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Synthesis of steroid-like analogues of cholesterol biosynthesis inhibitors

v o n

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aus

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Erklärung

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

Eidesstattliche Versicherung

Diese Dissertation wurde selbstständig und ohne unerlaubte Hilfe erarbeitet.

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Desirée Heerdegen

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Danke – Thank you – ありがとう

Für Mama und Papa

Table of contents

Summary

This thesis implies two chapters. The main topic of this thesis is presented in chapter one and discusses the synthesis of steroid-like analogues of cholesterol biosynthesis inhibitors. The potent DHCR24 inhibitor SH-42 and two related diols were the lead structures of the synthesised (*seco*-)steroidal analogues.

A chiral pool synthesis, starting from vitamin D_2, was performed to receive tri- and tetracyclic as well as *seco*-steroidal analogues with variation of ring A and B of the steroidal structure.

In total, 30 SH-42 analogues were synthesised and their inhibitory activity towards the cholesterol biosynthesis was tested using a whole-cell assay developed in our group. Three analogues showed an inhibition of a cholesterol biosynthesis enzyme: Diol **55b** showed a weak inhibition of the target enzyme DHCR24 and diols **97^{d}** and **169** inhibited the sterol C5 desaturase (SC5D) by accumulation of lathosterol. In general, variation of ring A and B resulted in a loss of DHCR24 inhibition. These studies revealed that the steroidal structure is necessary for potent DHCR24 inhibitors.

A part of these studies was published in the *European Journal of Organic Chemistry*[1]:

D. Heerdegen, D. Kremer, M. M. Kornmayer, K. N. Kriegler, C. Müller, P. Mayer, F. Bracher, *Eur. J. Org. Chem.* **2020**, accepted.

The topic of the second chapter is a traceless isoprenylation of aldehydes *via* *N*-Boc-*N*-allylhydrazones. In 2010, a publication by Thomson and co-workers presented a unique [3,3] sigmatropic rearrangement of *N*-Boc-*N*-allylhydrazones with the super acid triflimide as catalyst. In previous studies we designed and synthesised a novel *N*-Boc-*N*-allylhydrazine building block with two geminal methyl groups which form the isoprenyl group after rearrangement. In total, 17 *N*-Boc-*N*-allylhydrazones were synthesised and the scope and limitations of the rearrangement were studied. By variation of different acidic catalysts, protecting groups and solvents the optimum reaction conditions were explored and the reaction was carried out for six representative examples.

These studies