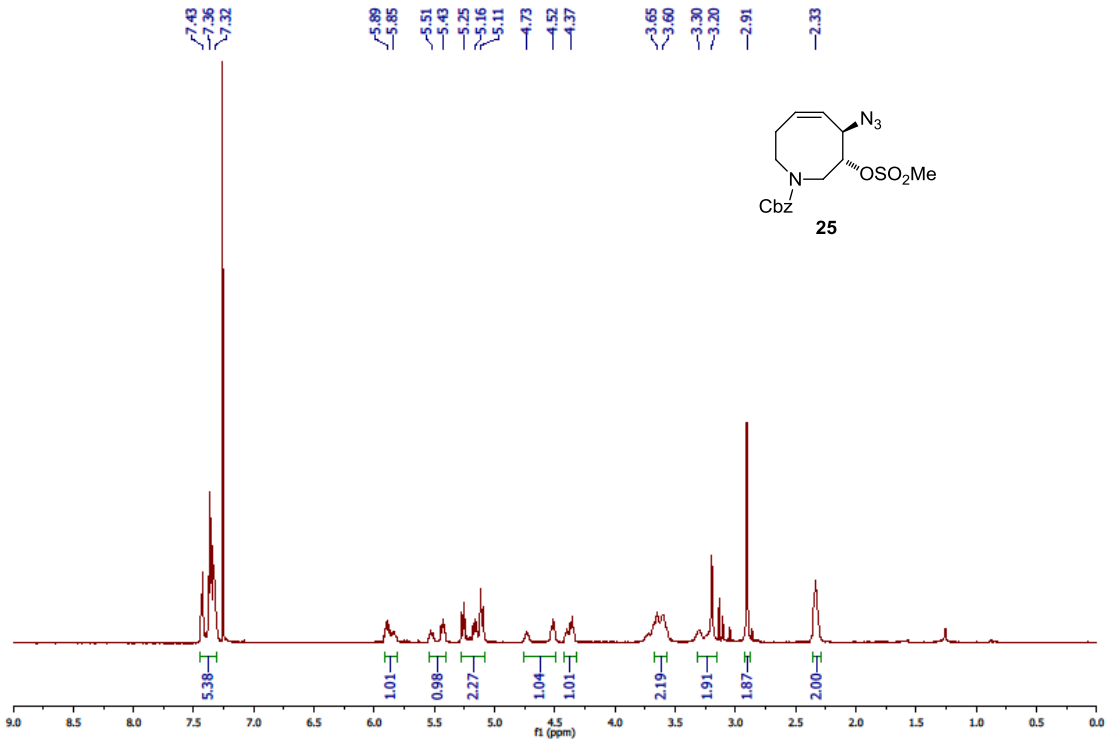

155.6
136.2
136.0
132.1
129.2
128.7
128.6
128.4
128.2
128.1
128.0
84.1
83.1
81.7
81.6
80.8
80.5
78.8
78.1
77.1
67.9
67.8
67.7
48.1
48.0
47.9
47.7
47.7
47.2
46.3
29.8
29.5
29.2
29.0
f1 (ppm)
H
O
S=O
O
N
H
Cbz
22

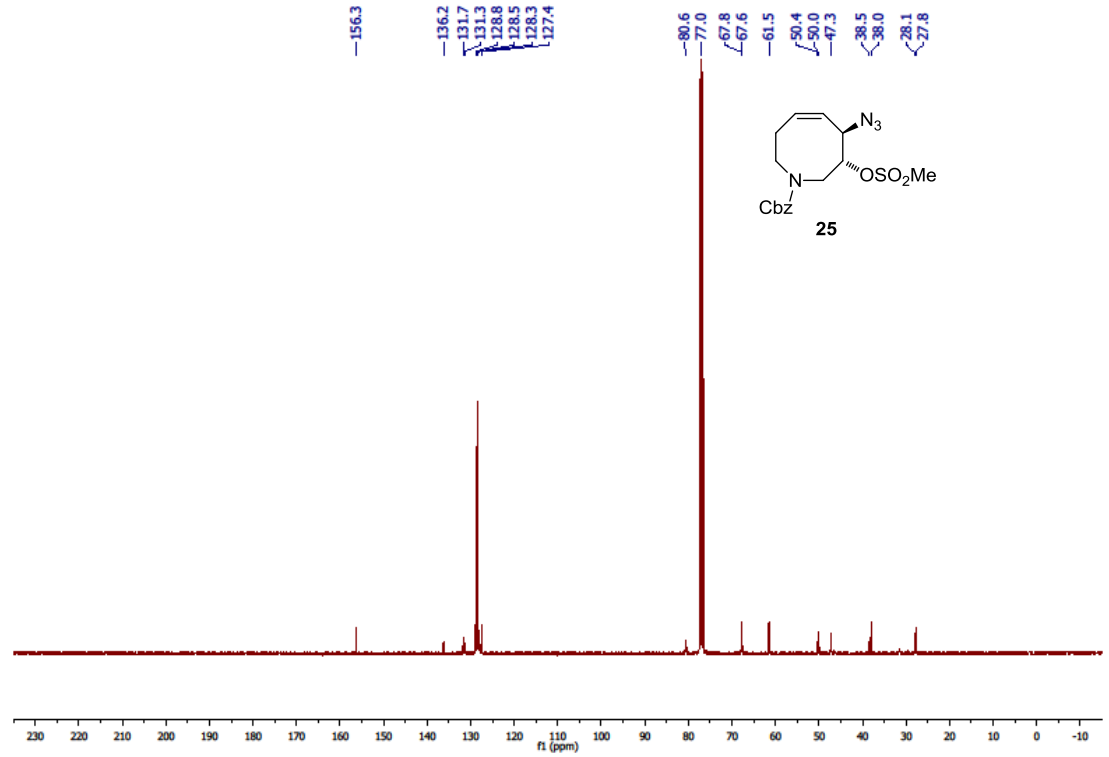

7.41
7.38
5.86
5.55
5.23
4.23
4.10
3.76
3.17
3.14
2.63
2.30
N3
OH
N
Cbz
23
6.45
1.00
0.97
2.76
2.68
1.05
0.98
0.87
1.87
f1 (ppm)

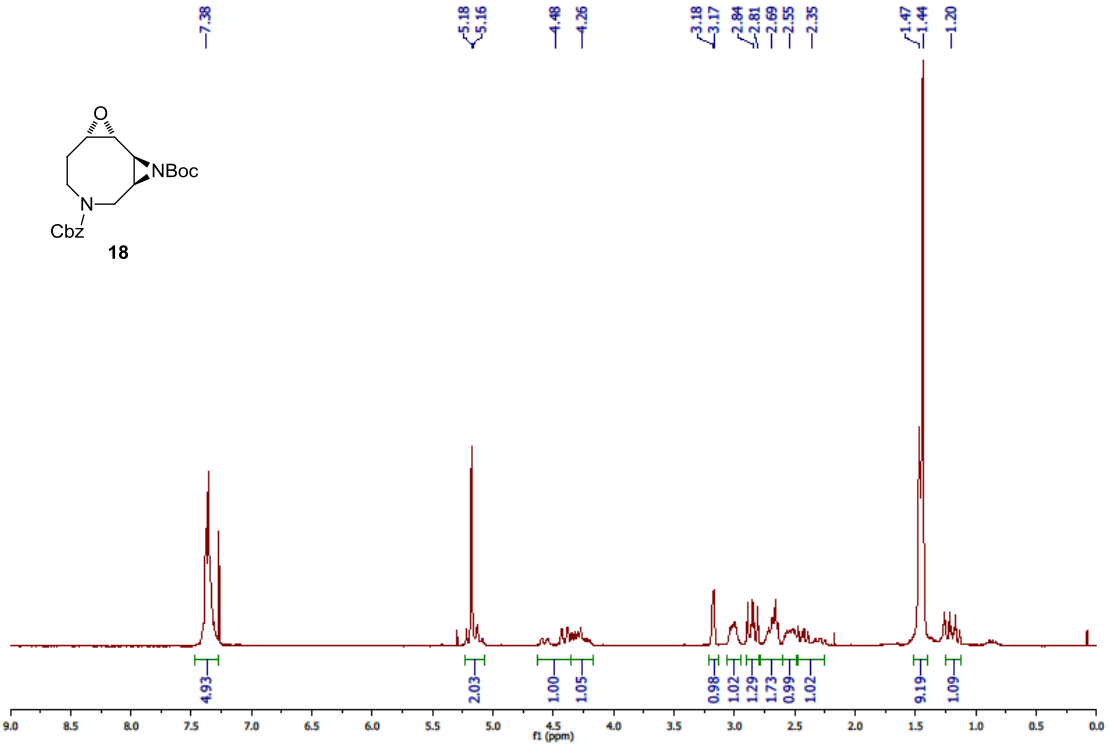

158.8
136.0
130.1
130.0
128.7
128.5
128.3
128.2
77.1
68.3
63.9
54.3
49.5
28.8
N3
OH
N
Cbz
23
f1 (ppm)

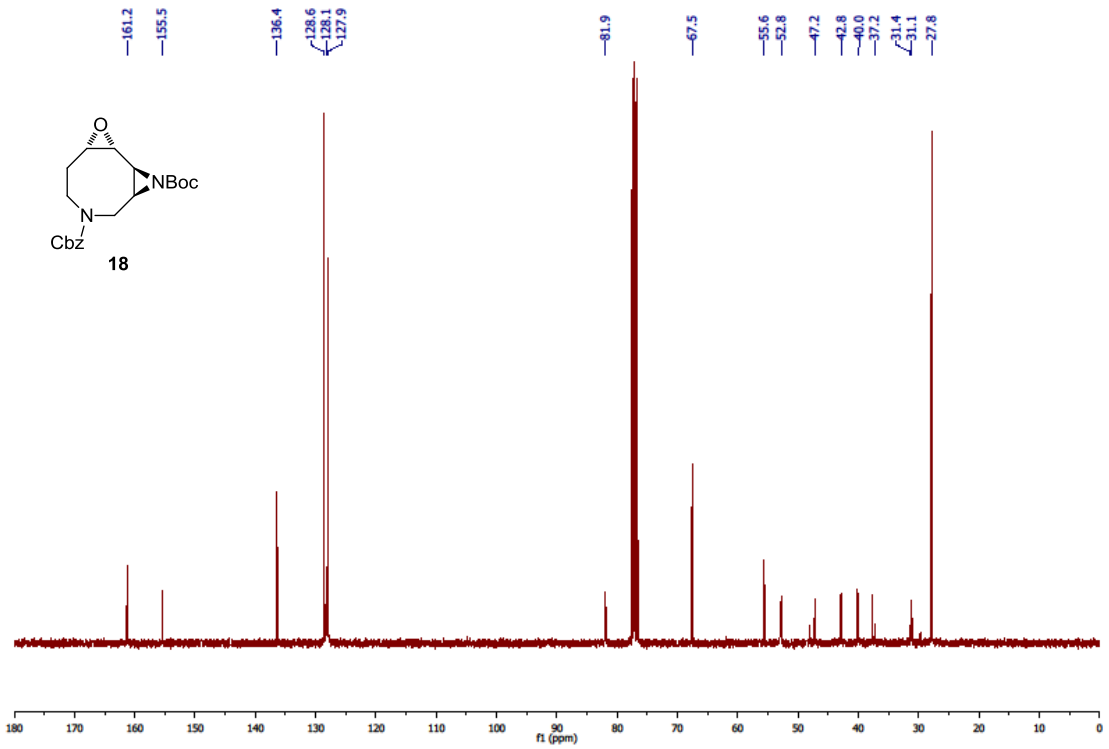

7.35
5.78
5.16
4.27
2.99
2.81
2.59
2.30
1.45
1.42
NBoc
N
Cbz
24
4.73
1.96
1.98
2.00
0.96
1.95
1.02
1.99
9.00
f1 (ppm)

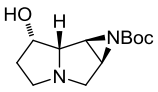

162.1
155.5
136.6
132.1
128.5
128.0
128.0
127.8
125.8
125.5
81.4
67.3
46.6
46.5
46.5
46.3
41.6
38.4
29.6
29.6
29.3
27.8
NBoc
N
Cbz
24
f1 (ppm)


7.43
7.36
7.32
5.89
5.85
5.51
5.43
5.25
5.16
5.11
4.73
4.52
4.37
3.65
3.60
3.30
3.20
2.91
2.33
N3
OSO2Me
N
Cbz
25
5.38
1.01
0.98
2.27
1.04
1.01
2.19
1.91
1.87
2.00
f1 (ppm)


156.3
136.2
131.7
131.3
128.8
128.5
128.3
127.4
80.6
77.0
67.8
67.6
61.5
50.4
50.0
47.3
38.5
38.0
28.1
27.8
N3
OSO2Me
N
Cbz
25
f1 (ppm)

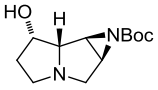

7.38
5.18
5.16
4.48
4.26
3.18
3.17
2.84
2.81
2.69
2.55
2.35
1.47
1.44
1.20
O
NBoc
N
Cbz
18
4.93
2.03
1.00
1.05
0.98
1.02
1.29
1.73
0.99
1.02
9.19
1.09
f1 (ppm)


161.2
155.5
136.4
128.6
128.1
127.9
81.9
67.5
55.6
52.8
47.2
42.8
40.0
37.2
31.4
31.1
27.8
O
NBoc
N
Cbz
18
f1 (ppm)


HO
H
NBoc
N

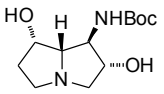
26

4.32
4.31
4.30
4.29
3.44
3.25
3.25
3.23
3.22
3.11
3.10
3.09
3.08
3.07
3.06
1.98
1.43
1.09
1.09
1.13
1.12
2.28
2.22
9.98
f1 (ppm)


HO
H
NBoc
N

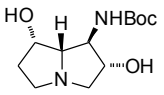
26

162.6
82.3
73.4
71.4
57.8
53.4
44.9
42.8
37.7
28.2
f1 (ppm)


HO
H
NHBoc
OH
N

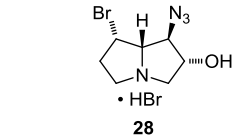
27

4.23
3.99
3.97
3.95
3.20
3.13
2.86
2.80
2.78
2.77
2.74
2.53
2.05
2.04
2.02
2.00
1.91
1.45
1.94
0.89
1.01
0.99
1.00
1.03
1.00
1.02
1.04
9.13
f1 (ppm)


HO
H
NHBoc
OH
N

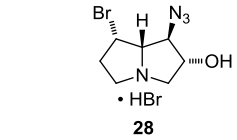
27

159.0
80.6
77.5
74.6
71.0
61.0
56.6
53.9
36.8
28.7
f1 (ppm)


Br
H
N3
OH
N
• HBr

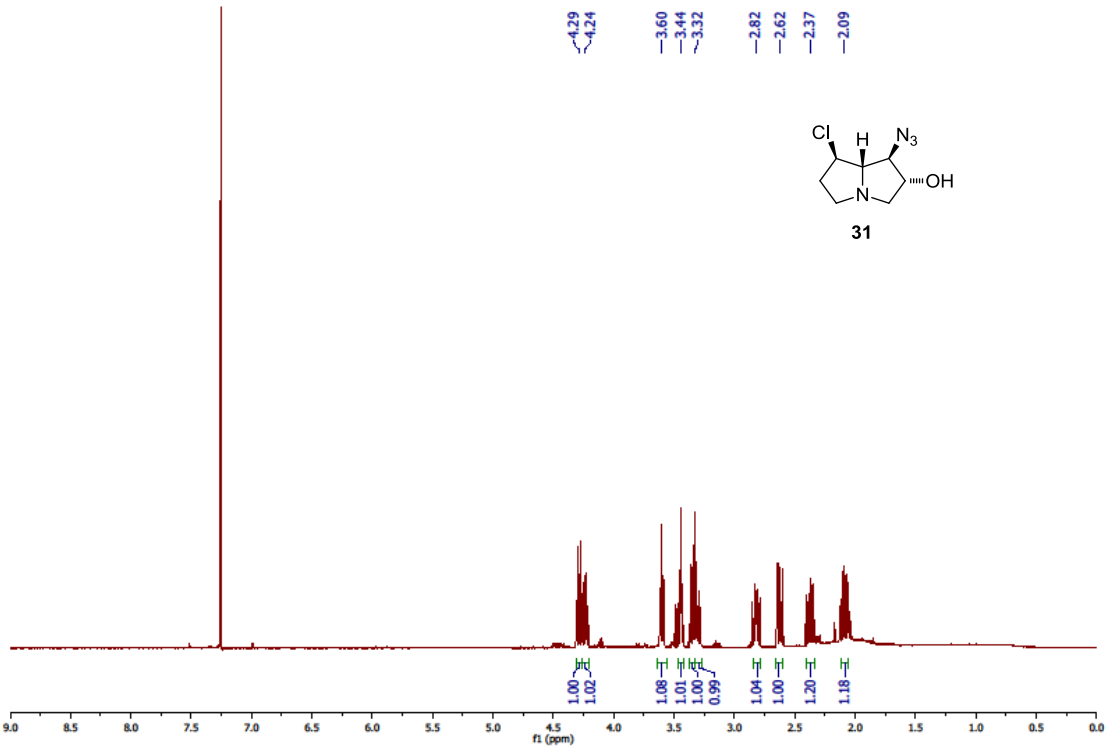
28

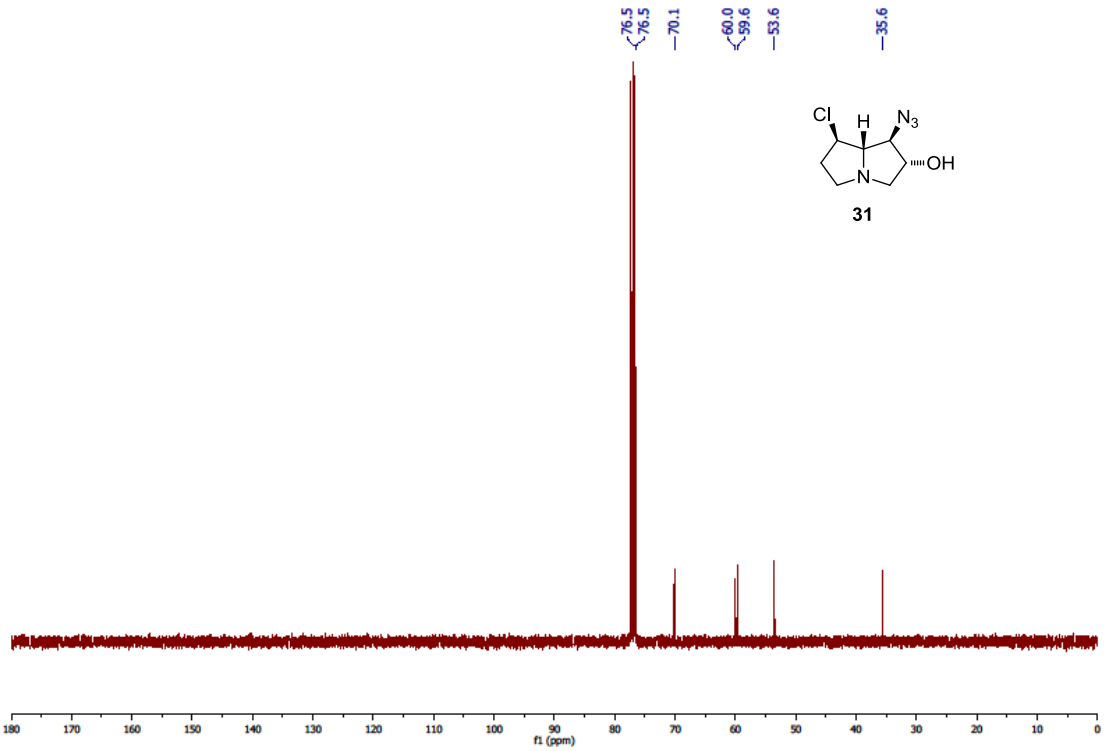
4.84
4.34
4.29
4.11
3.89
3.67
3.49
3.20
2.65
1.03
1.78
0.90
1.00
1.01
1.01
1.01
2.02
f1 (ppm)

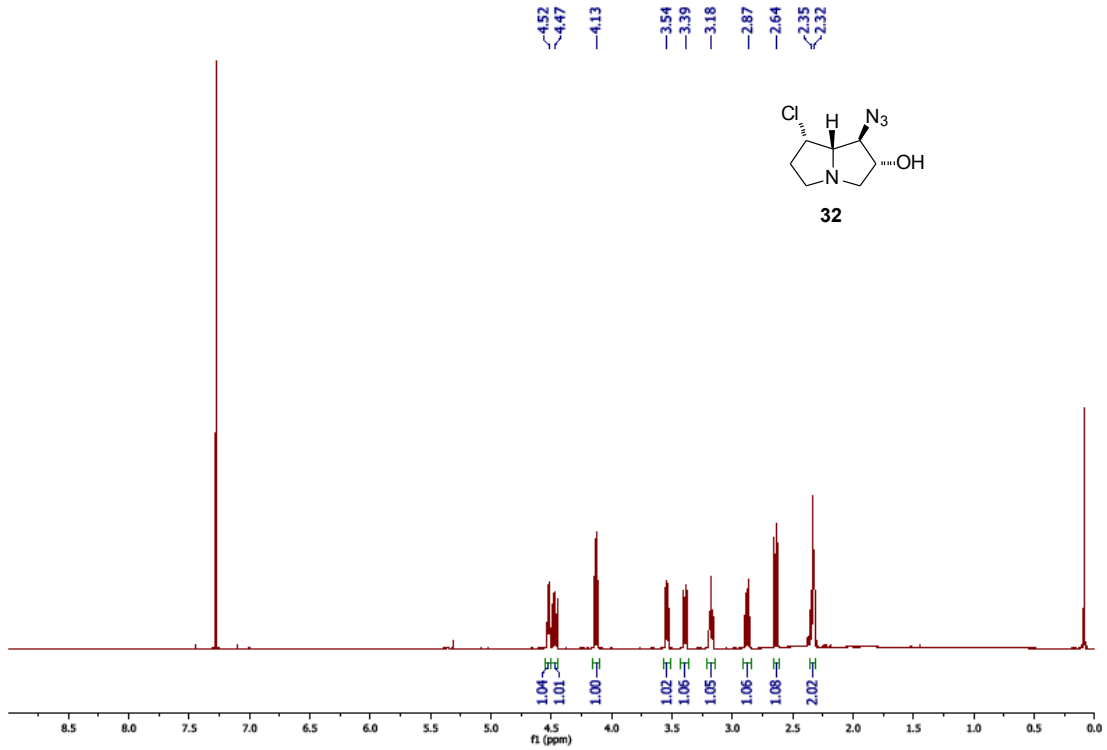

Br
H
N3
OH
N
• HBr

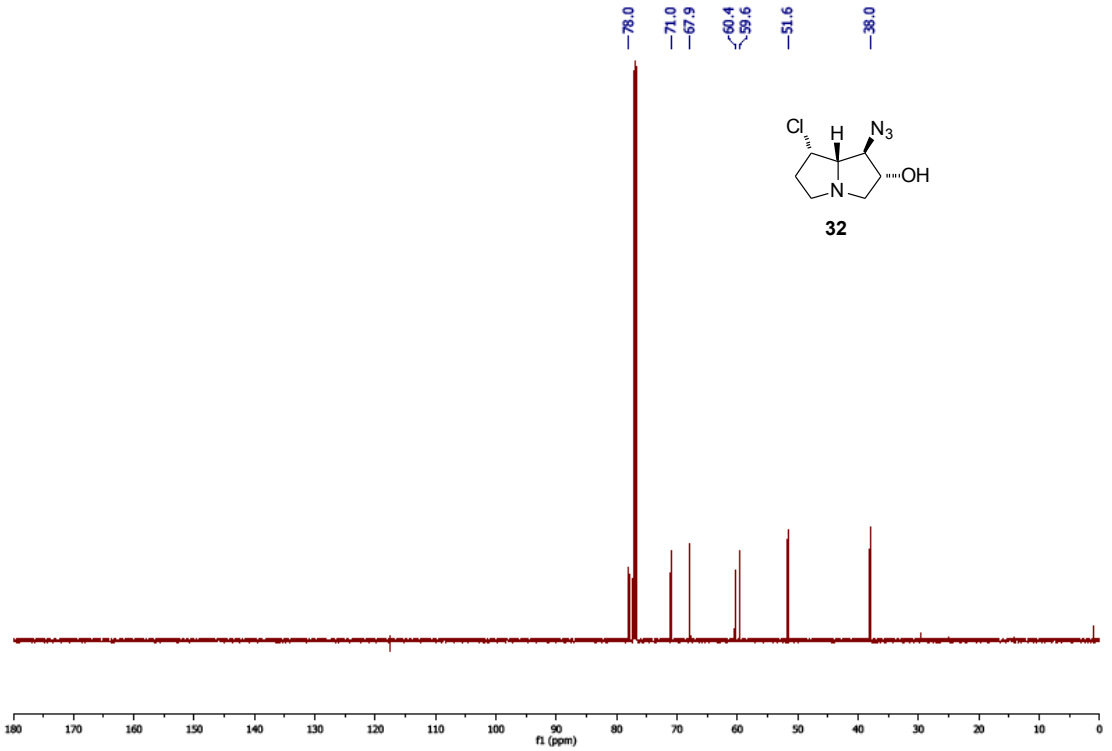
28

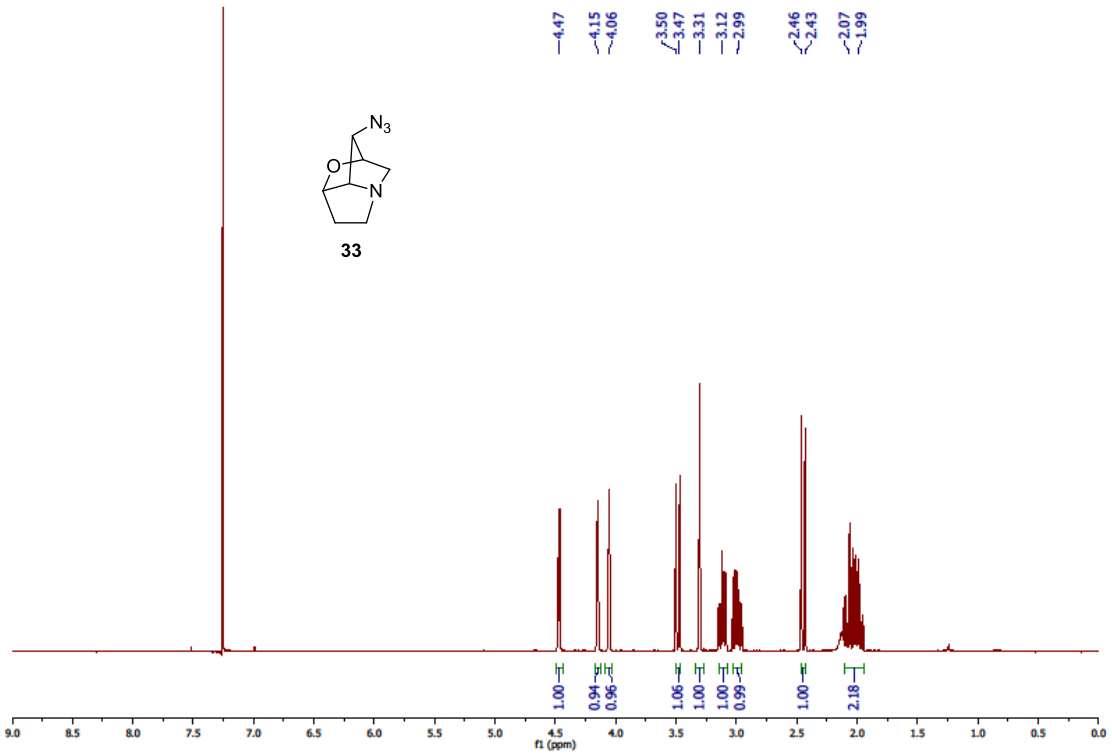
74.1
70.5
68.6
57.4
53.4
44.4
34.8
f1 (ppm)

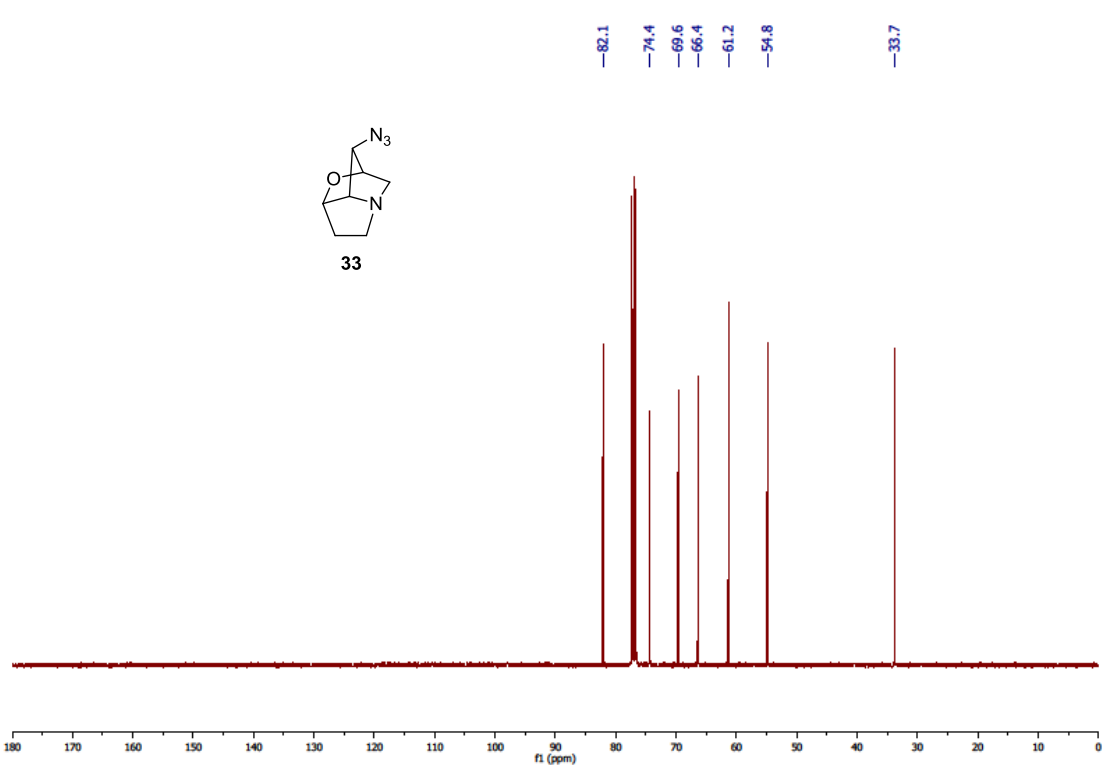

4.29
4.24
3.60
3.44
3.32
2.82
2.62
2.37
2.09
Cl
H
N3
OH
N
31
1.00
1.02
1.08
1.01
1.00
0.99
1.04
1.00
1.20
1.18
f1 (ppm)

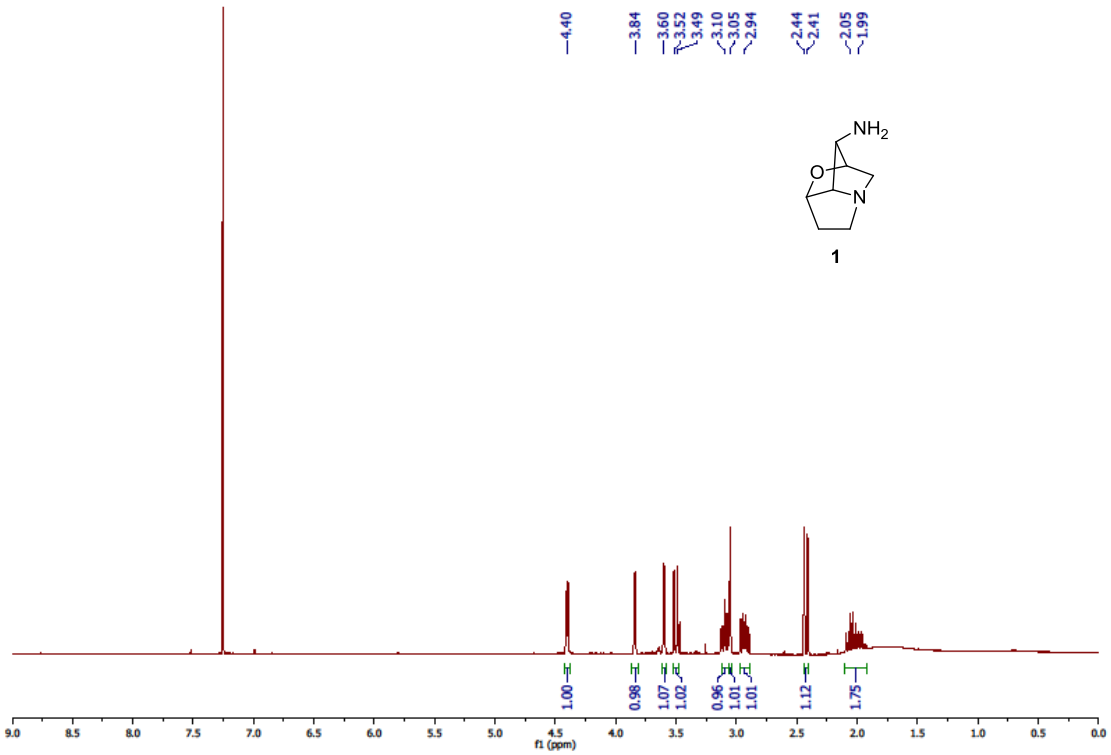

76.5
76.5
70.1
60.0
59.6
53.6
35.6
Cl
H
N3
OH
N
31
f1 (ppm)

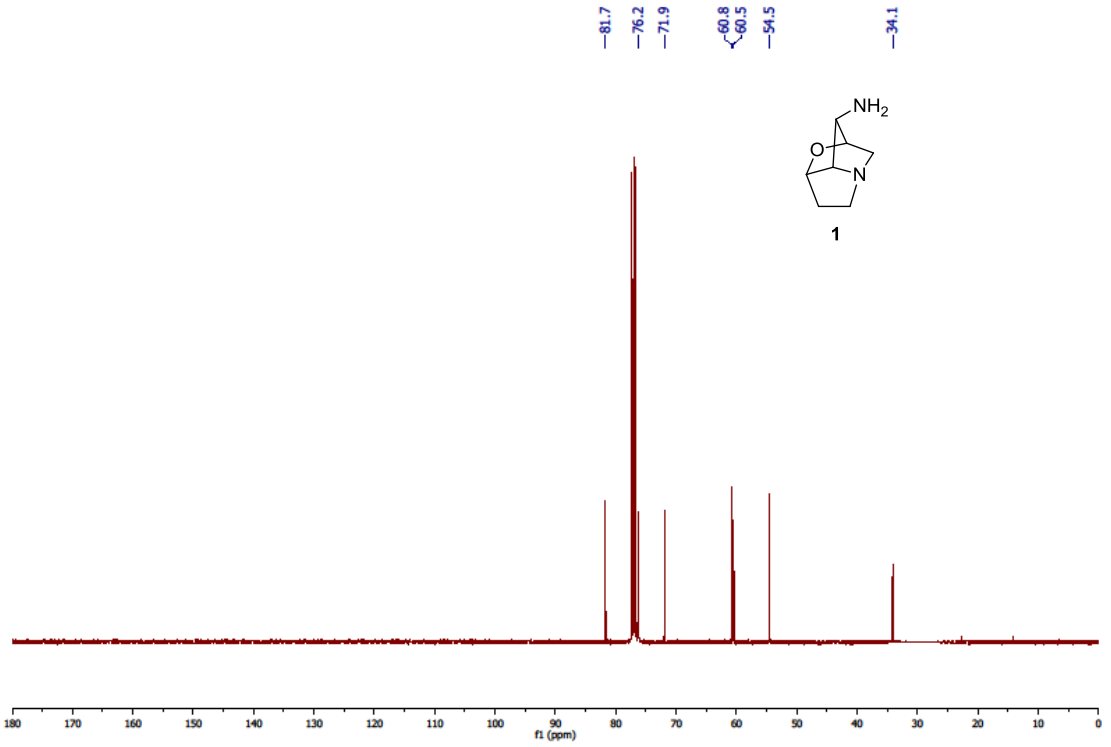

4.52
4.47
4.13
3.54
3.39
3.18
2.87
2.64
2.35
2.32
Cl
H
N3
OH
N
32
1.04
1.01
1.00
1.02
1.06
1.05
1.06
1.08
2.02
f1 (ppm)

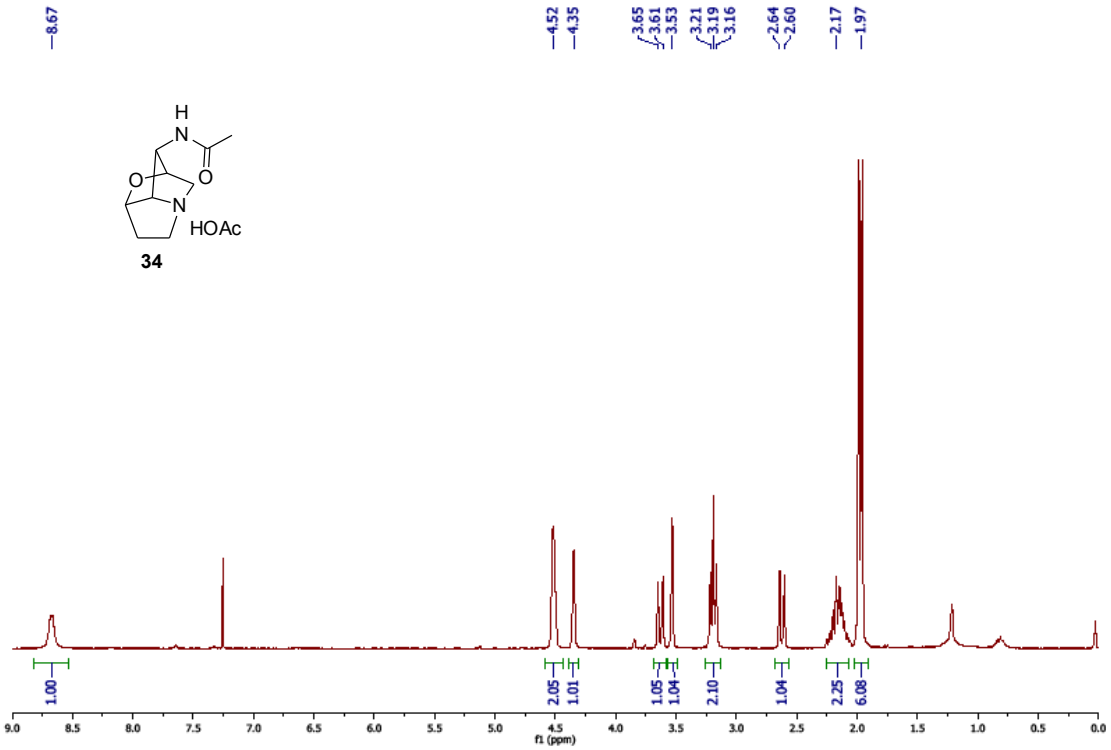

78.0
71.0
67.9
60.4
59.6
51.6
38.0
Cl
H
N3
OH
N
32
f1 (ppm)

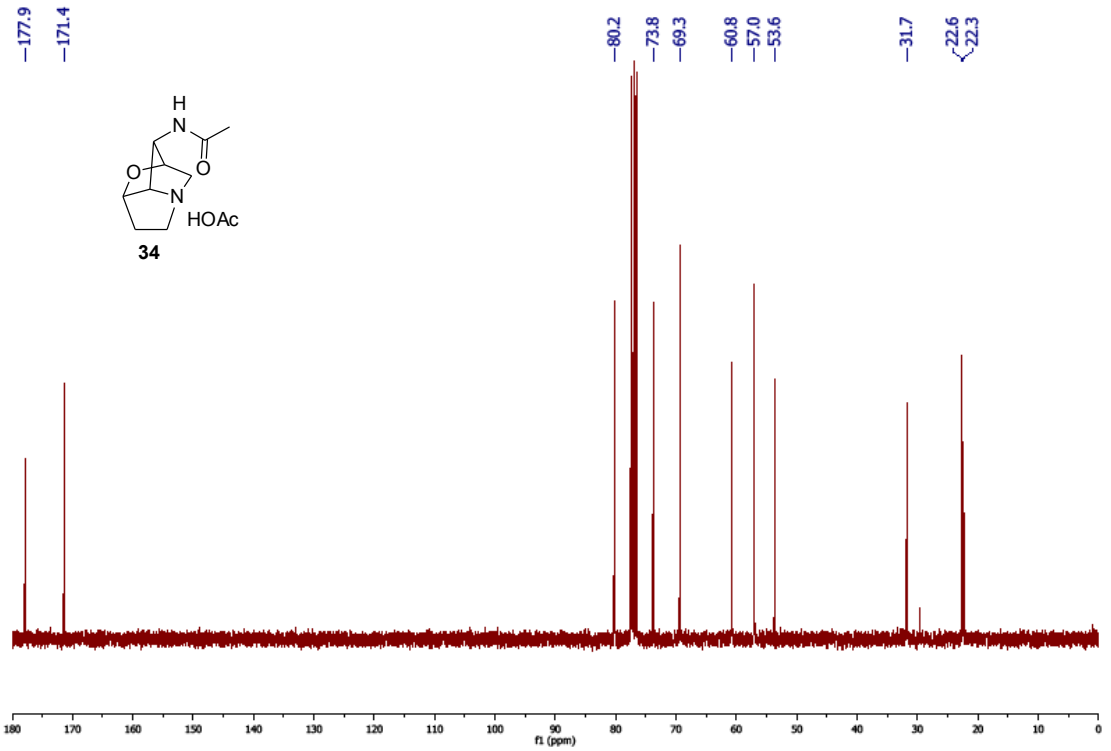

4.47
4.15
4.06
3.50
3.47
3.31
3.12
2.99
2.46
2.43
2.07
1.99
N3
O
N
33
1.00
0.94
0.96
1.06
1.00
1.00
0.99
1.00
2.18
f1 (ppm)

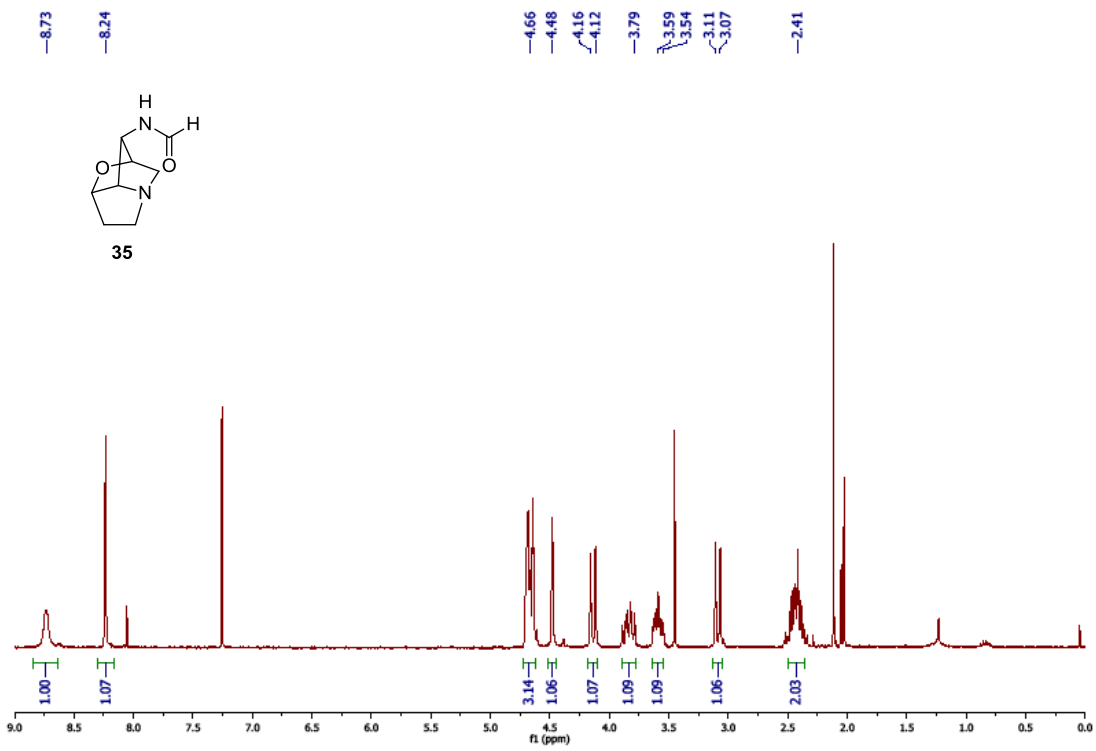

82.1
74.4
69.6
66.4
61.2
54.8
33.7
N3
O
N
33
f1 (ppm)

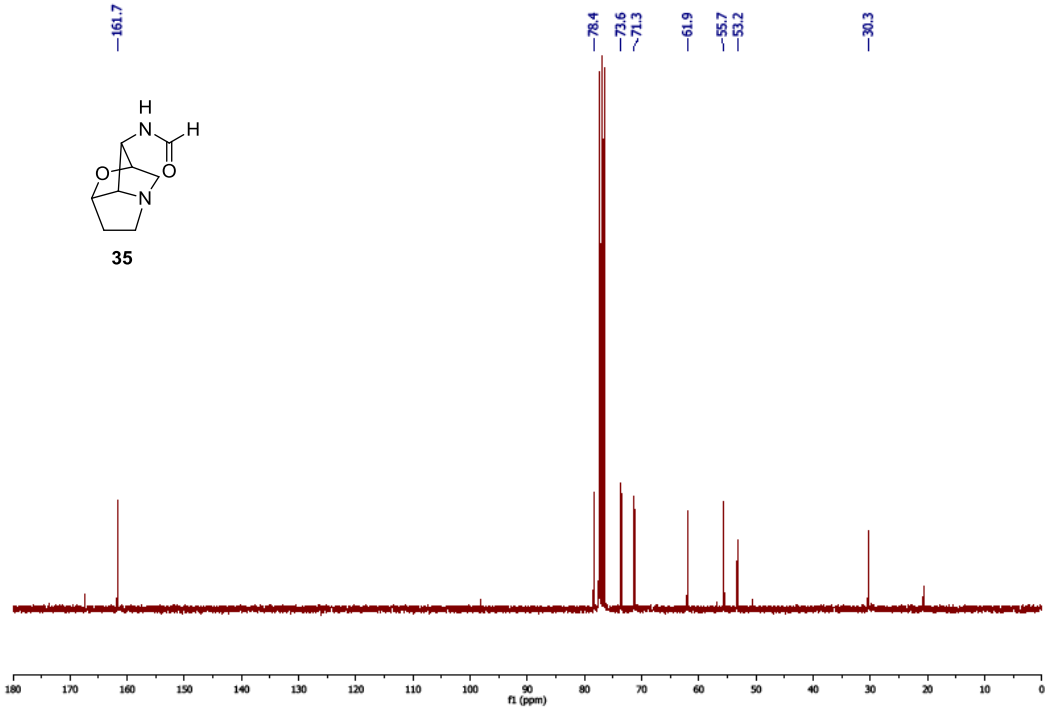

4.40
3.84
3.60
3.52
3.49
3.10
3.05
2.94
2.44
2.41
2.05
1.99
NH2
O
N
1
1.00
0.98
1.07
1.02
0.96
1.01
1.01
1.12
1.75
f1 (ppm)

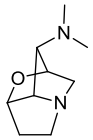

81.7
76.2
71.9
60.8
60.5
54.5
34.1
NH2
O
N
1
f1 (ppm)


8.67
4.52
4.35
3.65
3.61
3.53
3.21
3.19
3.16
2.64
2.60
2.17
1.97
H
N
O
O
N
HOAc
34
1.00
2.05
1.01
1.05
1.04
2.10
1.04
2.25
6.08
f1 (ppm)


177.9
171.4
80.2
73.8
69.3
60.8
57.0
53.6
31.7
22.6
22.3
H
N
O
O
N
HOAc
34
f1 (ppm)

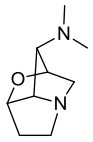

8.73
8.24
4.66
4.48
4.16
4.12
3.79
3.59
3.54
3.11
3.07
2.41
H
N
H
O
O
N
35
1.00
1.07
3.14
1.06
1.07
1.09
1.09
1.06
2.03
f1 (ppm)


161.7
78.4
73.6
71.3
61.9
55.7
53.2
30.3
H
N
H
O
O
N
35
f1 (ppm)



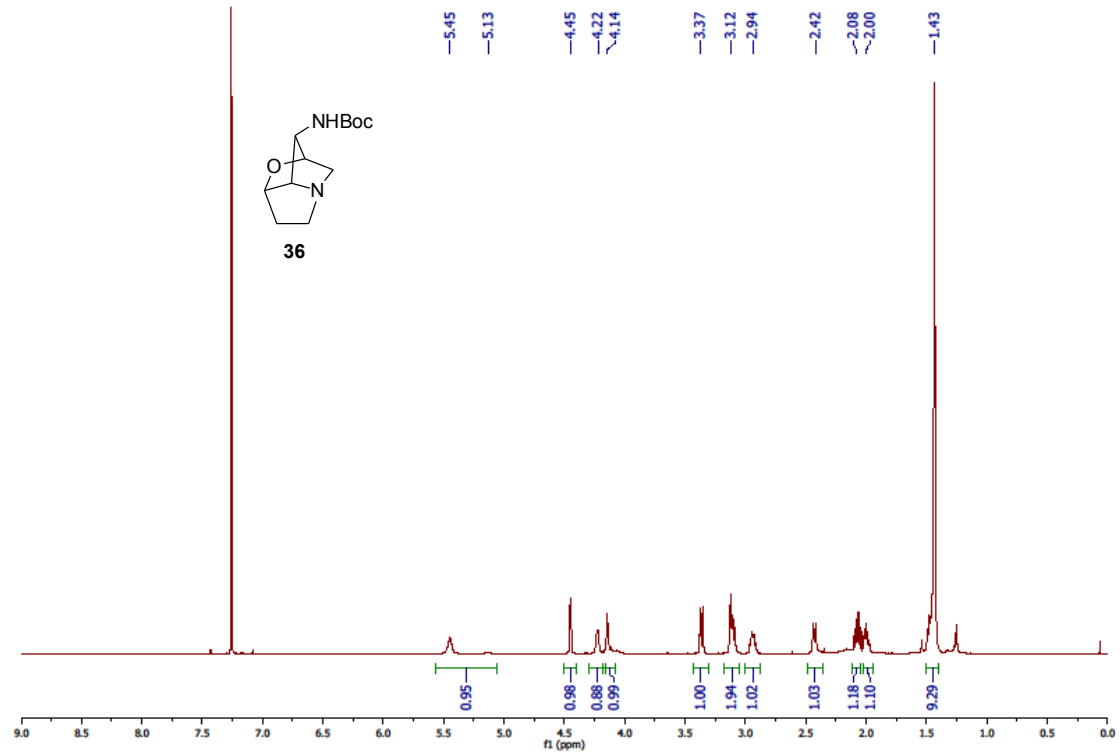
3

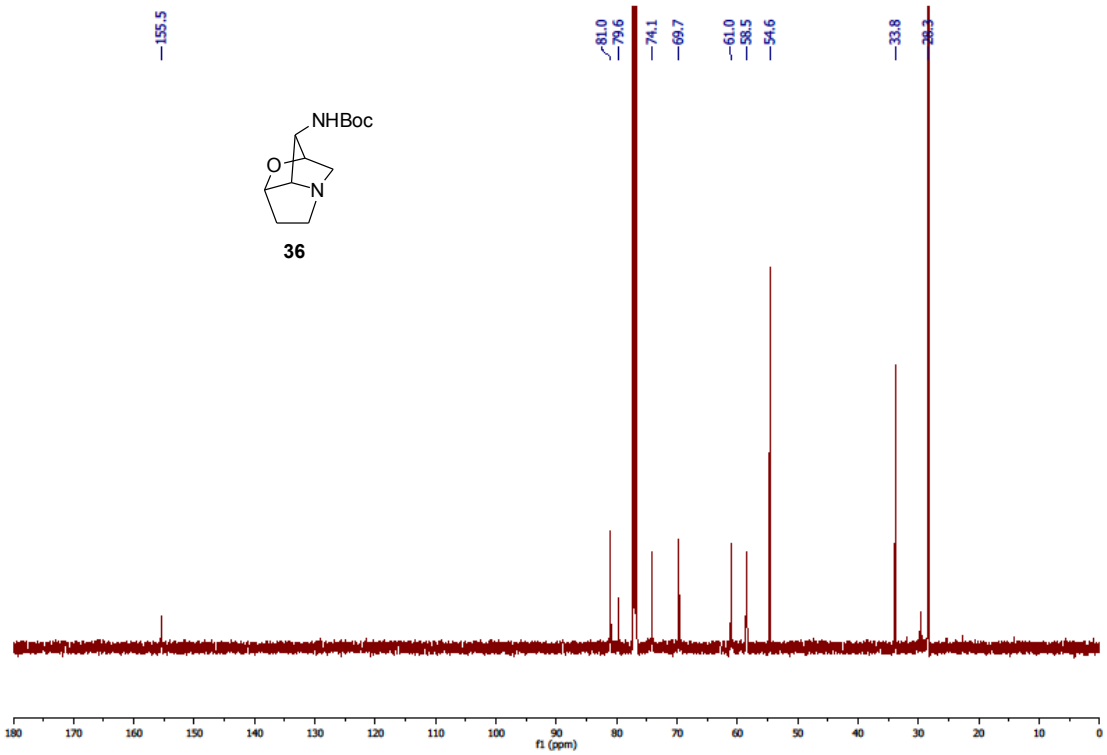
4.42
4.42
4.41
4.40
3.99
3.56
3.52
3.18
3.00
2.70
2.69
2.37
2.34
2.28
1.96
1.00
1.00
1.04
1.01
2.23
1.01
1.05
6.03
2.12
f1 (ppm)

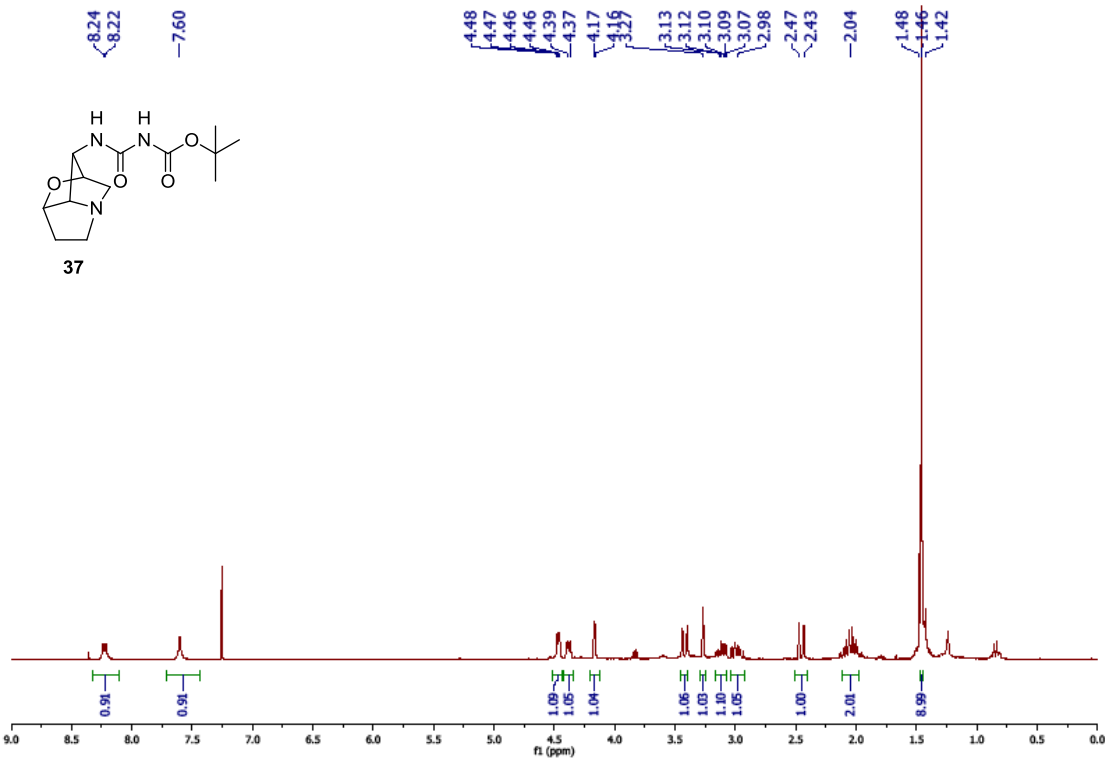


3

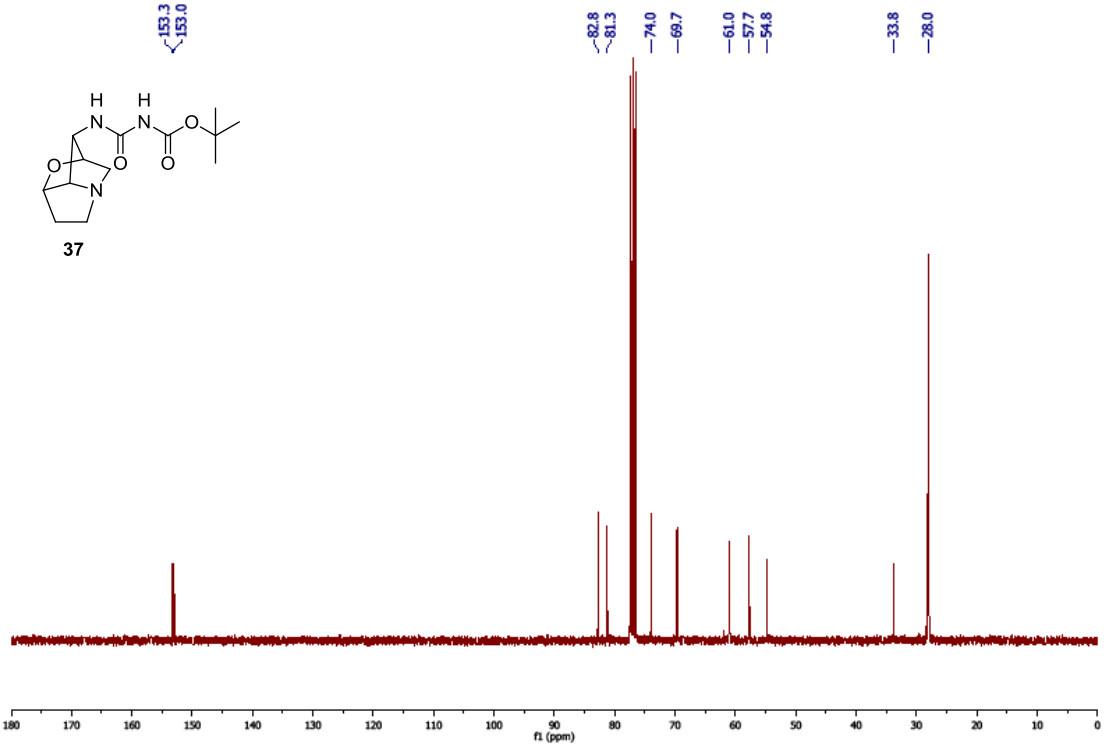
82.4
74.7
74.5
69.7
61.6
54.7
44.7
33.8
f1 (ppm)


5.45
5.13
4.45
4.22
4.14
3.37
3.12
2.94
2.42
2.08
2.00
1.43
NHBoc
O
N
36
0.95
0.98
0.88
0.99
1.00
1.94
1.02
1.03
1.18
1.10
9.29
f1 (ppm)

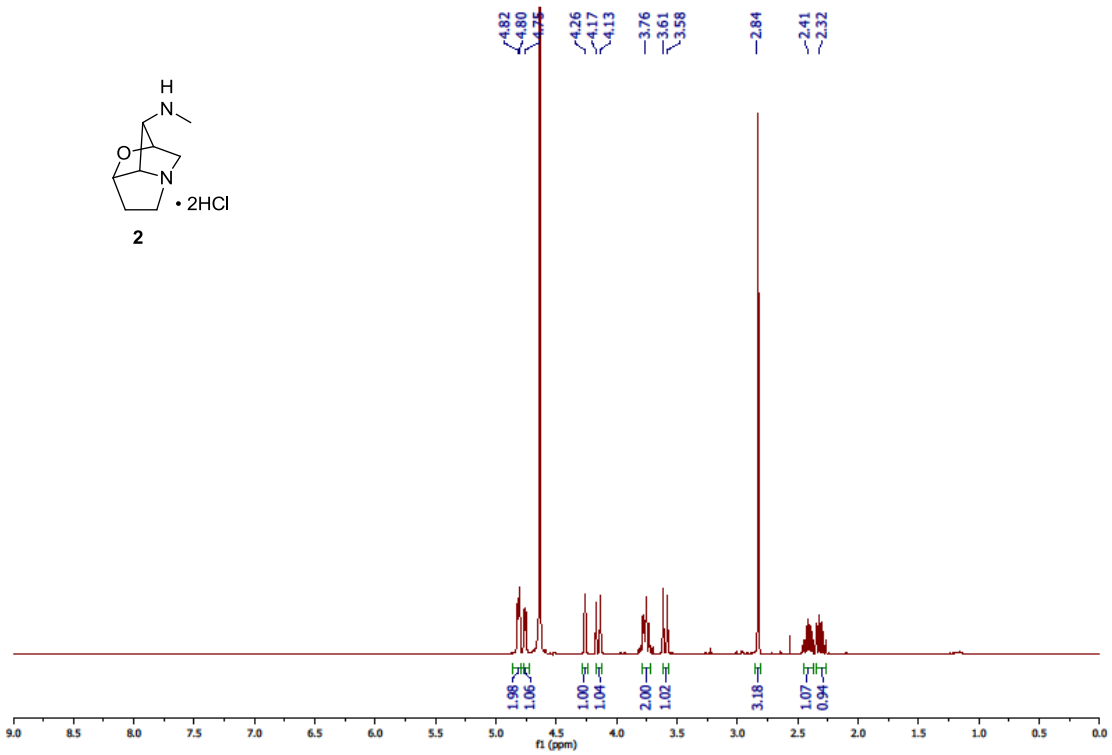

155.5
81.0
79.6
74.1
69.7
61.0
58.5
54.6
33.8
28.3
NHBoc
O
N
36
f1 (ppm)


8.24
8.22
7.60
4.48
4.47
4.46
4.46
4.39
4.37
4.17
4.16
3.27
3.13
3.12
3.10
3.09
3.07
2.98
2.47
2.43
2.04
1.48
1.46
1.42
0.91
0.91
1.09
1.05
1.04
1.06
1.03
1.10
1.05
1.00
2.01
8.99
f1 (ppm)

37


153.3
153.0
82.8
81.3
74.0
69.7
61.0
57.7
54.8
33.8
28.0
f1 (ppm)

37


4.82
4.80
4.26
4.17
4.13
3.76
3.61
3.58
2.84
2.41
2.32
1.98
1.06
1.00
1.04
2.00
1.02
3.18
1.07
0.94
f1 (ppm)

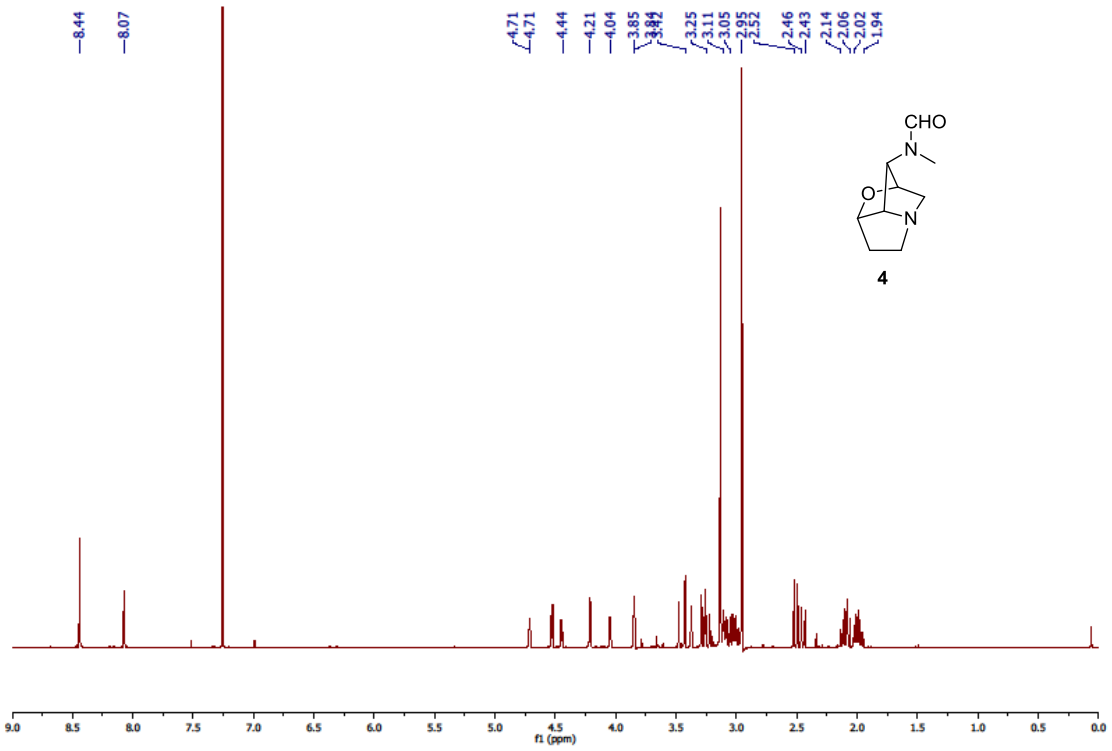

H
N
O
N
• 2HCl

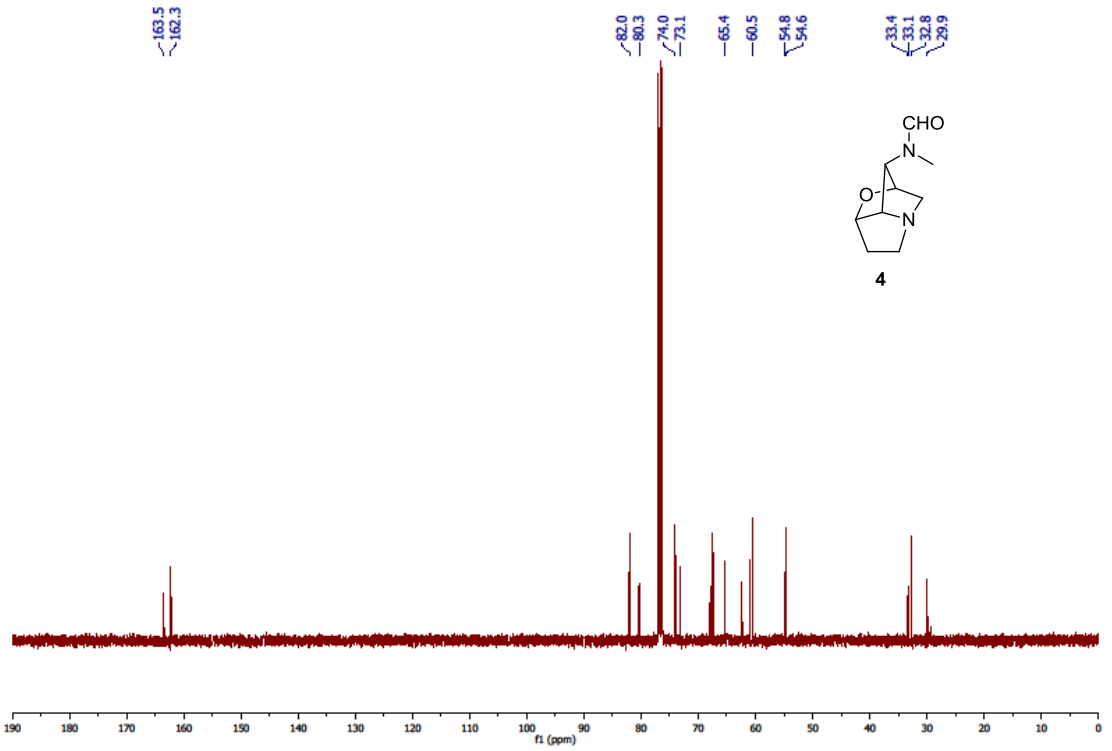
2

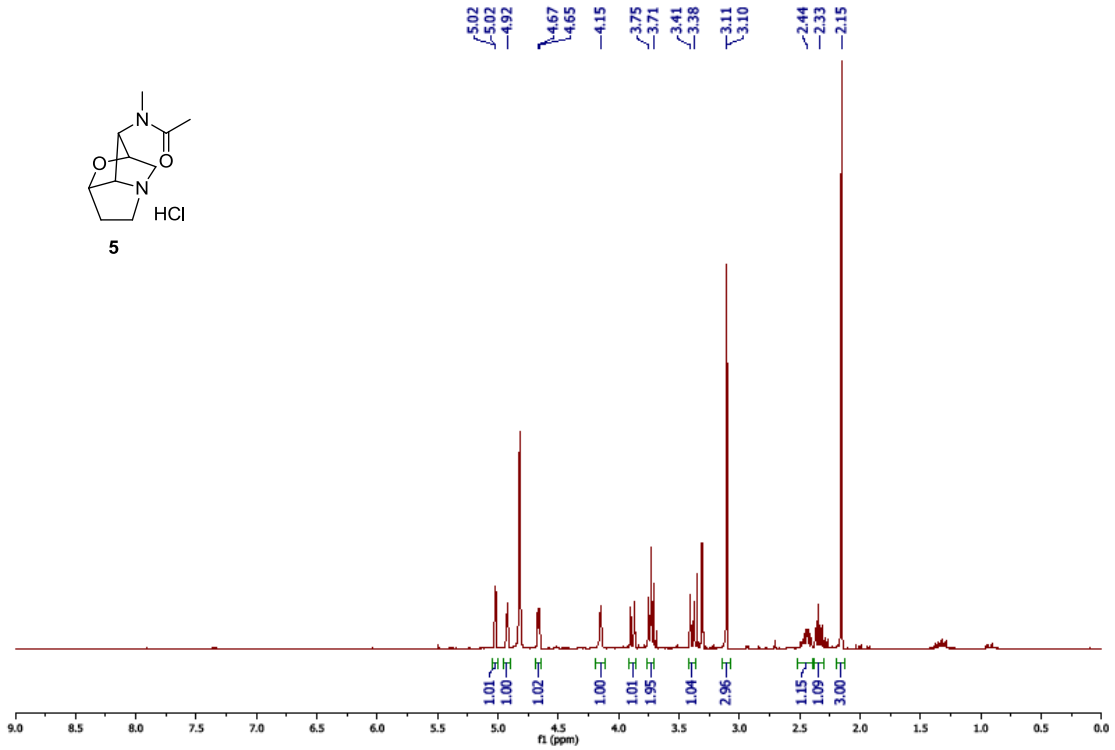
83.4
74.0
72.2
66.0
64.2
58.2
36.4
31.6
f1 (ppm)

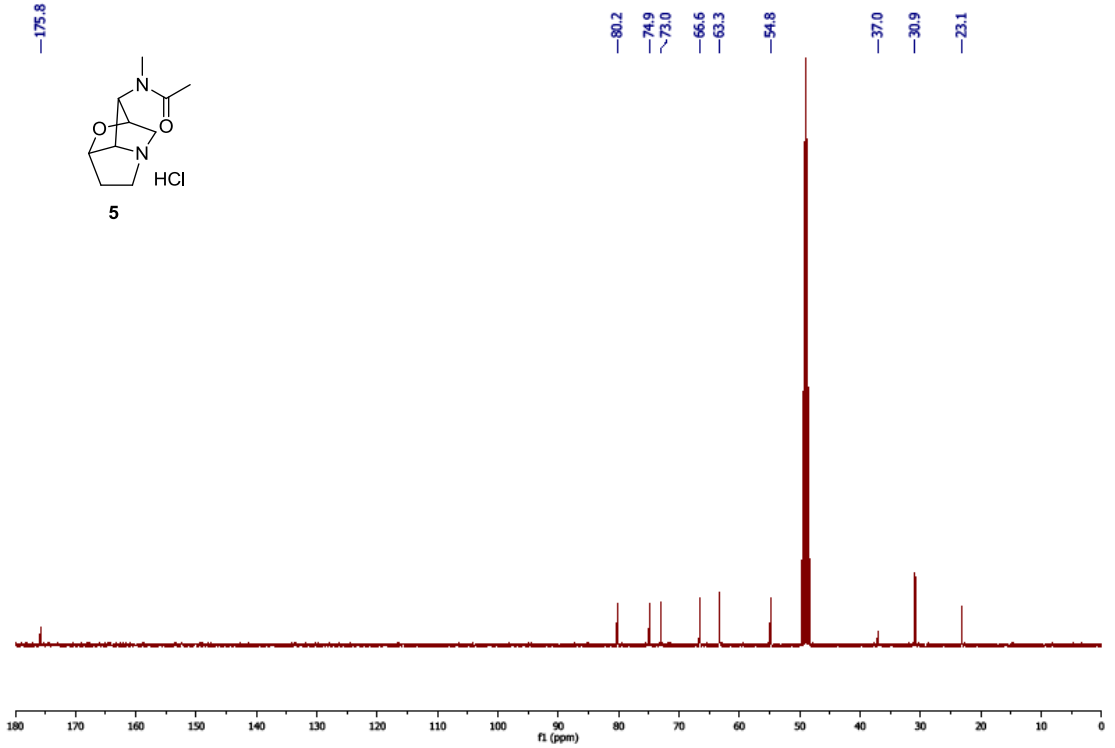
H
N
O
N
• 2HCl

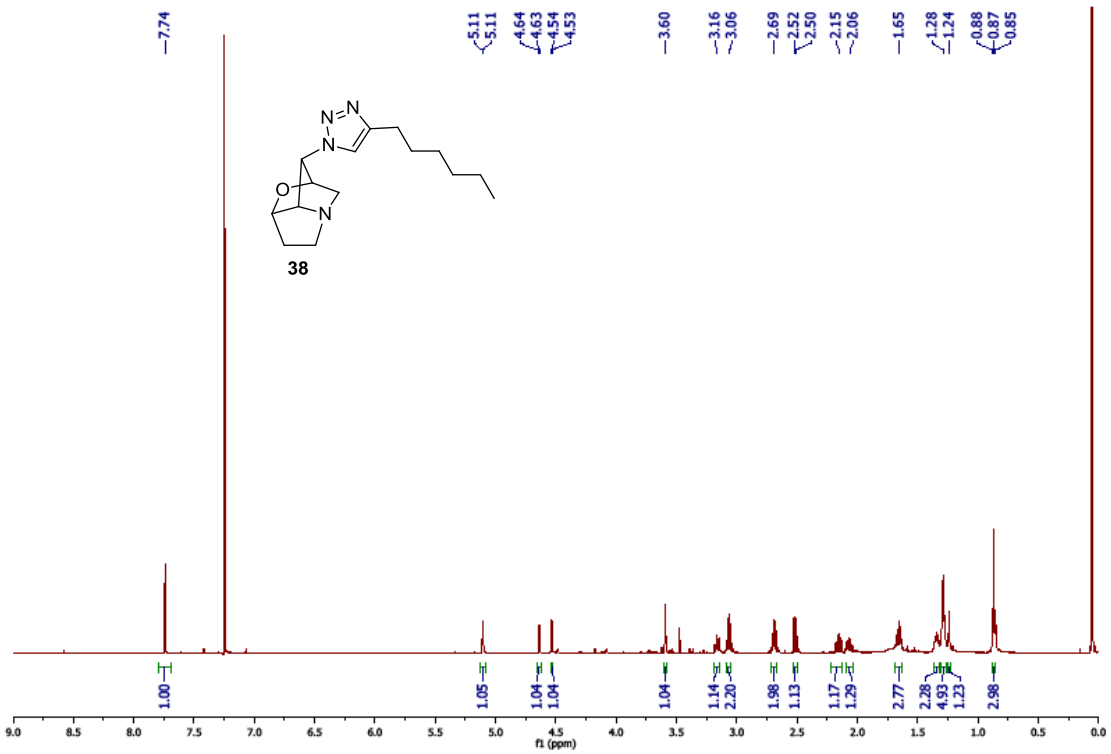
2


8.44
8.07
4.71
4.71
4.44
4.21
4.04
3.85
3.25
3.11
3.05
2.95
2.52
2.46
2.43
2.14
2.06
2.02
1.94
CHO
N
O
N
4
f1 (ppm)

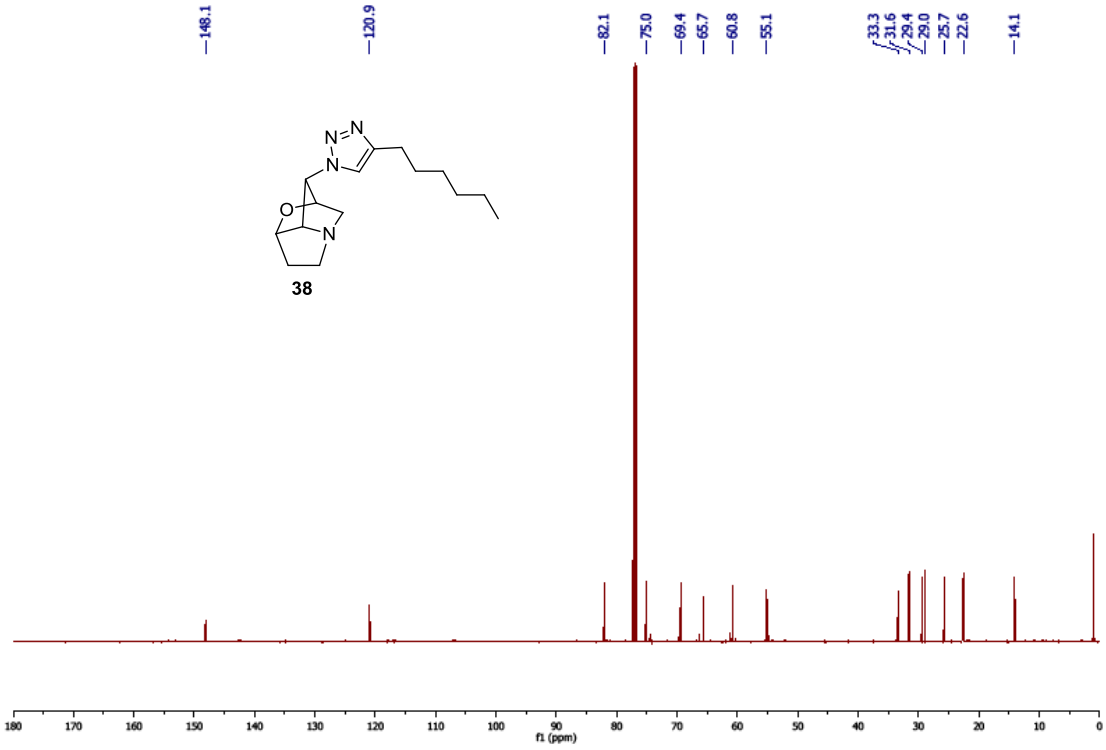

163.5
162.3
82.0
80.3
74.0
73.1
65.4
60.5
54.8
54.6
33.4
33.1
32.8
29.9
CHO
N
O
N
4
f1 (ppm)


5.02
5.02
4.92
4.67
4.65
4.15
3.75
3.71
3.41
3.38
3.11
3.10
2.44
2.33
2.15
HCl
5
1.01
1.00
1.02
1.00
1.01
1.95
1.04
2.96
1.15
1.09
3.00
f1 (ppm)

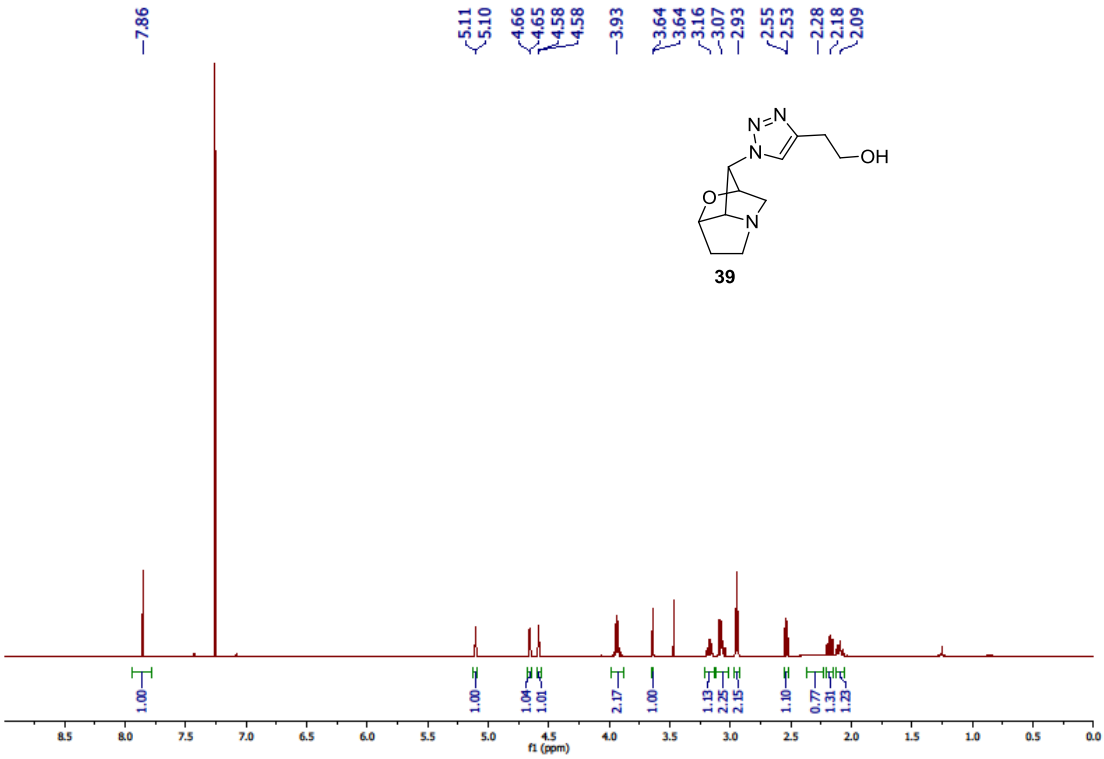

175.8
80.2
74.9
73.0
66.6
63.3
54.8
37.0
30.9
23.1
HCl
5
f1 (ppm)

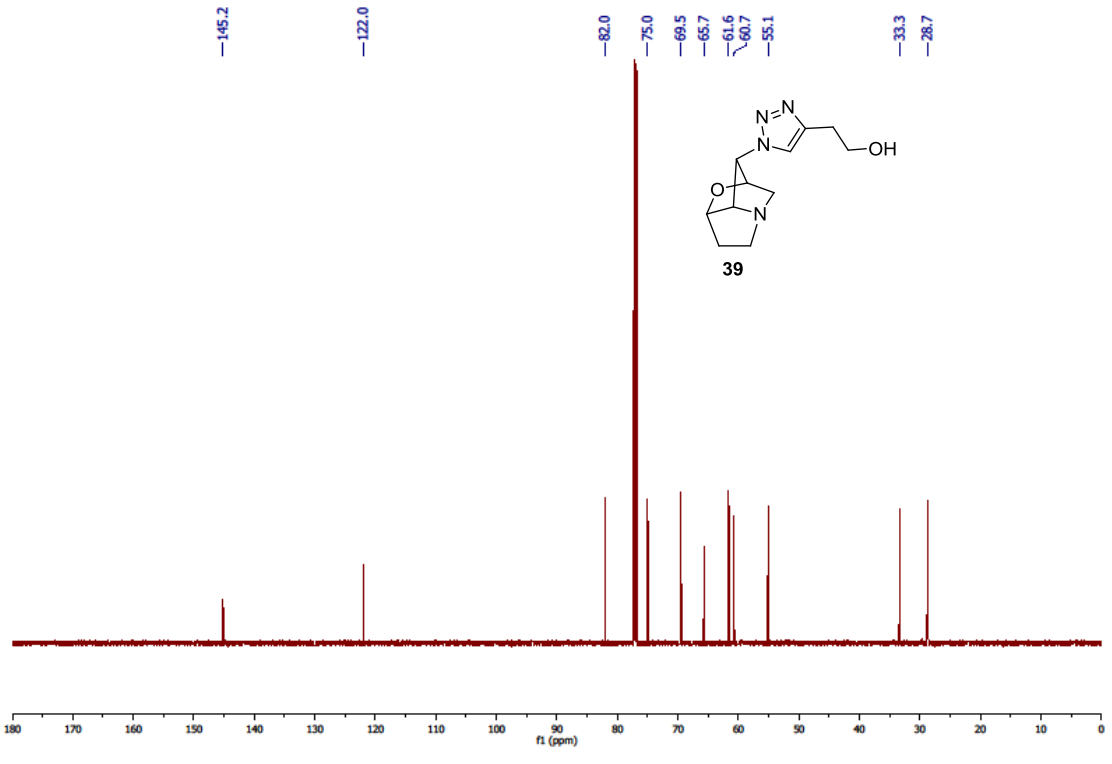

7.74
5.11
5.11
4.64
4.63
4.54
4.53
3.60
3.16
3.06
2.69
2.52
2.50
2.15
2.06
1.65
1.28
1.24
0.88
0.87
0.85
1.00
1.05
1.04
1.04
1.04
1.14
2.20
1.98
1.13
1.17
1.29
2.77
2.28
4.93
1.23
2.98
f1 (ppm)

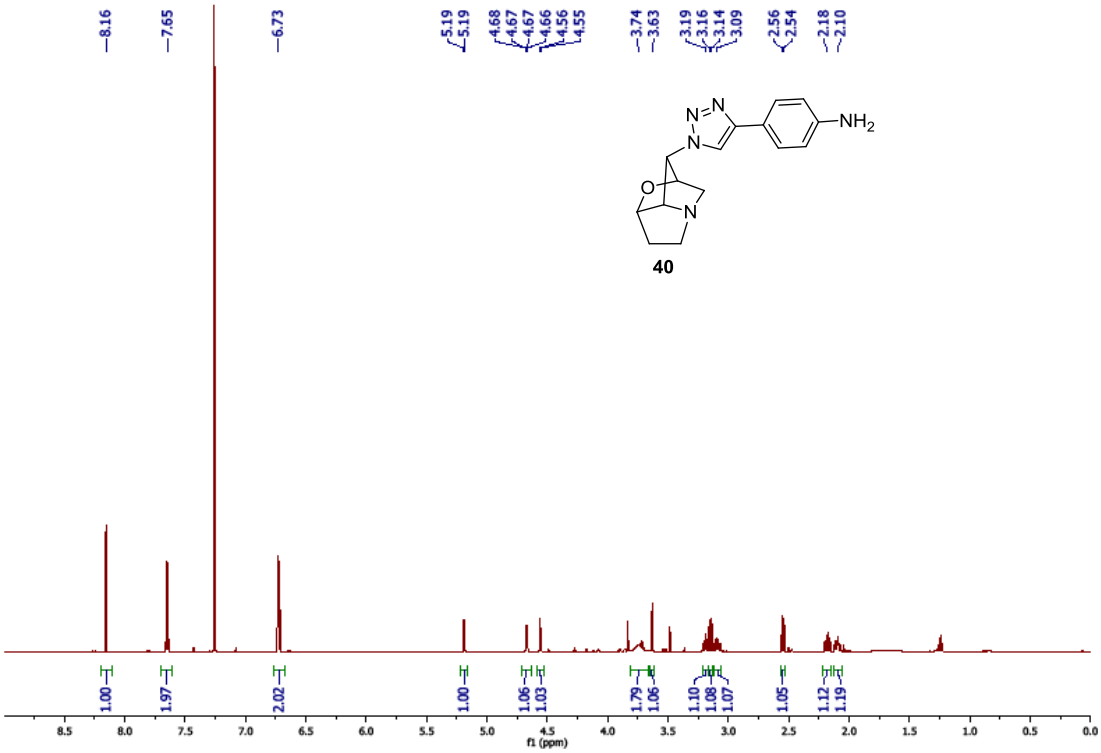
38

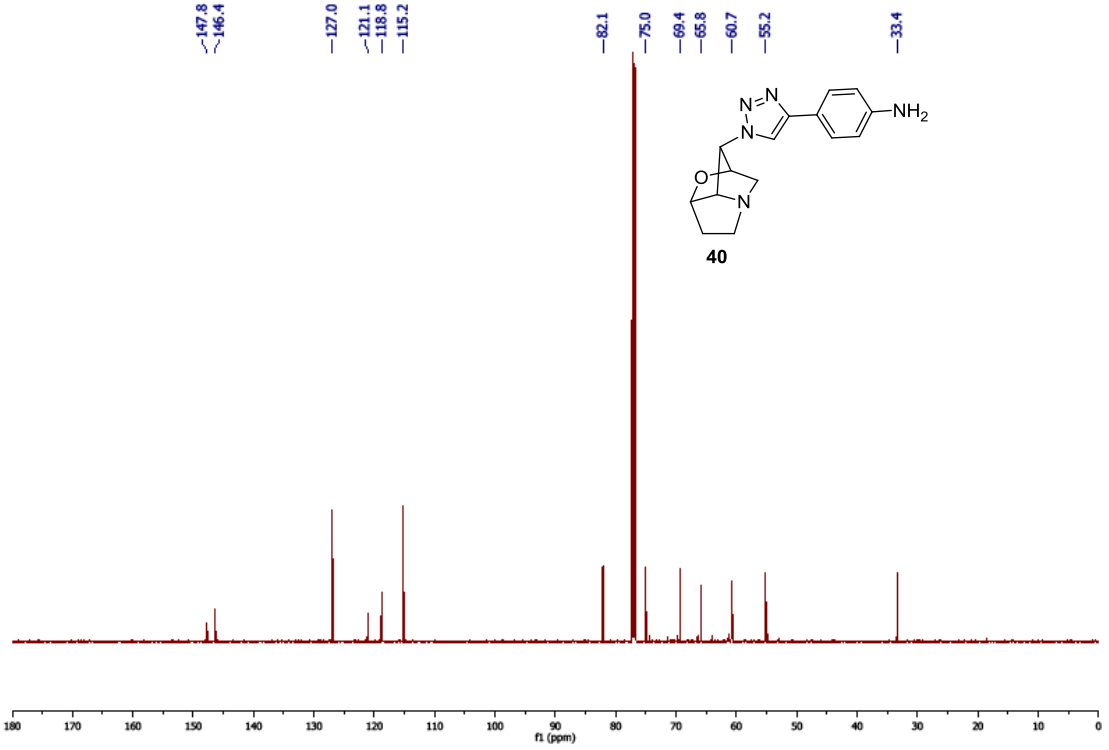

148.1
120.9
82.1
75.0
69.4
65.7
60.8
55.1
33.3
31.6
29.4
29.0
25.7
22.6
14.1
f1 (ppm)

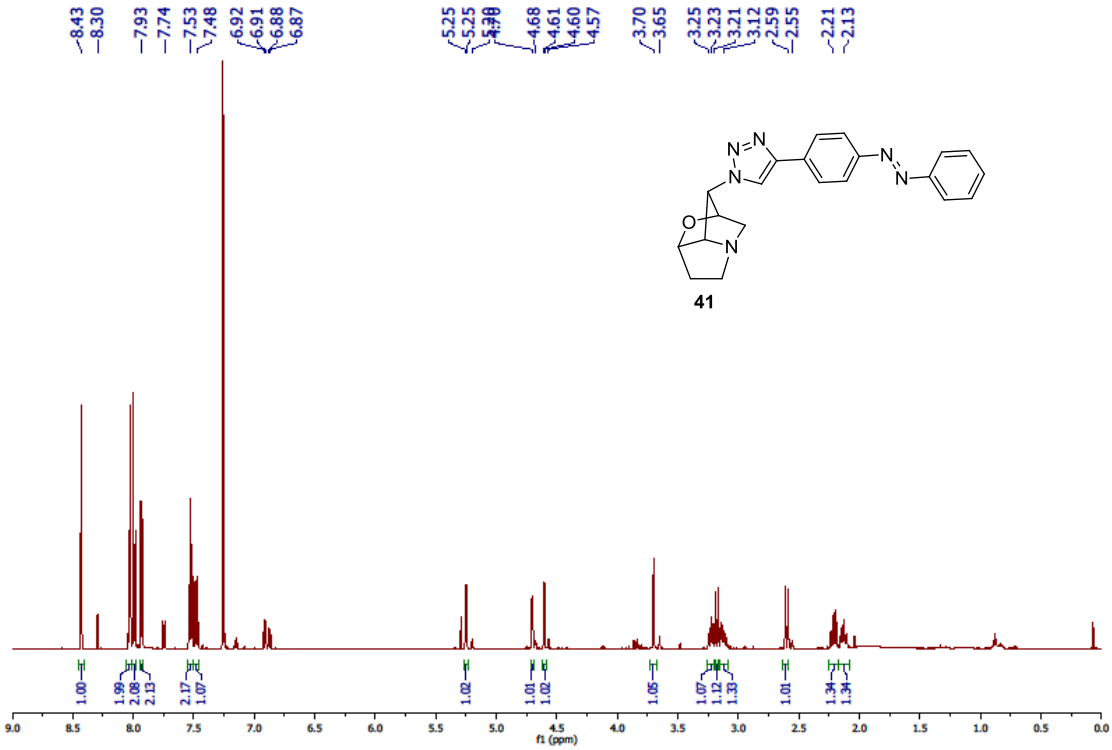
38


7.86
5.11
5.10
4.66
4.65
4.58
4.58
3.93
3.64
3.64
3.16
3.07
2.93
2.55
2.53
2.28
2.18
2.09
OH
39
f1 (ppm)

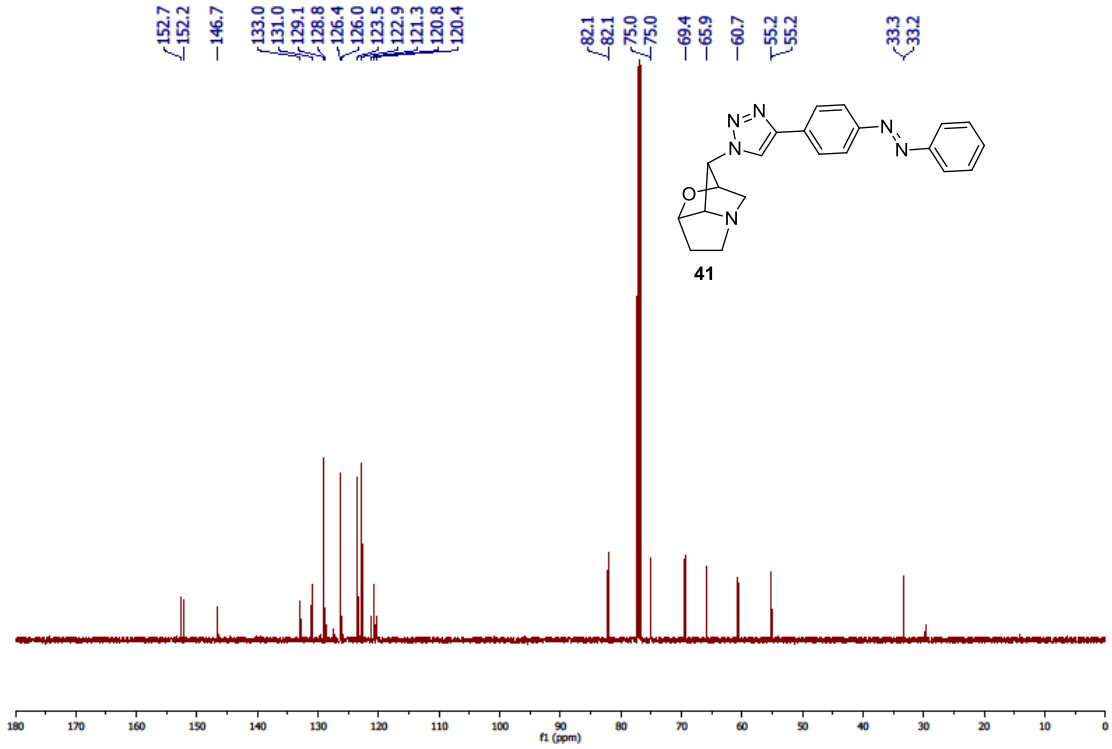

145.2
122.0
82.0
75.0
69.5
65.7
61.6
60.7
55.1
33.3
28.7
OH
39
f1 (ppm)


8.16
7.65
6.73
5.19
5.19
4.68
4.67
4.67
4.66
4.56
4.55
3.74
3.63
3.19
3.16
3.14
3.09
2.56
2.54
2.18
2.10
NH2
O
N
N
N
40
1.00
1.97
2.02
1.00
1.06
1.03
1.79
1.06
1.10
1.08
1.07
1.05
1.12
1.19
f1 (ppm)

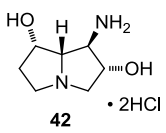

147.8
146.4
127.0
121.1
118.8
115.2
82.1
75.0
69.4
65.8
60.7
55.2
33.4
NH2
O
N
N
N
40
f1 (ppm)


8.43
8.30
7.93
7.74
7.53
7.48
6.92
6.91
6.88
6.87
5.25
5.25
4.68
4.61
4.60
4.57
3.70
3.65
3.25
3.23
3.21
3.12
2.59
2.55
2.21
2.13
1.00
1.99
2.08
2.13
2.17
1.07
1.02
1.01
1.02
1.05
1.07
1.12
1.33
1.01
1.34
1.34
f1 (ppm)

41

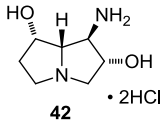

152.7
152.2
146.7
133.0
131.0
129.1
128.8
126.4
126.0
123.5
122.9
121.3
120.8
120.4
82.1
82.1
75.0
75.0
69.4
65.9
60.7
55.2
55.2
33.3
33.2
f1 (ppm)

41



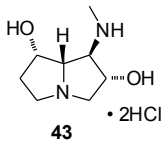
• 2HCl

42



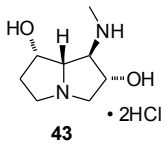
• 2HCl

42


HO
H
NH
OH
N
• 2HCl

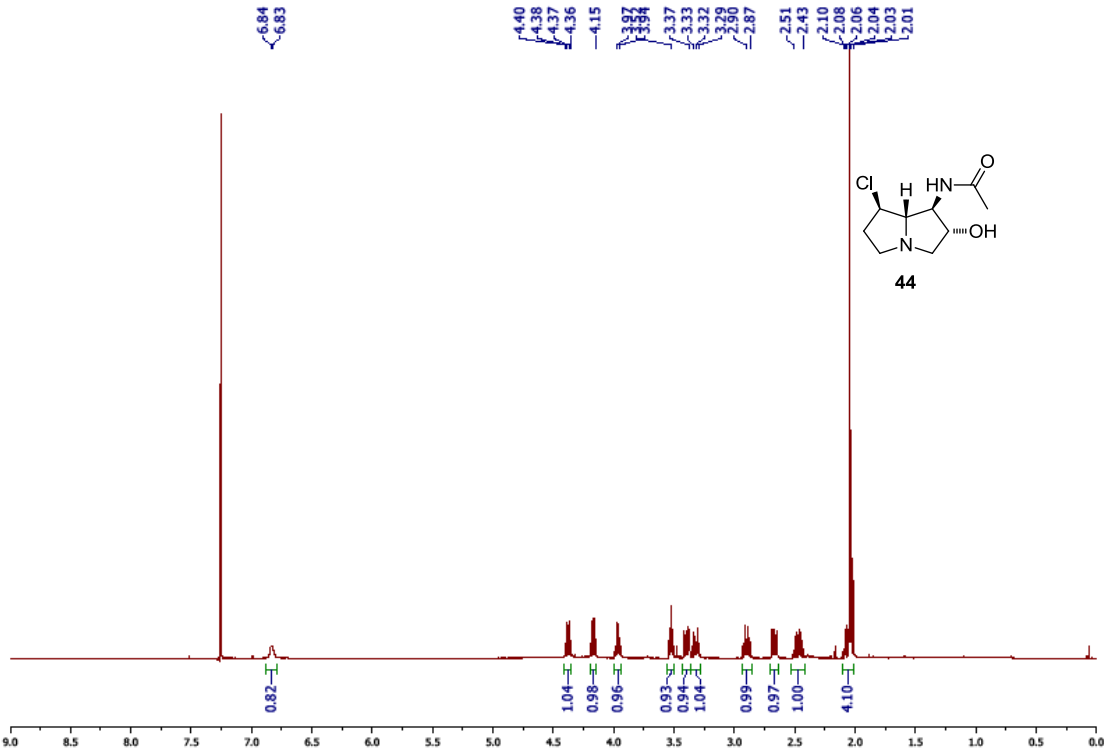
43

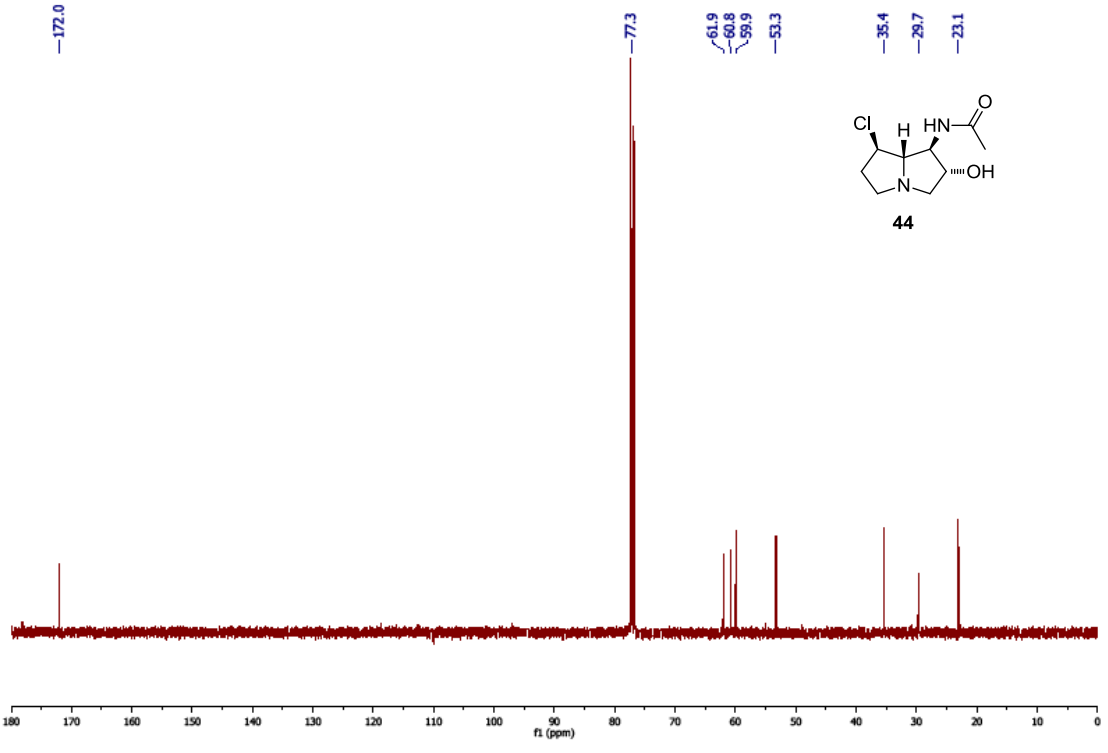
4.86
4.76
4.49
4.47
4.46
4.13
3.95
3.50
3.47
3.28
3.25
2.96
2.38
1.11
1.13
1.00
2.02
1.07
1.09
1.07
3.04
2.17
f1 (ppm)

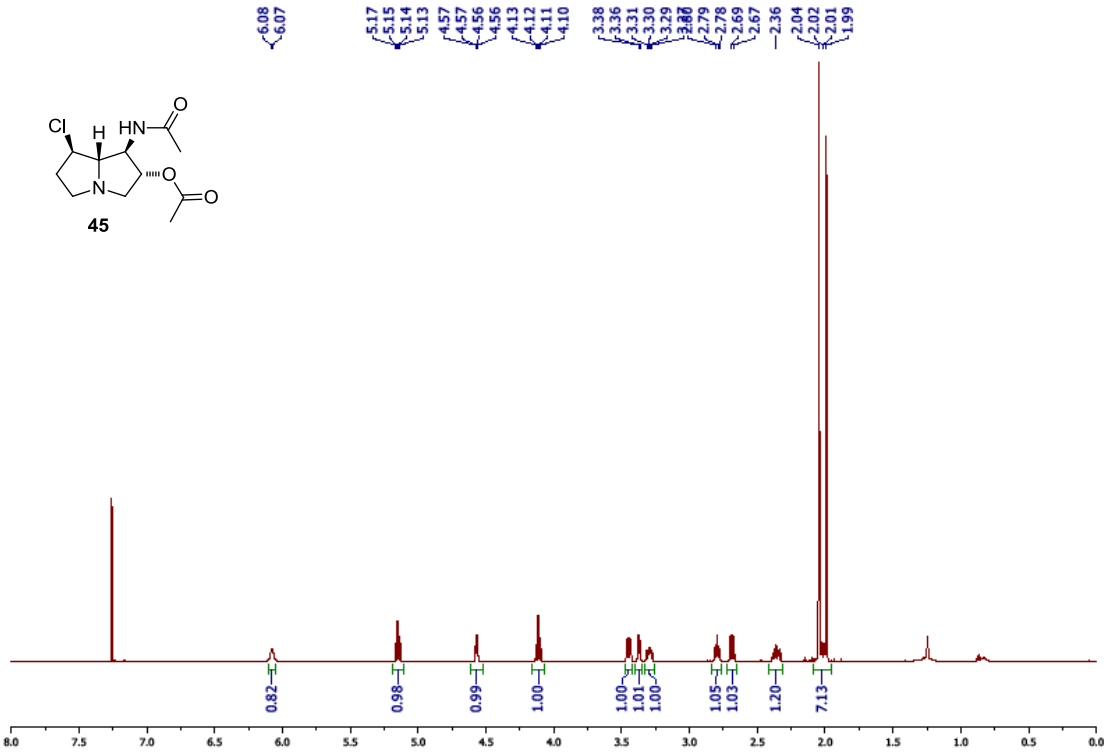

HO
H
NH
OH
N
• 2HCl

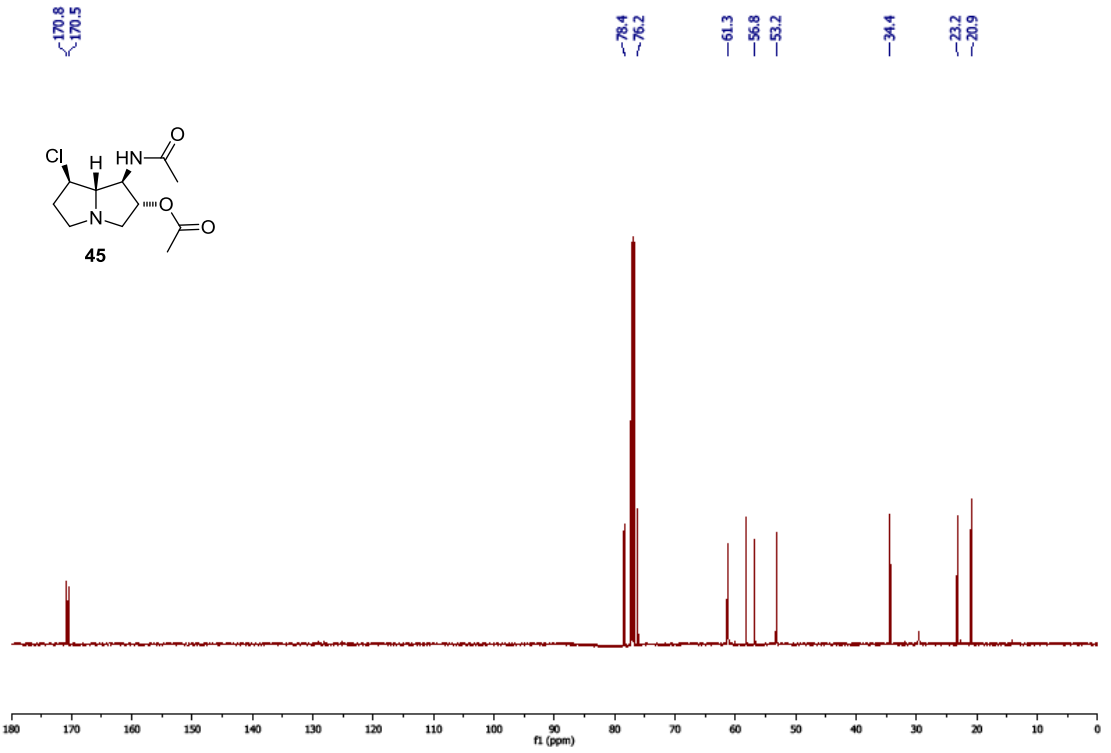
43

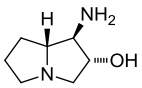
72.3
69.9
68.8
60.0
57.8
53.6
34.7
32.1
f1 (ppm)


6.84
6.83
4.40
4.38
4.37
4.36
4.15
3.37
3.33
3.32
3.29
2.90
2.87
2.51
2.43
2.10
2.08
2.06
2.04
2.03
2.01
Cl
H
HN
O
OH
N
44
0.82
1.04
0.98
0.96
0.93
0.94
1.04
0.99
0.97
1.00
4.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


172.0
77.3
61.9
60.8
59.9
53.3
35.4
29.7
23.1
Cl
H
HN
O
OH
N
44
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

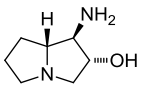

6.08
6.07
5.17
5.15
5.14
5.13
4.57
4.57
4.56
4.56
4.13
4.12
4.11
4.10
3.38
3.36
3.31
3.30
3.29
2.79
2.78
2.69
2.67
2.36
2.04
2.02
2.01
1.99
Cl
H
HN
O
O
O
N
45
0.82
0.98
0.99
1.00
1.00
1.01
1.00
1.05
1.03
1.20
7.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


170.8
170.5
78.4
76.2
61.3
56.8
53.2
34.4
23.2
20.9
Cl
H
HN
O
O
O
N
45
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



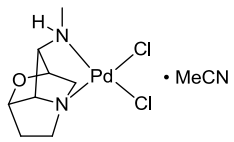
• 2HBr

46



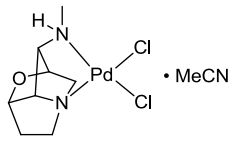
• 2HBr

46


H
N
Cl
O
Pd
• MeCN
N
Cl

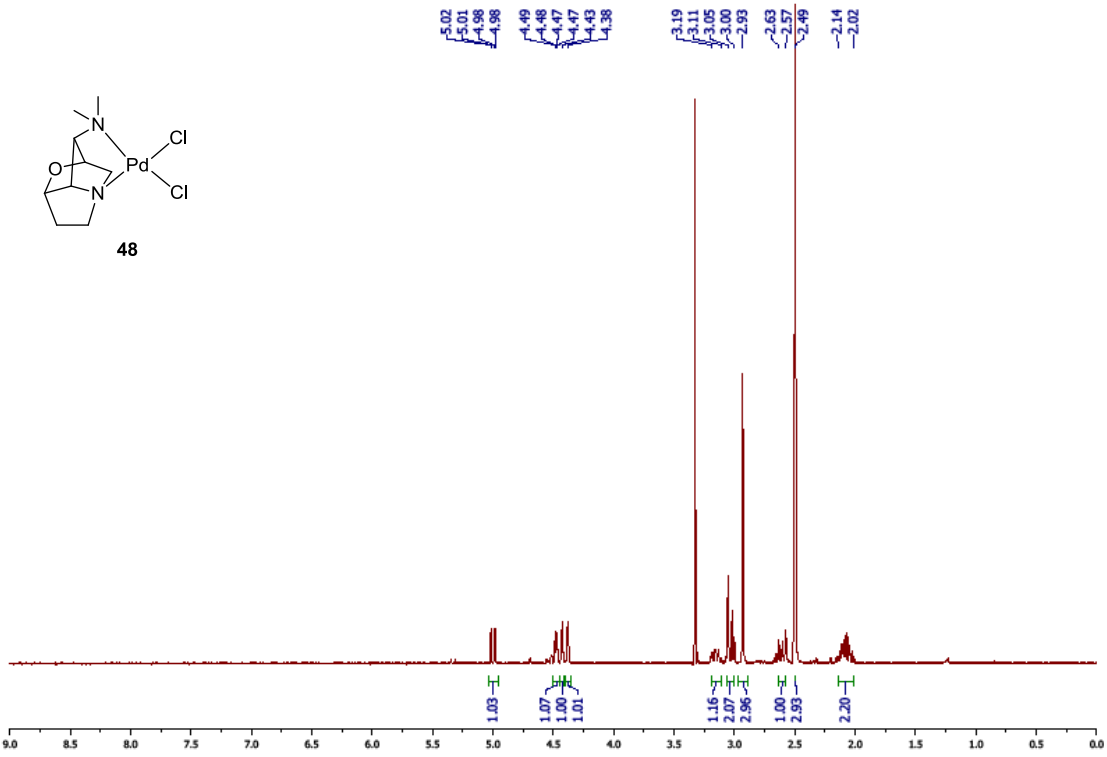
47

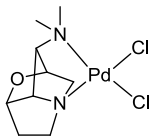
6.07
5.44
5.17
5.14
4.58
4.57
4.32
3.29
3.22
3.09
2.97
2.95
2.54
2.53
2.24
2.13
2.00
0.92
0.96
0.97
1.03
1.00
0.97
0.95
1.04
1.07
2.88
1.05
1.03
3.23
f1 (ppm)


H
N
Cl
O
Pd
• MeCN
N
Cl

47

116.3
79.6
78.1
72.5
65.3
64.2
54.8
37.0
31.8
1.9
f1 (ppm)


5.02
5.01
4.98
4.98
4.49
4.48
4.47
4.47
4.43
4.38
3.19
3.11
3.05
3.00
2.93
2.63
2.57
2.49
2.14
2.02
1.03
1.07
1.00
1.01
1.16
2.07
2.96
1.00
2.93
2.20
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

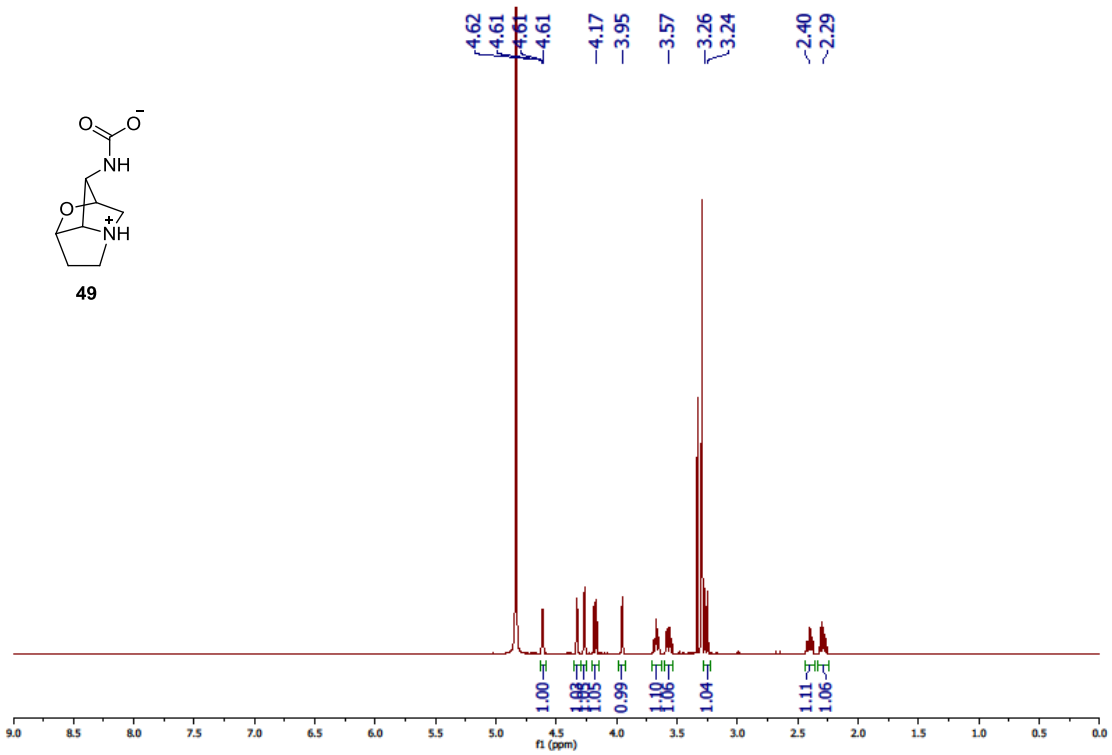

N
O
Pd
Cl
Cl
N

48

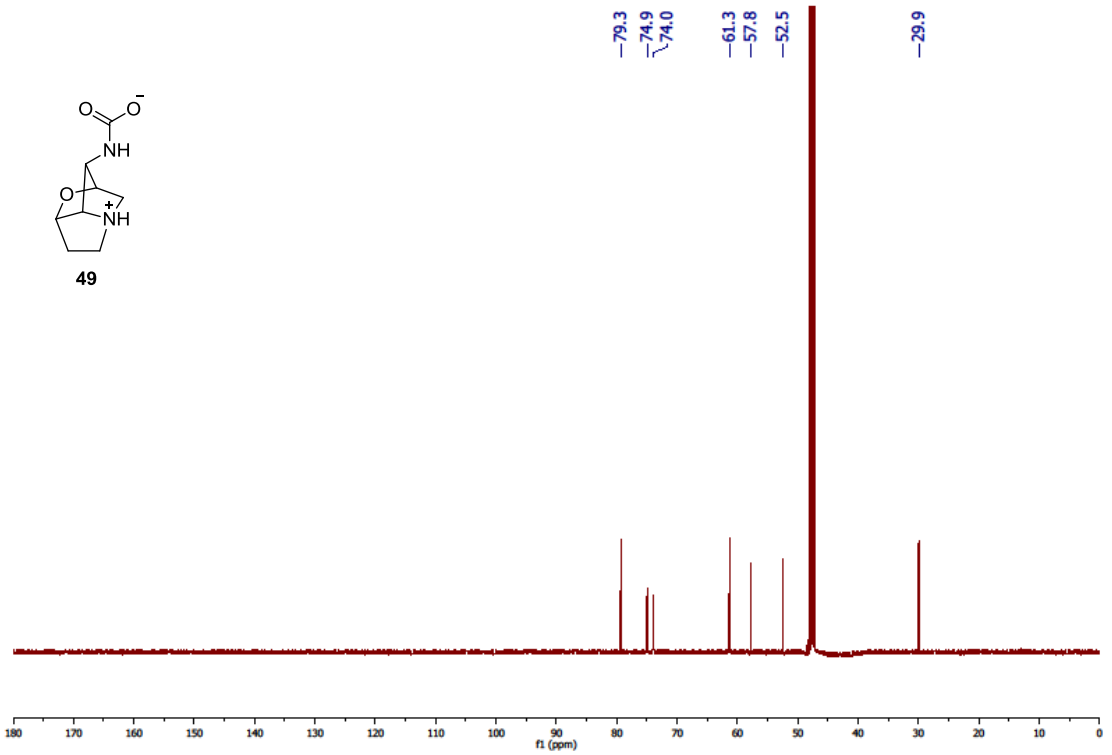
78.2
77.3
73.9
72.4
63.1
54.2
51.3
46.9
31.2
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

N
O
Pd
Cl
Cl
N

48



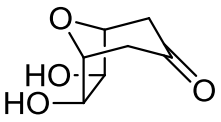
49



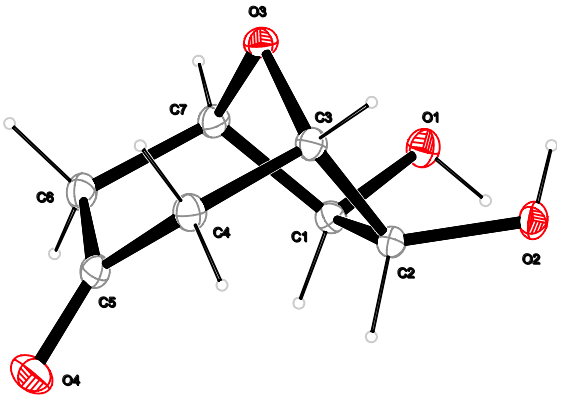
49

Crystal structures

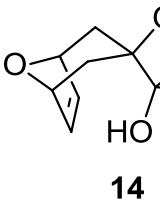
Crystal structure of **9**



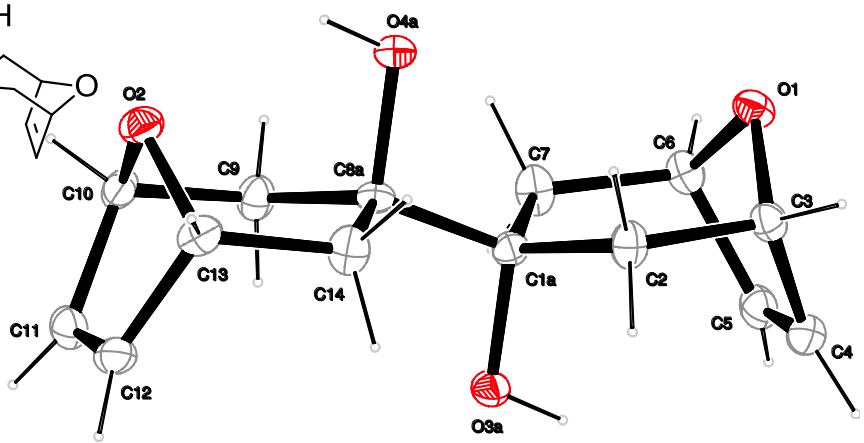
9



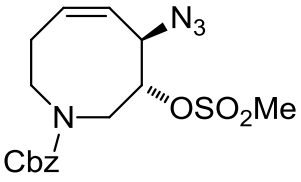
Crystal structure of **14**



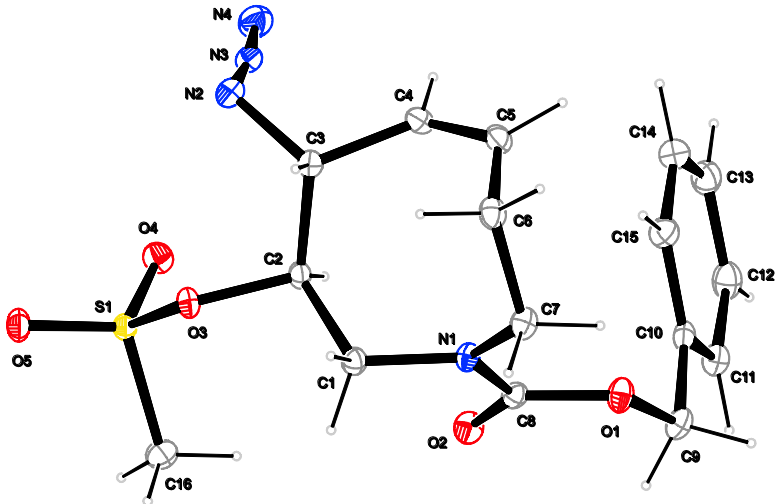
14



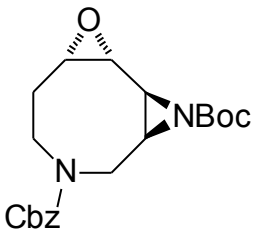
Crystal structure of **25**



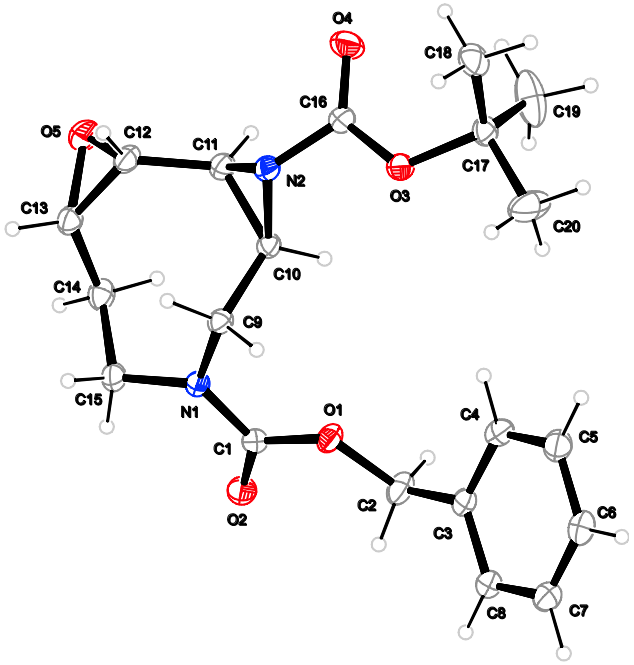
25



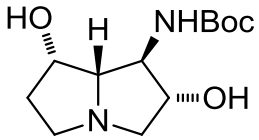
Crystal structure of **18**



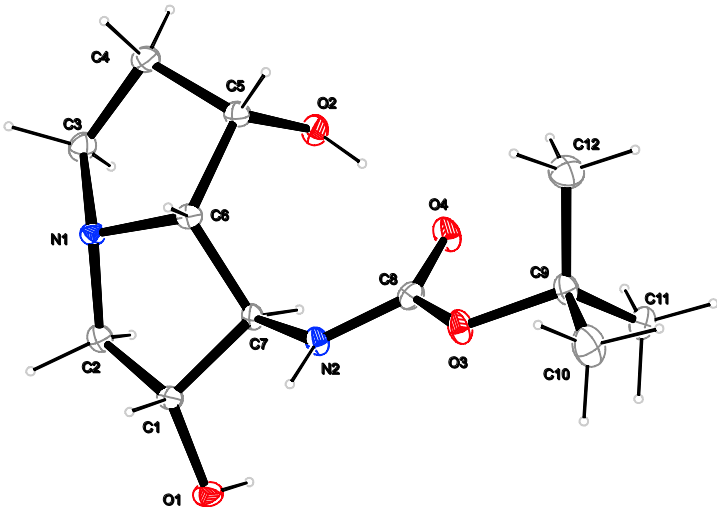
18



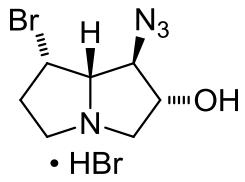
Crystal structure of **27**



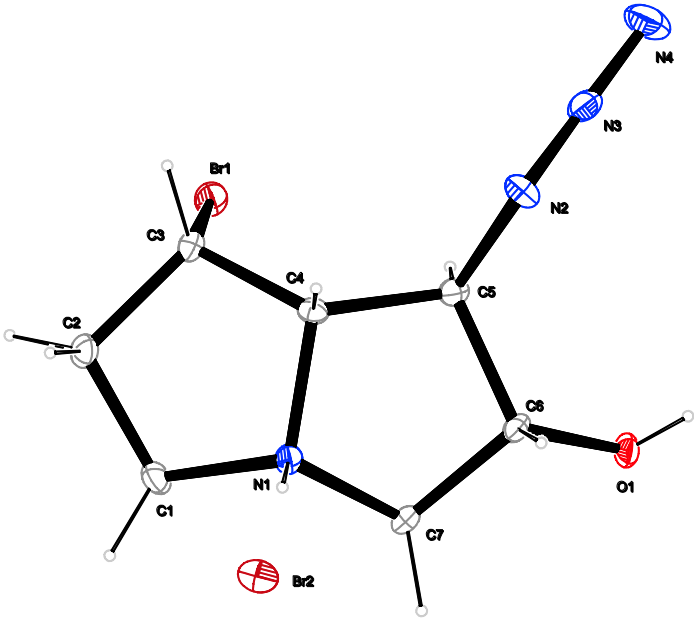
27



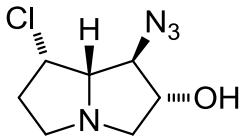
Crystal structure of **28**



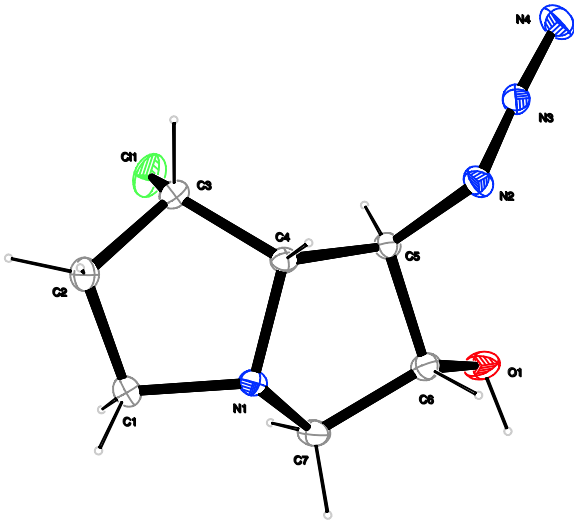
28



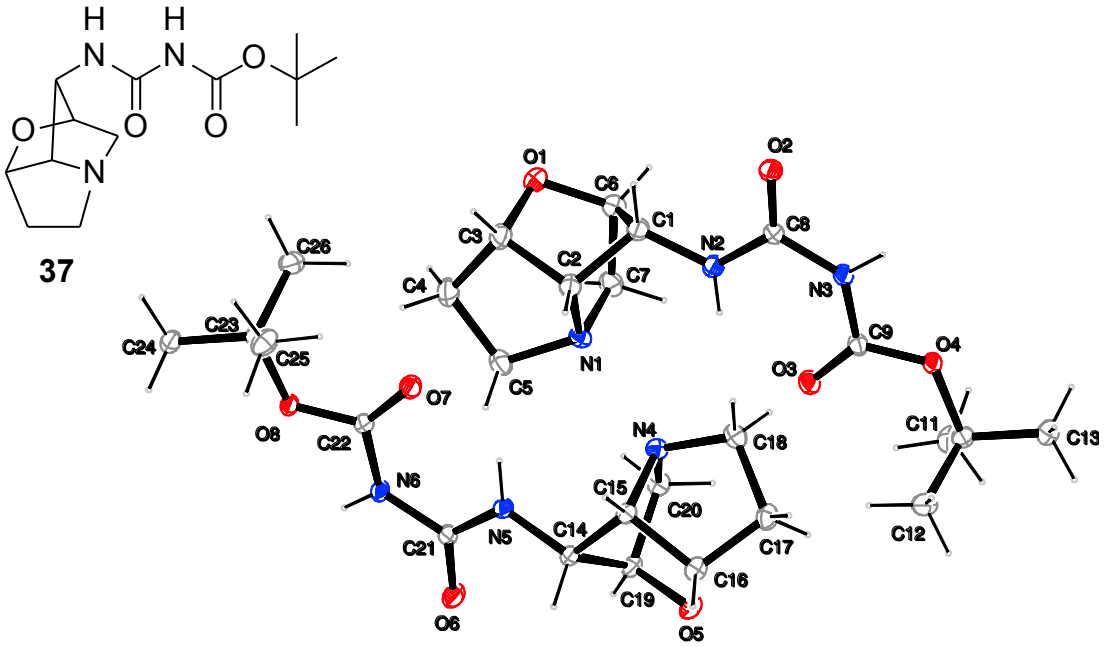
Crystal structure of **32**



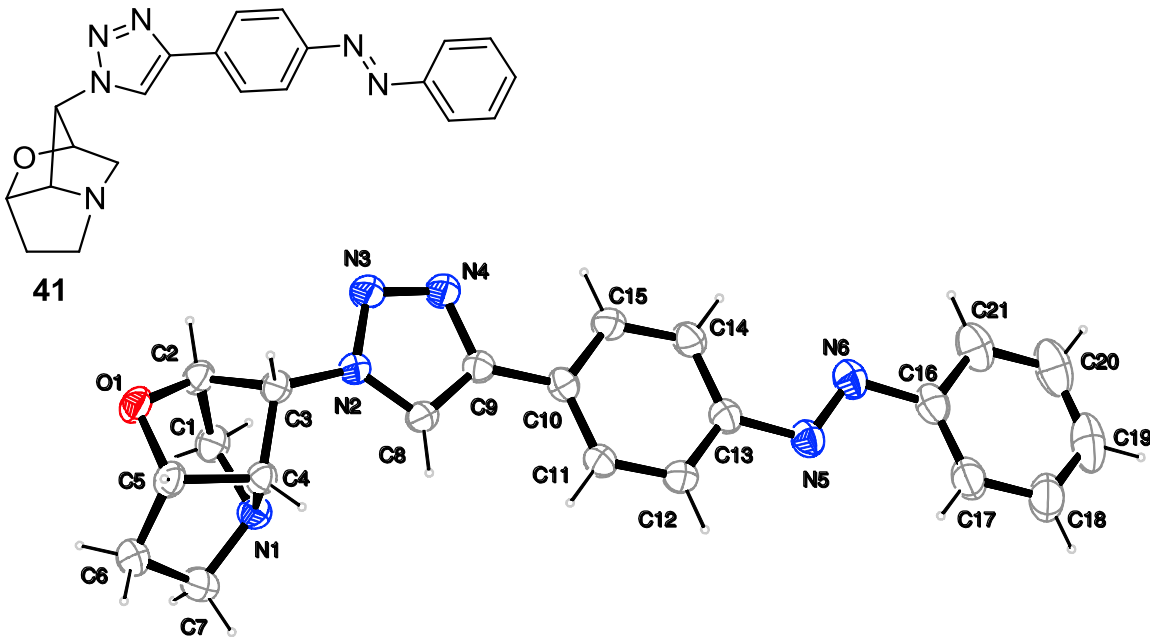
32



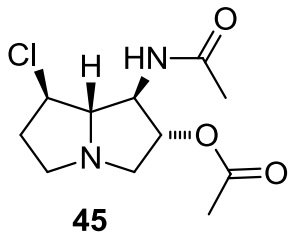
Crystal structure of **18**



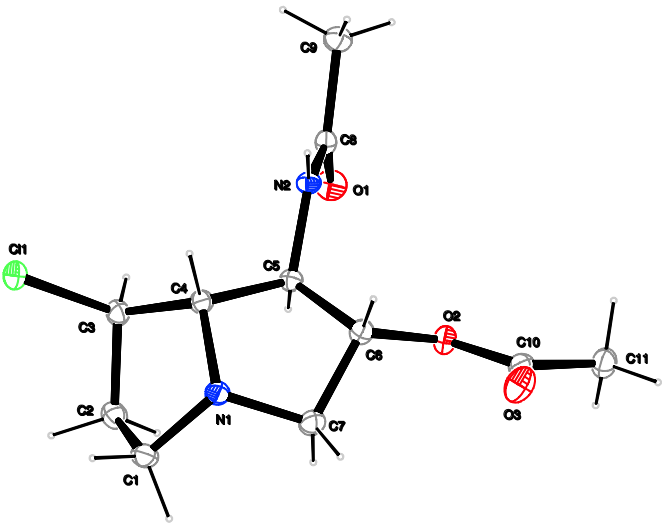
Crystal structure of **41**



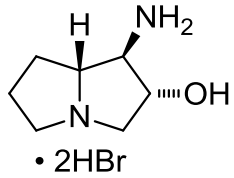
Crystal structure of **45**



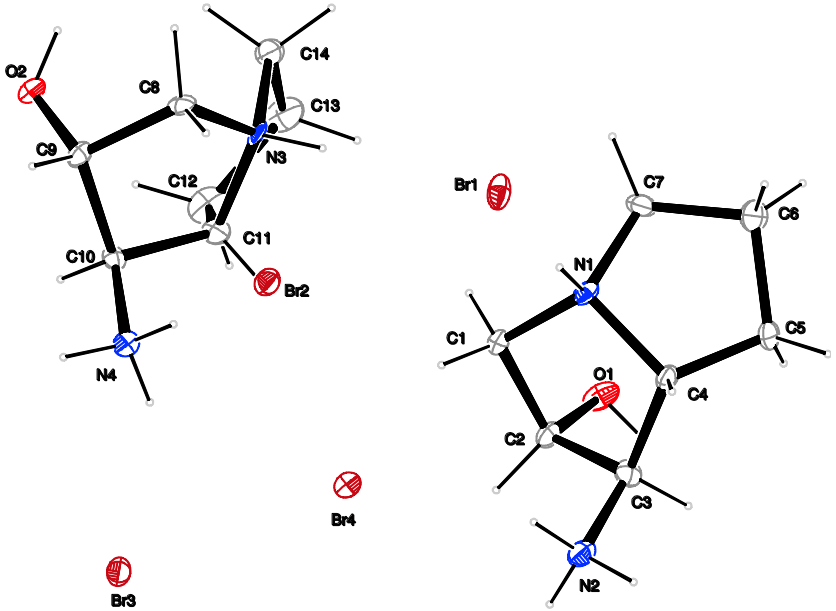
45



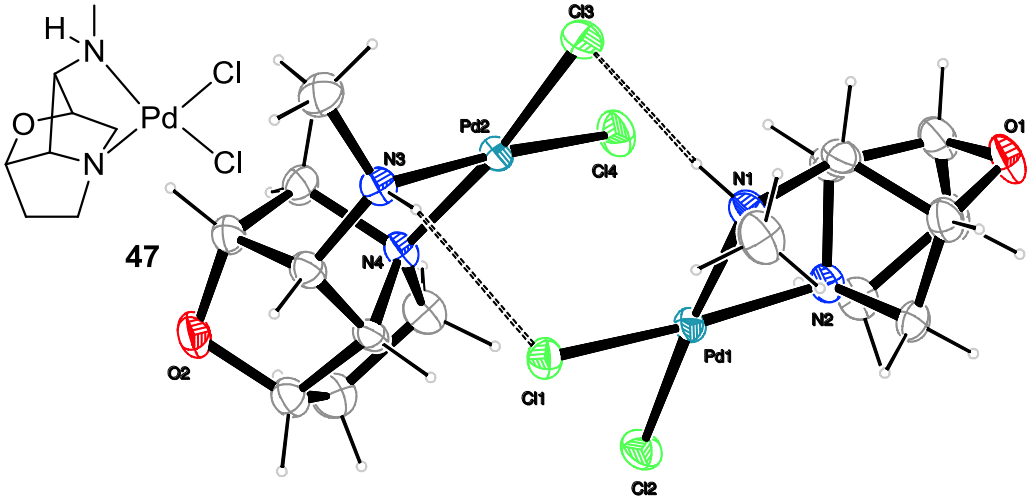
Crystal structure of **46**



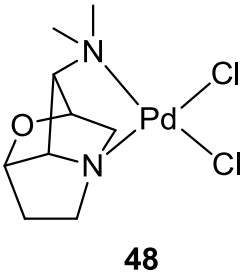
46

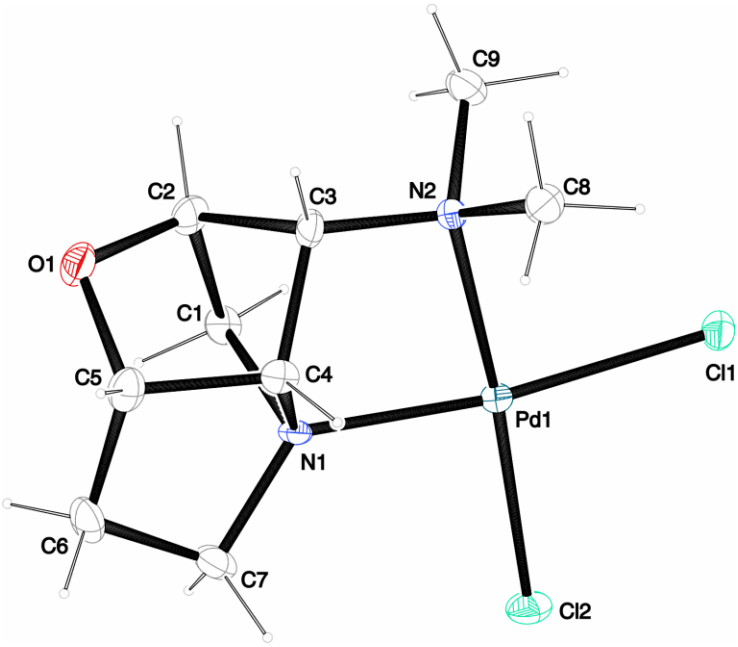


Crystal structure of **47**

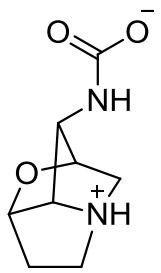


Crystal structure of **48**

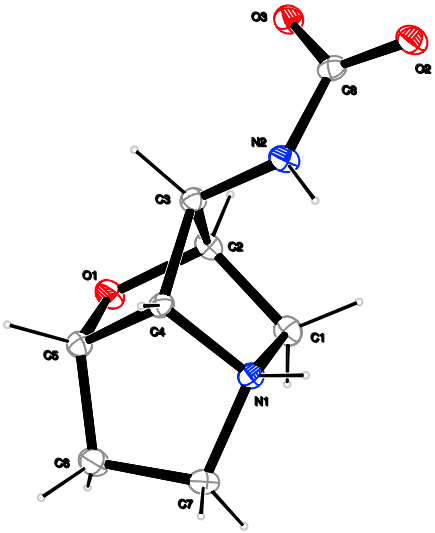




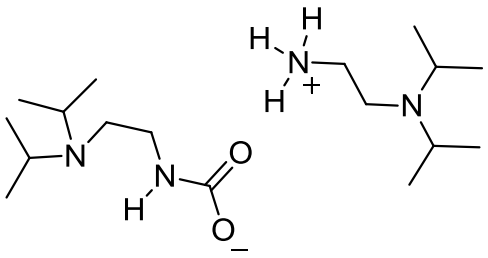
Crystal structure of **49**



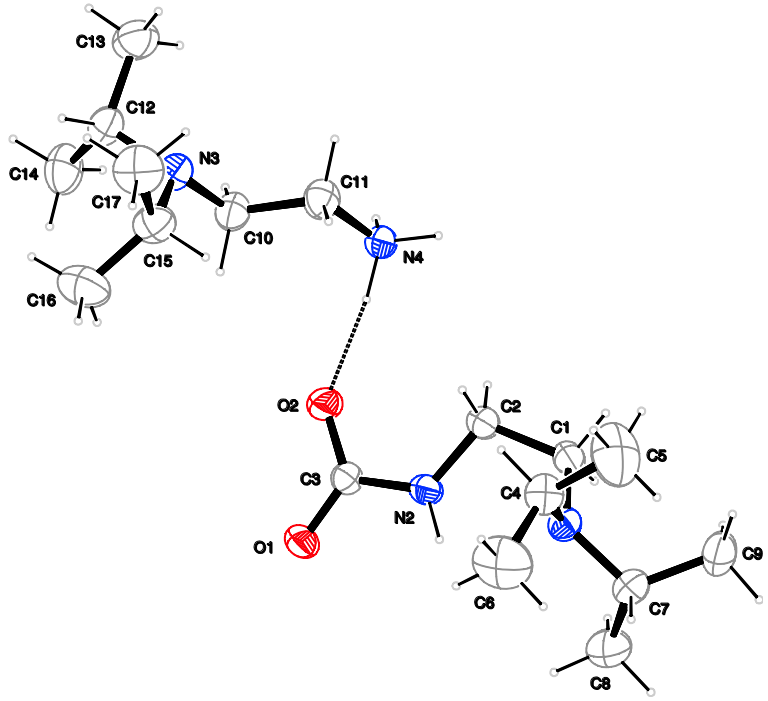
49



Crystal structure of **49**



51



II Studies toward Naphthomycin K

1. Introduction of Naphthomycins

1.1 History of Antibiotics

Paul Ehrlich, a German medicinal scientist, was awarded with the Nobel Prize in Physiology in 1908 for his work on immunity. He was the first researcher who developed a medical treatment of pox and is therefore the founder of chemotherapy. In 1910 he invented Salvarsan, also known as Arsphenamine, which was the first antibiotic drug.[1]

Figure 1: Paul Ehrlich and Salvarsan on the 200-Deutsche Mark bill.

Salvarsan is a narrow-spectrum antibiotic and only targets spirochetes. The first commercially available and more effective antibiotic Prontosil was developed by Gerhard Domagk in 1932.[2] Prontosil, which is a sulfonamide, opened a new era in medicine and was effectively used to treat wounds and ulcers during World War II. Sulfonamides inhibit the folate metabolism of bacteria and do not influence eukaryotic cells. Domagk received the 1939 Nobel Prize for Medicine for his efforts.

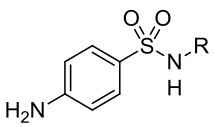


Figure 2: General structure of sulfonamides.

Penicillin, the next milestone in the history of antibiotics, could not be synthesized and had to be produced by microorganisms. Although the antibiotic properties of

fungus *Penicillium chrysogenum* had been known for many years[3], the first patient could be treated with Penicillin first in 1942 because of difficulties in purifying and isolating sufficient material. Penicillins bind to *DD*-transpeptidase, which only occurs in bacteria and inhibits the cell wall peptidoglycan formation. In 1945 the discovery of penicillin was awarded with the Nobel Prize in Medicine. Such a powerful antibiotic was unprecedented and its development led to a keen interest in the search for antibiotic compounds.

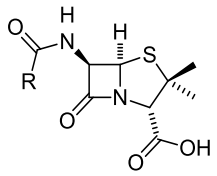


Figure 3: General structure of penicillins.

A common phenomenon is that many antibiotics, that had high initial efficacy against many bacterial species have become less effective over time because of increased resistance of many bacterial strains. The evolutionary stress of decades of antibacterial drug therapy has caused the emergence of resistance by means of natural selection. During antibiotic treatment the selection occurs when bacteria with enhanced fitness against antibiotics survive and sensitive bacteria are inhibited in growth. Another problem is cross-resistance, where bacteria tolerate antibiotics as a result of exposure to substances with similar chemical structure or acting mechanism. Bacteria showing resistance to multiple antibiotics are called multidrug resistant (MDR) or, informally, superbugs.

In addition to cell wall formation and folate metabolism, RNA translation and DNA replication are targets for successfully antagonize bacterial infections. The task of scientists is on the one hand to find new points of actions and the other hand to develop appropriate chemical compounds in order to treat bacterial infections.

1.2 Naphthomycins

Naphthomycins are antibiotics from the family of ansamycins and are potential candidates for antibacterial drugs. There is no total synthesis reported, which makes the evaluation of their biological activity difficult. For instance, naphthomycin K has known antifungal activity and shows cytotoxicity against P388 and A-549 cell lines,

but no inhibitory activity against *Staphylococcus aureus* and *Mycobacterium tuberculosis*.[4]

Naphthomycins are described having a basket like structure. All of them contain a naphthoquinone moiety that forms a planar portion and a polyketide chain, which forms a macrocyclic lactam and has a handle like structure.[5] Eleven various compounds of the naphthomycin family are known to date.[4-7] The letter of their names refers to their chronological discovery (Figure 4).

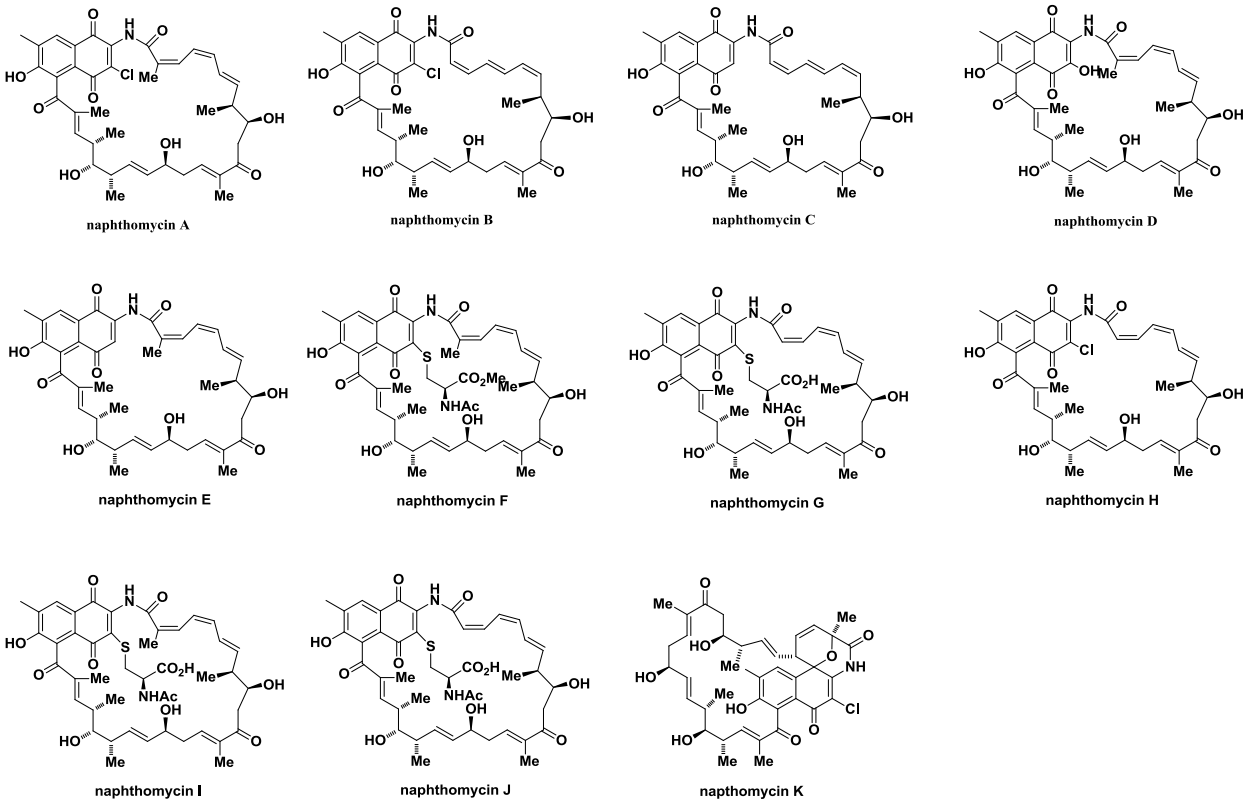
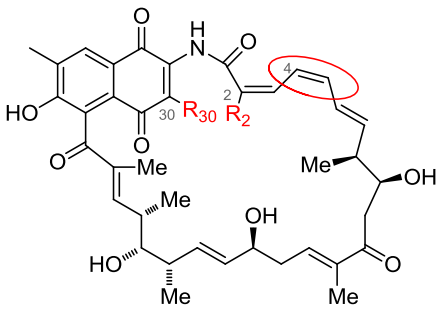


Figure 4: All members of the naphthomycin family.

All members of this family, excluding naphthomycin K, consist of the same structure with three modifications: the substituents at C2 and C30 and the conformation of the C4 double bond, highlighted in red (Figure 5).

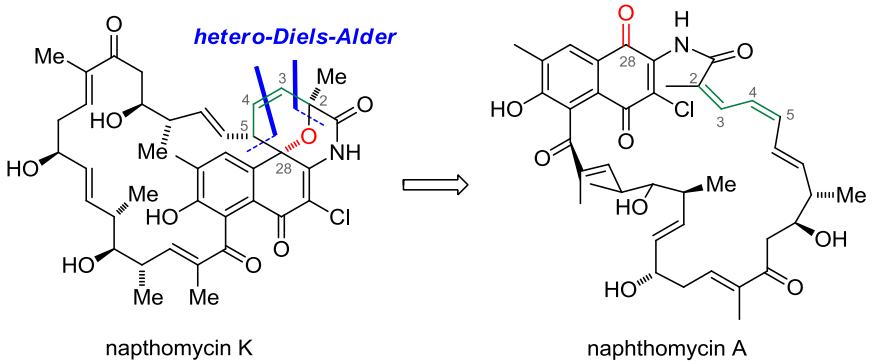


naphthomycin	R_{30}	R_2	DB-Geometry
A	Cl	Me	(Z)
B	Cl	H	(E)
C	H	H	(E)
D	OH	Me	(Z)
E	H	Me	(Z)
F	CysNAc (Me)	Me	(Z)
G	CysNAc	H	(Z)
H	Cl	H	(Z)
I	CysNAc	Me	(Z)
J	CysNAc	H	(Z)

Figure 5: Naphthomycins and their crucial distinctions.

The oldest member of this family, naphthomycin A, was first isolated in 1969 from *Streptomyces collinus* by Balerna *et al.*[7] The latest member, naphthomycin K, was isolated together with naphthomycin A in 2007. They were extracted from the chinese medical plant *Maytenus hookeri*, specifically from one of its commensal microorganisms: *Streptomyces* sp. CS.[4]

The distinctive feature of naphthomycin K compared to the other naphthomycins is its structure, which is not a result of modifying the above mentioned three positions. In naphthomycin K the bicyclic nucleus is extended by an additional oxa-azabicyclo-[3.3.1]nonen-one. In nature naphthomycin K probably arises out of naphthomycin A via a hetero-Diels-Alder reaction of C2 to C5 diene and to the C28 carbonyl, highlighted in red and green in Scheme 1.

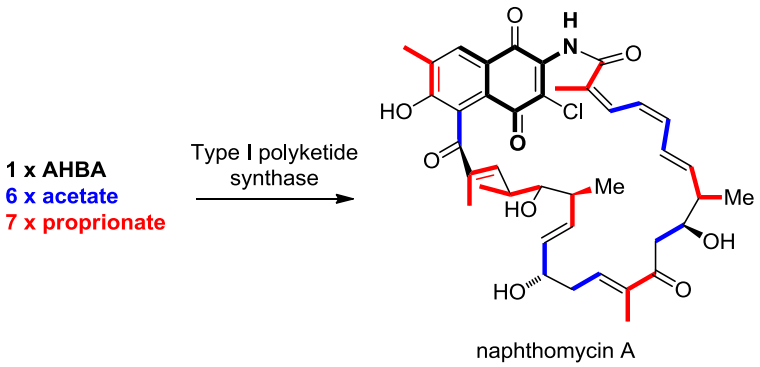


Scheme 1: Naphthomycin K and its arise from naphthomycin A.

1.3 Biosynthesis of Naphthomycin A

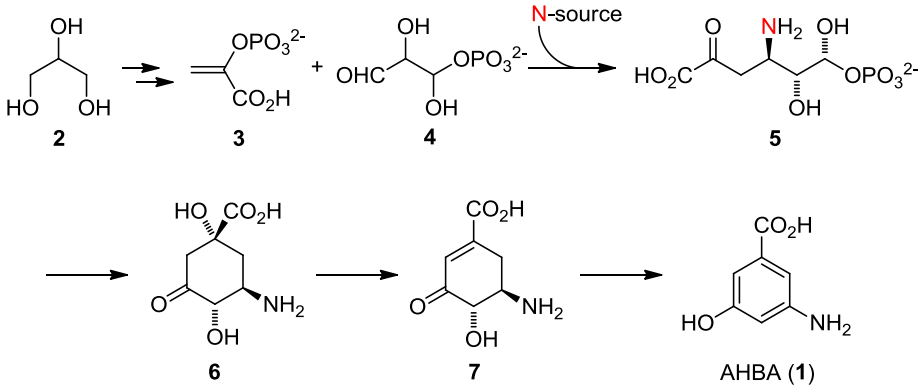
The biosynthesis of naphthomycin A was discovered by Lee *et al.* in 1994[8] and S. Chen *et al.* in 1999.[9] The polyketide macrocycle is formed by a type I polyketide

synthase using six acetate and seven proprionate units which are provided as malonyl-CoA and methylmalonyl-CoA (Scheme 2). The polyketide synthase uses a Coenzyme A thioester of 3-amino-5-hydroxybenzoic acid (**1**) (AHBA) as starter unit. This compound is synthesized by the aminoshikimate pathway.



Scheme 2: Biosynthetic origin of naphthomycin A.

The aminoshikimate starts with glycerol (**2),** out of which phosphoenolpyruvate (**3**) and erytrose 4-phosphate (**4**) In combination with a nitrogen source (e.g. glutamine) both merge to (amino)-deoxy-*arabino*-heptulosonate-7-phosphate (**5**). An enzymatic ring closing reaction creates the (amino)-dehydroquinic acid (**6**), which is converted to (amino)-dehydroshikimic acid (**7**) and further to AHBA (**1**).



Scheme 3: Biosynthesis of AHBA (**1**) via aminoshikimate pathway.

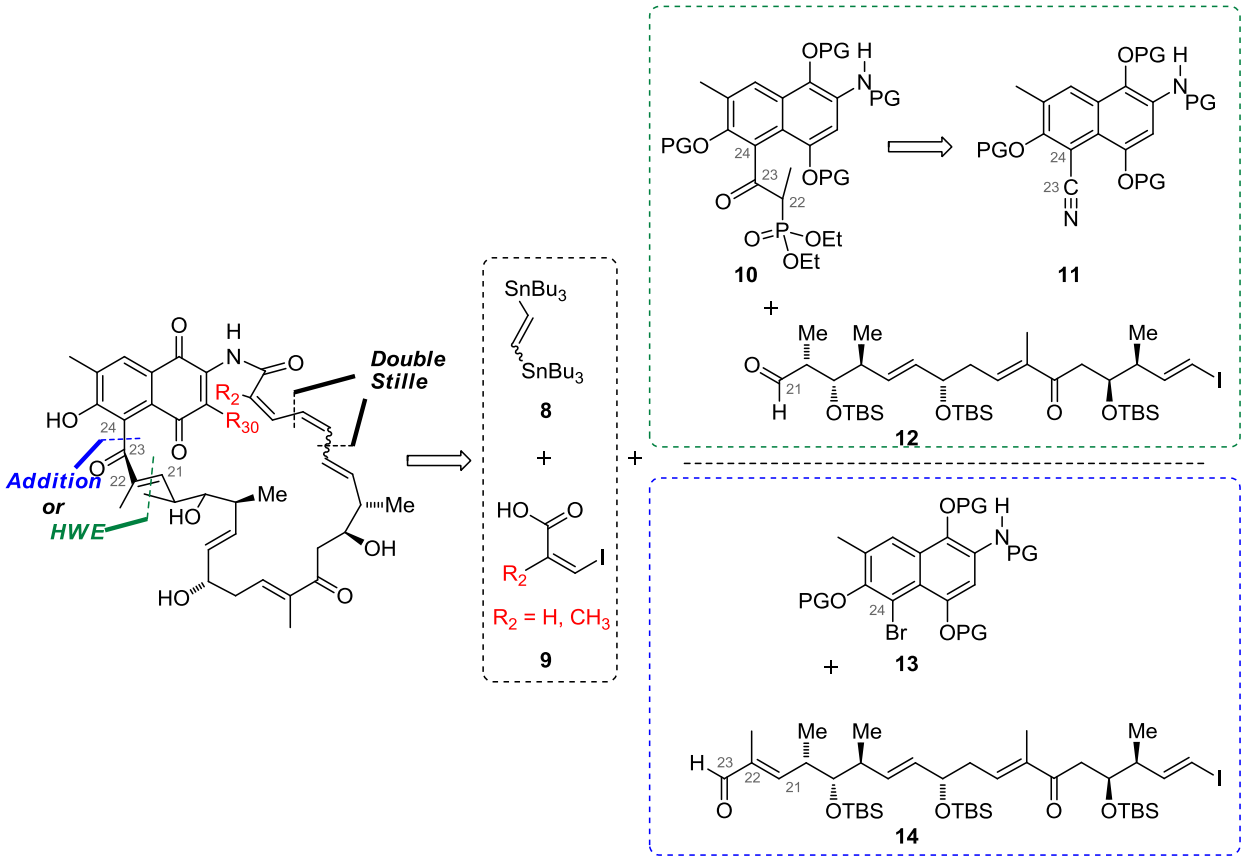
1.4 Retrosynthetic Analysis of Naphthomycins

Our aim is the biomimetic synthesis of naphthomycin K via Hetero-Diels-Alder shown in Scheme 1. That implies the key intermediate in the total synthesis of naphthomycin K is naphthomycin A.

Naphthomycin A has molecular weight of 720.25 g/mol and the formula $C_{40}H_{46}ClNO_9$. It has a napthoquinone portion and a polyketide chain, which has 23 carbons, 3 hydroxy- and 3 keto-groups as well as 3 double bonds, 6 stereocenters and a (*Z,Z,E*)-triene.

Our retrosynthetic plan, depicted in Scheme 4, primary targets naphthomycin A but is supposed to be applicable for the synthesis of all naphthomycins through simple modifications. The key step for making the macrocycle is a double Stille coupling[7, 8] with distannane (**8**), which can be made in both, (*E*)-and (*Z*)-configuration. The substituent in position 2 is either hydrogen or a methyl group, both accessible through known corresponding vinyl iodides (**9**). The final distinguishing feature is the substituent in position 30, which is planned to be introduced at a late stage through nucleophilic addition of the corresponding anion into the quinone functionality.

We envisioned two strategies for the crucial attachment of the polyketide chain to the naphthalenic portion in position 24. In the first strategy, phosphonate (**10**), which could be made out of the corresponding cyanide (**11**), and aldehyde (**12**) could be connected through a Horner-Wadsworth-Emmons reaction (HWE).[9] The second strategy envisions a lithiation of bromide (**13**) followed by a nucleophilic attack to the aldehyde (**14**).



Scheme 4: Two strategies for the synthesis of naphthomycins.

No matter which strategy will lead to success, both can be divided into two equally challenging subprojects. Hence, this project was distributed to two PhD students. One of them was me, focusing on the synthesis of the polyketide chain **12** or **14**, respectively. The synthesis of the aromatic moiety (**10** or **13**, respectively) was the focus of my team player Christian A. Kuttruff, who was temporary supported by Masters Student Simon Geiger. This segmentation should not give the impression of two separate and independent subprojects. Quite the contrary, there was a constant exchange of ideas and even crucial practical support. Progresses, failures and strategies of both subprojects were discussed on a daily basis, allowing both, me and Christian, to gain expertise in polyketide chemistry and aromatic chemistry.

References

(1) Lloyd, N. C.; Morgan, H. W.; Nicholson, B. K.; Ronimus, R. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 941–944.

(2) Domagk, G. *Deutsch. Med. Wschr.* **1935**, *61*, 250.

(3) Flemming, A. *J. Exp. Pathol.* **1929**, *10*, 226–236.

(4) Lu, C.; Shen, Y. *J. Antibiot.* **2007**, *60*, 649–653.

(5) Hooper, A. M.; Rickards, R. W. *J. Antibiot.* **1988**, *51*, 845–851.

(6) Keller-Schierlein, W.; Zeek, A.; Zähner, H. *J. Antibiot.* **1983**, *36*, 484–492.

(7) Balerna, M.; Keller-Schierlein, W.; Martius, C.; Wolf, H.; Zahner, H. *J. Antibiot.* **1969**, *65*, 303–317.

(8) Lee, J. P.; Tsao, S.; Chang, C.; He, X.; Floss, H. G. *Can. J. Chem* **1994**, *72*, 182–186.

(9) Chen, S.; Bamberg, v. D.; Hale, V.; Breuer, M.; Hardt, B.; Muller, R.; Floss, H. G.; Reynolds, K. A.; Leistner, E. *Eur. J. Biochem.* **1999**, *261*, 98–107.

2. Results

2.1 C. A. Kuttruff, S. Geiger, M. Cakmak, P. Mayer, D. Trauner, *Org. Lett.* **2012**, *14*, 1070–1073.

ORGANIC LETTERS

2012
Vol. 14, No. 4
1070–1073

An Approach to Aminonaphthoquinone Ansamycins Using a Modified Danishefsky Diene

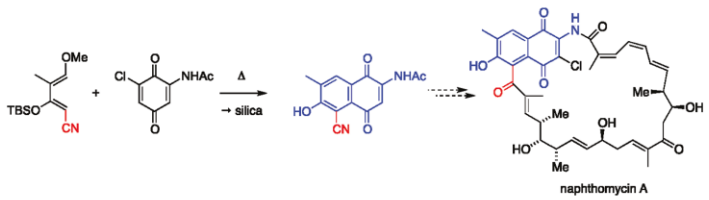
Christian A. Kuttruff, Simon Geiger, Mesut Cakmak, Peter Mayer, and Dirk Trauner*

Department of Chemistry and Pharmacology, Ludwig-Maximilians-Universität München and Center for Integrated Protein Science, 81377 Munich, Germany

dirk.trauner@lmu.de

Received December 23, 2011

ABSTRACT



A robust and scalable synthesis of a novel, cyano-substituted Danishefsky-type diene and its use in the Diels–Alder reaction with various dienophiles is reported. The diene allows for the rapid construction of highly substituted aminonaphthoquinones that occur in numerous ansamycin antibiotics.

Ansamycins are an important class of natural products that show potent antibacterial and antiviral activities. In addition to members of the family that have long been known, such as rifamycin or naphthomycin A (**1a**),[1] several new aminonaphthoquinone ansamycins with intriguing structures have recently been reported, including naphthomycin K (**1b**),[2] ansalactam (**2**),[3] and divergolides C (**3a**) and D (**3b**).[4] As depicted in Figure 1, these molecules possess structurally diverse *ansa* chains of varying lengths that are mounted to a shared naphthoquinone core (depicted in blue) through an acyl linkage in position 5 and an amide in position 2 (naphthoquinone nomenclature). Several members have additional C–C bonds between the aromatic core and the *ansa* chain, which is remarkable from both a synthetic and biosynthetic point of view.

Our interest in the total synthesis of these natural products prompted us to devise a unified approach to their aminonaphthoquinone core (Scheme 1). We reasoned that due to steric compression, attachment of an *ansa* chain to the arene would be a challenge. This led us to consider cyano naphthalene **4** as a key intermediate, which in turn could be traced back to cyano-substituted Danishefsky diene **5** and substituted aminoquinone **6** *via* Diels–Alder reaction.

The original Danishefsky diene[5] has been widely used in organic synthesis along with several variations, which have been developed to improve its reactivity and synthetic scope.[6] These include alterations of the electron-donating substituents in positions 1 and 3, as well as the introduction of further substituents in positions 2 and 4 (diene nomenclature) that are not lost following cycloaddition.[7] However, to the best of our knowledge, there is little, if any,

(1) Keller-Schierlein, W.; Meyer, M.; Cellai, L.; Cerrini, S.; Lamba, D.; Segre, A.; Fedeli, W.; Brufani, M. *J. Antibiot.* **1984**, *37*, 1357–1361.
(2) Lu, C.; Shen, Y. *J. Antibiot.* **2007**, *60*, 649–653.
(3) Wilson, M. C.; Nam, S.-J.; Gulder, T. A. M.; Kauffman, C. A.; Jensen, P. R.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc.* **2011**, *133*, 1971–1977.
(4) Ding, L.; Maier, A.; Fiebig, H.-H.; Goerls, H.; Lin, W.-H.; Peschel, G.; Hertweck, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1630–1634.
(5) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.
(6) (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406. (b) Herczegh, P.; Kovacs, I.; Erdoesi, G.; Varga, T.; Agocs, A.; Szilagyi, L.; Sztaricskai, F.; Berecibar, A.; Lukacs, G.; Olesker, A. *Pure Appl. Chem.* **1997**, *69*, 519–524. (c) Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293–6306.
(7) (a) Yu, Z.; Liu, X.; Dong, Z.; Xie, M.; Feng, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 1308–1311. (b) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252–5253. (c) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103–3105.

10.1021/ol203437a
Published on Web 02/01/2012

precedence for Danishefsky-type dienes that bear electron-withdrawing groups. We now report the synthesis of such a diene, compound **5**, as well as studies on its reactivity and use toward the synthesis of ansamycin antibiotics.

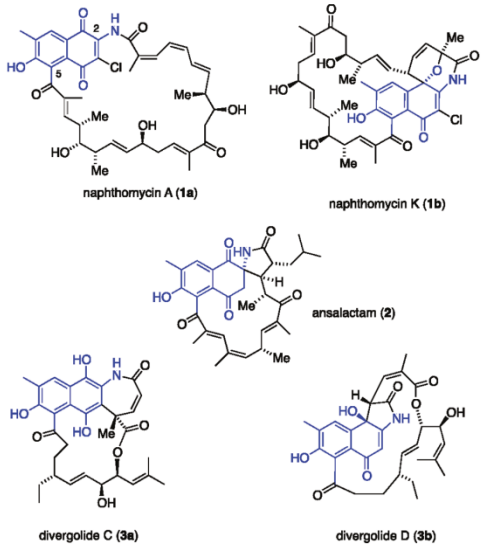
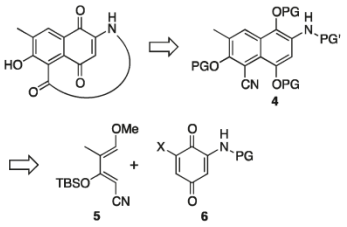


Figure 1. Structurally intriguing ansamycin antibiotics containing an aminonaphthoquinone core.

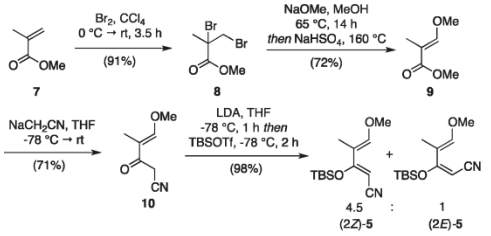
Scheme 1. Retrosynthetic Analysis of the Aminonaphthoquinone Core of Ansamycins with Suitable Functionalization



Our synthesis of **5** commenced with the bromination of commercially available methyl methacrylate[8] (**7**), followed by nucleophilic substitution and elimination to introduce a β-methoxy substituent (Scheme 2). Subsequent Claisen-type condensation with deprotonated acetonitrile gave ketonitrile **10**, which proved to be surprisingly stable. Next, conditions for its enolization and subsequent silylation were screened. Attempts to synthesize the TMS enol ether

(8) Werle, S.; Fey, T.; Neudoerfl, J. M.; Schmalz, H.-G. *Org. Lett.* **2007**, *9*, 3555–3558.

Scheme 2. Synthesis of Diene **5**



of **10** failed due to its high lability toward various workup conditions. However, we found that deprotonation with LDA and subsequent silylation with TBSOTf delivered silyloxy diene **5** as a 4.5:1 mixture of (2*Z*)- and (2*E*)-isomers in excellent overall yield. These isomers could be separated (see Supporting Information) but were usually employed as a mixture in subsequent reactions.

With multigram quantities of diene **5** in hand, we investigated its utility in the synthesis of naphthoquinones. Diels–Alder reaction of **5** with the known benzoquinone derivative **11**[9] gave intermediary product **12** as a mixture of stereoisomers, which was not further characterized. Treatment of this crude material with oven-dried silica gel in

Scheme 3. Synthesis of the Aminonaphthoquinone Core and Subsequent Reduction and Protection

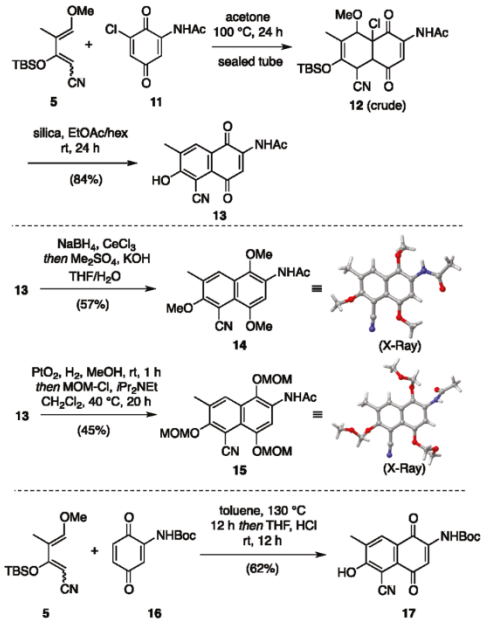
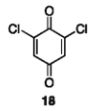
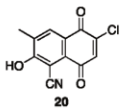
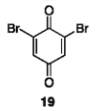
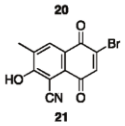
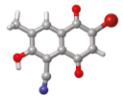
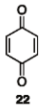
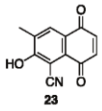
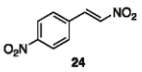
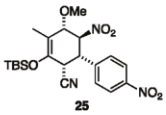
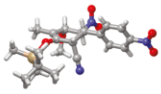
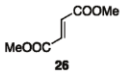
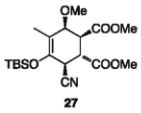
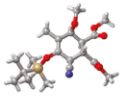
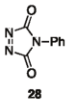
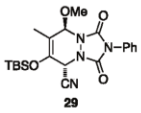
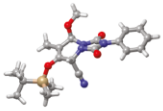


Table 1. Results of Diels–Alder Reactions of Diene **5** (4.5:1 Mixture of Stereoisomers) with Different Dienophiles

entry	dienophile	conditions	isolated product	crystal structure	yield [%]
1	 **18**	toluene, 120 °C, 29 h *then* silica, acetone, rt, 12 h	 **20**	–	79
2	 **19**	toluene, 150 °C, 3 h *then* THF, HCl, silica, rt, 12 h	 **21**		43
3	 **22**	$AlCl_3$, CH_2Cl_2, 0 °C, 3 h *then* silica	 **23**	–	79
4	 **24**	toluene, 120 °C, 2 h	 **25**		75
5	 **26**	toluene, 140 °C, 14 d	 **27**		23
6	 **28**	benzene, 80 °C, 12 h	 **29**		63

ethyl acetate/hexanes resulted in desilylation and aromatization to afford our key naphthoquionone **13** in 84% overall yield. Notably, only a single regioisomer was isolated.

To elaborate **13** into a more useful building block and confirm its structure, the naphthoquinone was reduced to the corresponding naphthohydroquinone using sodium borohydride. *In situ* protection of the phenolic hydroxy groups as methyl ethers then afforded hexasubstituted naphthalene **14**, the crystal structure of which is depicted in Scheme 3. Analogous protection of the three hydroxy groups as MOM ethers required reduction with hydrogen in the presence of Adam's catalyst, followed by treatment with MOM chloride and Hünig's base. This gave naphthalene derivative **15**, which was also characterized by X-ray crystallography. It should be noted that the alkylations required careful optimization to avoid *N*-methylation while ensuring that all three hydroxy groups were affected. Interestingly, the aromatization following the cycloaddition did not require an "inbuilt oxidant" in the form of a halogen substituent on the benzoquinone. Reaction of diene **5** with Moody's Boc-protected aminobenzoquinone **16**[10] gave naphthoquinone **17**, presumably through air oxidation of the intermediary cycloadduct.

To establish the synthetic scope of diene **5** in Diels–Alder reactions, we investigated its reactivity with other dienophiles (Table 1). Encouraged by our initial results, we first examined various quinones as dienophiles. Reaction of **5** with commercially available dichlorobenzoquinone (**18**) and the known dibromobenzoquinone (**19**)[11] provided naphthoquinones **20** and **21**, respectively, in satisfactory yields following aromatization (entries 1 and 2). When benzoquinone itself (**22**) was used as the dienophile, simple heating in toluene proved to be less effective than catalysis using $AlCl_3$ as a Lewis acid. Following aromatization, these catalytic conditions gave naphthoquinone **23** in good overall yield (entry 3). Reaction of **5** with nitrostyrene **24** afforded the desired cycloaddition product **25** as a single diastereomer (entry 4). Heating of diene **5** with dimethyl fumarate (**26**) over 14 days afforded cycloadduct **27** as a single diastereomer, but in only 23% yield. Reaction of **5** with phenyl triazoline dione (**28**) gave cycloadduct **29**,

(9) Kelly, T. R.; Echavarren, A.; Behforouz, M. *J. Org. Chem.* **1983**, *48*, 3849–3851.

(10) Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872–7881.

(11) Omura, K. *Synthesis* **1998**, *8*, 1145–1148.

which has the opposite relative stereochemistry with respect to the OMe and CN substituents compared to **25** and **27**. This stereochemical outcome presumably reflects isomerization of the initial cycloadduct to the thermodynamically more stable product *via* reversible cleavage of the *N*,*O*-acetal. The structures of **21**, **25**, **27**, and **29** were confirmed by X-ray crystallography (Table 1 and Supporting Information). Attempted reactions of diene **5** with tetracyanoethylene or maleic anhydride failed to give the desired products despite extensive screening of conditions.

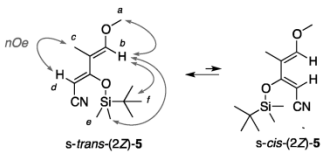


Figure 2. Conformational analysis of diene **5**.

From these data, it is apparent that diene **5** exhibits markedly reduced reactivity when compared to the parent Danishefsky diene. This can be partially attributed to the electronic effect of the cyano substituent but is probably also due to the influence of the methyl substituent on the preferred conformation of the diene. To undergo a [4 + 2] cycloaddition, **5** must adopt an s-*cis* conformation (Figure 2). NMR spectroscopy of pure (2*Z*)-**5** demonstrated a strong NOE correlation between olefinic proton *d* and the protons of the methyl group along with weak interactions between olefinic proton *b* and protons *e* and *f* of the TBS group. By contrast, no NOE could be observed between protons *b* and *d* or between proton *c* and the protecting group substituents. This strongly suggests that (2*Z*)-**5** mostly adopts an s-*trans* conformation and that the requisite s-*cis* conformation is sparsely populated. We assume that this effect is even more pronounced in the (2*E*)-isomer of **5** and that this isomer is essentially unreactive in Diels–Alder cycloadditions, or it may isomerize to its (2*Z*)-diastereomer under the reaction conditions.

In summary, we have reported the synthesis of a novel Danishefsky-type diene, which allows for the rapid assembly of substituted aminonaphthoquinones or other highly functionalized small molecules. Related studies on Diels–Alder dienes that bear substituents with opposing electronic effects will be further pursued. Our ongoing attempts to implement our synthetic strategy in the total synthesis of ansamycin antibiotics will also be reported in due course.

Acknowledgment. We thank Dr. Rob Webster (Ludwig-Maximilians-Universität München) for helpful discussions.

Supporting Information Available. Experimental procedures, spectroscopic and analytical data for compounds **5**–**29**, and X-ray data for compounds **14**, **15**, **21**, **25**, **27**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

An approach to aminonaphthoquinone ansamycins using a modified Danishefsky diene

Christian A. Kuttruff, Simon Geiger, Mesut Cakmak, Peter Mayer and Dirk Trauner*

Department of Chemistry and Biochemistry, Ludwig-Maximilians-Universität München, Butenandtstr. 5–13, 81377 Munich (Germany)

Supplementary Information

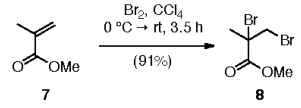
Index:

General Experimental Details. Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Triethylamine, diisopropylamine and diisopropylethylamine were distilled over calcium hydride immediately before use. Reactions were magnetically stirred and monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F_{254} precoated glass plates. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of ceric ammoniummolybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$), an acidic solution of vanillin or a solution of ninhydrin in ethanol followed by heating with a heat gun. Flash column chromatography was performed as described by Still *et al.* employing silica gel (60 Å, 40-63 μm, Merck) and a forced flow of eluant at 1.3–1.5 bar pressure.[1] Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure material.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$: δ 7.26, DMSO-d_6: δ 2.50, $(CD_3)_2CO$: δ 2.05, CD_3OD: δ 3.31). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, *br* = broad, app = apparent, or combinations thereof. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, DMSO-d_6: δ 39.5, $(CD_3)_2CO$: δ 29.8, CD_3OD: δ 49.00). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System). IR data is reported in frequency of absorption (cm^{-1}). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Synthetic procedures.



7 8

Methyl 2,3-dibromo-2-methylpropanoate (8):

Br_2 (5.27 mL, 103 mmol, 1.03 equiv) in CCl_4 (40 mL) was added dropwise over 2.5 h to a solution of methyl methacrylate (7) (10.7 mL, 99.9 mmol, 1.00 equiv) in CCl_4 (100 mL) at 0 °C. After complete addition, the orange solution was stirred at this temperature for further 1 h. A solution of sat. aq. $Na_2S_2O_3$ (70 mL) was then added to the colorless reaction mixture at 0 °C and it was allowed to warm to rt. The solution was extracted with TBME (1 × 200 mL then 3 × 100 mL) and the combined organic phases were dried over Na_2SO_4 and the solvent evaporated to afford dibromide **8** (23.5 g, 90.4 mmol, 91%) as a pale yellow liquid.

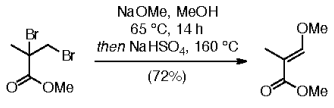
TLC (hexanes:EtOAc = 5:1), R_f = 0.86 (UV/CAM)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.22 (dd, J = 9.8 Hz, 0.7 Hz, 1 H), 3.83 (s, 3 H), 3.72 (d, J = 9.8 Hz, 1 H), 2.03 (d, J = 0.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.1, 55.3, 53.4, 38.1, 26.4.

IR (Diamond-ATR, neat) ν_{max}: 1741, 1450, 1381, 1291, 1235, 1197, 1169, 1103, 1078, 1048, 990, 925, 871, 831, 772, 666 cm^{-1}.

HRMS (EI) calcd for $C_5H_8{}^{79}Br^{81}BrO_2$ $[M]^{+\bullet}$: 259.8871; found: 259.9019.



8 9

(*E*)-methyl 3-methoxy-2-methylacrylate (9):

Freshly cut sodium (7.77 g, 338 mmol, 2.00 equiv) was dissolved in methanol (120 mL) and the highly viscous solution heated to 68 °C. A solution of **8** (43.98 g, 169 mmol, 1.00 equiv) in MeOH (50 mL) was added rapidly and the mixture stirred at 68 °C for 14 h. The reaction mixture was allowed to cool to rt and filtered. The filter residue was washed with a small amount of cold MeOH, the filtrate concentrated to 1/3 of its volume *in vacuo* and filtered again. To the resulting solution was added H_2O (30 mL) and the biphasic system was extracted with Et_2O (4 × 60 mL). The combined organic layers were dried over Na_2SO_4 and

the solvent was evaporated. $NaHSO_4 \cdot H_2O$ (160 mg, 1.16 mmol, 0.006 equiv) was added to the reaction mixture and the suspension was heated to 160 °C under ambient pressure. When no more evolution of MeOH was observed, the residue was subjected to fractional distillation (90 °C, 45 mbar) to afford the product **9** (15.8 g, 71.8 mmol, 72%) as a colorless oil.

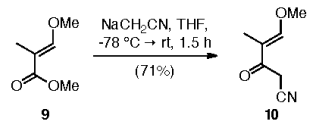
TLC (hexanes:EtOAc = 2:1), R_f = 0.63 (UV/CAM)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27–7.26 (m, 1 H), 3.94 (s, 3 H), 3.62 (s, 3 H), 1.75 (d, J = 1.3 Hz, 3 H).

^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.2, 158.5, 106.1, 61.1, 51.2, 9.0.

IR (Diamond-ATR, neat) ν_{max}: 2950, 1706, 1645, 1436, 1389, 1356, 1295, 1241, 1189, 1144, 1112, 1024, 993, 943, 905, 836, 757, 718 cm^{-1}.

HRMS (EI) calcd for $C_6H_{10}O_3$ $[M]^{+\bullet}$: 130.0630; found: 130.0621.



9 **10**

(*E*)-5-methoxy-4-methyl-3-oxopent-4-enenitrile (10):

To a solution of NaHMDS (1 M solution in THF, 7.74 mL, 7.74 mmol, 2.2 equiv) in THF (10 mL) was added MeCN (0.441 mL, 8.45 mmol, 2.4 equiv) dropwise at -78 °C. After 20 minutes, this solution was transferred via canula to a solution of **9** (458 mg, 3.52 mmol, 1.0 equiv) in THF (40 mL) at -78 °C over a period of 20 minutes. The reaction mixture was maintained at -78 °C for 30 minutes and then warmed to 0 °C. After 40 minutes, the reaction was quenched by addition of sat. aq. NH_4Cl (30 mL) and subsequently extracted with Et_2O (3 × 50 mL) and EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude orange oil, which tended to crush out in less polar solvents, was dissolved in a small amount of $CHCl_3$ and purified by flash column chromatography (silica gel packed in $CHCl_3$, gradient: hexanes:EtOAc = 2:1 → 1:1) to afford the title compound **10** (350 mg, 2.52 mmol, 71%) as a white solid.

TLC (hexanes:EtOAc = 1:1), R_f = 0.36 (UV/$KMnO_4$)

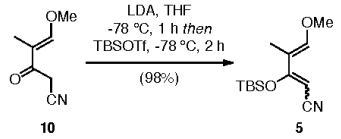
M.p.: 101–103 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.26 (dd, J = 2.4, 1.2 Hz, 1 H), 3.94 (s, 3 H), 3.62 (s, 2 H), 1.75 (d, J = 1.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 186.0, 161.7, 115.8, 114.5, 62.1, 28.1, 8.5.

IR (Diamond-ATR, neat) ν_{max}: 2956, 2920, 2259, 1652, 1626, 1452, 1410, 1393, 1369, 1336, 1256, 1217, 1149, 1059, 993, 967, 912, 890, 824, 713 cm^{-1}.

HRMS (EI) calcd for $C_7H_9NO_2$ $[M]^{+\bullet}$: 139.0633; found: 139.0635.



10 5

(2*Z*,4*E*)-3-((tert-butyldimethylsilyl)oxy)-5-methoxy-4-methylpenta-2,4-dienenitrile (5):

To a solution of diisopropylamine (2.54 mL, 18.0 mmol, 1.25 equiv) in THF (60 mL) was added *n*-BuLi (2.5 M solution in hexanes, 6.3 mL, 15.8 mmol, 1.10 equiv) dropwise at -78 °C. The solution was stirred at -78 °C for 10 min, warmed to 0 °C and stirred at this temperature for 15 min and subsequently cooled back to -78 °C. A solution of **10** in THF (20 mL) was then added to the freshly prepared LDA solution. After stirring at -78 °C for 2 h, TBSOTf was added to the orange reaction mixture and the solution was stirred for 1 h. A 1:1 mixture of H_2O (20 mL) and sat. aq. NH_4Cl (20 mL) and EtOAc (30 mL) were added and the reaction mixture was warmed to rt. The organic phase was separated and the aq. phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (silica gel, hexanes:EtOAc = 20:1) to provide silyl-enol ether **5** (3.57 g, 14.1 mmol, 98%) as a pale-yellow oil.

Note: Since the product hydrolyzes on silica gel, it is recommended to quickly flush the crude over a relatively short column.

TLC (hexanes:EtOAc = 20:1), R_f = 0.46 (2*Z*)-**5**, 0.38 (2*E*)-**5** (UV/ $KMnO_4$)

(2*E*)-**5**:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.90 (q, *J* = 1.3 Hz, 1 H), 4.38 (s, 1 H), 3.77 (s, 3 H), 1.87 (d, *J* = 1.2 Hz, 3 H), 0.95 (s, 9 H), 0.22 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 153.5, 119.2, 110.4, 74.0, 60.8, 25.5, 18.2, 10.7, -4.6.

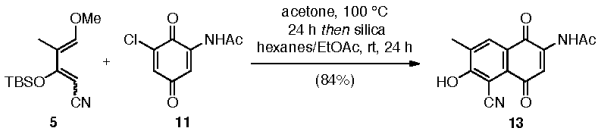
(2*Z*)-**5**:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.75 (q, *J* = 1.2 Hz, 1 H), 4.55 (s, 1 H), 3.76 (s, 3 H), 1.67 (d, *J* = 1.1 Hz, 3 H), 1.03 (d, *J* = 0.2 Hz, 9 H), 0.28 (d, *J* = 0.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 152.5, 118.5, 110.2, 74.6, 60.9, 25.8, 18.5, 9.9, -3.6.

IR (Diamond-ATR, neat) ν_{max}: 2954, 2932, 2887, 2860, 2208, 1704, 1641, 1585, 1472, 1464, 1394, 1368, 1329, 1238, 1141, 1116, 1046, 1004, 978, 939, 893, 841, 824, 807, 783, 746, 702, 679, 637 cm^{-1}.

HRMS (EI) calcd for $C_{13}H_{23}NO_2Si$ $[M]^{+\bullet}$: 253.1498; found: 253.1502.



Aminonaphthoquinone 13:

Quinone **11**[2] (501 mg, 2.51 mmol, 1.0 equiv) and a solution of diene **5** (700 mg, 2.76 mmol, 1.1 equiv) in acetone (10 mL) were combined in a pressure tube and heated to 100 °C for 24 h under an atmosphere of argon. After evaporation of the solvent, the brown residue was suspended in a 1:1 mixture of hexanes/EtOAc (50 mL), oven-dried silica (5 g) was added and the mixture was stirred overnight. The solvent was removed and the residue was purified by flash column chromatography (silica gel, hexanes:EtOAc = 1:1 → $CHCl_3$/acetone = 5:1 → 1:2) to provide aminonaphthoquinone **13** (624 mg, 2.31 mmol, 84%) as a purple-black solid.

M.p.: decomposition without melting

TLC (CH_2Cl_2:acetone:AcOH:H_2O = 70:10:0.5:0.5), R_f = 0.45 (visible/CAM)

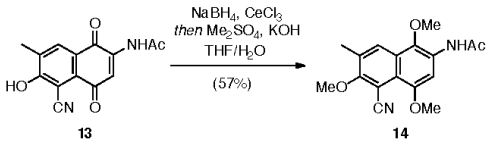
^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.56 (s, 1 H), 7.58 (d, J = 0.9 Hz, 1 H), 7.28 (s, 1 H), 2.20 (s, 3 H), 1.97 (d, J = 0.9 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 186.1, 177.7, 175.4, 170.9, 141.0, 135.1, 133.4, 128.7, 119.2, 113.3, 111.2, 94.7, 24.5, 17.1.

IR (Diamond-ATR, neat) ν_{max}: 3302, 2213, 1648, 1581, 1490, 1365, 1335, 1273, 1212, 1086, 1013, 874, 852, 805, 742, 706 cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_9N_2O_4$ $[M-H]^-$: 269.0568; found: 269.0567.

[2] Kelly, T. R.; Echavarren, A.; Behforouz, B. *J. Org. Chem.* **1983**, *48*, 3849–3851.



13 14

Cyano naphthalene 14:

A solution of **13** (80 mg, 0.29 mmol, 1.00 equiv) in a mixture of THF (10 mL) and H_2O (5 mL) was degassed with Argon in a sonicator for 5 minutes and Cerium(III) chloride heptahydrate (162 mg, 0.44 mmol, 1.50 equiv) was added. The reaction mixture was cooled to 0 °C and $NaBH_4$ (20 mg, 0.52 mmol, 1.80 equiv) was added in two portions over 20 min. After H_2 evolution had ceased, the reaction was warmed to rt, Me_2SO_4 (550 µL, 5.80 mmol, 20 equiv) was added and the flask was evacuated and filled with argon. A solution of KOH (325 mg, 5.80 mmol, 20 equiv) in H_2O (5 mL) was added dropwise. The reaction mixture was stirred at rt for 15 h, cooled to 0 °C and conc. NH_4OH (3 mL) and H_2O (10 mL) were added. The reaction mixture was extracted with EtOAc (6 × 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, gradient: $CHCl_3$:acetone = 20:1 → 10:1) afforded the title compound **14** (52 mg, 0.17 mmol, 57%) as an orange solid.

TLC ($CHCl_3$:acetone = 3:1), R_f = 0.67 (UV/CAM)

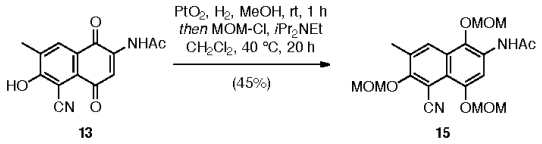
M.p.: 215–220 °C

^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.09 (s, 1 H), 7.93 (s, 1 H), 7.78 (*br* s, 1 H), 4.05 (s, 3 H), 4.03 (s, 3 H), 2.47 (d, J = 0.8 Hz, 3 H), 2.28 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 168.5, 163.1, 151.1, 136.1, 132.2, 128.5, 127.6, 124.9, 120.6, 116.5, 101.1, 99.7, 61.8, 61.7, 56.0, 25.0, 16.9.

IR (Diamond-ATR, neat) ν_{max}: 3241, 2941, 2221, 1693, 1659, 1622, 1602, 1497, 1458, 1443, 1400, 1364, 1350, 1278, 1234, 1213, 1168, 1144, 1097, 1055, 1001, 968, 894, 865, 848, 818, 789, 732, 707, 683 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{19}N_2O_4$ $[M+H]^+$: 315.1345; found: 315.1336.



Naphthalene 15:

To a suspension of **13** (100 mg, 0.37 mmol, 1.00 equiv) in MeOH (6 mL) was added PtO_2 (12.6 mg, 55.5 µmol, 0.15 equiv) and the inner atmosphere of the flask was exchanged three times with hydrogen and the resulting mixture was stirred under hydrogen atmosphere (double layer balloon) for 1 h at rt. The reaction mixture was filtered through a syringe filter and the solvent was removed under reduced pressure under exclusion of air. The residue was dissolved in CH_2Cl_2 (10 mL), Chloromethyl methyl ether (298 mg, 3.70 mmol, 10 equiv) and diisopropylamine (0.83 mL, 4.81 mmol, 13 equiv) were added and the reaction mixture was sealed with a yellow cap and stirred at 40 °C. After 20 h, the reaction mixture was cooled to rt and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (silica gel, gradient: $CHCl_3$:acetone = 10:1 → 2:1) afforded the title compound **15** (68 mg, 168 mµol, 45%) as a white solid.

TLC ($CHCl_3$:acetone = 10:1), R_f = 0.27 (UV/CAM)

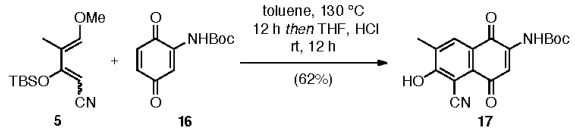
M.p.: 120–122 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (*br* s, 1 H), 8.31 (s, 1 H), 7.92 (d, J = 0.7 Hz, 1 H), 5.40 (s, 2 H), 5.32 (s, 2 H), 5.10 (s, 2 H), 3.70 (s, 3 H), 3.66 (s, 3 H), 3.61 (s, 3 H), 2.49 (d, J = 0.9 Hz, 3 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.4, 161.3, 148.4, 135.8, 132.4, 129.1, 127.7, 125.8, 120.9, 116.8, 105.4, 101.2, 100.9, 100.0, 95.1, 58.2, 57.7, 56.9, 24.8, 17.6.

IR (Diamond-ATR, neat) ν_{max}: 3252, 2922, 2829, 2361, 2338, 1662, 1620, 1605, 1526, 1497, 1430, 1398, 1413, 1360, 1347, 1284, 1242, 1152, 1144, 1086, 1078, 1035, 986, 967, 919, 888, 820, 734, 668 cm^{-1}.

HRMS (EI) calcd for $C_{20}H_{24}N_2O_7Na$ $[M+Na]^+$: 427.1476; found: 427.1477.



_N_-Boc naphthoquinone 17:

To a solution of **5** (37 mg, 0.15 mmol, 1.00 equiv) in toluene (3.5 mL) in a pressure tube was added **16**[3] (33 mg, 0.15 mmol, 1.00 equiv). The reaction mixture was stirred for 12 h at 130 °C and subsequently cooled to rt. The solvent was evaporated, the crude product was dissolved in THF (5 mL) and aq. HCl (2 M, 3 drops) was added and the reaction mixture was stirred for further 12 h at rt. Silica (2 g) was added to the solution and the solvent removed *in vacuo*. Purification by flash column chromatography (silica gel, gradient: $CHCl_3$:acetone = 1:1 → 1:9) yielded the desired product **17** (30 mg, 0.091 mmol, 62%) as a purple solid.

TLC ($CHCl_3$:acetone = 1:2), R_f = 0.31 (visible/$KMnO_4$)

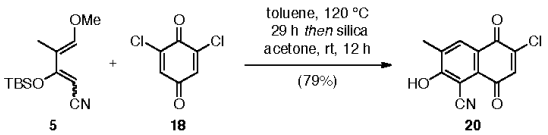
M.p.: decomposition without melting

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.20 (s, 1 H), 7.56 (d, J = 1.0 Hz, 1 H), 6.84 (s, 1 H), 1.96 (d, J = 0.9 Hz, 3 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6) δ: 185.2, 177.9, 174.5, 151.2, 141.3, 135.5, 133.2, 128.8, 119.2, 111.0, 95.3, 90.6, 81.5, 27.7, 17.1.

IR (Diamond-ATR, neat) ν_{max}: 3361, 2223, 1732, 1650, 1584, 1503, 1476, 1367, 1333, 1272, 1147, 1032, 844 cm^{-1}.

HRMS (ESI) calcd for $C_{17}H_{16}N_2O_5$ $[M+Na]^+$: 351.0957; found: 351.0953.



Chloro naphthoquinone 20:

A solution of diene **5** (424 mg, 1.67 mmol, 1.50 equiv) in toluene (8 mL) was added to 2,6-dichlorobenzoquinone (**18**) (187 mg, 1.12 mmol, 1.00 equiv) in a pressure tube. The brown-orange mixture was heated to 120 °C for 29 h. The solvent was removed *in vacuo* and the brown, amorphous residue dissolved in acetone (30 mL). Silica gel (5 g) was added and the brown-purple slurry stirred at ambient temperature for 12 h. The solvent was evaporated and

[3] Nawrat, C. C.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2011**, *76*, 7872–7881.

the residue was purified by flash column chromatography (silica gel, $CHCl_3$:acetone = 1:2) to yield naphthoquinone **20** (220 mg, 0.89 mmol, 79%) as a dark purple solid.

TLC ($CHCl_3$:acetone = 1:10), R_f = 0.19 (visible/CAM)

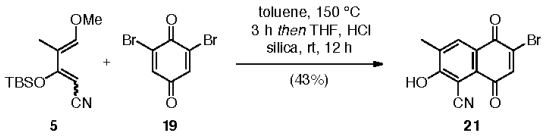
M.p.: no melting point or visible decomposition in the range of 20-400 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.60 (d, J = 1.0 Hz, 1 H), 7.07 (s, 1 H), 1.99 (d, J = 1.0 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6) δ: 183.3, 176.8, 173.4, 145.4, 134.5, 134.5, 133.5, 129.3, 118.9, 112.9, 94.8, 17.2.

IR (Diamond-ATR, neat) ν_{max}: 3571, 3358, 3052, 2218, 1675, 1650, 1599, 1577, 1534, 1463, 1421, 1355, 1324, 1258, 1210, 1036, 1006, 936, 924, 905, 892, 826, 800, 717, 654 cm^{-1}.

HRMS (EI) calcd for $C_{12}H_5{}^{35}ClNO_3$ $[M]^{+\bullet}$: 245.9958; found: 245.9962.



5 19 21

Bromo naphthoquinone 17:

A solution of diene **5** (200 mg, 0.79 mmol, 1.50 equiv) in toluene (5 mL) was added to 2,6-dibromobenzoquinone (**19**)[4] (140 mg, 0.53 mmol, 1.00 equiv) in a pressure tube. The orange mixture was heated to 150 °C for 3 h. The solvent was removed *in vacuo* and the residue dissolved in THF (5 mL). Conc. HCl (3 drops) and silica gel (2 g) was added and the brown-purple slurry stirred at ambient temperature for 12 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel, gradient: $CHCl_3$:acetone = 1:1 → 1:3) gave naphthoquinone **21** (66 mg, 0.23 mmol, 43%) as a dark purple solid.

TLC (CH_2Cl_2:acetone:AcOH:H_2O = 70:10:0.5:0.5), R_f = 0.5 (visible/CAM)

M.p.: decomposition without melting

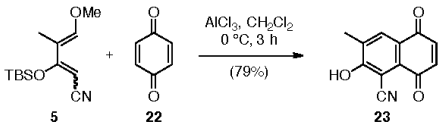
^{1}H NMR (600 MHz, DMSO-d_6) δ: 8.03 (d, J = 0.9 Hz, 1 H), 7.67 (s, 1 H), 2.35 (d, J = 0.9 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6) δ: 180.7, 175.9, 140.0, 138.3, 133.1, 132.6, 132.6, 122.9, 114.8, 96.8, 90.6, 16.9.

[4] Omura, K. *Synthesis* **1998**, *8*, 1145–1148.

IR (Diamond-ATR, neat) ν_{max}: 2361, 2340, 1662, 1576, 1539, 1492, 1473, 1456, 1436, 1367, 1321, 1252, 1054, 1032, 1004, 911, 884, 826, 813, 798, 699 cm^{-1}.

HRMS (ESI) calcd for $C_{12}H_5BrNO_3$ $[M-H]^-$: 289.9458; found: 289.9462.



5 **22** **23**

Naphthoquinone 23:

$AlCl_3$ (2.1 mg, 15.7 µmol, 0.11 equiv) was added to a solution of diene **5** (35.4 mg, 140 µmol, 1.00 equiv) and *p*-benzoquinone (**22**) (30.2 mg, 279 µmol, 2.00 equiv) in CH_2Cl_2 (0.7 mL) at 0 °C. The mixture was stirred at this temperature for 3 h and turned dark green. H_2O (1 mL) was added and the mixture was concentrated *in vacuo*. The yellow residue was purified by flash column chromatography (silica gel, $CHCl_3$:acetone = 1:4) to afford the desired product **23** (23.6 mg, 111 µmol, 79%) as a dark purple solid.

TLC ($CHCl_3$:acetone = 1:2), R_f = 0.14 (visible/CAM)

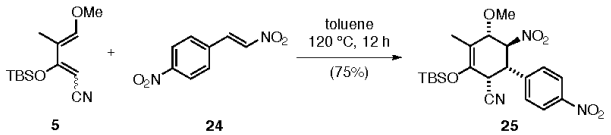
M.p.: No melting point or visible decomposition in the range of 20-400 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.55 (d, J = 1.0 Hz, 1 H), 6.70 (s, 2 H), 2.01 (d, J = 1.0 Hz, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6) δ: 185.6, 181.4, 176.4, 138.6, 136.4, 134.5, 134.1, 128.6, 119.2, 114.4, 93.9, 17.3.

IR (Diamond-ATR, neat) ν_{max}: 3347, 2921, 2212, 1668, 1651, 1582, 1539, 1500, 1456, 1389, 1374, 1361, 1327, 1273, 1192, 1164, 1084, 1026, 986, 845, 810, 765, 687, 625 cm^{-1}.

HRMS (ESI) calcd for $C_{12}H_6NO_3$ $[M-H]^-$: 212.0353; found: 212.0352.



5 **24** **25**

Cycloadduct 25:

To a solution of **5** (30 mg, 118 µmol, 1.00 equiv) in toluene (2 mL) was added **24** (25 mg, 129 µmol, 1.09 equiv) in a pressure tube and the reaction mixture was heated to 120 °C for

12 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, gradient: hexanes:EtOAc = 15:1 → 10:1 → 5:1) to afford the desired product **25** (39 mg, 87.1 µmol, 75%) as a colorless wax.

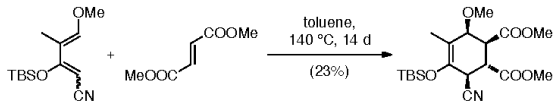
TLC (hexanes:EtOAc = 5:1), R_f = 0.47 (UV/CAM)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.29–8.25 (m, 1 H), 7.60–7.56 (m, 1 H), 5.47–5.40 (dd, *J* = 12.5, 8.1 Hz, 1 H), 4.66 (d, *J* = 8.1 Hz, 1 H), 3.87 (dd, *J* = 12.6, 4.9 Hz, 1 H), 3.41 (s, 3 H), 3.30 (d, *J* = 4.6 Hz, 1 H), 1.77 (s, 3 H), 0.97 (s, 9 H), 0.26 (d, *J* = 2.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.5, 140.4, 139.9, 129.1, 124.5, 116.3, 115.3, 85.8, 81.3, 55.6, 44.5, 39.8, 25.7, 18.3, 12.6. -3.7, -4.0.

IR (Diamond-ATR, neat) ν_{max}: 2933, 2898, 1684, 1640, 1602, 1556, 1518, 1470, 1412, 1378, 1343, 1293, 1260, 1222, 1194, 1184, 1111, 1069, 966, 951, 913, 838, 823, 808, 782, 774, 742 cm^{-1}.

HRMS (ESI) calcd for $C_{21}H_{29}N_3O_6Si$ $[M-H]^-$: 446.1826, found 446.1759.



5 **26** **27**

Methylester 27:

A solution of diene **5** (88.9 mg, 0.35 mmol, 1.00 equiv) in toluene (3 mL) and dimethylfumarate (**26**) (75.8, 0.53 mmol, 1.50 equiv) were dissolved in toluene and the resulting mixture heated in a pressure tube to 140 °C fourteen days. The solvent was evaporated and the resulting crude brown solid purified by flash column chromatography (silica gel, hexanes:EtOAc = 8:1) to afford the title compound **27** (32.1 mg, 80.7 µmol, 23%) as a white amorphous solid.

TLC (hexanes:EtOAc = 8:1), R_f = 0.25 (UV/$KMnO_4$)

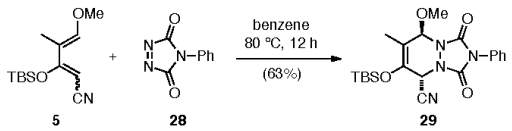
M.p.: 105 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.06 (d, *J* = 3.4 Hz, 1 H), 3.83 (s, 3 H), 3.74 (s, 3 H), 3.50 (ddd, *J* = 12.2, 11.0, 0.3 Hz, 1 H), 3.39 (s, 3 H), 3.28 (ddq, *J* = 11.0, 2.1, 0.8 Hz, 1 H), 2.88 (dd, *J* = 12.2. Hz, 3.4 Hz, 1 H), 1.77 (dd, *J* = 2.1 Hz, 0.2 Hz, 1 H), 0.99 (s, 9 H), 0.19 (s, 3 H), 0.15 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.3, 170.7, 138.0, 116.9, 115.6, 78.1, 60.0, 52.8, 52.2, 46.8, 41.5, 36.5, 25.6, 18.2, 15.7, -3.8, -4.2.

IR (Diamond-ATR, neat) ν_{max}: 2954, 2932, 2888, 2859, 1730, 1690, 1473, 1462, 1436, 1381, 1350, 1314, 1276, 1254, 1230, 1178, 1165, 1011, 978, 947, 912, 872, 841, 827, 815, 782, 747, 714, 687, 608 cm^{-1}.

HRMS (ESI) calcd for $C_{19}H_{31}NO_6NaSi$ $[M+Na]^+$: 420.1813, found 420.1812.



Cycloadduct 29:

To a solution of **5** (42 mg, 166 µmol, 1.00 equiv) in benzene (3 mL) was added **28** (32 mg, 182 µmol, 1.10 equiv) in a pressure tube and the reaction mixture was heated to 80 °C for 12 h. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel, gradient: hexanes:EtOAc = 10:1 → 5:1 → 2:1) to afford the desired product **29** (45 mg, 0.11 mmol, 63%) as a white crystalline solid.

TLC (hexanes:EtOAc = 5:1), R_f = 0.24 (UV/CAM)

M.p.: 102 °C

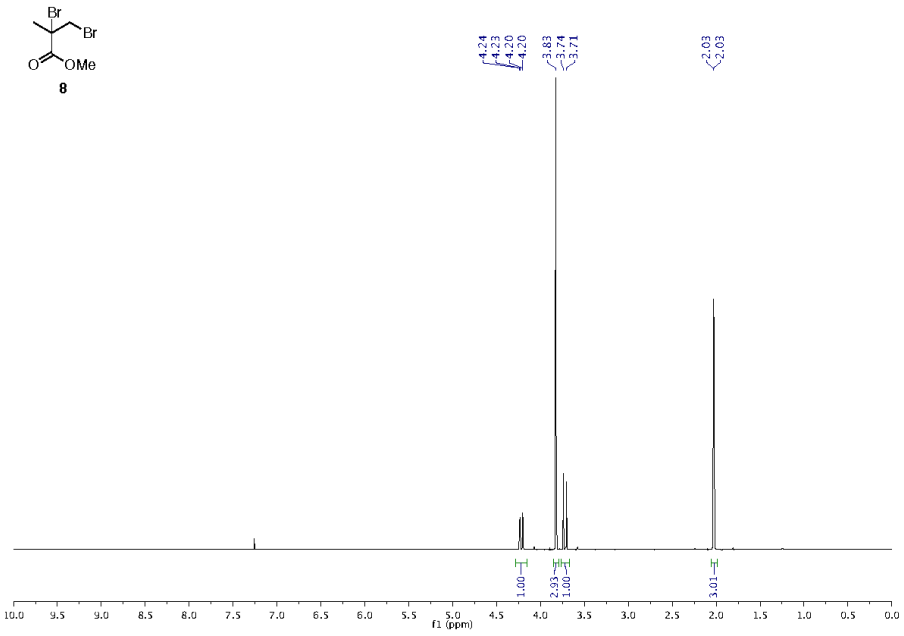
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.54–7.48 (m, 4 H), 7.44–7.38 (m, 1 H), 5.57 (s, 1 H), 4.98 (m, 1 H), 3.55 (s, 3 H), 1.83 (d, J = 1.4 Hz, 3 H), 1.02 (s, 9 H), 0.28 (d, J = 4.8 Hz, 6 H).

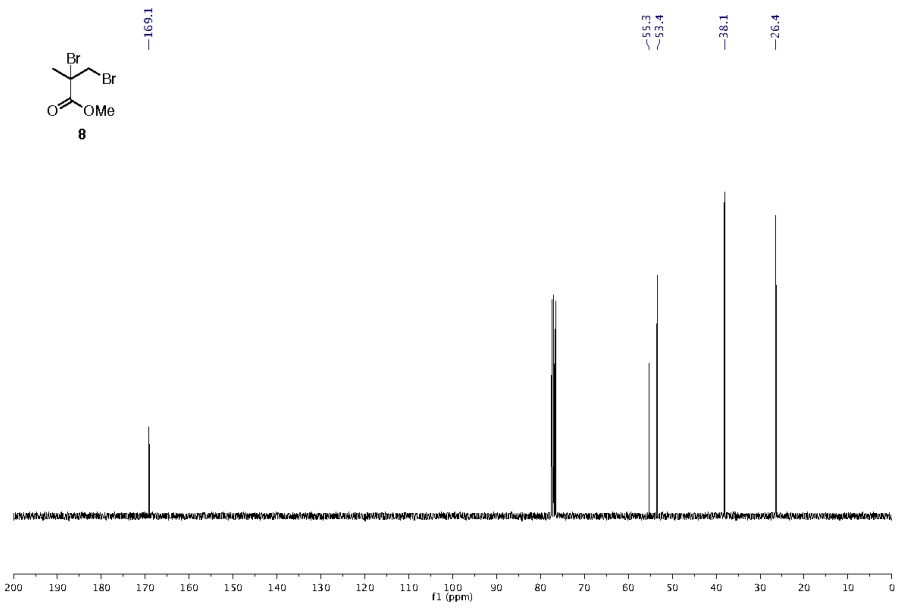
^{13}C NMR (150 MHz, $CDCl_3$) δ: 151.3, 150.4, 137.5, 130.5, 129.3, 129.3, 128.7, 125.3, 113.2, 113.1, 83.1, 56.1, 47.1, 25.5, 18.2, 13.3, -3.8, -3.9.

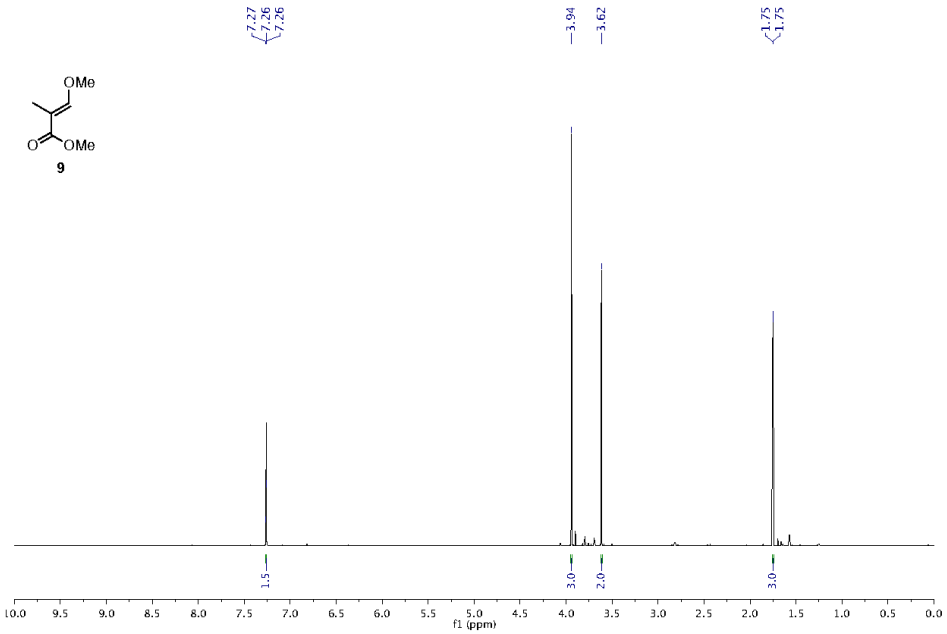
IR (Diamond-ATR, neat) ν_{max}: 2953, 2926, 2856, 1729, 1689, 1461, 1436, 1379, 1350, 1313, 1274, 1253, 1229, 1177, 1164, 1077, 1010, 978, 946, 911, 871, 840, 826, 814, 781, 746, 714, 686 cm^{-1}.

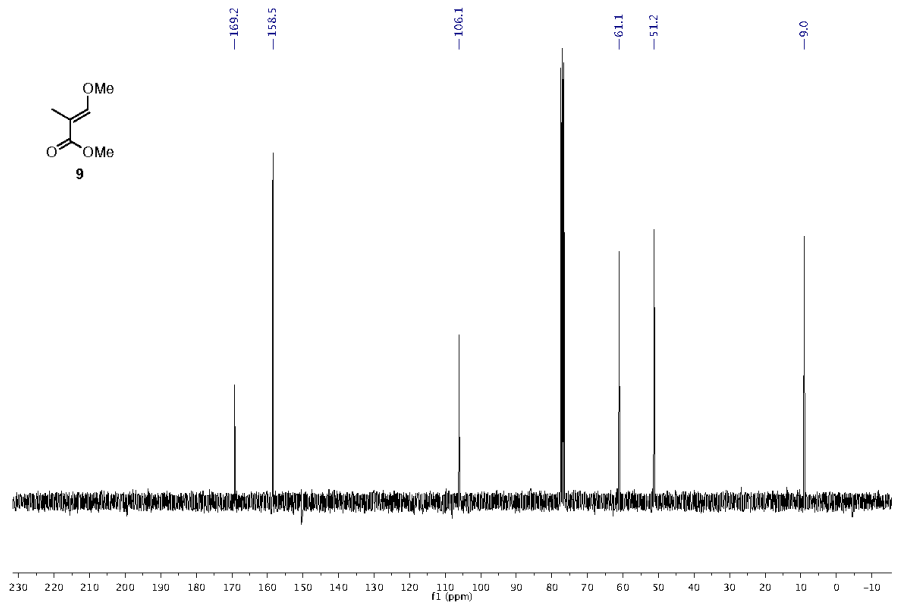
HRMS (ESI) calcd for $C_{21}H_{28}N_4O_4NaSi$ $[M+Na]^+$: 451.1772, found 451.1777.

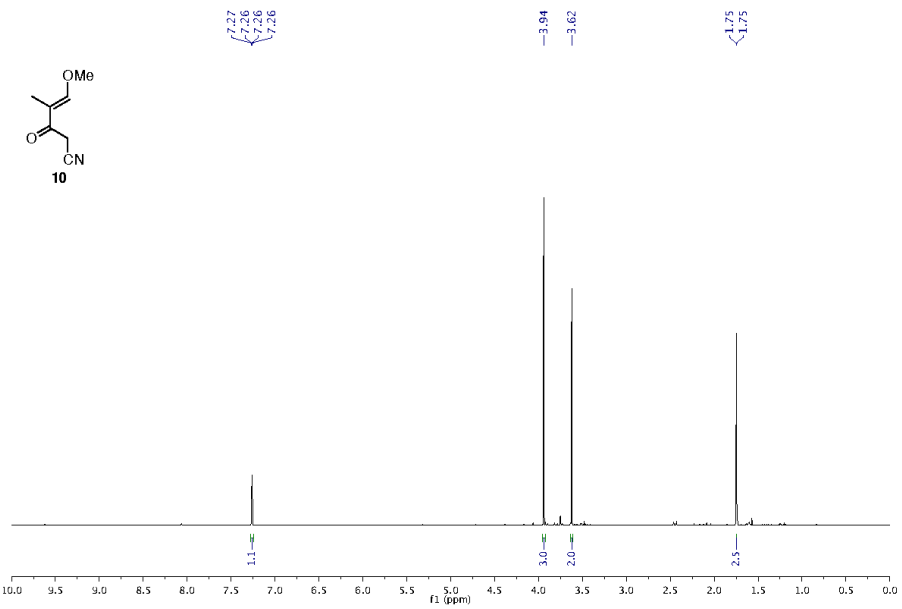
NMR spectra.

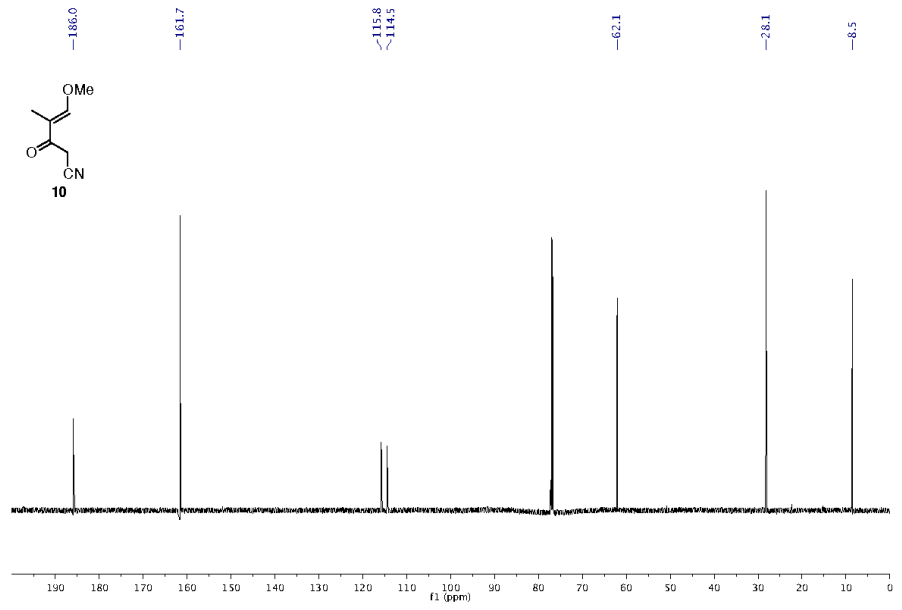

Br
Br
O
OMe
8
4.24
4.23
4.20
4.20
3.83
3.74
3.71
2.03
2.03
1.00
2.03
1.00
3.01
f1 (ppm)

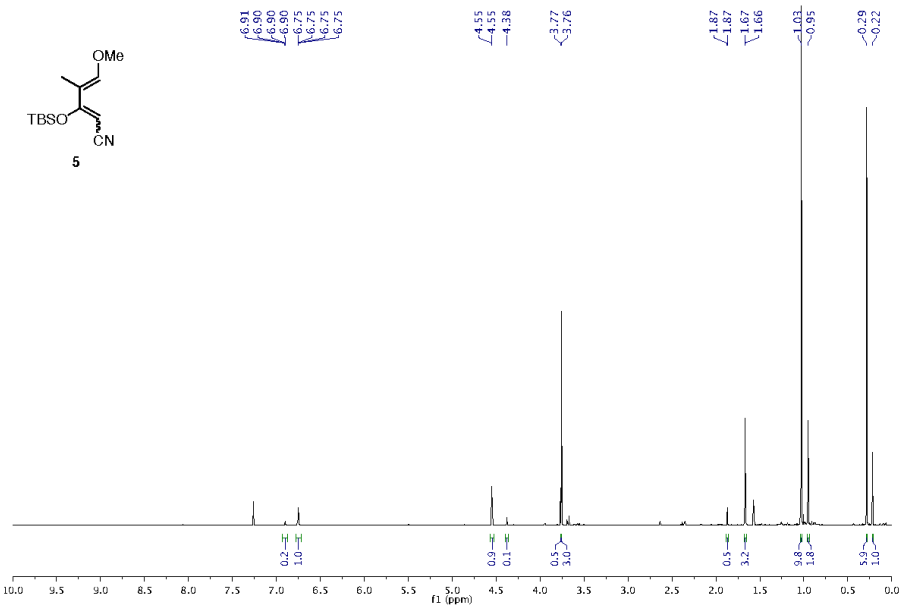

169.1
55.3
53.4
38.1
26.4
Br
Br
O
OMe
8
f1 (ppm)

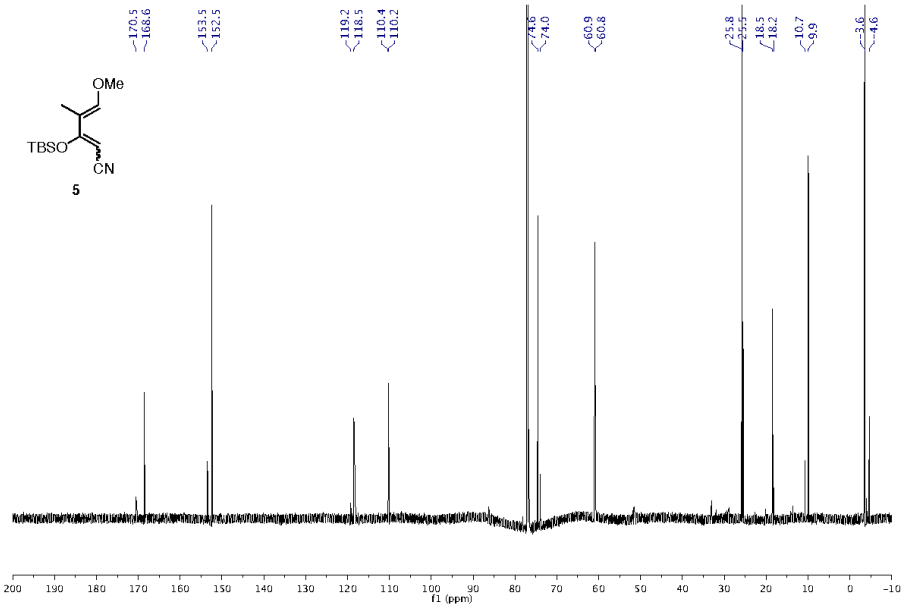

7.27
7.26
7.26
3.94
3.62
1.75
1.75
OMe
OMe
9
1.5
3.0
2.0
3.0
f1 (ppm)

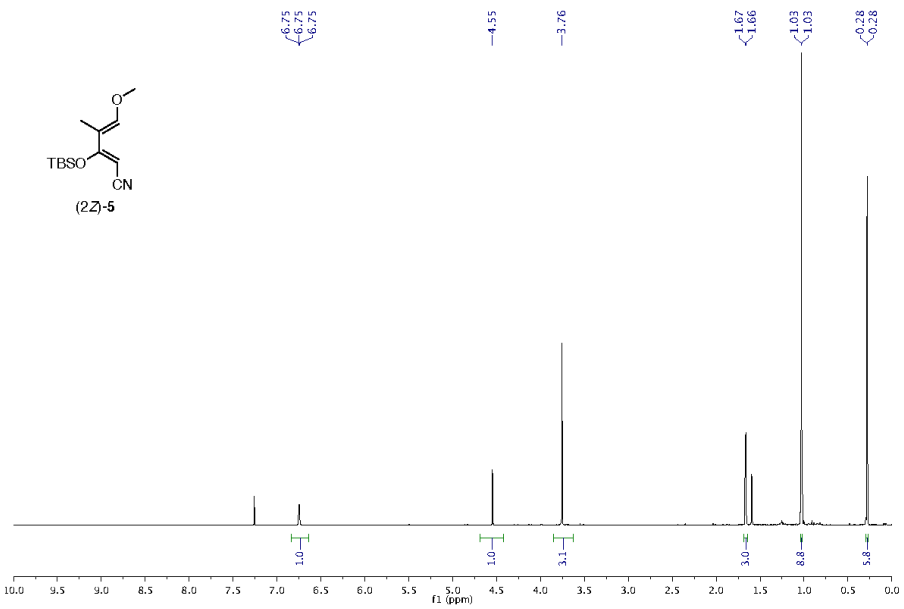

169.2
158.5
106.1
61.1
51.2
9.0
OMe
OMe
9
f1 (ppm)

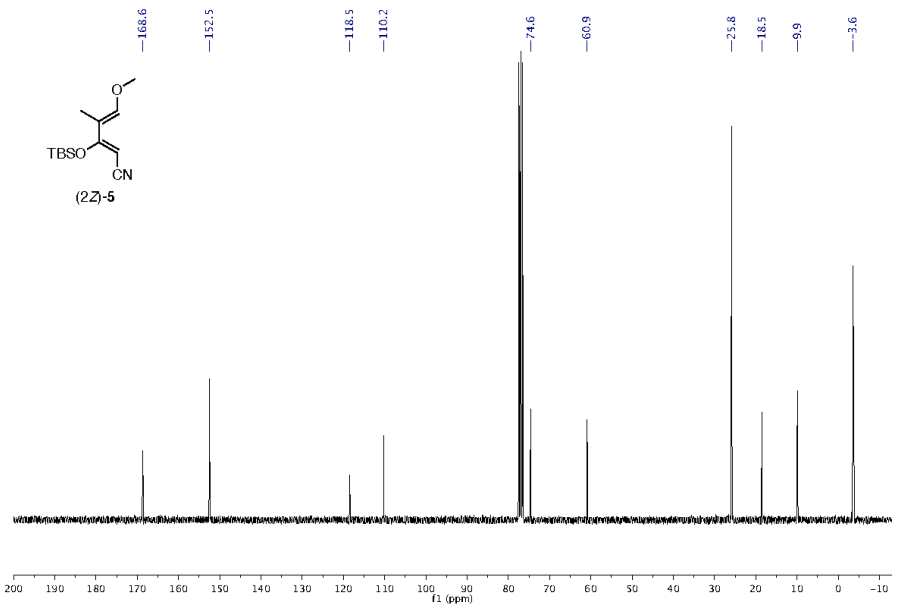

7.27
7.26
7.26
7.26
7.26
3.94
3.62
1.75
1.75
OMe
O
CN
10
1.1
3.0
2.0
2.5
f1 (ppm)

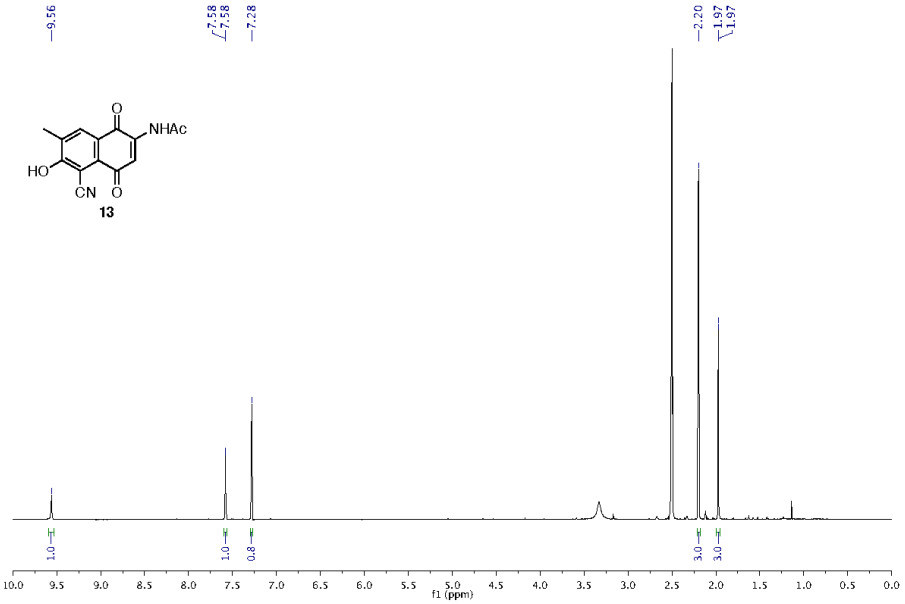

186.0
161.7
115.8
114.5
62.1
28.1
8.5
OMe
O
CN
10
f1 (ppm)

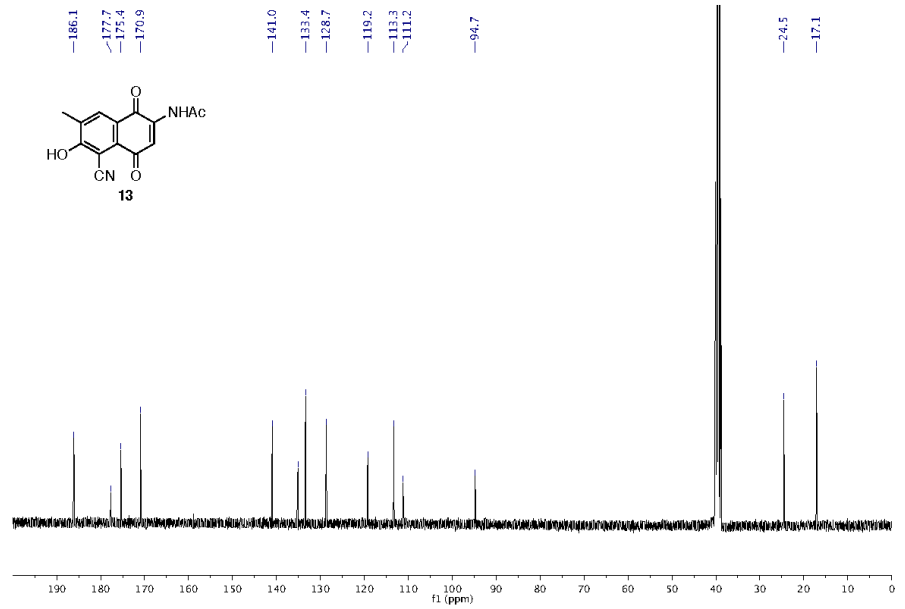

OMe
TBSO
CN
5
f1 (ppm)

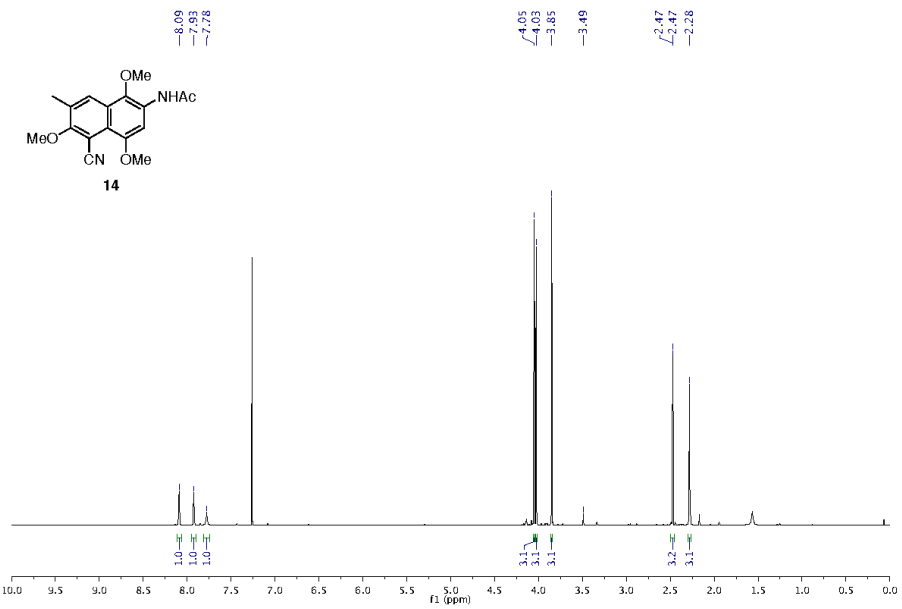

OMe
TBSO
CN
5
f1 (ppm)

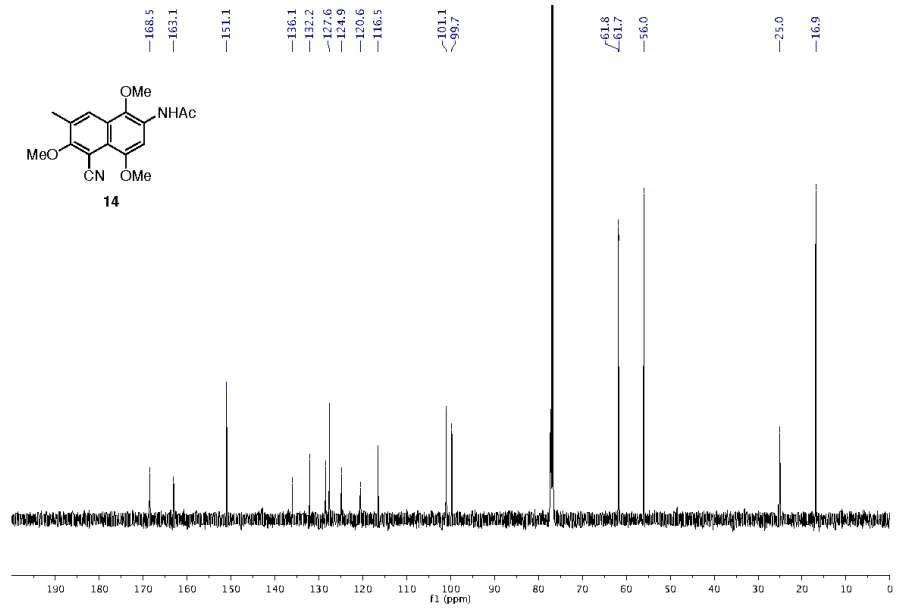

6.75
6.75
6.75
4.55
3.76
1.67
1.66
1.03
1.03
0.28
0.28
TBSO
CN
(2Z)-5
1.0
1.0
3.1
3.0
8.8
5.8
f1 (ppm)

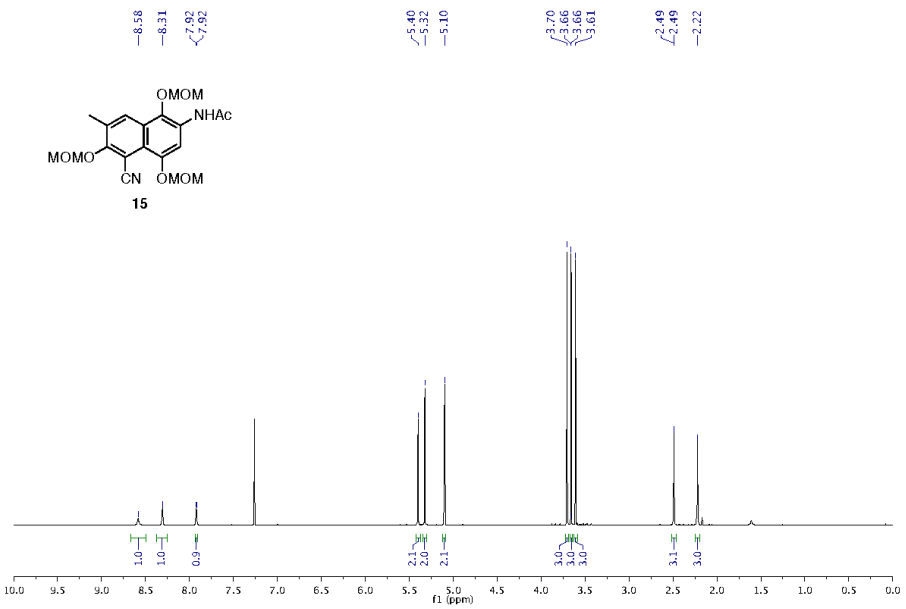

168.6
152.5
118.5
110.2
74.6
60.9
25.8
18.5
9.9
-3.6
TBSO
CN
(2Z)-5
f1 (ppm)

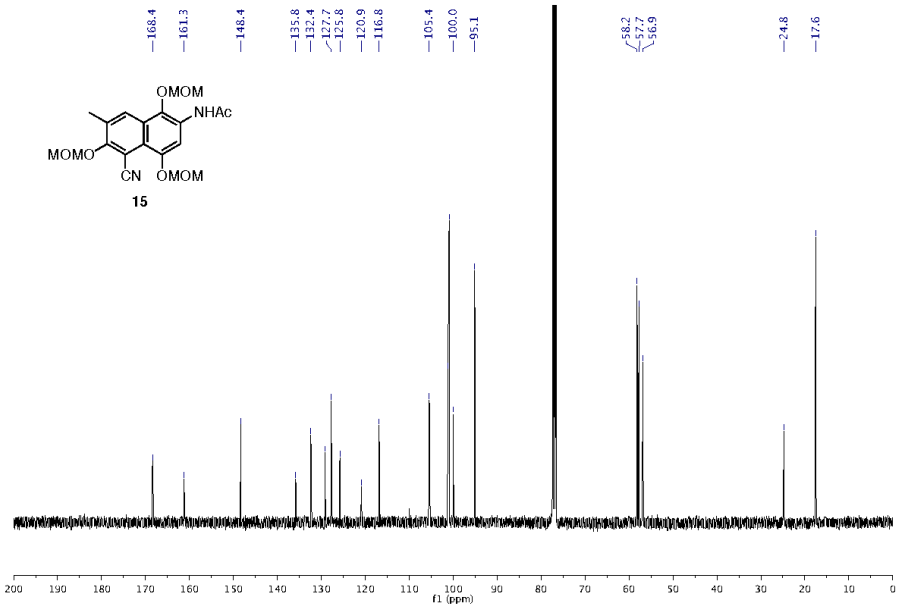

9.56
7.58
7.58
7.28
2.20
1.97
1.97
NHAc
HO
CN
O
13
1.0
1.0
0.8
3.0
3.0
f1 (ppm)

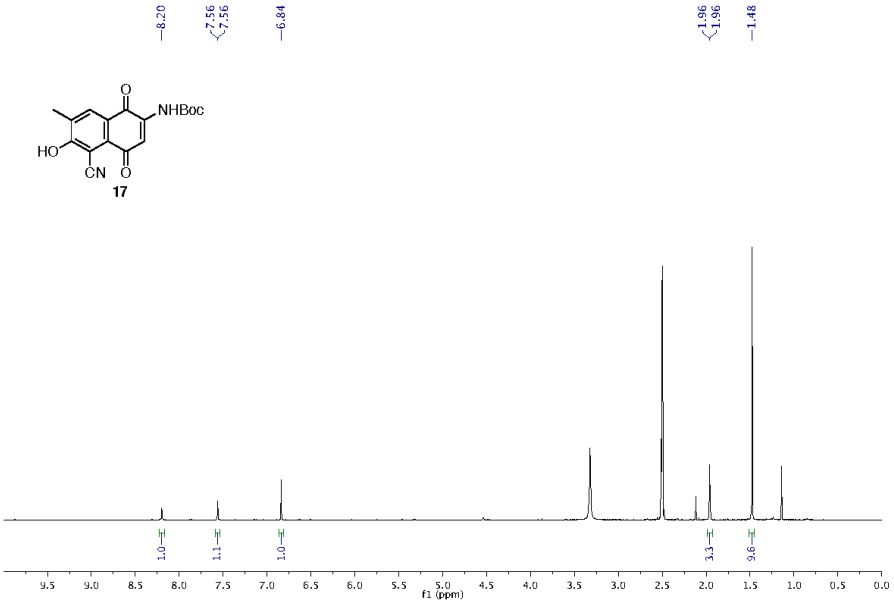

186.1
177.7
175.4
170.9
141.0
133.4
128.7
119.2
113.3
111.2
94.7
24.5
17.1
NHAc
HO
CN
O
13
f1 (ppm)

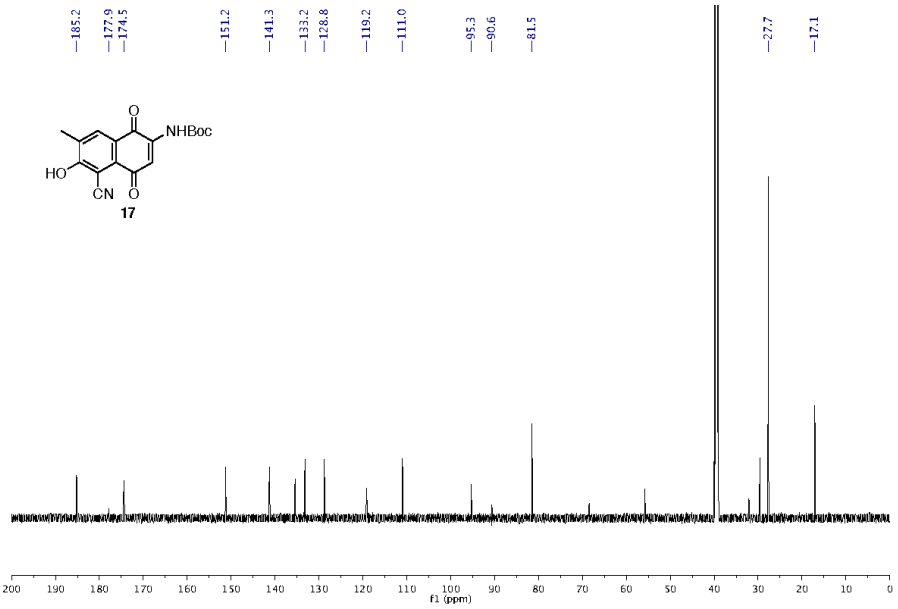

8.09
7.93
7.78
4.05
4.03
3.85
3.49
2.47
2.47
2.28
OMe
NHAc
MeO
CN
OMe
14
1.0
1.0
1.0
3.1
3.1
3.1
3.2
3.1
f1 (ppm)

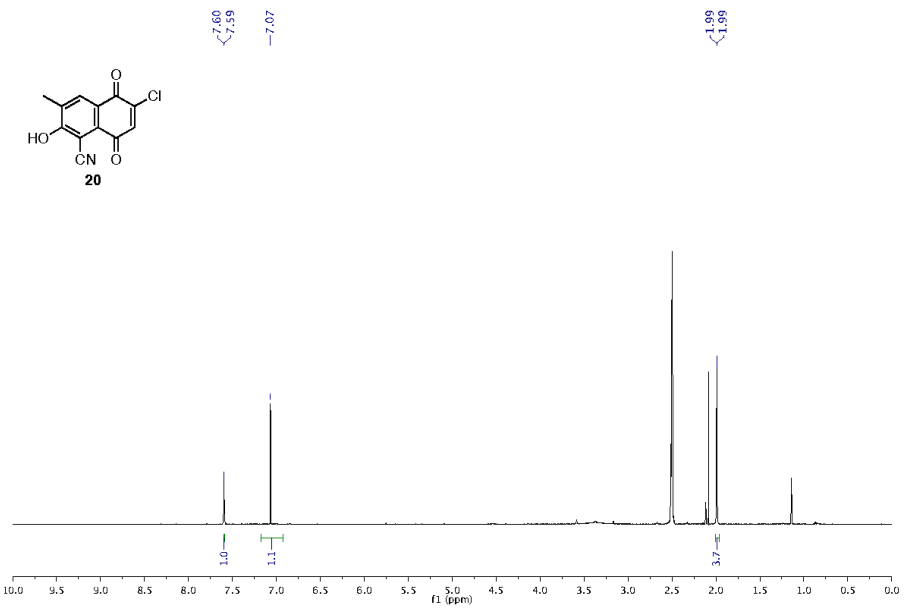

168.5
163.1
151.1
136.1
132.2
127.6
124.9
120.6
116.5
101.1
99.7
61.8
61.7
56.0
25.0
16.9
OMe
NHAc
MeO
CN
OMe
14
f1 (ppm)

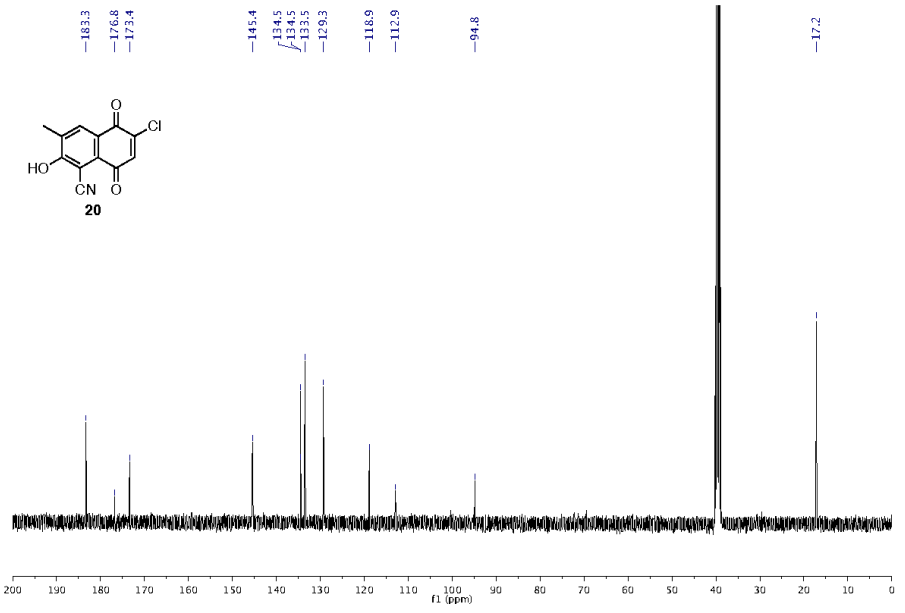

8.58
8.31
7.92
7.92
5.40
5.32
5.10
3.70
3.66
3.66
3.61
2.49
2.49
2.22
OMOM
NHAc
MOMO
CN
OMOM
15
1.0
1.0
0.9
2.1
2.0
2.1
3.0
3.0
3.0
3.1
3.0
f1 (ppm)

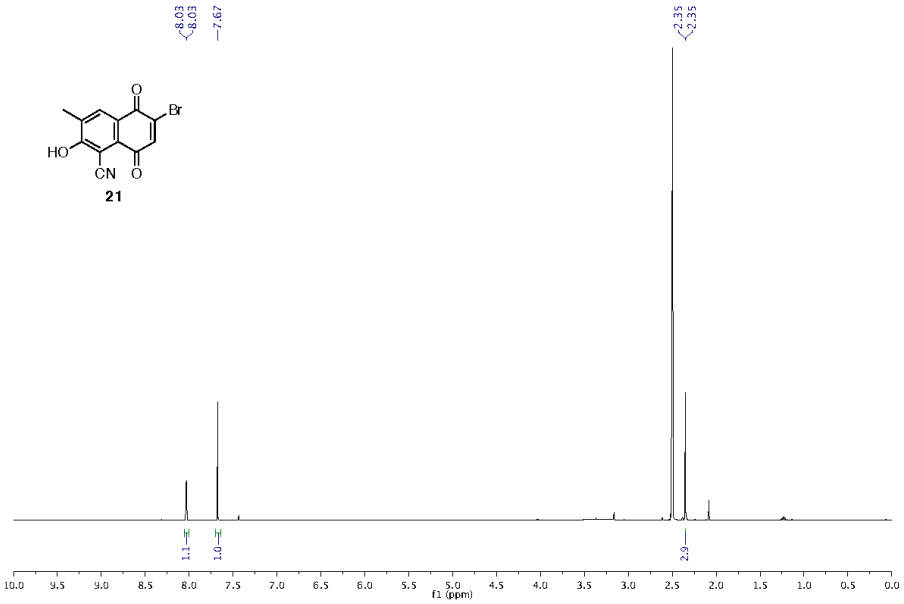

168.4
161.3
148.4
135.8
132.4
127.7
125.8
120.9
116.8
105.4
100.0
95.1
58.2
57.7
56.9
24.8
17.6
OMOM
NHAc
MOMO
CN
OMOM
15
f1 (ppm)

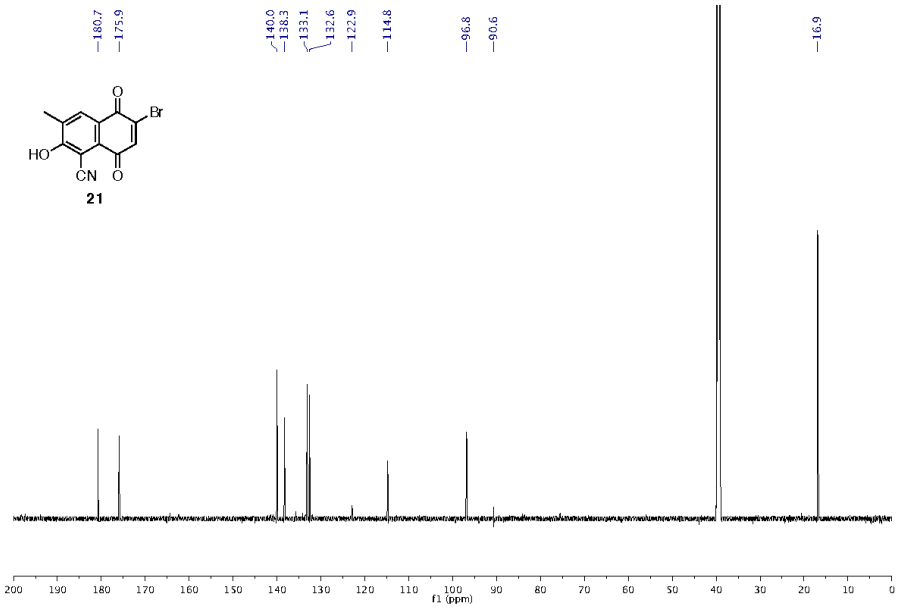

8.20
7.56
7.56
6.84
1.96
1.96
1.48
NHBoc
HO
CN
O
17
1.0
1.1
1.0
3.3
9.6
f1 (ppm)

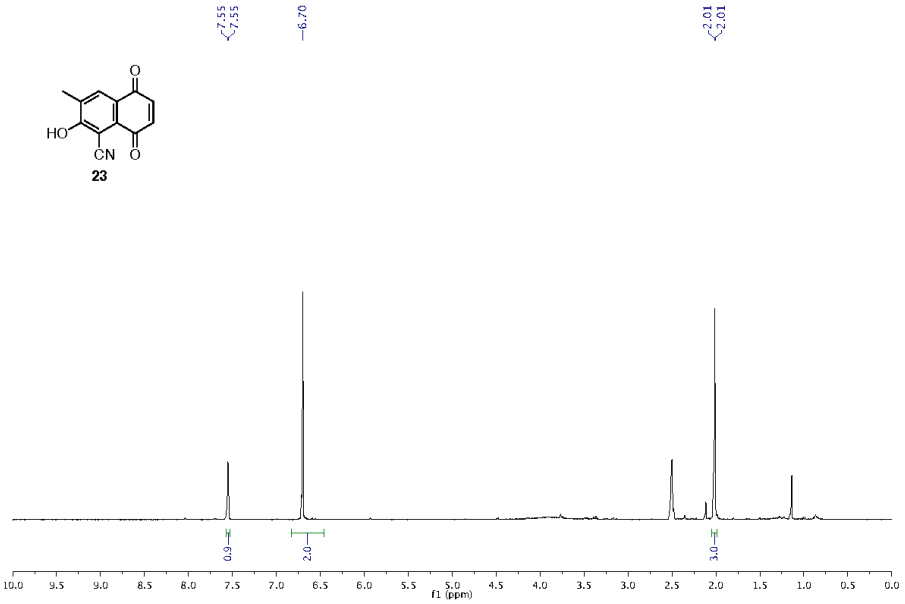

185.2
177.9
174.5
151.2
141.3
133.2
128.8
119.2
111.0
95.3
90.6
81.5
27.7
17.1
NHBoc
HO
CN
O
17
f1 (ppm)

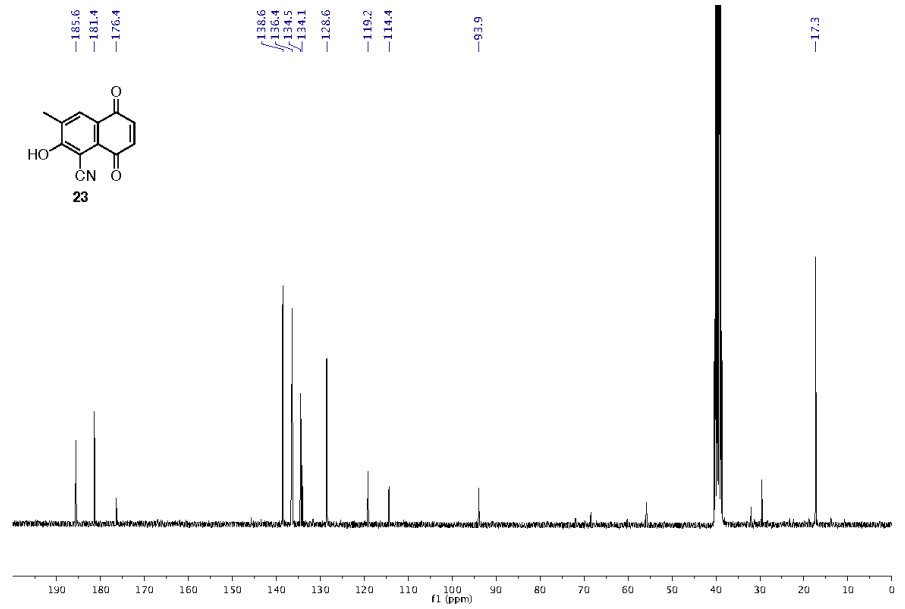

7.60
7.59
7.07
1.99
1.99
O
Cl
HO
CN
O
20
1.0
1.1
3.7
f1 (ppm)

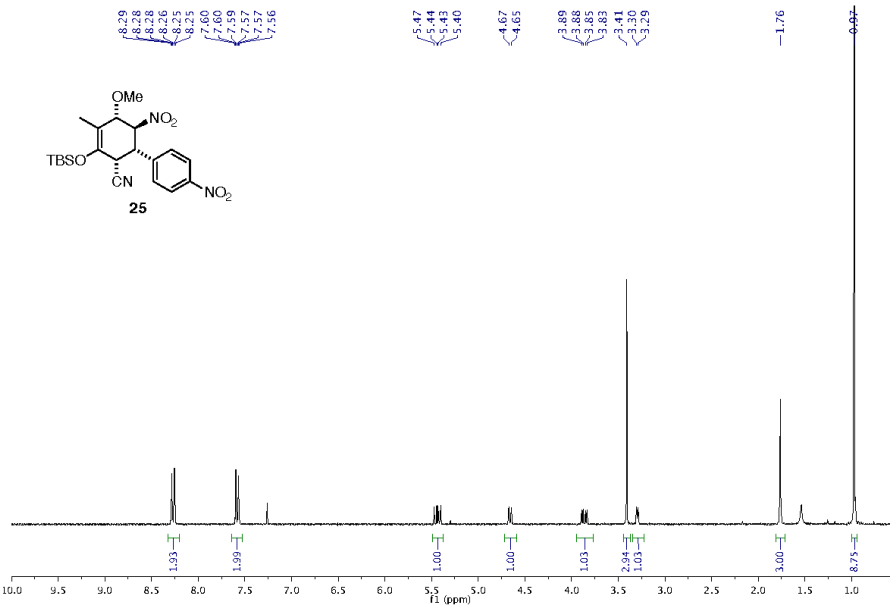

183.3
176.8
173.4
145.4
134.5
134.5
133.5
129.3
118.9
112.9
94.8
17.2
O
Cl
HO
CN
O
20
f1 (ppm)

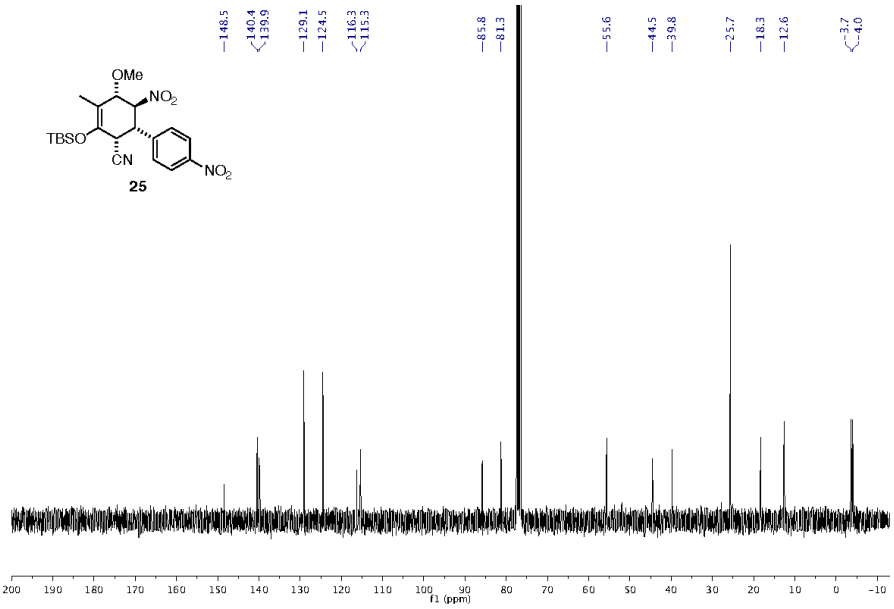

8.03
8.03
7.67
2.35
2.35
Br
HO
CN
O
O
21
1.1
1.0
2.9
f1 (ppm)

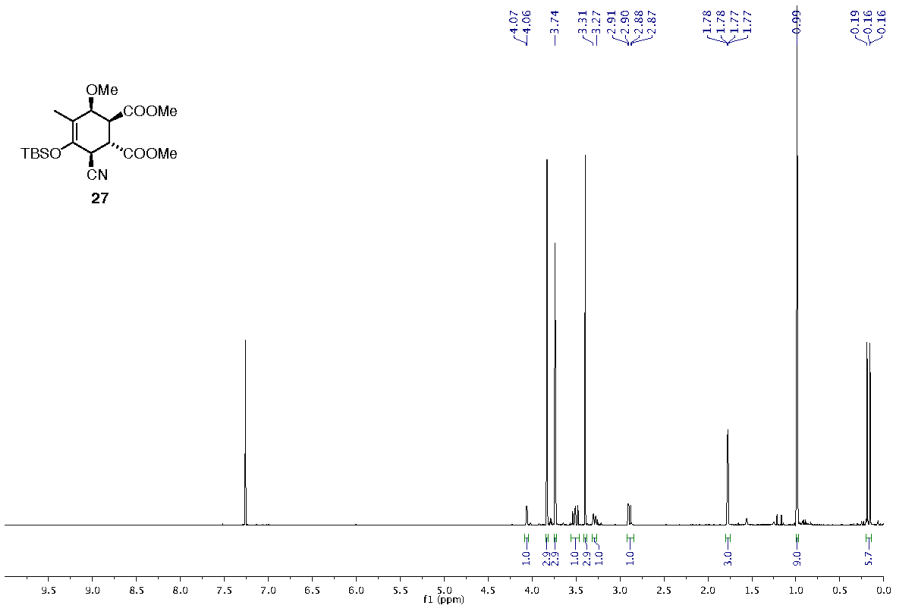

180.7
175.9
140.0
138.3
133.1
132.6
122.9
114.8
96.8
90.6
16.9
Br
HO
CN
O
O
21
f1 (ppm)

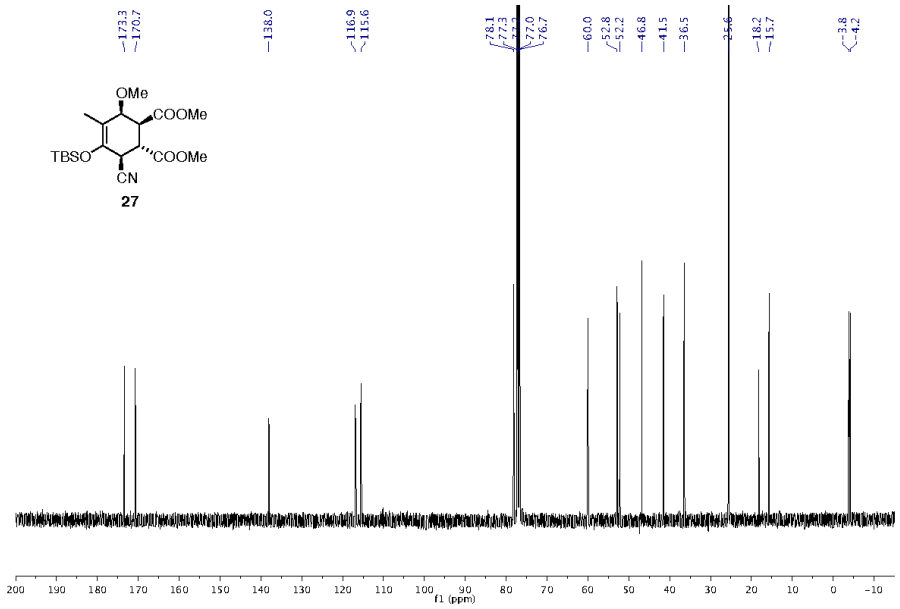

7.55
7.55
6.70
2.01
2.01
HO
CN
O
O
23
0.9
2.0
3.0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

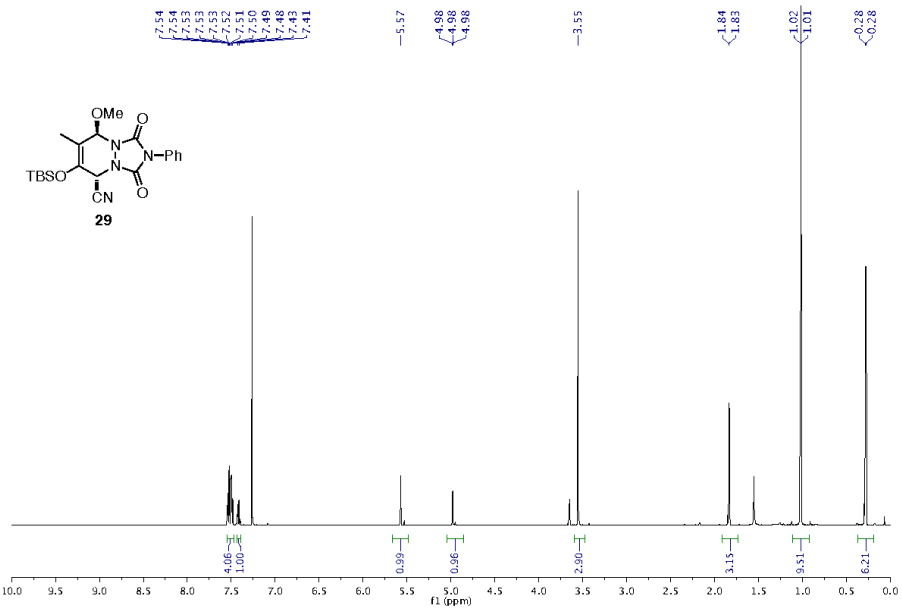

185.6
181.4
176.4
138.6
136.4
134.5
134.1
128.6
119.2
114.4
93.9
17.3
HO
CN
O
O
23
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

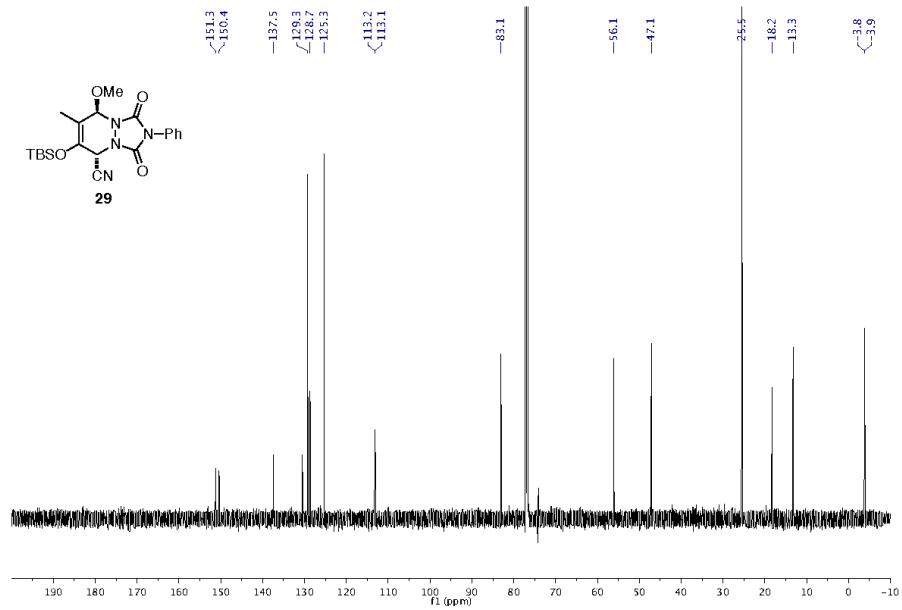

8.29
8.28
8.28
8.26
8.25
8.25
7.60
7.60
7.59
7.57
7.57
7.56
5.47
5.44
5.43
5.40
4.67
4.65
3.89
3.88
3.85
3.83
3.41
3.30
3.29
1.76
0.97
OMe
NO2
TBSO
CN
NO2
25
1.93
1.99
1.00
1.00
1.03
2.94
1.03
3.00
8.79
f1 (ppm)


148.5
140.4
139.9
129.1
124.5
116.3
115.3
85.8
81.3
55.6
44.5
39.8
25.7
18.3
12.6
3.7
4.0
OMe
NO2
TBSO
CN
NO2
25
f1 (ppm)


OMe
COOMe
TBSO
COOMe
CN
27
4.07
4.06
3.74
3.31
3.27
2.91
2.90
2.88
2.87
1.78
1.78
1.77
1.77
0.99
0.19
0.16
0.16
1.0
2.3
2.3
1.0
2.9
1.0
1.0
3.0
9.0
5.7
f1 (ppm)


173.3
170.7
138.0
116.9
115.6
78.1
77.3
77.0
76.7
60.0
52.8
52.2
46.8
41.5
36.5
25.6
18.2
15.7
3.8
4.2
OMe
COOMe
TBSO
COOMe
CN
27
f1 (ppm)

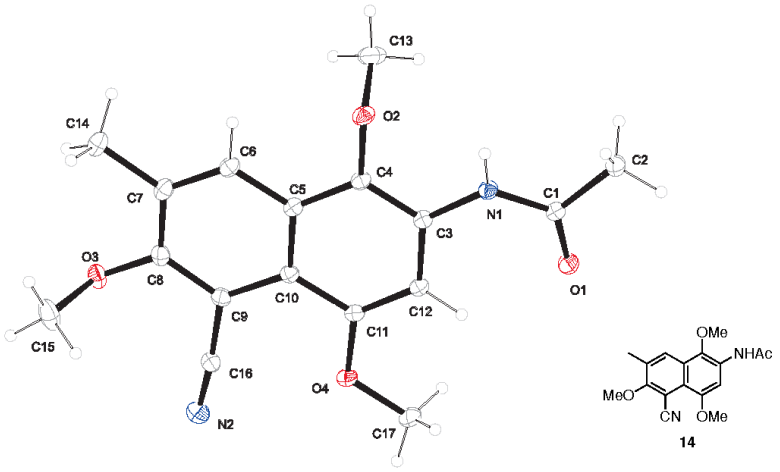

OMe
O
N
N
N–Ph
TBSO
CN
O
29
7.54
7.54
7.53
7.53
7.53
7.52
7.51
7.50
7.49
7.48
7.43
7.41
5.57
4.98
4.98
4.98
3.55
1.84
1.83
1.02
1.01
0.28
0.28
4.06
1.00
0.99
0.96
2.90
3.15
9.51
6.21
f1 (ppm)


OMe
O
N
N
N–Ph
TBSO
CN
O
29
151.3
150.4
137.5
129.3
128.7
125.3
113.2
113.1
83.1
56.1
47.1
25.5
18.2
13.3
3.8
-3.9
f1 (ppm)

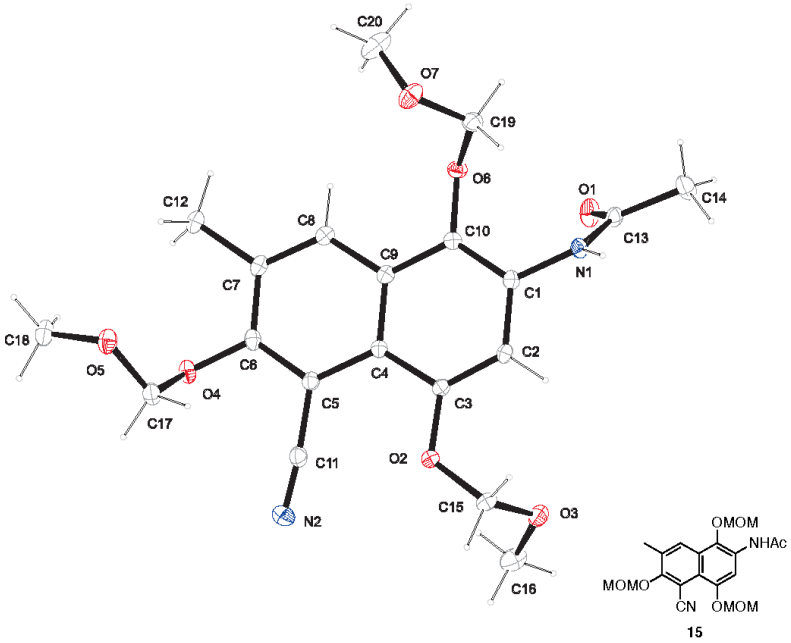
Crystal structures

Note: Crystallographic data for compounds **14**, **15**, **21**, **25**, **27** and **29** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 859806, 859805, 859804, 864199, 859807, and 859808, respectively).

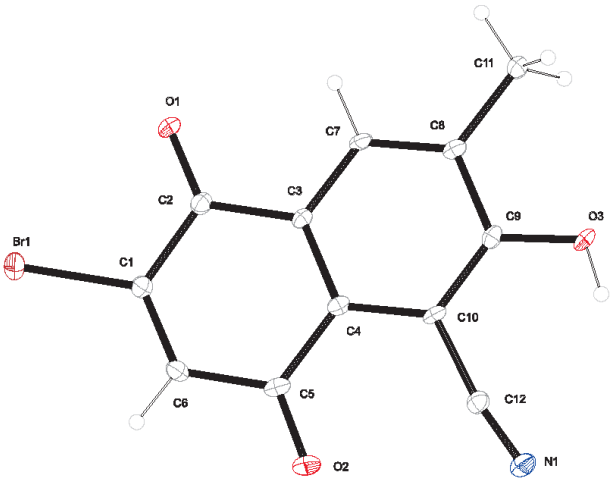
a) X-Ray structure of **14**:



b) X-Ray structure of **15**:

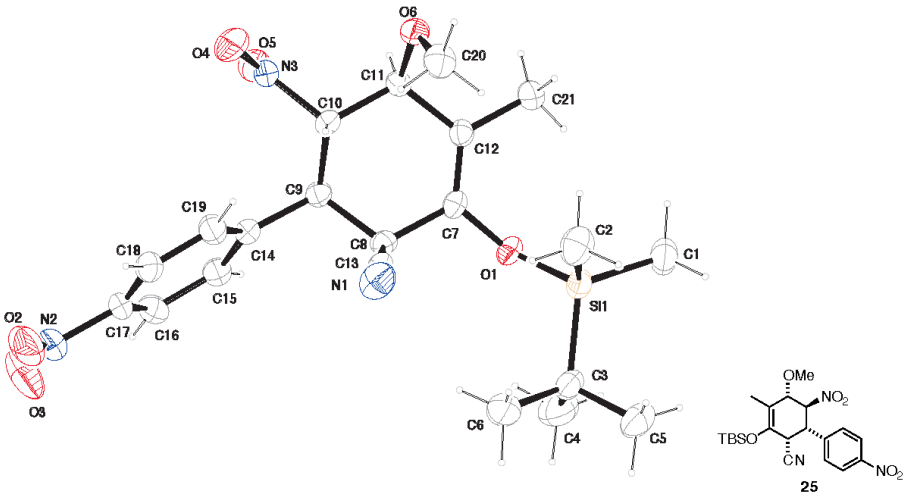


c) X-Ray structure of **21**:



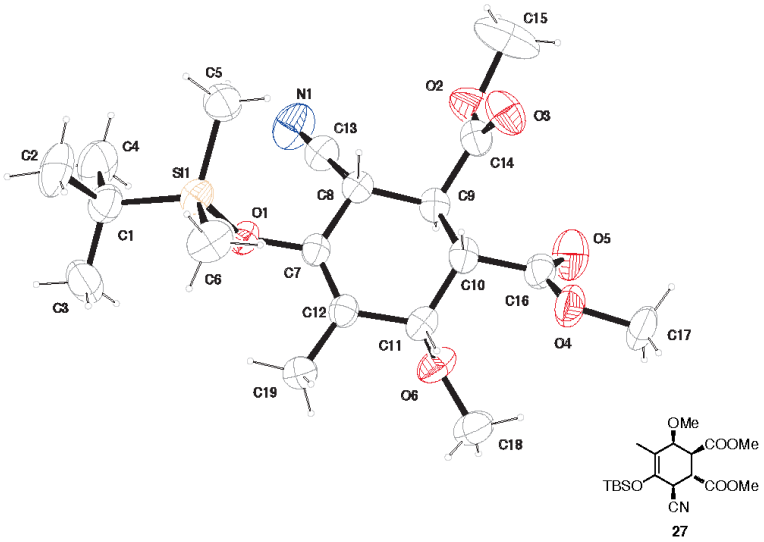
21

d) X-Ray structure of **25**:

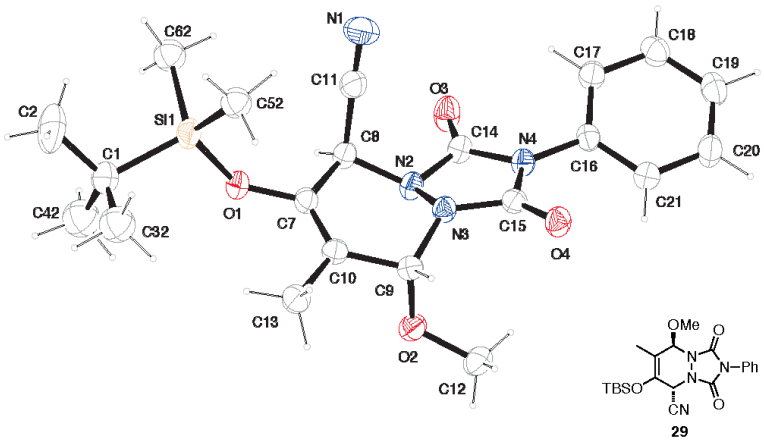


25

e) X-Ray structure of **27**:



f) X-Ray structure of **29**:

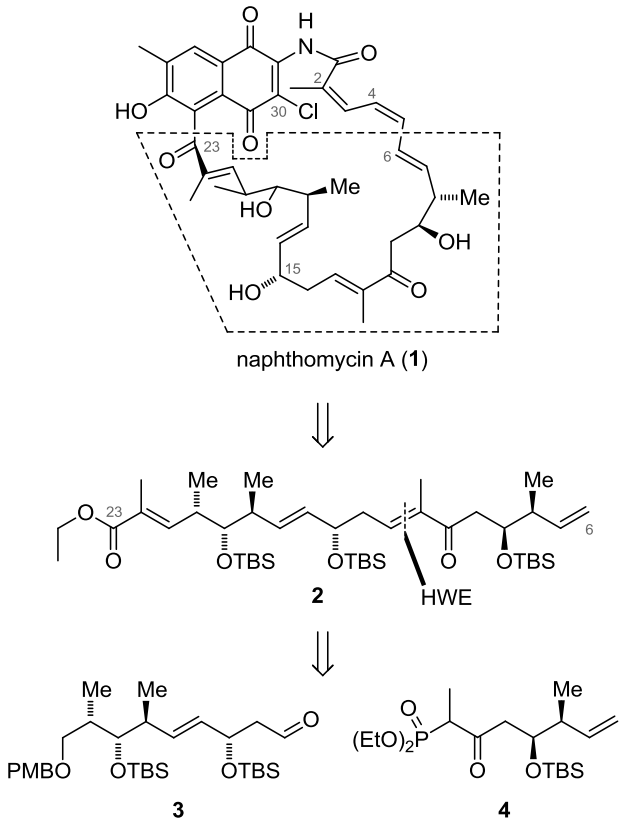


2.2 Synthesis of the C6–C23 Fragment of Naphthomycins

Naphthomycins, exemplified by naphthomycin A (**1**) depicted in Scheme 1, are described as having a basket like structure.[1] All of them contain a naphthoquinone moiety, which forms the flat part and is linked to a polyketide chain, that forms a macrocyclic lactam. Distinguishing features in the naphthomycin family are a variety of substituents at C30, methyl or hydrogen substitution at C2 and the double bond configuration of C4. Recently, results from our laboratories have been published, dealing with the synthesis of the aminonaphthoquinone core of naphthomycins and other ansamycins.[2] To date, there is no total synthesis of any naphthomycin reported. Our ongoing interest in ansamycines and their potential biological activity render the naphthomycins as attractive synthetic targets.

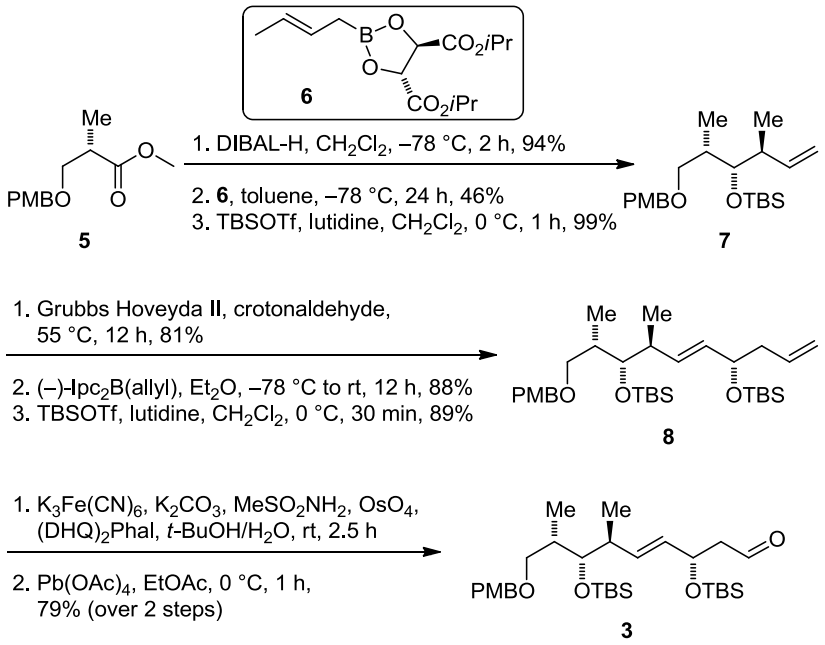
The polyketide chain from C6 to C23 is a shared moiety in all naphthomycins. This common fragment (**2**) is characterized by six stereogenic centers, two enones and a labile hydroxyl group at C15. Access to this fragment (**2**) would allow its incorporation in the syntheses of all naphthomycins. Retrosynthetically, we anticipated this general building block to arise from aldehyde **3** and phosphonate **4** by means of a Horner-Wadsworth-Emmons (HWE) reaction.

Scheme 1. Synthetic Approach to C6-C23 Fragment **2** of Naphthomycin A (**1**)



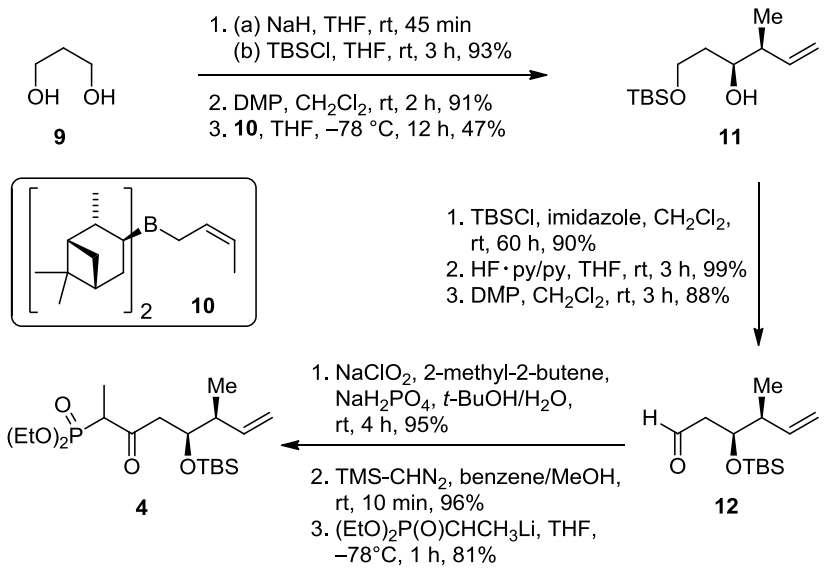
Our synthesis of aldehyde **3** is outlined in Scheme 2 and commenced with DIBAL-H reduction of PMB protected Roche ester **5** to the corresponding aldehyde in very good yield. Roush crotylation with borane **6** followed by protection of the resulting alcohol with TBSOTf yielded literature known alkene **7**.[3] Subsequent exposure to cross metathesis conditions with crotonaldeyde and Grubbs Hoveyda 2nd Generation catalyst afforded an α,β-unsaturated aldehyde, which was allylated with commercially available (□)-Ipc$_2$B(allyl) followed by protection to give TBS ether **8**. With all carbon atoms in place, oxidative cleavage of the terminal double bond was required. Various conditions have been tried to achieve the final transformation, but the desired aldehyde **3** could not be isolated in higher than 32% yield. This is due to its sensitivity towards elimination of the TBS ether under slightly acidic or basic conditions giving a dienenale (not shown in Scheme 2), which further decomposes. However, exposure to Sharpless dihydroxylation conditions followed by glycol cleavage with Pb(OAc)$_4$ gave rise to the desired aldehyde **3** in 79% yield.

Scheme 2. Synthesis of Aldehyde Building Block (**3**)



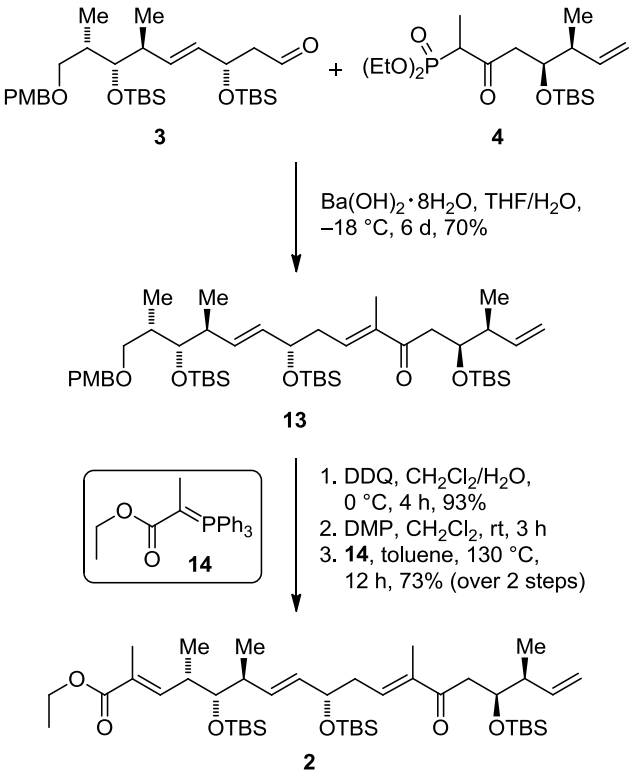
Being able to synthesize multigram quantities of building block **3**, a scalable route for building block **4** was next targeted. Our successful synthesis is outlined in Scheme 3 and started with mono-protection of diol **9**.[4] Dess-Martin periodane (DMP) oxidation followed by Brown crotylation with borane **10** set the two stereocenters and gave alcohol **11**.[5] Subsequent protection of the secondary alcohol followed by selective primary deprotection and DMP oxidation afforded aldehyde **12**. Efforts to convert aldehyde **12** or further oxidized derivatives, such as the corresponding acyl chloride or the Weinreb amide, into the desired building block **4** were all fruitful. Eventually the best yield was achieved when the corresponding methyl ester, prepared by Pinnick oxidation followed by methylation with TMS-diazomethane, was treated with lithiated phosphonate to give building block **4** as a 1:1 mixture of diastereomers.

Scheme 3. Synthesis of Phosphonate Building Block (**4**)



With multigram quantities of both building blocks in hand, the crucial HWE was investigated. Standard bases, such as LDA, NaH, LiHMDS, KO*t*Bu amongst others, mostly led to decomposition of aldehyde **3** and reisolation of phosphonate **4**. Mild conditions for sensitive compounds have been reported[6], but in this case only gave poor yield and were not scalable. The best result was obtained when a modified procedure with dried $Ba(OH)_2$ at –18 °C for six days was applied.[7] These conditions allowed for a multigram synthesis of desired enone **13** in reliable 70% yield. Finally, PMB-ether was selectively cleaved by means of DDQ and the liberated alcohol was oxidized with DMP. Treatment of the later with phosphanylidene **14** at 130 °C for 12 hours gave access to the complete fragment **2** in 73% over two steps.

Scheme 4. Completion of the Synthesis of Fragment (**2**)



In conclusion, a synthesis of the C6–C23 fragment of naphthomycins has been accomplished within nine steps and in an overall yield of 30.6%. Building blocks **3** and **4** were both prepared in each five steps from literature known compounds in multigram quantities. The preparation of sensitive aldehyde building block **3** and its linkage in a Horner-Wadsworth-Emmons reaction were crucial steps in the synthesis and required careful optimization.

References

[1] I. E. Wrona, V. Agouridas, J. S. Panek, *Comptes-Rendus Académie des Sciences*, **2008**, *11*, 1483–1522.

[2] C. A. Kuttruff, S. Geiger, M. Cakmak, P. Mayer, D. Trauner, *Org. Lett.* **2012**, *14*, 1070–1073.

[3] M. Ying, W. R. Roush, *Tetrahedron* **2011**, *67*, 10274–10280.

[4] S. Lou, J. A. Westbrook, S. E. Schaus, *J. Am. Chem. Soc.*, **2004**, 126, 11440–11441.

[5] Y.-J. Kim, P. Wang, M. Navarro-Villalobos, B. D. Rohde, J. Mark, D. Berry, D. Y. Gin, *J. Am. Chem. Soc.*, **2006**, *128*, 11906–11915.

[6] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186; M. W. Rathke, M. Nowak, J. Org. Chem. 1**985**, *50*, 2624; D. Simoni, M. Rossi, R. Rondanin, A. Mazzali, R. Baruchello, C. Malagutti, M. Roberti, F. P. Invidiata, *Org. Lett.* **2000**, *2*, 3765–3768; L. K. Blasdel, A. G. Myers, *Org. Lett.* **2005**, *7*, 4281–4283.

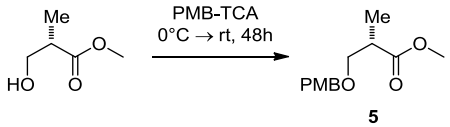
[7] I. Paterson, K.-S. Yeung, J. B. Smaill, *Synlett* **1993**, 774.

2.2.1 Supplementary Information

General Experimental Details. Unless stated otherwise, all reactions were performed in oven-dried or flame-dried glassware under a positive pressure of nitrogen. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from benzophenone and sodium immediately prior to use. Diisopropylethylamine (DIPEA) and Triethylamine (TEA) were distilled over calcium hydride immediately before use. Reactions were magnetically stirred and monitored by crude NMR or analytical thin-layer chromatography (TLC) using E. Merck 0.25 mm silica gel 60 F_{254} precoated glass plates. TLC plates were visualized by exposure to ultraviolet light (UV, 254 nm) and/or exposure to an aqueous solution of ceric ammoniummolybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating with a heat gun. Flash column chromatography was performed as described by *Still et al.* employing silica gel (60 Å, 40-63 μm, Merck) and a forced flow of eluant at 1.3–1.5 bar pressure.[1] Yields refer to spectroscopically (^{1}H NMR and ^{13}C NMR) pure material.

Instrumentation. Proton nuclear magnetic resonance (1H NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Proton chemical shifts are expressed in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference (CHCl3: δ 7.26, MeOH: δ 3.31, H2O: δ 4.79). Data for 1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. Carbon nuclear magnetic resonance (13C NMR) spectra were recorded on Varian VNMRS 300, VNMRS 400, INOVA 400 or VNMRS 600 spectrometers. Carbon chemical shifts are expressed in parts per million (δ scale) and are referenced from the carbon resonances of the solvent (CDCl3: δ 77.0, MeOH: δ 49.0). Infrared (FTIR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System). FTIR Data is reported in frequency of absorption (cm-1). Mass spectroscopy (MS) experiments were performed on a Thermo Finnigan MAT 95 (EI) or on a Thermo Finnigan LTQ FT (ESI) instrument. Microwave reactions were performed on a CEM machine (Model: Discovery System, No. 908010).

Synthetic procedures.

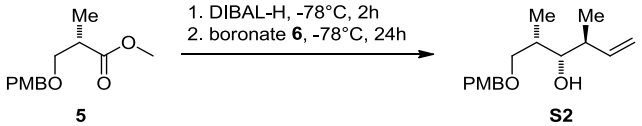


PMB-ether 5

A solution of 1.34 g (11.3 mmol, 1 eq.) (*S*)-methyl 3-hydroxy-2-methylpropanoate in CH_2Cl_2 (10 mL) was cooled to 0 °C and a solution of 4.49 g (15.9 mmol, 1.4 eq.) PMB trichloroacetimidate (freshly prepaired) in CH_2Cl_2 (2 mL) was added dropwise. 130 mg (0.6 mmol, 0.05 eq.) CSA was added and the reaction mixture was allowed to warm to rt and stirred for 48 h. The precipitate was removed by filtration through a plug of silica and the silica was washed with CH_2Cl_2 (50 mL). Combined filtrates were washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 19:1) to yield 1.77 g (7.4 mmol, 81%) PMB ether **5** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 5:1): R_f = 0.40 (CAM, UV).

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.27–7.20 (m, 2H), 6.89–6.83 (m, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.62 (dd, *J*=7.3, 9.1 Hz, 1H), 3.45 (dd, *J*=5.9, 9.1 Hz, 1H), 2.85–2.68 (m, 1H), 1.16 (d, *J*=7.1 Hz, 3H).



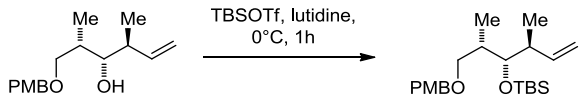
Alcohol S2

1.83 g (7.68 mmol, 1 eq.) methyl ester **5** was dissolved in CH_2Cl_2 (30 mL) and cooled to −78 °C. 9.2 mL (9.20 mmol, 1.2 eq., 1 M solution in CH_2Cl_2) DIBAL-H was added dropwise and the reaction mixture was stirred for 2 h at −78 °C. $^1/_3$ sat. aq. Rochelles-salt (30 mL) was added and the reaction mixture was allowed to warm to rt and further stirred for 1 h. The reaction mixture was diluted with Et_2O (100 mL) and the layers were separated. The organic layer was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 1.5 g (7.20 mmol, 94%) of the desired aldehyd **S1** as a greenish oil (one spot on TLC).

Flame dried 4Å mol sieves (1 g) were treated with 25.5 mL (10.1 mmol, 1.4 eq., 0.4 M solution in toluene) boronate **6** and stirred for 30 min at rt. The reaction mixture was cooled to −78 °C and 1.5 g (7.203 mmol, 1 eq.) aldehyde **S1** in toluene (5 mL) was added dropwise via syringe pump over 1 h. The reaction mixture was stirred for 24 h at −78 °C and subsequently quenched with 10% aq. NaOH (25 mL) and allowed to warm to rt. 50 % aq. H_2O_2 (25 mL) was added dropwise and stirred for 3 h. The reaction mixture was diluted with Et_2O (60 mL) and the layers were separated. The milky water layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 9:1) to yield 885 mg (3.354 mmol, 46%) alcohol **S2** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 4:1): R_f = 0.44 (CAM, UV).

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.29–7.21 (m, 2H), 6.90–6.83 (m, 2H), 5.79 (ddd, *J*=8.4, 10.4, 17.1 Hz, 1H), 5.16–5.06 (m, 2H), 4.44 (s, 2H), 3.80 (s, 3H), 3.57–3.42 (m, 3H), 2.35–2.17 (m, 2H), 2.01–1.87 (m, 1H), 0.97 (d, *J*=2.9 Hz, 3H), 0.93 (d, *J*=3.1 Hz, 3H).



S2 **7**

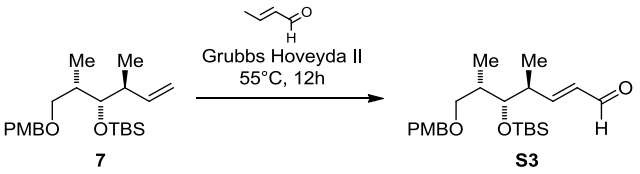
TBS ether 7

A solution of 5.10 g (47.34 mmol, 2.0 eq.) 2,6-lutidine and 6.25 g (23.67 mmol, 1.0 eq.) homoallylic alcohol **S2** in CH_2Cl_2 (35 mL) was cooled to 0 °C and 9.37 g (35.51 mmol, 1.5 eq.) TBSOTf was added dropwise. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with sat. aq. NH_4Cl (50 mL) and CH_2Cl_2 (50 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 94:4) to yield 8.93 g (23.6 mmol, 99%) TBS ether **7** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1): R_f = 0.54 (CAM, UV).

^{1}H-NMR ($CDCl_3$, 200 MHz): δ = 7.29–7.21 (m, 2H), 6.91–6.84 (m, 2H), 5.84 (ddd, *J*=7.8, 10.4, 17.2 Hz, 1H), 5.03–4.93 (m, 2H), 4.46–4.33 (m, 2H), 3.81 (s, 3H), 3.65 (dd, *J*=3.3, 5.0

Hz, 1H), 3.37 (dd, *J*=6.6, 9.1 Hz, 1H), 3.21 (dd, *J*=6.8, 9.0 Hz, 1H), 2.42 (m, 1H), 1.94, (ddd, *J*=3.3, 6.8, 13.6 Hz, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).



7 **S3**

Aldehyde S3

A solution of 7.30 g (19.3 mmol, 1.0 eq) alkene **7** and 27.0 g (386 mmol, 20.0 eq) crotonaldehyde in CH_2Cl_2 (800 mL) was treated with 604 mg (0.966 mmol, 0.05 eq) Grubbs Hoveyda 2nd Generation catalyst. The reaction mixture was stirred at 55 °C for 12 h. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash column chromatography (hexanes/EtOAc = 19:1→7:1) to yield 6.36 g (15.64 mmol, 81%) aldehyde **S3** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1): R_f = 0.33 (CAM).

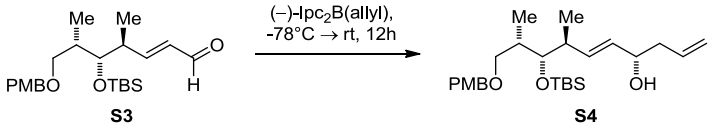
^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.49 (d, *J*=7.9 Hz, 1H), 7.25–7.21 (m, 2H), 6.92 (dd, *J*=7.9, 15.8 Hz, 1H), 6.89–6.86 (m, 2H), 6.07 (ddd, *J*=1.1, 7.9, 15.8 Hz, 1H), 4.43–4.34 (m, 2H), 3.81 (s, 3H), 3.78 (dd, *J*=3.5, 4.8 Hz, 1H), 3.34 (dd, *J*=6.9, 9.1 Hz, 1H), 3.19 (dd, *J*=6.2, 9.1 Hz, 1H), 2.70–2.59 (m, 1H), 1.97–1.85 (ddd, *J*=3.5, 6.9, 13.2 Hz, 1H), 1.09 (d, *J*=6.9 Hz, 3H), 0.91–0.88 (m, 12H), 0.04 (s, 3H), 0.04 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 194.2, 161.8, 159.2, 132.2, 130.5, 129.2, 113.8, 75.8, 72.6, 72.5, 55.3, 41.9, 37.9, 26.1, 18.4, 17.1, 12.3, –3.7, –4.1.

IR (Diamond-ATR, neat) ν_{max}: 2956, 2930, 2884, 2856, 2361, 1691, 1613, 1513, 1471, 1462, 1248, 1172, 1141, 1083, 1035, 1006, 835, 773 cm^{-1}.

$[\alpha]^{20}_D$ = -10.8° (*c* = 0.42, $CHCl_3$).

HRMS (ESI) calcd for $C_{23}H_{38}O_4Si$ $[M+H]^+$: 407.2618; found: 407.2607.



S3 **S4**

Alcohol S4

25 mL (25 mmol, 3.0 eq., 1M solution in pentane) (−)-Ipc_2B(allyl) was dissolved in Et_2O (50 mL) and cooled to −78 °C. A solution of 3.38 g (8.31 mmol, 1.0 eq.) aldehyde **S3** in Et_2O (50 mL) was added dropwise and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was cooled to 0 °C, aq. 2 M NaOH (30 mL) and aq. 30 % H_2O_2 (30 mL) were subsequently added dropwise and stirred for 12 h at rt. The reaction mixture was diluted with H_2O (40 mL) and extracted with Et_2O (4 x 100 mL). The combined organic layers were washed with sat. aq. NH_4Cl (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Ipc-alcohol was removed from the crude product on high *vacuo* (96 h at 50 °C). Further purification by flash column chromatography (hexanes/EtOAc = 19:1 → 12:1) yielded 3.29 g (7.33 mmol, 88%) alcohol **S4** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1): R_f = 0.33 (CAM).

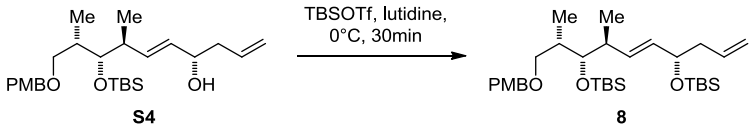
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.25–7.22 (m, 2H), 6.89–6.85 (m, 2H), 5.85–5.72 (m, 1H), 5.69 (ddd, *J*=1.0, 7.6, 15.6 Hz, 1H), 5.44 (ddd, *J*=1.0, 6.7, 15.6 Hz, 1H), 5.15–5.10 (m, 2H), 4.43–4.36 (m, 2H), 4.10 (q, *J*=6.4 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J*=3.4, 4.6 Hz, 1H), 3.35 (dd, *J*=6.6, 9.0 Hz, 1H), 3.20 (dd, *J*=6.8, 9.0 Hz, 1H), 2.39–2.31 (m, 1H), 2.30–2.25 (m, 2H), 1.98–1.81 (m, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 159.0, 135.0, 134.5, 131.6, 130.7, 129.1, 117.9, 113.7, 76.0, 73.3, 72.5, 72.0, 55.2, 41.9, 41.3, 37.2, 26.1, 18.4, 17.5, 12.6, –3.8, –4.2.

IR (Diamond-ATR, neat) ν_{max}: 3396, 2956, 2929, 2904, 2856, 1513, 1472, 1462, 1361, 1302, 1247, 1462, 1361, 1302, 1247, 1172, 1069, 1036, 1005, 834, 772 cm^{-1}.

$[\alpha]^{20}_D$ = -18.9° (*c* = 0.42, $CHCl_3$).

HRMS (ESI) calcd for $C_{26}H_{44}O_4Si$ $[M+NH_4]^+$: 466.3353; found: 466.3345.



S4 **8**

Protected alcohol 8

1.06 g (4.02 mmol, 1.2 eq.) TBSOTf and 860 mg (8.04 mmol, 2.4 eq.) lutidine were dissolved in CH_2Cl_2 (45 mL) and cooled to 0 °C. 1.50 g (3.35 mmol, 1.0 eq.) alcohol **S4** was added dropwise and the reaction mixture was stirred at 0°C for 30 min. The reaction was quenched with sat. aq. NH_4Cl (20 mL), diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$,

filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes/EtOAc = 29:1 → 19:1) to yield 1.67 mg (2.99 mmol, 89%) of protected alcohol **8** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1): R_f = 0.58 (CAM).

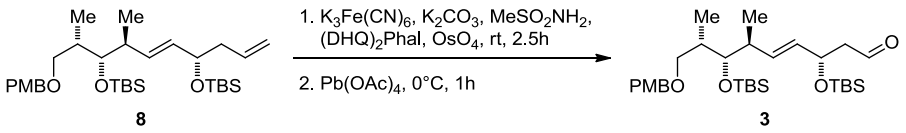
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.26–7.23 (m, 2H), 6.90–6.86 (m, 2H), 5.84–5.73 (m, 1H), 5.63 (ddd, *J*=1.1, 7.8, 15.6 Hz, 1H), 5.38 (ddd, *J*=1.0, 6.15, 15.6 Hz, 1H), 5.05–4.99 (m, 2H), 4.43–4.35 (m, 2H), 4.08 (q, *J*=6.7 Hz, 1H), 3.80 (s, 3H), 3.64 (t, *J*=3.9 Hz, 1H), 3.36 (dd, *J*=6.1, 9.0 Hz, 1H), 3.21 (dd, *J*=6.9, 9.0 Hz, 1H) 2.37–2.28 (m, 1H), 2.27–2.16 (m, 2H), 1.94–1.88 (m, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.92–0.87 (m, 21H), 0.04 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 159.0, 135.4, 132.6, 132.5, 130.8, 129.1, 116.5, 113.7, 76.1, 73.3, 73.2, 72.5, 55.2, 43.2, 41.4, 37.5, 26.1, 25.9, 18.4, 18.2, 18.0, 13.2, -3.9, -4.1, -4.3, -4.8.

IR (Diamond-ATR, neat) ν_{max}: 2955, 2928, 2855, 1613, 1513, 1472, 1462, 1247, 1171, 1079, 1037, 1004, 833, 772, 677 cm^{-1}.

$[\alpha]^{22}_D$ = - 18.2° (*c* = 0.48, $CHCl_3$).

HRMS (ESI) calcd for $C_{32}H_{58}O_4Si_2$ $[M+NH_4]^+$: 580.4217; found: 580.4221.



Aldehyde 3

A solution of 3 g (5.34 mmol, 1.0 eq.) alkene **8** in *tert*-butanol (90 mL) was treated with 5.27 g (16.01 mmol, 3.0 eq.) $K_3Fe(CN)_6$, 2.21 g (16.01 mmol, 3.0 eq.) K_2CO_3, 0.51 g (5.34 mmol, 1.0 eq.) $MeSO_2NH_2$ and 1.66 g (2.1 mmol, 0.4 eq.) $(DHQ)_2Phal$. H_2O (90 mL) was added to the reaction mixture was stirred for 15 min and treated dropwise with 870 µL (0.85 mmol, 0.016 eq., 2,5% wt in *tert*-butanol) OsO_4. The reaction mixture was stirred for 2.5 h at rt before quenching with 16.8 g (133 mmol, 25 eq.) Na_2SO_3. The reaction mixture was stirred for 30 min at rt, diluted with H_2O (50 mL), extracted with EtOAc (3 x 250 mL), washed with 1 M HCl (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 4.4 g of crude diol **S5** as a yellowish oil.

A solution of crude diol **S5** (100% yield assumed from Sharpless dihydroxylation reaction, 5.34 mmol) in EtOAc (290 mL) was cooled to 0°C and treated with 3.07 g (6.94 mmol,

1.3 eq.) $Pb(OAc)_4$. The reaction mixture was stirred for 1 h at 0°C. The reaction mixture was filtered through a pad of silica, washed with 1 L Et_2O/hexanes (1:1) and the combined filtrates were concentrated *in vacuo* to yield 2.95 g aldehyde **3** as a brown oil.

For characterization purpose the crude product from a previous batch was purified by flash column chromatography* (hexanes:EtOAc = 19:1) to yield the desired aldehyde **FF10 (**in 79% isolated yield) as a colorless oil (one spot on TLC).

**Product is not very stable on silica, a quick column is recommended. Purification is not necessary for the next step.*

TLC (hexanes:EtOAc = 9:1): R_f = 0.38 (CAM).

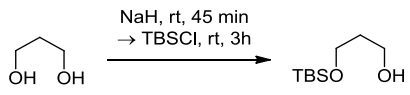
^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 9.75 (t, *J*=2.5 Hz, 1H), 7.25–7.23 (m, 2H), 6.88–6.86 (m, 2H), 5.73 (ddd, *J*=1.2, 7.8, 15.6 Hz, 1H), 5.42 (ddd, *J*=1.0, 6.1, 15.6 Hz, 1H), 4.62–4.57 (m, 1H), 4.39 (q, *J*=11.6 Hz, 2H), 3.80 (s, 3H), 3.65 (t, *J*=3.8 Hz, 1H), 3.33 (dd, *J*=6.3, 9.0 Hz, 1H), 3.19 (dd, *J*=6.7, 9.0 Hz, 1H), 2.55 (ddd, *J*=2.8, 7.2, 15.5 Hz, 1H), 2.44 (ddd, *J*=2.2, 4.8, 15.5 Hz, 1H), 2.34 (td, J=4.0, 7.1 Hz, 1H), 1.91–1.85 (ddd, *J*=3.9, 6.6, 13.3 Hz, 1H), 0.99 (d, *J*=7.0 Hz, 3H), 0.91–0.86 (m, 21H), 0.05, (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 201.9, 159.1, 133.8, 131.4, 130.8, 129.2, 113.7, 76.0, 73.2, 72.6, 69.2, 55.3, 51.7, 41.3, 37.7, 26.1, 25.8, 18.4, 18.1, 18.0, 13.1, -3.9, –4.1, –4.2, –5.0.

IR (Diamond-ATR, neat) ν_{max}: 2956, 2929, 2885, 2856, 1513, 1472, 1463, 1248, 1082, 1035, 832, 773 cm^{-1}.

$[\alpha]^{22}_{D}$ = - 17.7° (*c* = 0.57, $CHCl_3$).

HRMS (ESI) calcd for $C_{31}H_{56}O_5Si_2$ $[M+NH_4]^+$: 582.4010; found: 582.4009.



9 **S6**

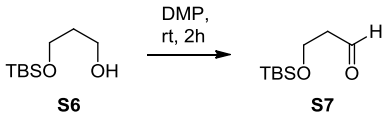
3-((*tert*-butyldimethylsilyl)oxy)propan-1-ol (S6)

6.7 g (100 mmol, 1.0 eq., 60% dispersion in mineral oil) NaH was dissolved in THF (50 mL) and 7.6 g (100 mmol, 1.0 eq.) 1,3-propanediol (**9**) in THF (20 mL) was added dropwise at rt. The reaction mixture was stirred for 45 min and 15.7 g (100 mmol, 1.0 eq.) TBSCl in THF (50 mL) was added dropwise. After 3 h, the reaction was quenched with sat. aq. $NaHCO_3$ (150 mL). The reaction mixture was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography

(hexanes:EtOAc = 4:1) to yield 17.6 g (93 mmol, 93%) of the desired product **S6** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 2:1), R_f = 0.60 (CAM).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.86–3.78 (m, 4H), 1.78 (dt, *J*=5.6, 11.1 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H).



S6 **S7**

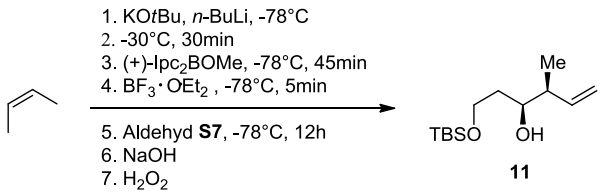
3-((*tert*-butyldimethylsilyl)oxy)propanal (S7)

11.0 g (57.9 mmol, 1.0 eq.) TBS-alcohol **S6** was dissolved in CH_2Cl_2 (500 mL) and 31.8 g (75.0 mmol, 1.3 eq.) Dess-Martin periodinane was added portion wise at rt. The reaction mixture was stirred for 2 h at rt before it was quenched with sat. aq. $NaHCO_3/Na_2S_2O_3/H_2O$ 1:1:1 (500 mL) and stirred further for 1 h. The reaction mixture was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The obtained crude product was purified by flash column chromatography (hexanes:Et_2O = 6:1) to yield 9.9 g (52.7 mmol, 91%) aldehyde **S7** as a colorless liquid (one spot on TLC).*

**Product is volatile.*

TLC (hexanes:EtOAc = 3:1), R_f = 0.74 (CAM).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 9.78 (t, *J*=2.1 Hz, 1H), 3.97 (t, *J*=6.0 Hz, 2H), 2.58 (td, *J*=2.1, 6.0 Hz, 2H), 0.86 (s, 9H), 0.05 (s, 6H).



11

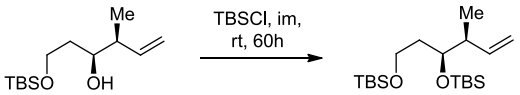
Alcohol 11

In a flame dried flask equipped with a mechanical stirrer 4.17 g (74.4 mmol, 2.0 eq.) *cis*-butene was condensed at −78 °C. 4.17 g (37.2 mmol, 1.0 eq.) KO*t*Bu and THF (10 mL) were added and the solution was treated dropwise with 15.5 mL (37.2 mmol, 1.0 eq., 2.4 M

solution in hexanes) *n*-BuLi. The reaction mixture was warmed to −30 °C for 30 min, recooled to −78 °C and 14.11 g (44.6 mmol, 1.2 eq.) (+)-Ipc_2BOMe in THF (20 mL) was added. The viscous solution was stirred 45 min at −78 °C, treated with 5.26 g (37.2 mmol, 1.0 eq.) $BF_3 \cdot Et_2O$ and after 5 min with 7.00 g (37.2 mmol, 1.0 eq.) aldehyde **S7** in THF (10 mL). After stirring for 12 h at −78 °C, the reaction mixture was quenched carefully with 3 N aq. NaOH (36 mL) and 50% aq. H_2O_2 solution (20 mL), allowed to warm to rt and stirred for 12 h. The reaction mixture was extracted with Et_2O (3 × 150 mL) and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 19:1) to yield 4.24 g (17.4 mmol, 47%) alcohol **11** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 4:1), R_f = 0.72 (CAM).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 5.78 (ddd, *J*=7.7, 10.5, 17.3 Hz, 1H), 5.07–4.96 (m, 2H), 4.04–3.59 (m, 3H), 2.38–2.12 (m, 1H), 1.75–1.49 (m, 2H), 1.05 (d, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).



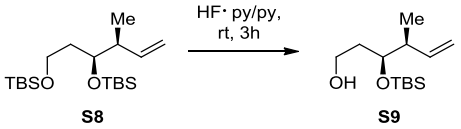
11 **S8**

Alkene S8

2.81 g (41.3 mmol, 2.4 eq.) imidazole was dissolved in CH_2Cl_2 (12 mL) and treated with 4.20 g (17.2 mmol, 1.0 eq.) alcohol **10** in CH_2Cl_2 (5 mL). 3.10 g (20.6 mmol, 1.2 eq.) TBSCl was added in one portion and the reaction mixture was stirred for 60 h at rt, filtered through Celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 29:1) to yield 5.54 g (15.5 mmol, 90%) product **S8** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 10:1), R_f = 0.49 (CAM).

^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 6.00–5.81 (m, 1H), 5.05–4.94 (m, 2H), 3.77–3.57 (m, 3H), 2.38–2.22 (m, 1H), 1.67–1.48 (m, 2H), 0.96 (d, *J*=6.9 Hz, 3H), 0.89 (s, 18H), 0.04 (m, 12H).



S8 **S9**

Primary alcohol S9

HF·pyridine (18 mL) was cooled to 0 °C in a plastic vessel, diluted with THF (150 mL) and carefully treated with pyridine (72 mL). 5.7 g (15.9 mmol, 1 eq.) protected alcohol **S8** in THF (60 mL) was added dropwise to the HF-solution and the reaction mixture was stirred for 3 h at rt before it was quenched with sat. aq. $NaHCO_3$ (200 mL) and solid $NaHCO_3$ (20 g). After extraction with Et_2O (4 × 150 mL) the combined organic layers were washed with sat. aq. $CuSO_4$ (6 × 150 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 3.85 g (15.8 mmol, 99%) product **S9** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 3:1), R_f = 0.53 (CAM).

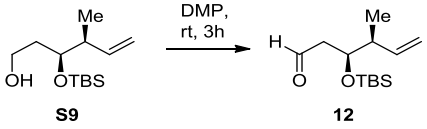
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.87 (ddd, *J*=6.9, 9.8, 18.0 Hz, 1H), 5.08–5.00 (m, 2H), 3.85–3.66 (m, 3H), 2.50–2.35 (m, 1H), 2.20 (br s, 1H), 1.77–1.62 (m, 2H), 1.00 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 140.3, 114.6, 74.7, 60.1, 42.8, 35.0, 25.9, 18.0, 15.7, –4.4, –4.6.

IR (Diamond-ATR, neat) ν_{max}: 3330, 2930, 1253, 1060, 1005, 912, 834, 773, 666 cm^{-1}.

$[\alpha]^{20}_D$ = – 33.0° (*c* = 0.48, $CHCl_3$).

HRMS (ESI) calcd for $C_{13}H_{29}O_2Si_1$ $[M+H]^+$: 245.1931; found: 245.1931.



S9 **12**

Aldehyde 12

570 mg (2.33 mmol, 1.0 eq.) alcohol **S9** was dissolved in CH_2Cl_2 (25 mL) and 1.98 g (4.67 mmol, 2.0 eq.) Dess-Martin periodinane was added in one portion. The reaction mixture was stirred for 3 h at rt, quenched with sat. aq. $NaHCO_3/Na_2S_2O_3/H_2O$ 1:1:1 (200 mL) and stirred further for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 49:1) to yield 495 mg (2.04 mmol, 88%) aldehyde **12** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 5:1), R_f = 0.72 (CAM).

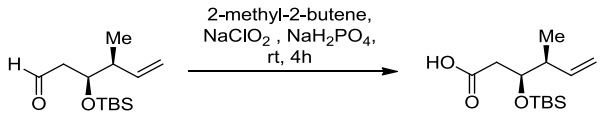
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 9.80 (t, *J*=2.4 Hz, 1H), 5.82 (ddd, *J*=6.9, 10.4, 17.3 Hz, 1H), 5.09–5.07 (m, 1H), 5.03 (ddd, *J*=1.6, 17.2 Hz, 1H), 4.11–4.05 (m, 1H), 2.58–2.33 (m, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 202.2, 139.7, 115.5, 71.7, 48.1, 43.8, 25.8, 18.0, 15.4, −4.4, −4.6.

IR (Diamond-ATR, neat) ν_{max}: 2957, 2930, 2858, 1726, 1253, 1089, 834, 774 cm^{-1}.

$[\alpha]^{20}_D$ = – 34.3° (*c* = 0.46, $CHCl_3$).

HRMS (ES) calcd for $C_{13}H_{26}O_2Si$ $[M]^+$: 242.1702; found: 242.1694.



12 **S10**

Carboxylic acid S10

1.20 g (4.94 mmol, 1.0 eq.) aldehyde **12** was dissolved in 72 mL *t*BuOH/H_2O (1:1) and 2-methyl-2-butene (5.3 mL) was added. To the biphasic solution 5.93 g (49.4 mmol, 10.0 eq.) NaH_2PO_4 and 4.47 g (49.4 mmol, 10.0 eq.) $NaClO_2$ were added and the reaction mixture was stirred for 4 h at rt under exclusion of light. The reaction was quenched with solid NH_4Cl (15 g) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 9:1 → 3:1) to yield 1.21 g (4.69 mmol, 95%) carboxylic acid **S10** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 3:1), R_f = 0.38 (CAM).

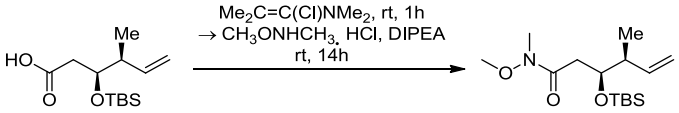
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.93–5.81 (m, 1H), 5.10–5.04 (m, 2H), 4.07 (dt, *J*=5.0, 6.8 Hz, 1H), 2.55–2.36 (m, 3H), 1.03 (d, *J*=6.9 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 177.8, 139.7, 115.3, 72.8, 43.3, 39.3, 25.8, 18.0, 14.9, −4.5, −4.8.

IR (Diamond-ATR, neat) ν_{max}: 2957, 2930, 2888, 2858, 1710, 1253, 1083, 830, 774 cm^{-1}.

$[\alpha]^{20}_D$ = – 32.6° (*c* = 0.48, $CHCl_3$).

HRMS (ESI) calcd for $C_{13}H_{25}O_3Si_1$ $[M-H]^-$: 257.1578; found: 257.1577.



S10 **S11**

Weinreb amide S11

100 mg (0.388 mmol, 1.0 eq.) acid **S10** in CH_2Cl_2 (10 mL) was treated dropwise with the 78 mg (0.582 mmol, 1.5 eq.) 1-chloro-N,N,2-trimethylprop-1-en-1-amine (Ghosez-reagent). After stirring for 1 h at rt, 42 mg (0.427 mmol, 1.1 eq.) *N*,*O*-dimethylhydroxylamine·HCl was added to the reaction mixture. The reaction mixture was cooled to 0 °C and treated dropwise with 110 mg (0.854 mmol, 2.2 eq.) DIPEA. The reaction was allowed to warm to rt and stirred 14 h before it was diluted with 1 N aq. HCl (10 mL). The resulting layers were separated and the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 9:1 → 5:1) to yield 78 mg (0.259 mmol, 67%) Weinreb amide **S11** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 4:1), R_f = 0.43 (CAM).

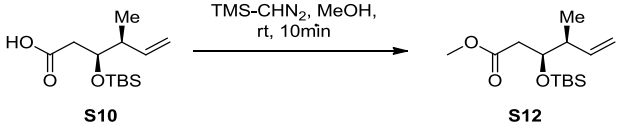
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.96–5.85 (m, 1H), 5.04–4.98 (m, 2H), 4.20 (dt, *J*=4.4, 8.4 Hz, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 2.68–2.60 (m, 1H), 2.40–2.30 (m, 2H), 0.99 (d, *J*=6.9 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H).

^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 172.7, 140.5, 114.5, 72.7, 61.3, 43.5, 37.6, 36.3, 25.9, 18.1, 14.5, −4.6, −4.8.

IR (Diamond-ATR, neat) ν_{max}: 2957, 2930, 2857, 1664, 1385, 1075, 1004, 829, 775 cm^{-1}.

$[\alpha]^{20}_D$ = – 65.8° (*c* = 0.46, $CHCl_3$).

HRMS (ESI) calcd for $C_{15}H_{32}N_1O_3Si_1$ $[M+H]^+$: 302.2146; found: 302.2145.



S10 **S12**

Methy ester S12

1.24 g (4.8 mmol, 1.0 eq.) acid **S10** in MeOH (11 mL) and benzene (36 mL) was treated with 3.6 mL (7.2 mmol, 1.5 eq., 2 M solution in hexanes) TMS-CHN_2. After 10 min the reaction mixture was concentrated *in vacuo* and the crude product was purified by flash column

chromatography (hexanes:EtOAc = 49:1) to yield 1.12 g (4.1 mmol, 96%) methyl ester **S12** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1), R_f = 0.81 (CAM).

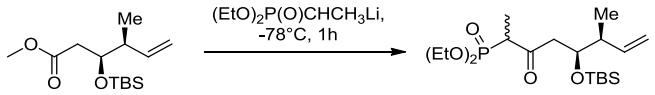
^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 5.86 (ddd, *J*=6.7, 10.8, 17.0 Hz, 1H), 5.07–4.99 (m, 2H), 4.08 (dt, *J*=4.9, 7.4 Hz, 1H), 3.66 (s, 3H), 2.45–2.33 (m, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H).

^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 172.6, 140.0, 114.9, 73.0, 51.5, 43.3, 39.4, 25.8, 18.0, 14.7, −4.5, −4.8.

IR (Diamond-ATR, neat) ν_{max}: 2955, 2930, 2858, 1741, 1251, 1172, 1081, 830, 775 cm^{-1}.

$[\alpha]^{20}_D$ = – 50.8° (*c* = 0.48, $CHCl_3$).

HRMS (EI) calcd for $C_{13}H_{25}O_3Si_1$ $[M-CH_3]^-$: 257.1578; found: 257.1566.



S12 **4**

Phosphonate 4

1.81 g (10.90 mmol, 3.0 eq.) diethyl ethylphosphonate in THF (40 mL) was treated with 4.45 mL (10.90 mmol, 3.0 eq., 2.45 M solution in hexanes) *n*-BuLi dropwise at −78 °C and stirred for 1 h at −78 °C. 990 mg (3.63 mmol. 1.0 eq.) methylester **S12** in THF (30 mL) was added dropwise to the solution and stirred 1 h at −78 °C before it was quenched with sat. aq. NH_4Cl (150 mL). The reaction mixture was extracted with CH_2Cl_2 (4 × 150 mL) and the combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (hexanes:EtOAc = 6:1 → 2:1) to yield 1.20 g (2.95 mmol, 81%) phosphonate **4** as a mixture of diastereomers (two spots on TLC).

TLC (hexanes:EtOAc = 1:1), R_f = 0.41 (CAM).

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 5.93 (ddd, *J*=6.7, 10.7, 17.7 Hz, 1H), 5.82 (ddd, *J*=6.7, 10.7, 17.7 Hz, 1H), 5.09–5.00 (m, 4H), 4.20–4.07 (m, 10H), 3.29–3.10 (m, 2H), 2.88–2.67 (m, 4H), 2.38–2.24 (m, 2H), 1.39–1.27 (m, 18H), 0.97 (d, *J*=6.9 Hz, 6H), 0.88 (s, 9H), 0.86 (s, 9H), 0.09– –0.02 (m, 12H).

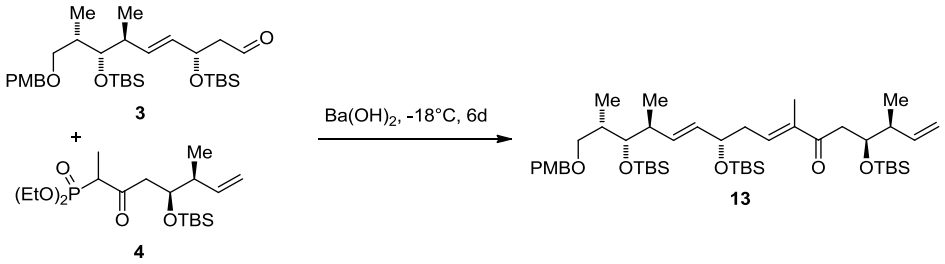
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 204.8, 204.8, 204.2, 204.1, 140.5, 140.0, 114.7, 114.7, 72.2, 71.6, 62.6, 62.5, 62.5, 62.4, 47.9, 47.4, 43.8, 43.0, 25.8, 18.0, 18.0, 16.4, 16.4, 16.3, 16.3, 15.0, 14.4, 10.9, 10.8, 10.6, 10.5, −4.6, −4.6, −4.7.

^{31}P-NMR ($CDCl_3$, 162 MHz) δ: 23.54, 23.50.

IR (Diamond-ATR, neat) ν_{max}: 2931, 1715, 1250, 1049, 1021, 960, 832, 813, 775, 673 cm^{-1}.

$[\alpha]^{20}_D$ = – 55.4° (*c* = 0.50, $CHCl_3$).

HRMS (ESI) calcd for $C_{19}H_{39}Na_1O_5P_1Si_1$ $[M+Na]^+$: 429.2197; found: 429.2196.



Alkene 13

4.04 g (12.82 mmol, 2.4 eq.) $Ba(OH)_2 \cdot 8H_2O$ was dried on *high vacuo* at 130 °C for 4 h. The salt was cooled to rt and 2.60 g (6.41 mmol, 1.2 eq.) phosphonate **4** in THF (90 mL) was added and the reaction mixture was stirred for 1 h at rt. The reaction mixture was cooled to 0 °C and crude aldehyde **3** (100% yield assumed from glycol cleavage, 5.34 mmol) dissolved in THF (56 mL) and H_2O (3 mL) was added and stirred for 2 min at 0 °C before placing the reaction flask in the freezer for 6 d. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with sat. aq. $NaHCO_3$ (150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (hexanes/EtOAc = 49:1 → 29:1) to yield 2.42 g (2.96 mmol, 55% over 3 steps) of alkene **13** as a colorless oil (one spot on TLC).

TLC (hexanes:EtOAc = 9:1): R_f = 0.45 (CAM).

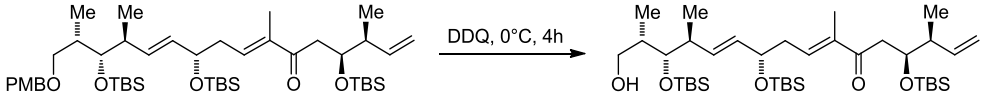
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.24–7.23 (m, 2H), 6.88–6.86 (m, 2H), 6.67 (td, *J*=0.9, 7.1 Hz, 1H), 5.90 (ddd, *J*=6.6, 10.7, 17.2 Hz, 1H), 5.66 (dd, *J*=7.9, 15.6 Hz, 1H), 5.39 (dd, *J*=6.3, 15.5 Hz, 1H), 5.03–4.99 (m, 2H), 4.38 (dd, *J*=11.6, 26.2 Hz, 2H), 4.24–4.22 (m, 1H), 4.18 (q, *J*=6.1 Hz, 1H), 3.80 (s, 3H), 3.65 (t, *J*=3.8 Hz, 1H), 3.34 (dd, *J*=6.3, 9.0 Hz, 1H), 3.21 (dd, *J*=6.6, 9.0 Hz, 1H), 2.85 (dd, *J*=7.7, 15.8 Hz, 1H), 2.52 (dd, *J*=4.1, 15.8 Hz, 1H), 2.39 (t, *J*=6.7 Hz, 2H), 2.32 (ddd, *J*=4.1, 7.4, 11.1 Hz, 2H), 1.89 (ddd, *J*=3.9, 6.7, 13.3 Hz, 1H), 1.74 (s, 3H), 0.98 (t, *J*=6.8 Hz, 6H), 0.91–0.90 (m, 12H), 0.89 (s, 9H), 0.83 (s, 9H), 0.06 (s, 3H), 0.04 (s, 6H), 0.02 (s, 6H), –0.07 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 200.5, 159.1, 140.6, 139.5, 138.9, 133.4, 132.3, 130.8, 129.1, 114.4, 113.7, 76.0, 73.3, 72.7, 72.6, 72.6, 55.3, 43.6, 41.5, 41.3, 38.3, 37.6, 26.1, 25.9, 25.9, 18.4, 18.1, 18.1, 14.5, 13.0, 11.6, -3.8, –4.1, –4.2, –4.6, –4.7, –4.8.

IR (Diamond-ATR, neat) ν_{max}: 2955, 2928, 2856, 2895, 1669, 1513, 1472, 1462, 1249, 1078, 1038, 830, 774 cm^{-1}.

$[\alpha]^{22}_{D}$ = - 25.1° (*c* = 0.34, $CHCl_3$).

HRMS (ESI) calc'd for $C_{46}H_{84}O_6Si_3$ $[M+NH_4]^+$: 834.5919; found: 834.5927



13 **S13**

Alcohol S13

A solution of 20 mg (24.8 µmol, 1.0 eq.) PMB-ether **13** in CH_2Cl_2 (0.8 mL) and H_2O (0.2 mL) was cooled to 0 °C and 7 mg (0.030 mmol, 1.2 eq.) DDQ was added in one portion and the reaction mixture was stirred for 4h at 0 °C. Sat. aq. $NaHCO_3$ (3 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash column chromatography (hexanes/EtOAc 19:1 → 14:1). To remove the PMB-aldehyde the product was put on *high vacuo* to yield 16 mg (0.0230 mmol, 93%) of deprotected alcohol **S13**.

TLC (hexanes:EtOAc = 9:1): R_f = 0.15 (CAM).

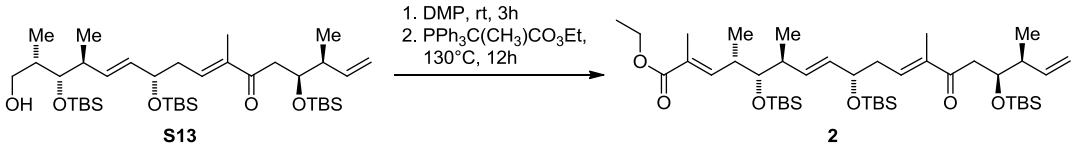
^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 6.66 (td, *J*=1.2, 7.1 Hz, 1H), 5.90 (ddd, *J*=6.6, 10.8, 17.2 Hz, 1H), 5.73 (ddd, *J*=0.9, 7.9, 15.6 Hz, 1H), 5.45 (ddd, *J*=0.8, 6.3, 15.6 Hz, 1H), 5.03–4.99 (m, 2H), 4.24–4.21 (m, 2H), 3.67 (t, *J*=3.6 Hz, 1H), 3.63–3.59 (m, 1H), 3.46–3.42 (m, 1H), 2.84 (dd, *J*=7.6, 15.9 Hz, 1H), 2.54 (dd, *J*=4.1, 15.9 Hz, 1H), 2.42 (m, 3H), 2.35–2.30 (m, 1H), 1.89–1.79 (m, 1H), 1.76 (s, 3H), 1.02 (d, *J*=7.0 Hz, 3H), 0.98 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 3H), 0.83 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), –0.06 (s, 3H).

^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 200.6, 140.6, 139.2, 138.9, 133.2, 132.5, 114.5, 72.7, 72.4, 65.8, 43.6, 41.4, 40.5, 39.9, 38.2, 26.0, 25.9, 25.8, 18.6, 18.3, 18.1, 18.1, 14.6, 12.9, 11.7, –4.1, –4.2, –4.3, –4.6, –4.7, –4.8.

IR (Diamond-ATR, neat) ν_{max}: 3460, 2955, 2928, 2886, 2856, 1666, 1472, 1462, 1251, 1074, 1031, 834, 769 cm^{-1}.

$[\alpha]^{22}_{D}$ = - 108.2° (*c* = 0.77, $CHCl_3$).

HRMS (ESI) calcd for $C_{38}H_{76}O_5Si_3$ $[M+Na]^+$: 719.4898; found: 719.4911.



S13 **2**

Ethylester 2

A solution of 81 mg (0.116 mmol, 1.0 eq.) alcohol **S13** and 100 mg (0.233 mmol, 2.0 eq.) Dess-Martin-periodinane in CH_2Cl_2 (15 mL) was stirred at rt for 3 h. The reaction mixture was quenched with sat. aq. $NaHCO_3/Na_2S_2O_3/H_2O$ 1:1:1 (20 mL) and stirred further for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was triturated with hexanes (20 mL), filtered and concentrated *in vacuo* to yield 88 mg aldehyde **S14** as a yellowish oil.

88 mg (100% yield assumed from DMP oxidation, 0.112 mmol) crude aldehyde **S14** and 122 mg (0.337 mmol, 3.0 eq.) phosphoranylidene **14** were dissolved in toluene (6 mL) and stirred at 130 °C for 12 h in a pressure tube. The reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (hexanes/EtOAc 49:1) yielded 66 mg (0.085 mmol, 73% over two steps) ester **2**.

TLC (hexanes:EtOAc = 9:1): R_f = 0.50 (CAM).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 6.65 (td, *J*=1.2, 7.0 Hz, 1H), 6.58 (dd, *J*=1.4, 10.3 Hz, 1H), 5.90 (ddd, *J*=6.6, 10.8, 17.2 Hz, 1H), 5.62 (ddd, *J*=0.8, 8.4, 15.5 Hz, 1H), 5.37 (dd, *J*=6.6, 15.5 Hz, 1H), 5.02–4.99 (m, 2H), 4.25–4.16 (m, 4H), 3.43 (dd, *J*=2.4, 7.6 Hz, 1H), 2.83 (dd, *J*=7.6, 15.9 Hz, 1H), 2.66–2.59 (m, 1H), 2.52 (dd, *J*=4.1, 15.8 Hz, 1H), 2.41–2.39 (dd, *J*=4.1, 9.4 Hz, 2H), 2.34–2.29 (dq, *J*=6.8, 13.5 Hz, 1H), 2.25–2.22, (m, 1H), 1.82 (d, *J*=1.4 Hz, 3H), 1.75 (s, 3H), 1.29 (t, *J*=7.1 Hz, 3H), 1.00 (d, *J*=7.0 Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.93 (s, 9H), 0.89 (s, 9H), 0.83 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 6H), 0.04 (s, 3H), –0.07 (s, 3H).

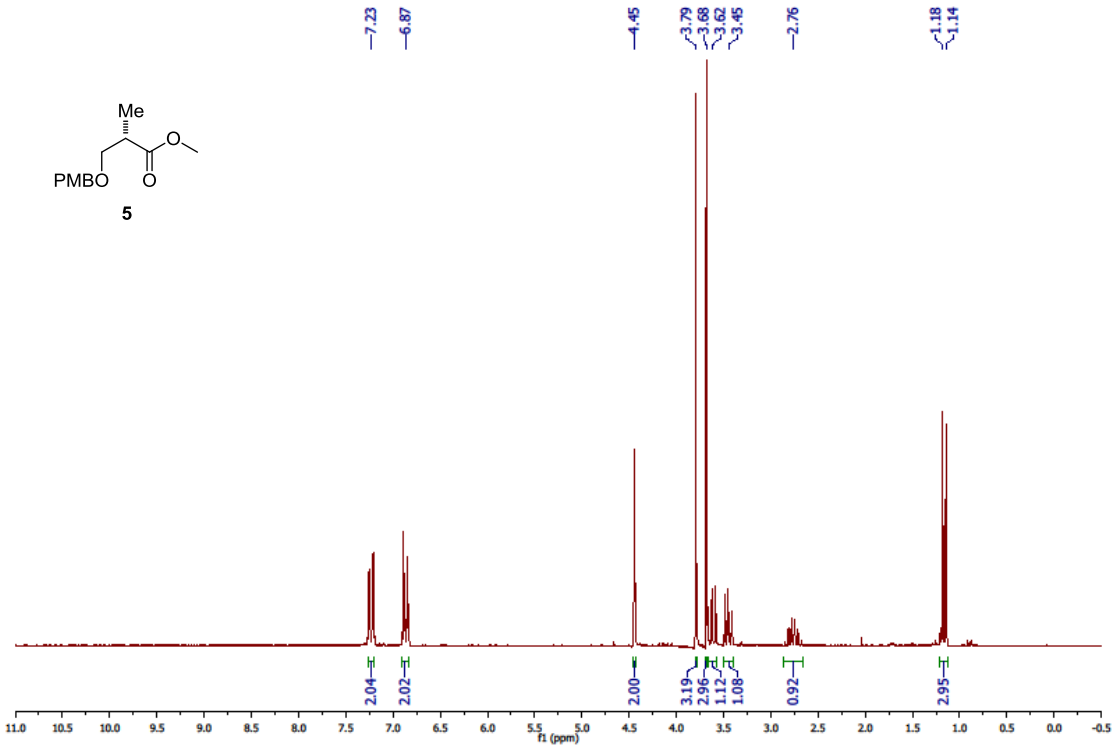
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 200.4, 168.3, 145.2, 140.6, 139.4, 138.9, 133.2, 132.6, 126.5, 114.4, 95.8, 79.7, 72.6, 60.5, 43.5, 41.8, 41.2, 38.3, 38.0, 26.2, 25.9, 25.8, 18.5, 18.4, 18.1, 18.0, 16.6, 14.5, 14.3, 12.8, 11.7, –3.6, –3.8, –4.2, –4.6, –4.7, –4.8.

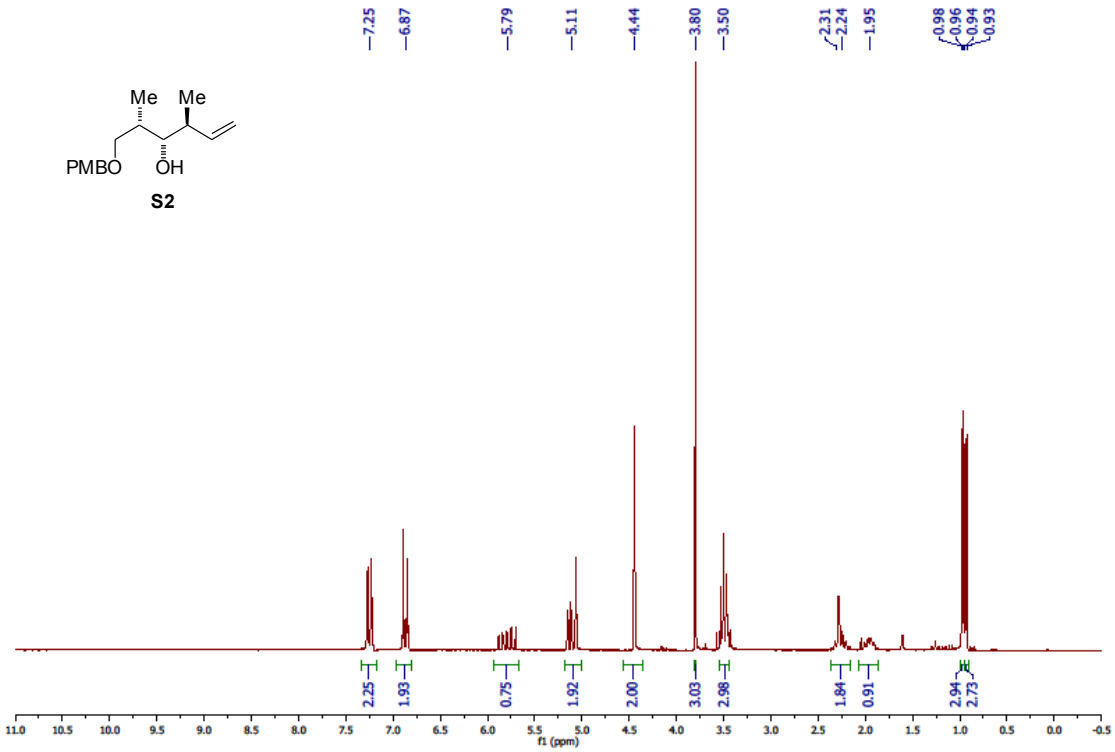
IR (Diamond-ATR, neat) ν_{max}: 2957, 2930, 2886, 2857, 1712, 1671, 1472, 1463, 1388, 1368, 1290, 1250, 1081, 1033, 1005, 833, 773 cm^{-1}.

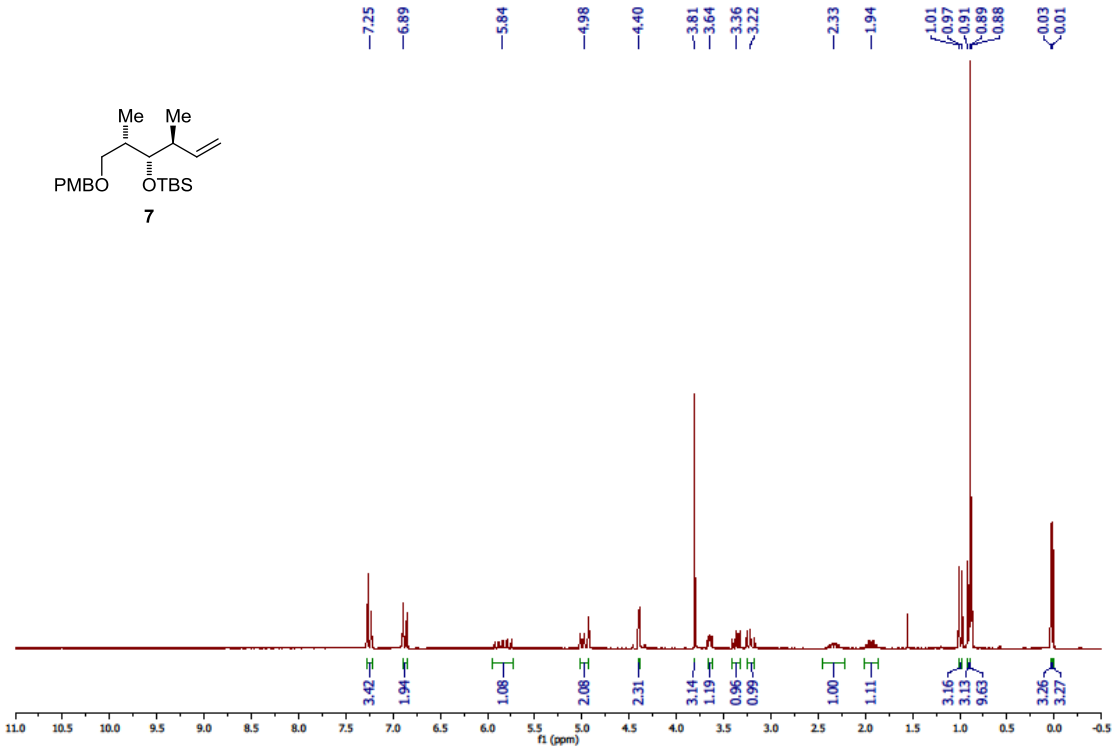
$[\alpha]^{19}_{D}$ = -44.4° (*c* = 0.44, $CHCl_3$).

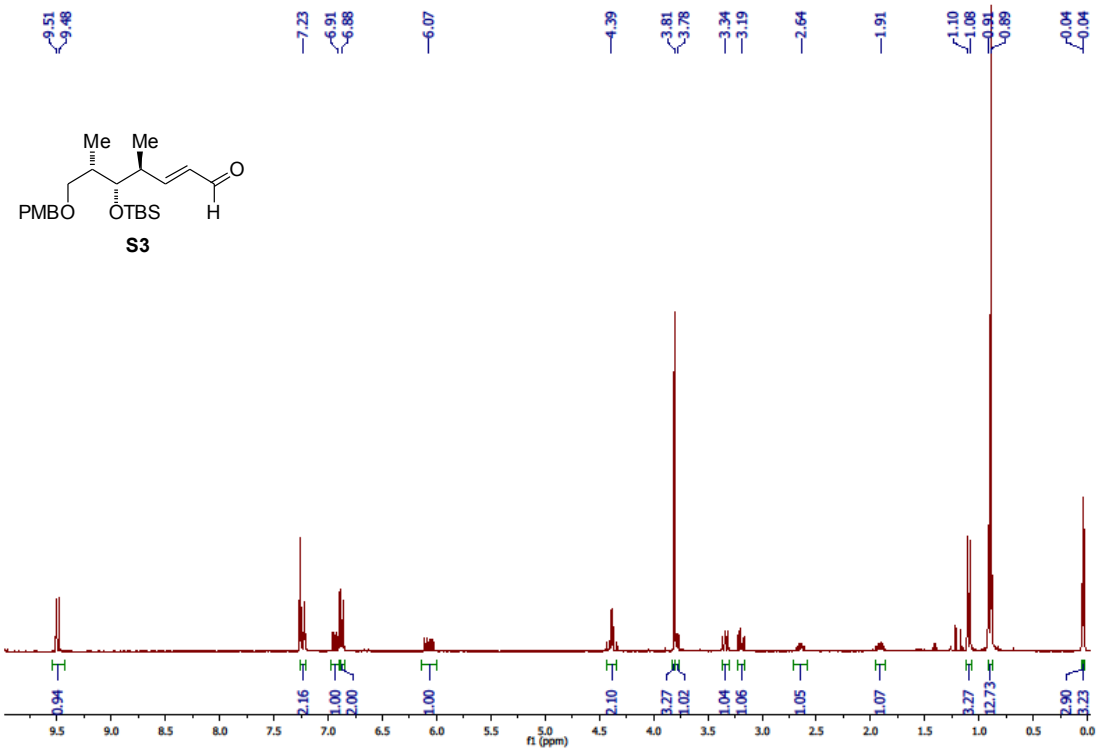
HRMS (ESI) calcd for $C_{43}H_{82}O_6Si_3$ $[M+Na]^+$: 801.5317; found: 801.5311.

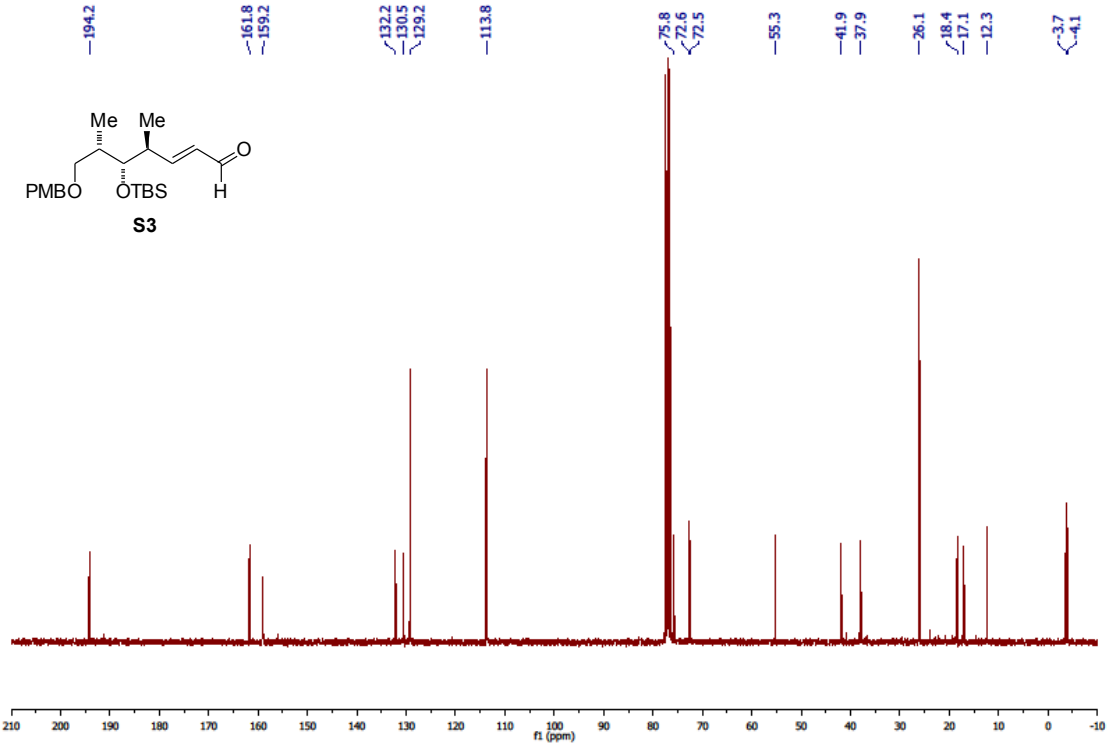
NMR Spectra

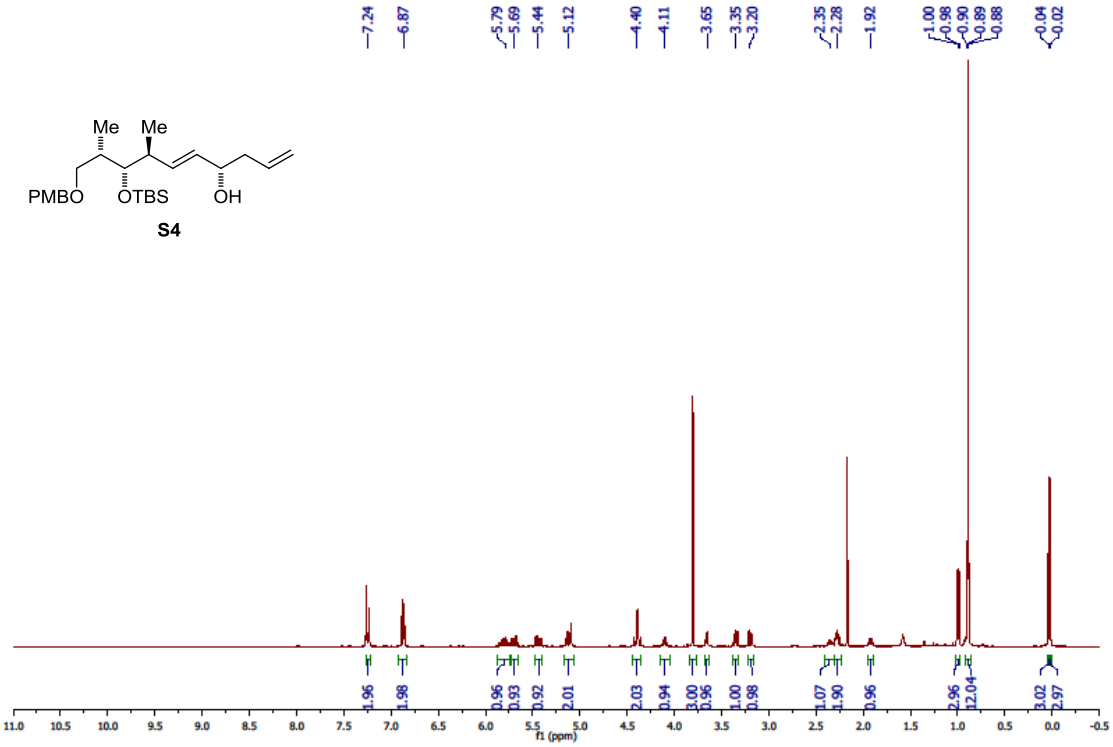

Me
O
PMBO
O
5
7.23
6.87
4.45
3.79
3.68
3.62
3.45
2.76
1.18
1.14
2.04
2.02
2.00
3.19
2.96
1.12
1.08
0.92
2.95
f1 (ppm)

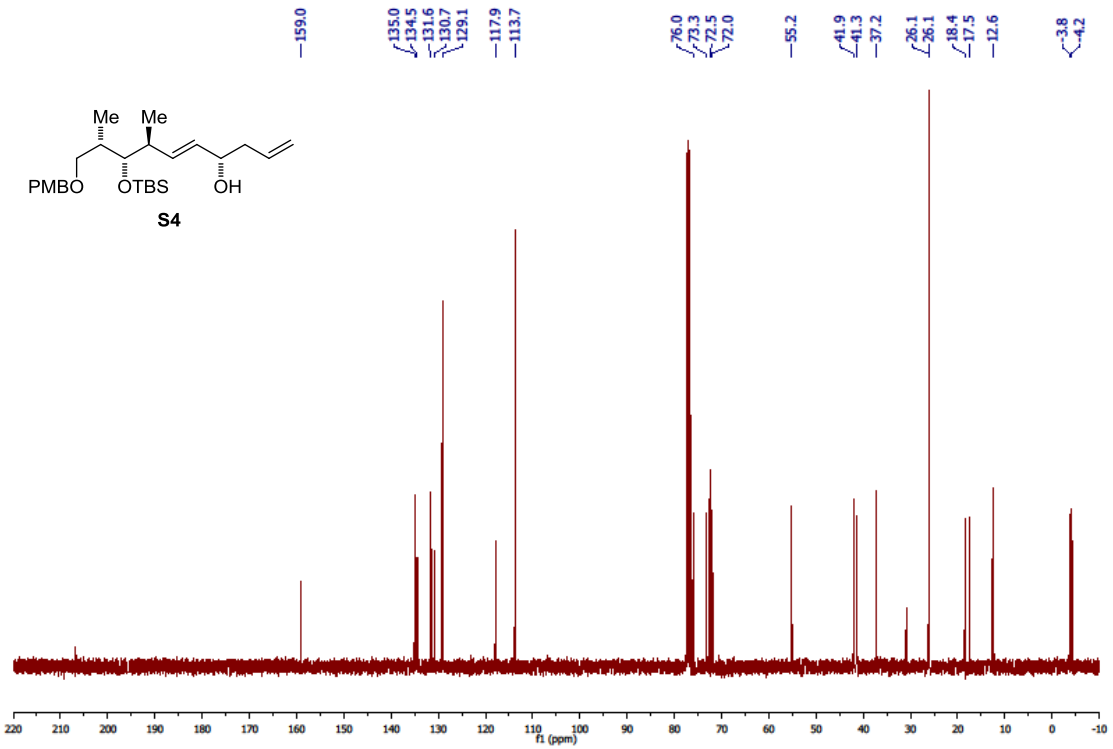

Me
Me
PMBO
OH
S2
7.25
6.87
5.79
5.11
4.44
3.80
3.50
2.31
2.24
1.95
0.98
0.96
0.94
0.93
2.25
1.93
0.75
1.92
2.00
3.03
2.98
1.84
0.91
2.94
2.73
f1 (ppm)

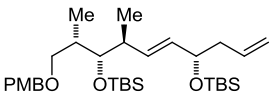

Me
Me
PMBO
OTBS
7
7.25
6.89
5.84
4.98
4.40
3.81
3.64
3.36
3.22
2.33
1.94
1.01
0.97
0.91
0.89
0.88
0.03
0.01
3.42
1.94
1.08
2.08
2.31
3.14
1.19
0.96
0.99
1.00
1.11
3.16
3.13
9.63
3.26
3.27
f1 (ppm)


9.51
9.48
7.23
6.91
6.88
6.07
4.39
3.81
3.78
3.34
3.19
2.64
1.91
1.10
1.08
0.91
0.89
0.04
0.04
Me
Me
O
PMBO
OTBS
H
S3
0.94
2.16
1.00
2.00
1.00
2.10
3.27
1.02
1.04
1.06
1.05
1.07
3.27
12.73
2.90
3.23
f1 (ppm)


194.2
161.8
159.2
132.2
130.5
129.2
113.8
75.8
72.6
72.5
55.3
41.9
37.9
26.1
18.4
17.1
12.3
-3.7
-4.1
Me
Me
O
PMBO
OTBS
H
S3
f1 (ppm)

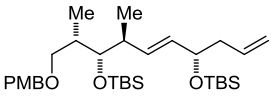

Me
Me
PMBO
OTBS
OH
S4
7.24
6.87
5.79
5.69
5.44
5.12
4.40
4.11
3.65
3.35
3.20
2.35
2.28
1.92
1.00
0.98
0.90
0.89
0.88
0.04
0.02
1.96
1.98
0.96
0.93
0.92
2.01
2.03
0.94
3.00
0.96
1.00
0.98
1.07
1.90
0.96
2.96
12.04
3.02
2.97
f1 (ppm)


Me
Me
PMBO
OTBS
OH
S4
159.0
135.0
134.5
131.6
130.7
129.1
117.9
113.7
76.0
73.3
72.5
72.0
55.2
41.9
41.3
37.2
26.1
26.1
18.4
17.5
12.6
-3.8
-4.2
f1 (ppm)


Me
Me
PMBO
OTBS
OTBS

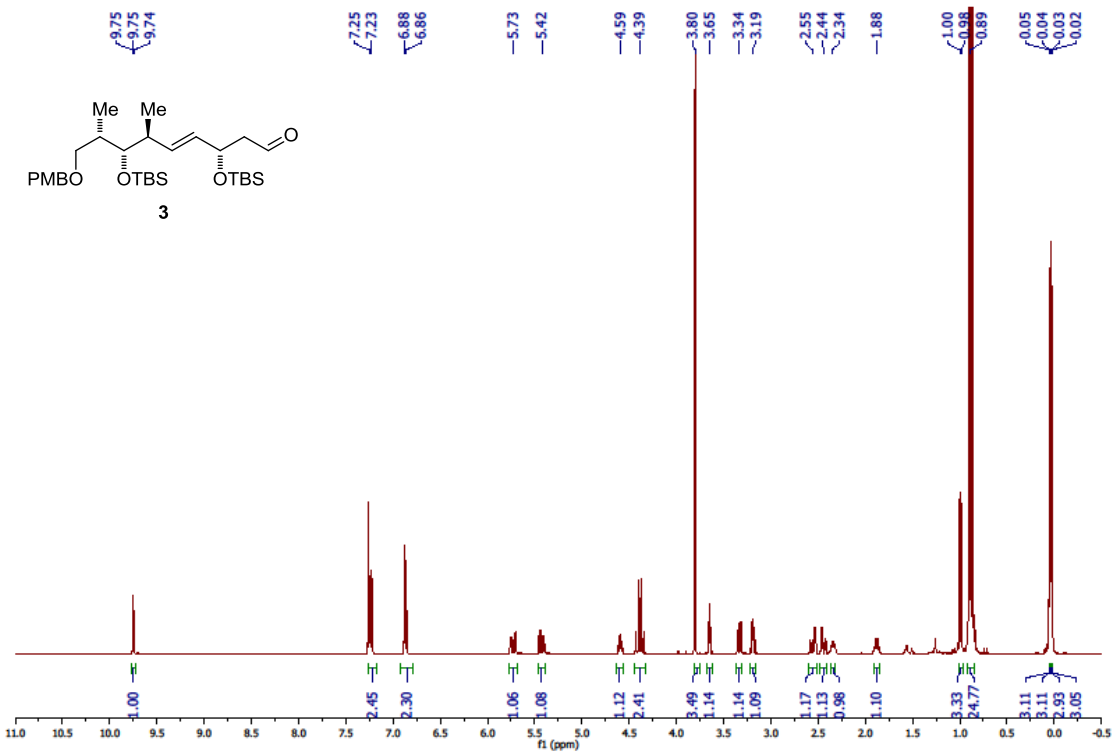
8

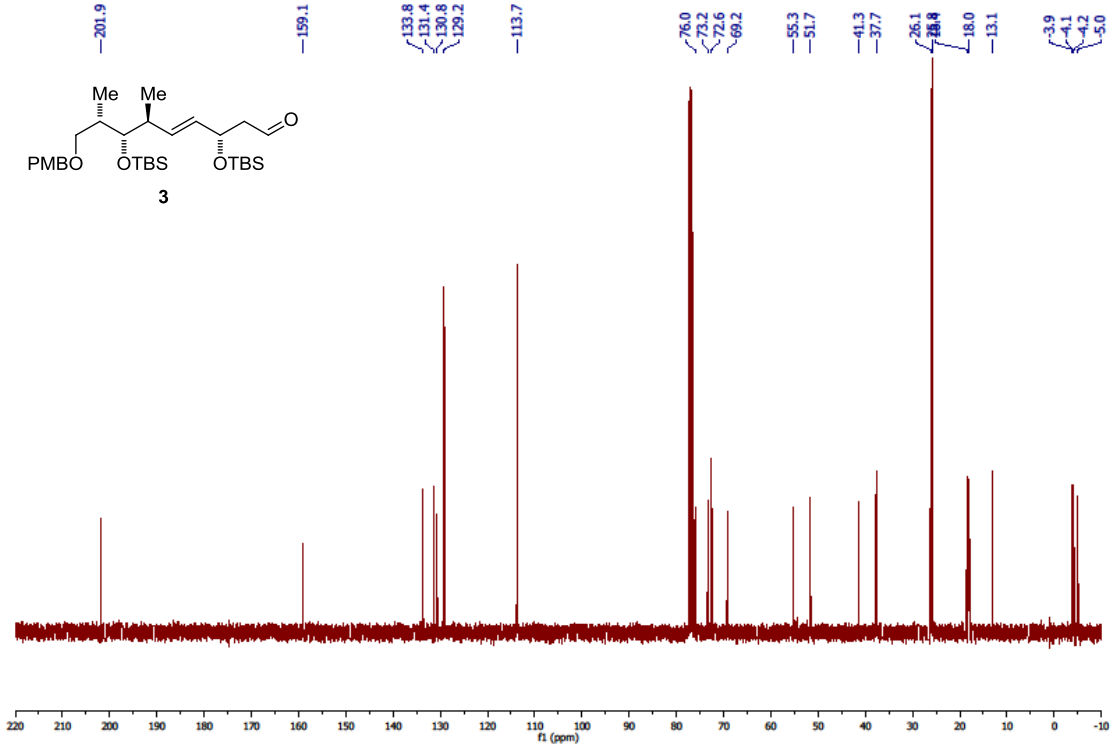
7.26
7.23
6.88
6.86
5.79
5.63
5.38
5.02
4.38
4.08
3.64
3.36
3.21
2.32
2.21
1.91
1.00
0.98
0.90
0.89
0.04
0.04
0.02
0.01
1.96
2.04
1.05
0.97
1.02
2.12
2.25
1.00
3.18
1.01
1.01
0.99
1.01
2.17
1.08
3.04
21.26
2.91
2.93
3.06
3.05
f1 (ppm)

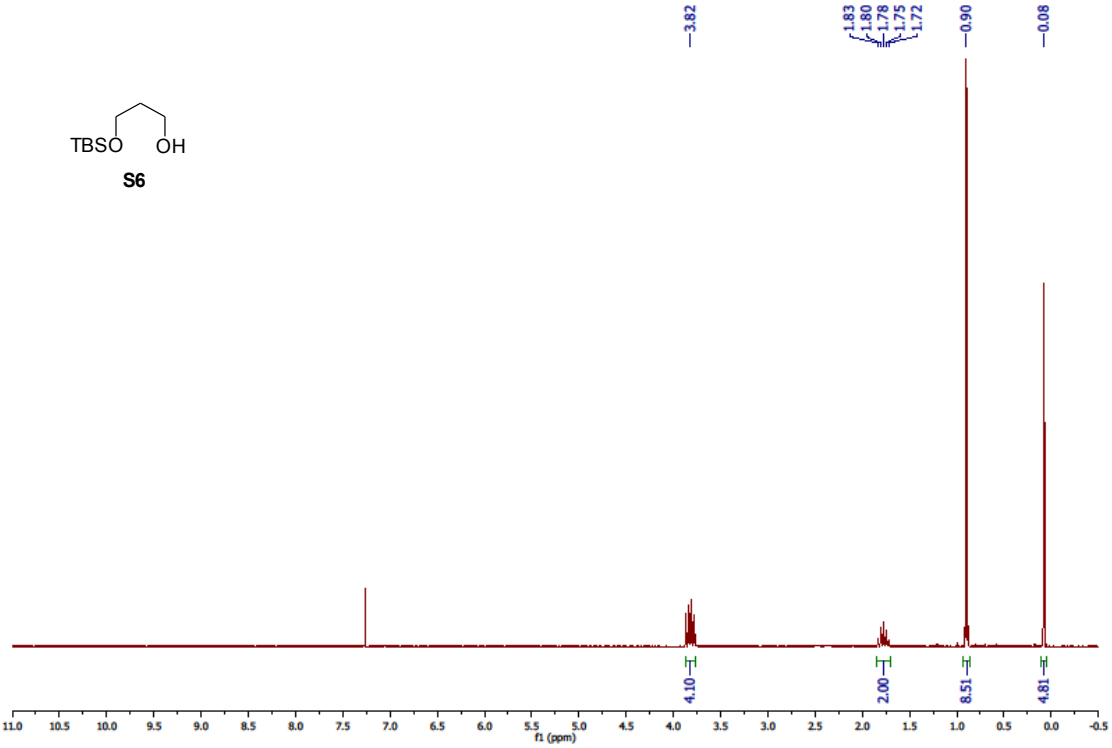

Me
Me
PMBO
OTBS
OTBS

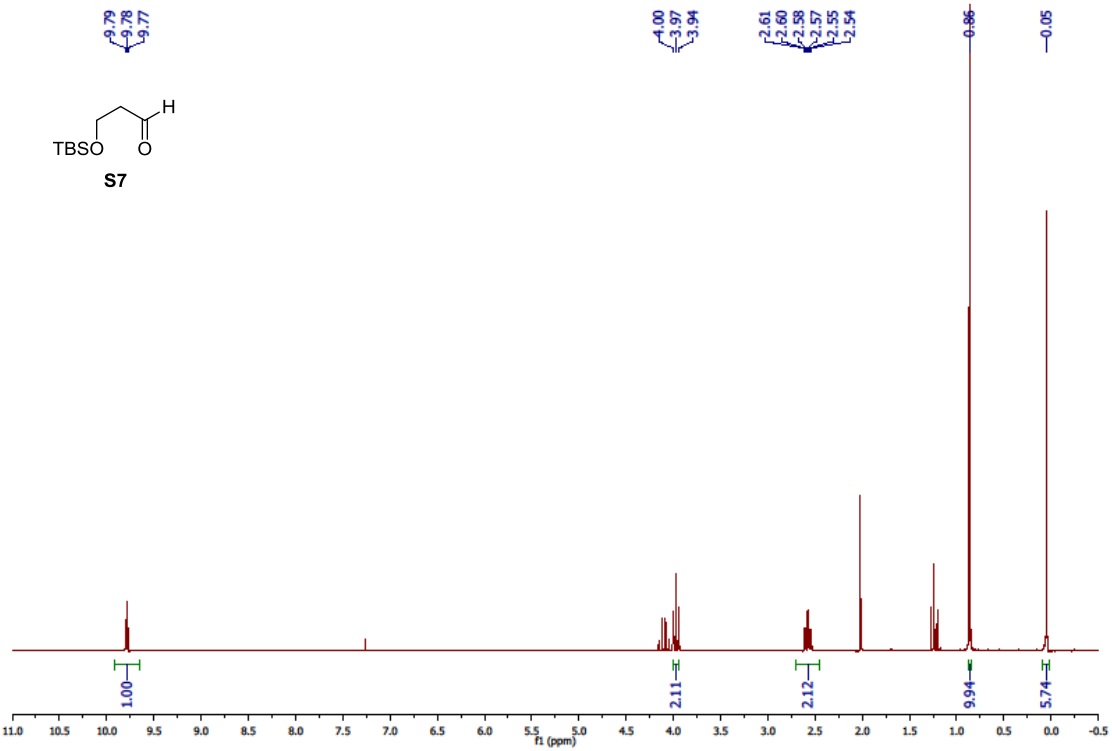
8

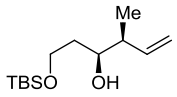
159.0
135.4
132.6
132.5
130.8
129.1
116.5
113.7
76.1
73.3
73.2
72.5
55.2
43.2
41.4
37.5
26.1
18.0
13.2
-3.9
-4.1
-4.3
-4.8
f1 (ppm)


Me
Me
PMBO
OTBS
OTBS
O
3
f1 (ppm)


Me
Me
PMBO
OTBS
OTBS
O
3
f1 (ppm)

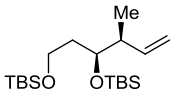

TBSO
OH
S6
3.82
1.83
1.80
1.78
1.75
1.72
0.90
0.08
4.10
2.00
8.51
4.81
f1 (ppm)


TBSO
O
H
S7
9.79
9.78
9.77
4.00
3.97
3.94
2.61
2.60
2.58
2.57
2.55
2.54
0.86
0.05
1.00
2.11
2.12
9.94
5.74
f1 (ppm)


Me
TBSO
OH

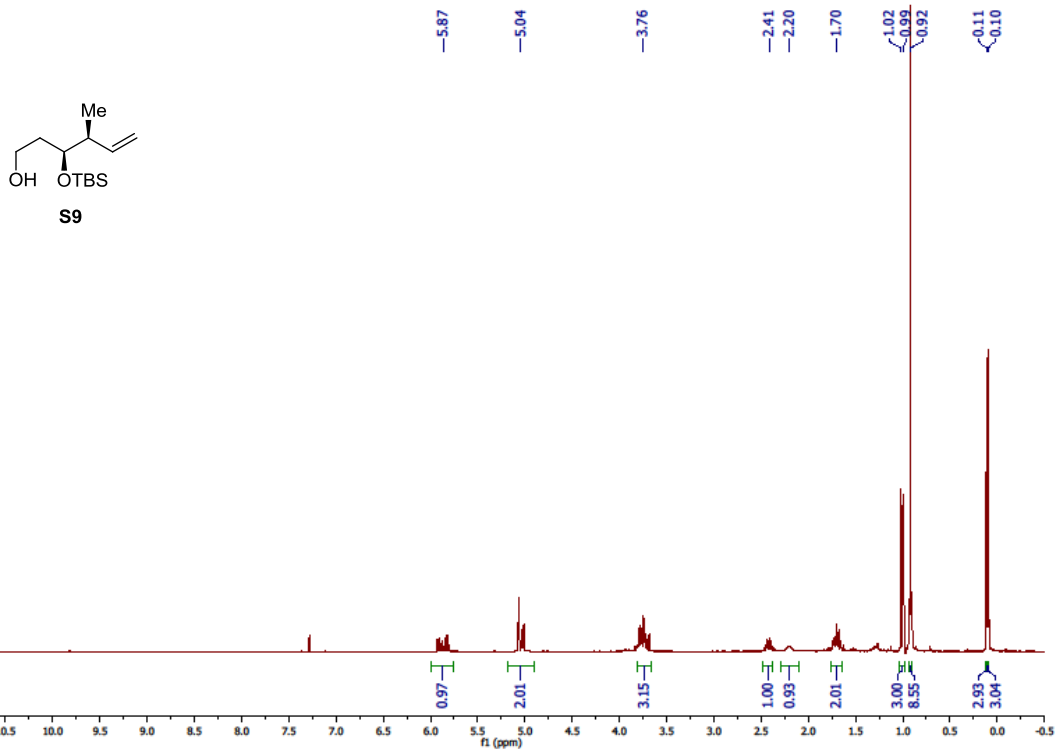
11

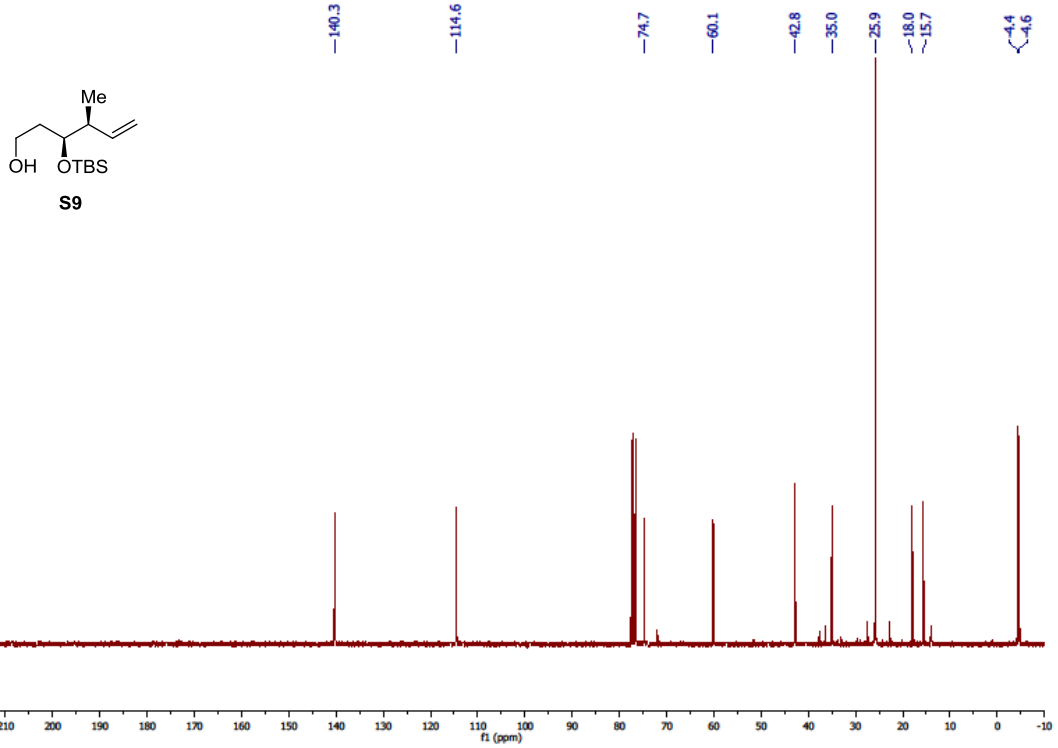
5.78
5.04
3.80
2.24
1.66
1.07
1.04
0.89
0.07
0.92
2.28
3.29
1.00
2.40
3.55
11.68
7.57
f1 (ppm)

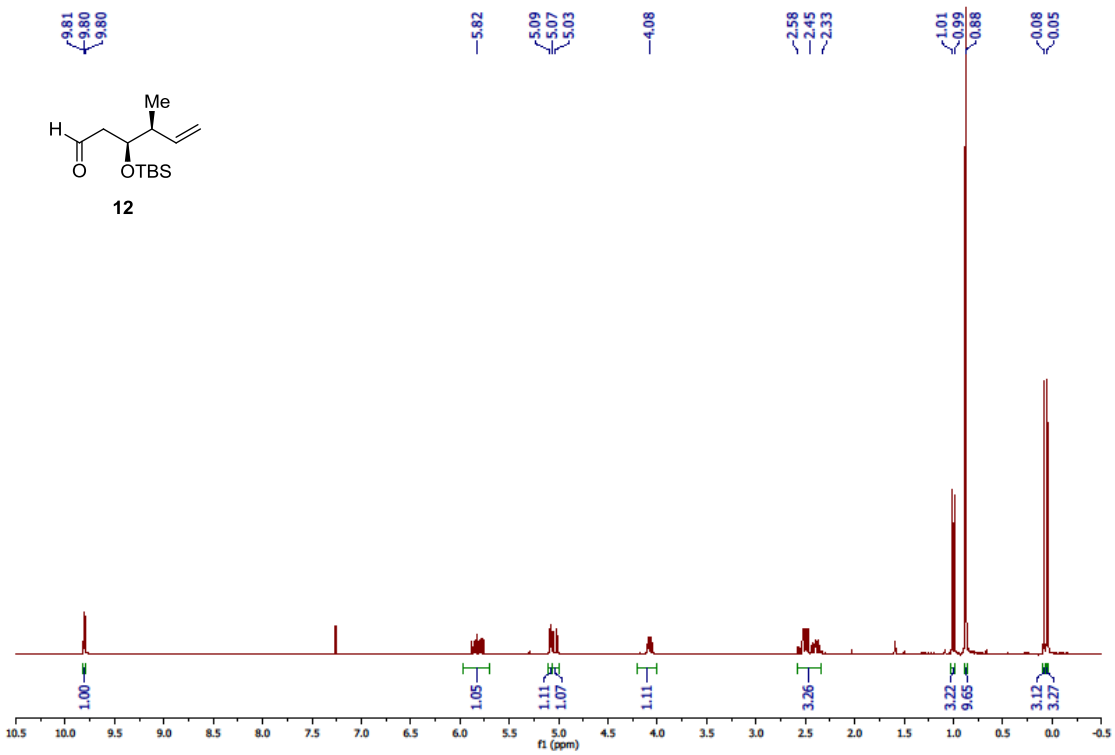

Me
TBSO
OTBS

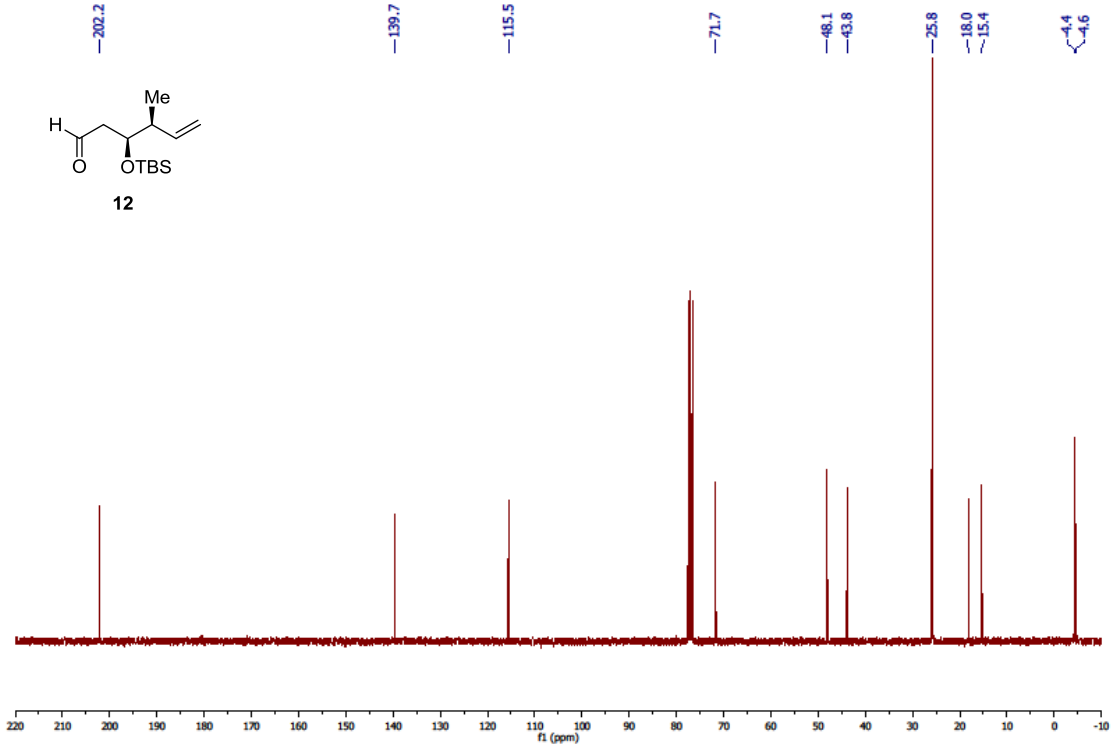
S8

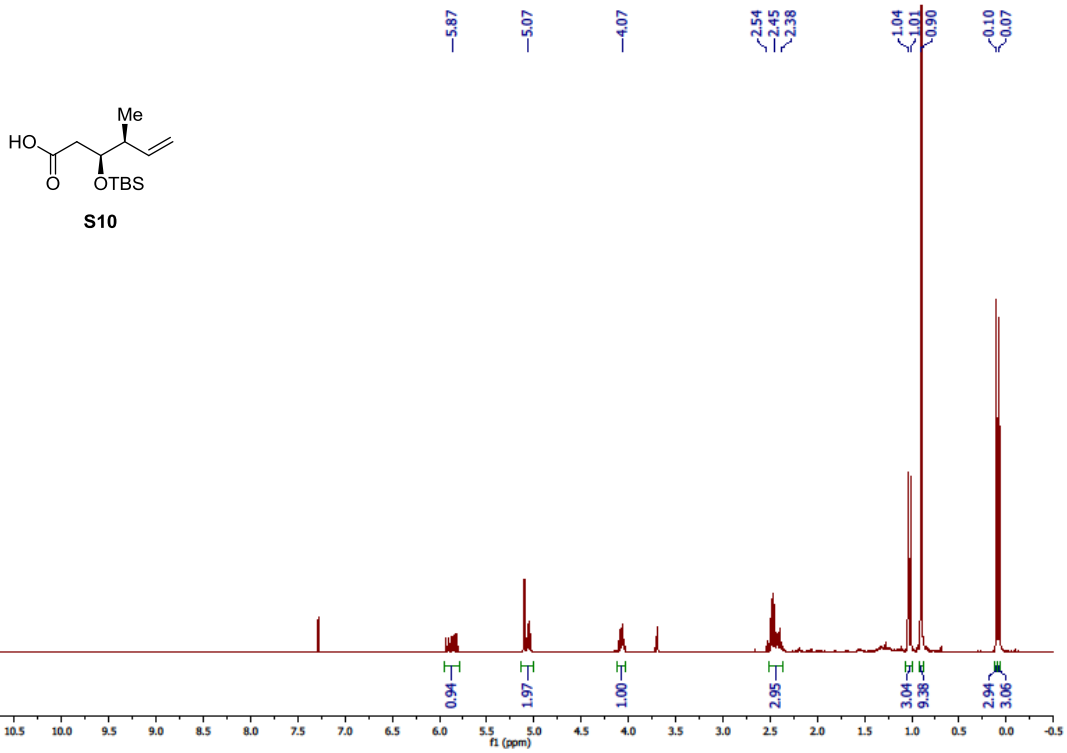
5.90
5.00
3.67
2.30
0.97
0.94
0.89
0.04
0.85
2.00
3.07
0.64
1.74
2.90
18.11
10.40
f1 (ppm)

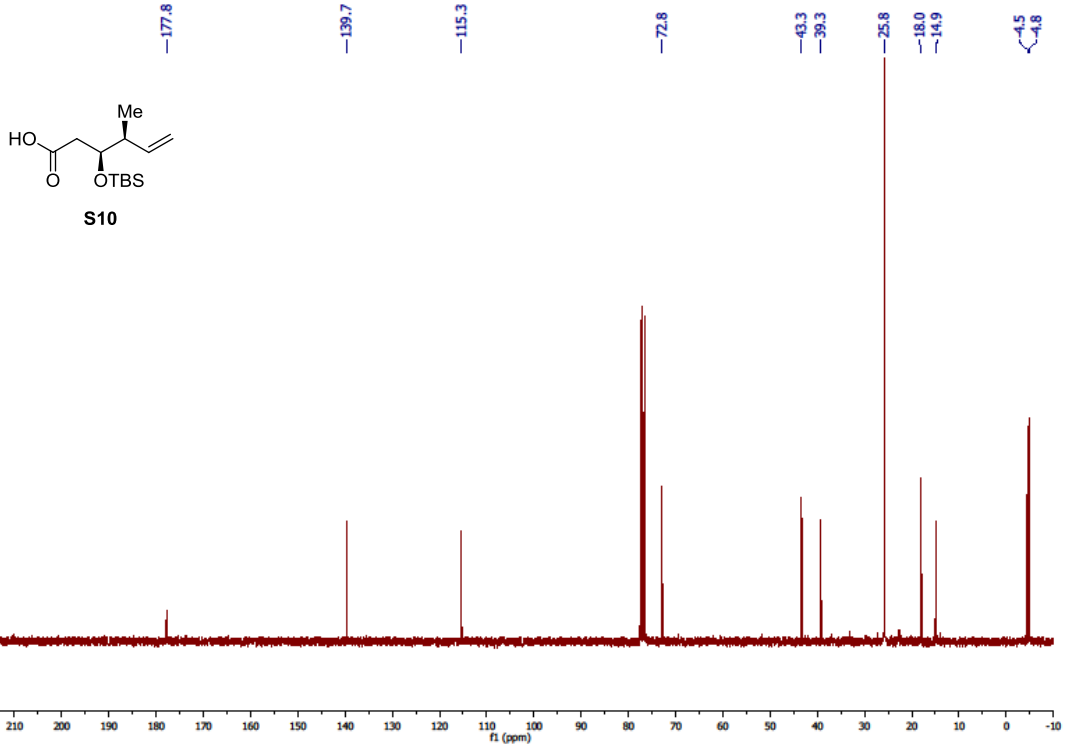

Me
OH
OTBS
S9
5.87
5.04
3.76
2.41
2.20
1.70
1.02
0.99
0.92
0.11
0.10
0.97
2.01
3.15
1.00
0.93
2.01
3.00
8.55
2.93
3.04
f1 (ppm)

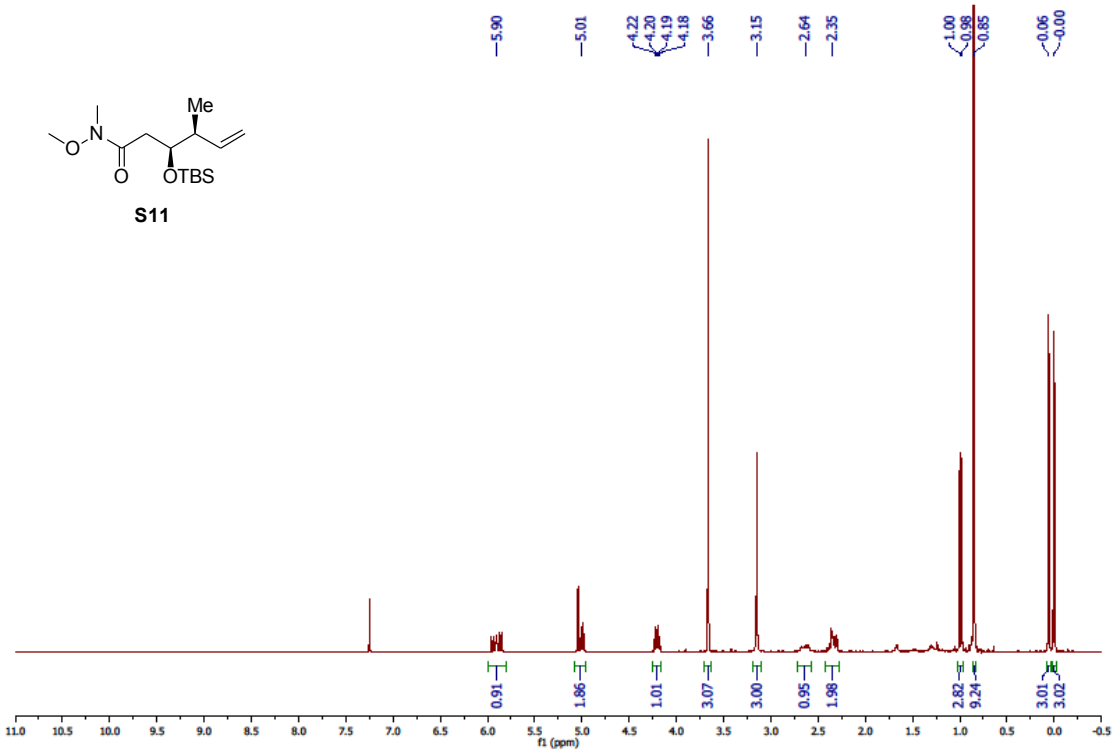

Me
OH
OTBS
S9
140.3
114.6
74.7
60.1
42.8
35.0
25.9
18.0
15.7
-4.4
-4.6
f1 (ppm)

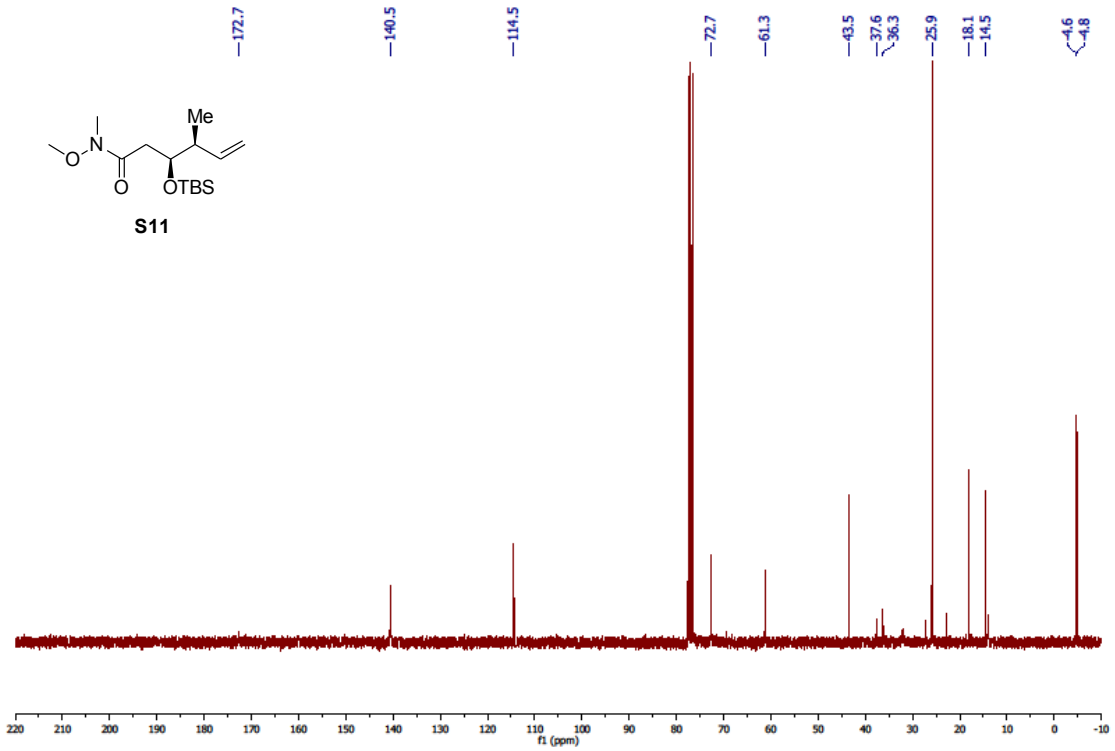

9.81
9.80
9.80
5.82
5.09
5.07
5.03
4.08
2.58
2.45
2.33
1.01
0.99
0.88
0.08
0.05
Me
H
O
OTBS
12
1.00
1.05
1.11
1.07
1.11
3.26
3.22
9.65
3.12
3.27
f1 (ppm)

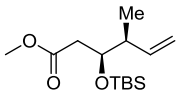

202.2
139.7
115.5
71.7
48.1
43.8
25.8
18.0
15.4
4.4
4.6
Me
H
O
OTBS
12
f1 (ppm)


HO
O
Me
OTBS
S10
5.87
5.07
4.07
2.54
2.45
2.38
1.04
1.01
0.90
0.10
0.07
0.94
1.97
1.00
2.95
3.04
9.38
2.94
3.06
f1 (ppm)


HO
O
Me
OTBS
S10
177.8
139.7
115.3
72.8
43.3
39.3
25.8
18.0
14.9
-4.5
-4.8
f1 (ppm)

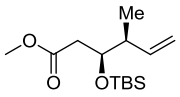

Me
N
O
O
OTBS
S11
5.90
5.01
4.22
4.20
4.19
4.18
3.66
3.15
2.64
2.35
1.00
0.98
0.85
0.06
0.00
0.91
1.86
1.01
3.07
3.00
0.95
1.98
2.82
9.24
3.01
3.02
f1 (ppm)


Me
N
O
O
OTBS
S11
172.7
140.5
114.5
72.7
61.3
43.5
37.6
36.3
25.9
18.1
14.5
-4.6
-4.8
f1 (ppm)


Me
O
O
OTBS

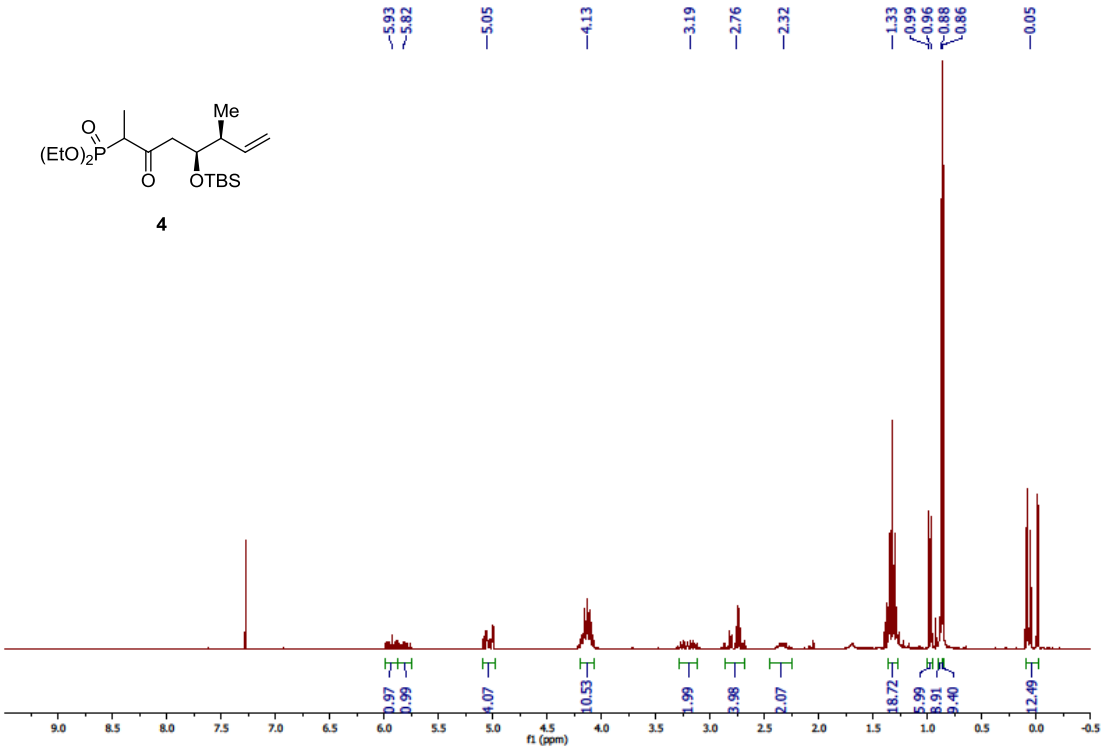
S12

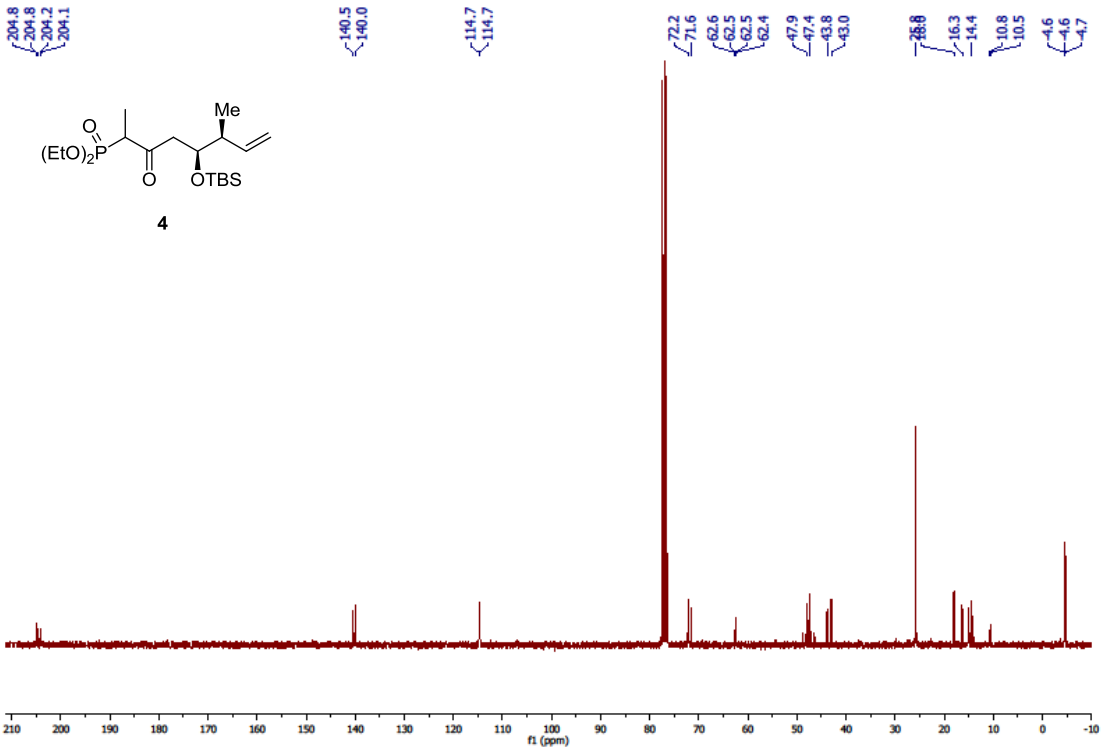
5.87
5.03
4.08
3.66
2.39
1.01
0.99
0.87
0.08
0.03
0.89
1.86
1.01
3.00
3.07
2.91
9.06
3.00
2.90
f1 (ppm)

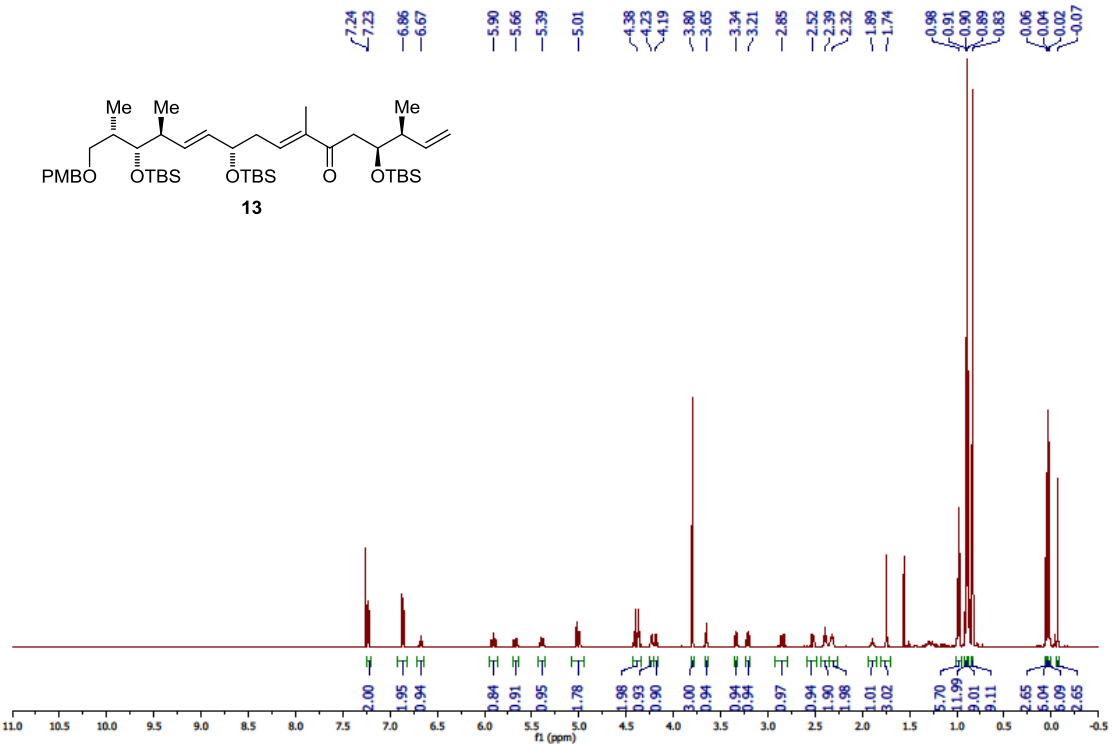

Me
O
O
OTBS

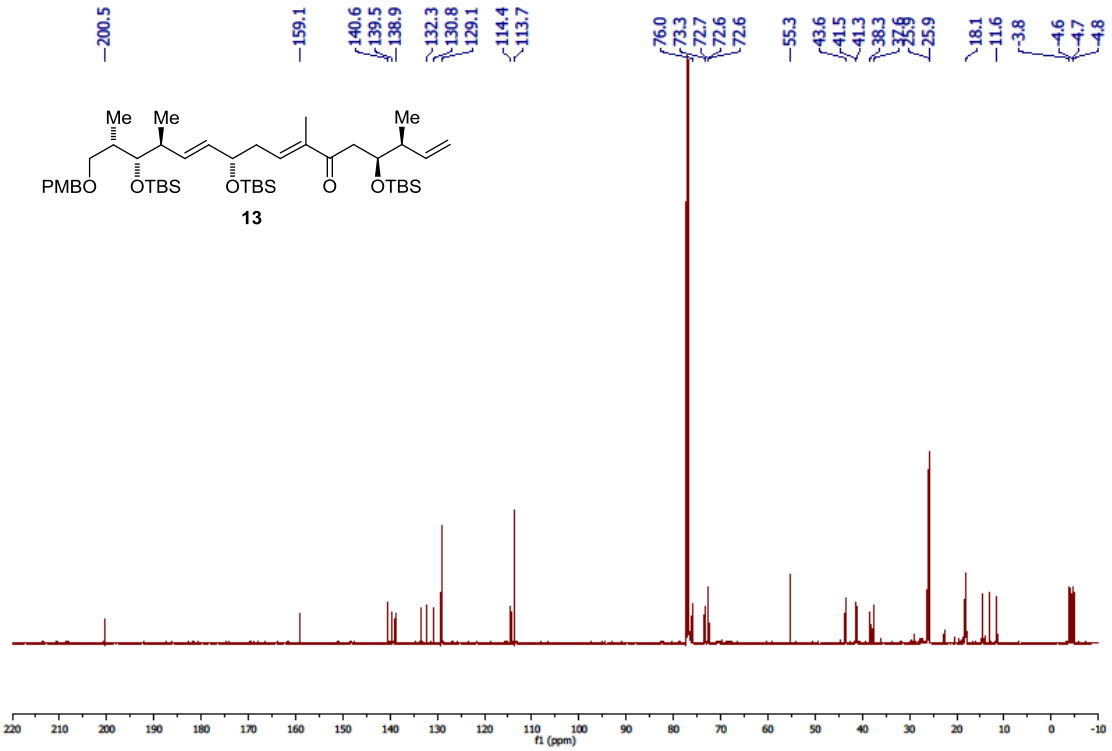
S12

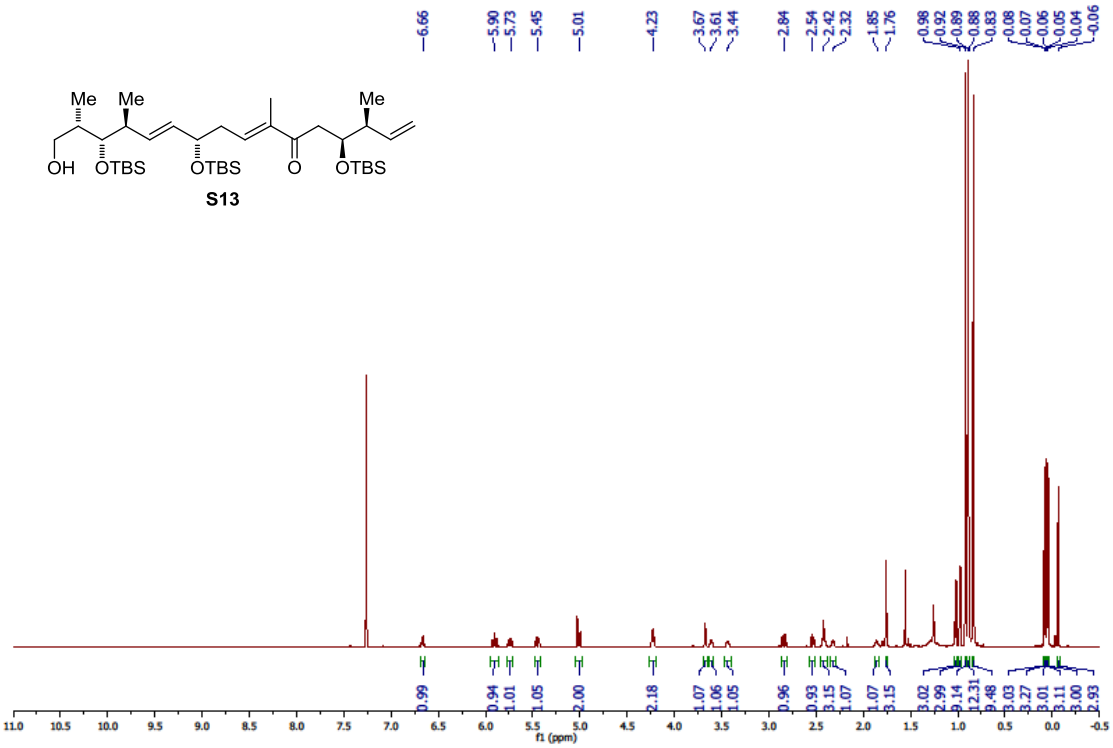
172.6
140.0
114.9
73.0
51.5
43.3
39.4
25.8
18.0
14.7
-4.5
-4.8
f1 (ppm)

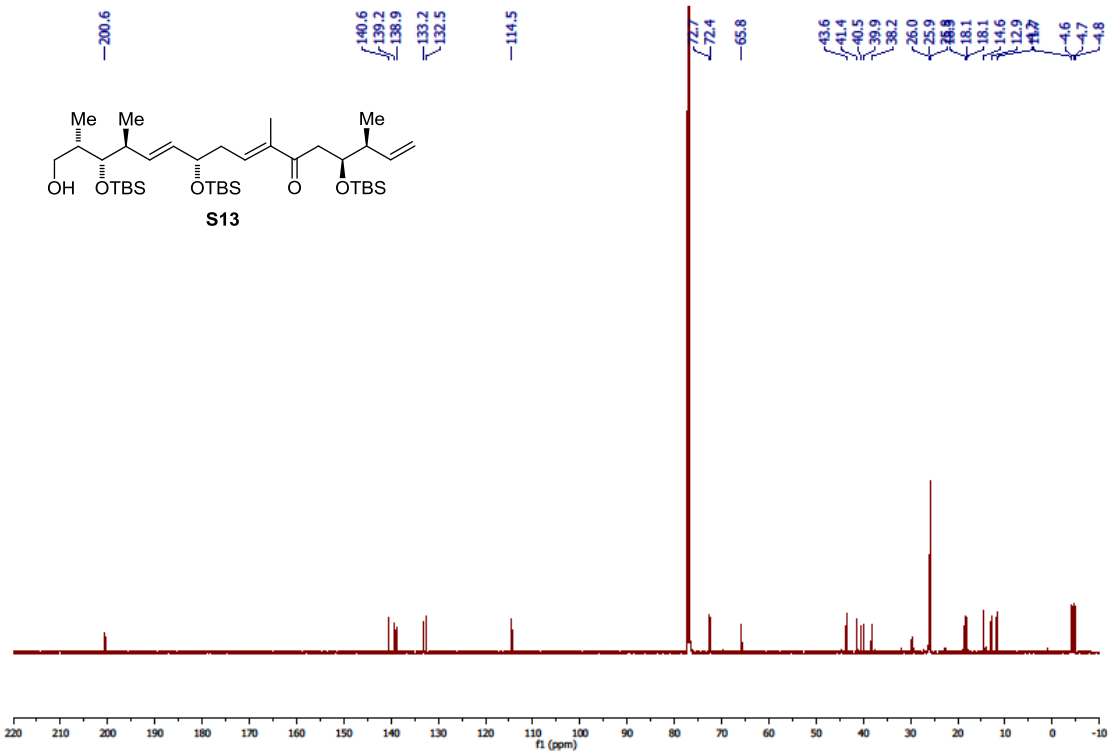

5.93
5.82
5.05
4.13
3.19
2.76
2.32
1.33
0.99
0.96
0.88
0.86
0.05
Me
O
(EtO)2P
O
OTBS
4
0.97
0.99
4.07
10.53
1.99
3.98
2.07
18.72
5.99
8.91
3.40
12.49
f1 (ppm)

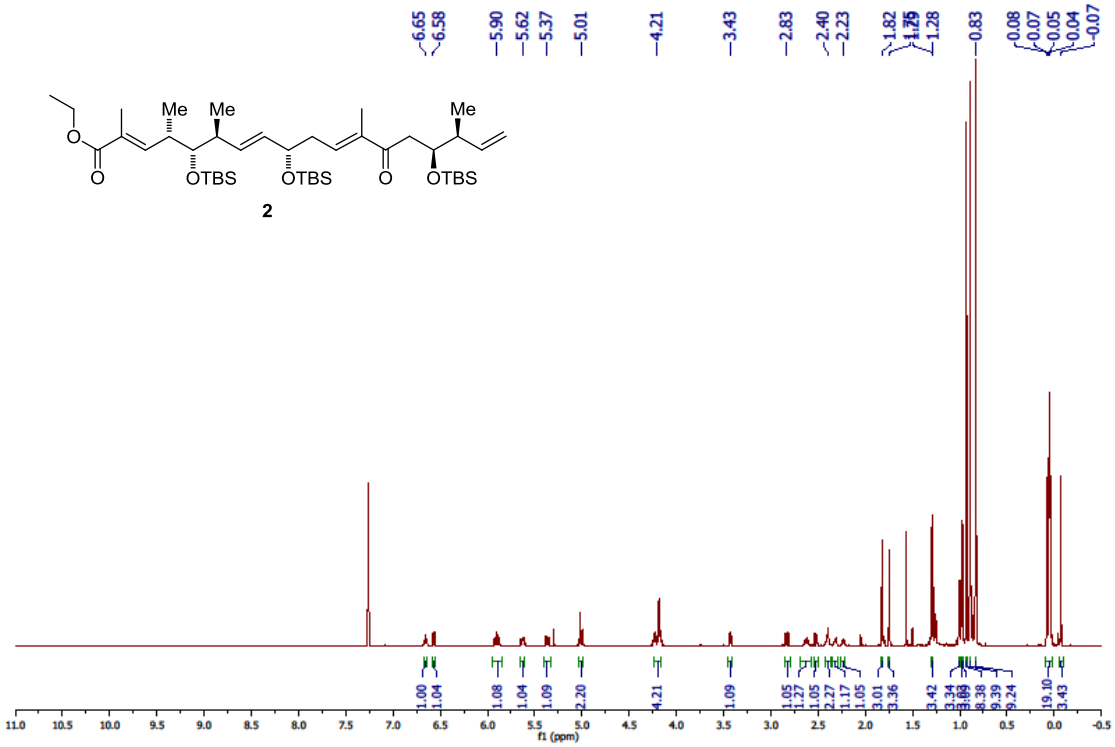

204.8
204.8
204.2
204.1
140.5
140.0
114.7
114.7
72.2
71.6
62.6
62.5
62.5
62.4
47.9
47.4
43.8
43.0
26.8
26.8
16.3
14.4
10.8
10.5
-4.6
-4.6
-4.7
Me
O
(EtO)2P
O
OTBS
4
f1 (ppm)

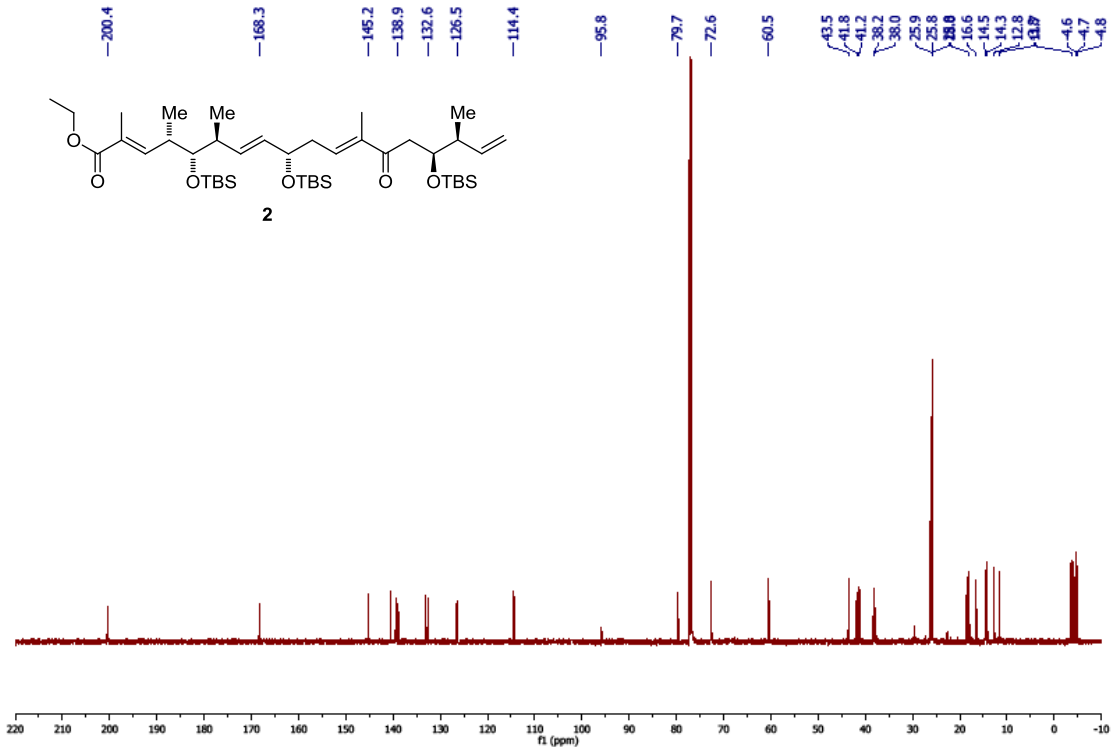

7.24
7.23
6.86
6.67
5.90
5.66
5.39
5.01
4.38
4.23
4.19
3.80
3.65
3.34
3.21
2.85
2.52
2.39
2.32
1.89
1.74
0.98
0.91
0.90
0.89
0.83
0.06
0.04
0.02
-0.07
Me
Me
Me
PMBO
OTBS
OTBS
O
OTBS
13
2.00
1.95
0.94
0.84
0.91
0.95
1.78
1.98
0.93
0.90
3.00
0.94
0.94
0.94
0.97
0.94
1.90
1.98
1.01
3.02
5.70
11.99
9.01
9.11
2.65
6.04
6.09
2.65
f1 (ppm)


200.5
159.1
140.6
139.5
138.9
132.3
130.8
129.1
114.4
113.7
76.0
73.3
72.7
72.6
72.6
55.3
43.6
41.5
41.3
38.3
25.9
18.1
11.6
-3.8
-4.6
-4.7
-4.8
Me
Me
Me
PMBO
OTBS
OTBS
O
OTBS
13
f1 (ppm)


Me
Me
Me
OH
OTBS
OTBS
O
OTBS
S13
6.66
5.90
5.73
5.45
5.01
4.23
3.67
3.61
3.44
2.84
2.54
2.42
2.32
1.85
1.76
0.98
0.92
0.89
0.88
0.83
0.08
0.07
0.06
0.05
0.04
-0.06
0.99
0.94
1.01
1.05
2.00
2.18
1.07
1.06
1.05
0.96
0.93
3.15
1.07
1.07
3.15
3.02
2.99
9.14
12.31
9.48
3.03
3.27
3.01
3.11
3.00
2.93
f1 (ppm)


Me
Me
Me
OH
OTBS
OTBS
O
OTBS
S13
200.6
140.6
139.2
138.9
133.2
132.5
114.5
72.7
72.4
65.8
43.6
41.4
40.5
39.9
38.2
26.0
25.9
18.1
18.1
14.6
12.9
-4.6
-4.7
-4.8
f1 (ppm)


Me
Me
Me
O
O
OTBS
OTBS
O
OTBS
2


Me
Me
Me
O
O
OTBS
OTBS
O
OTBS
2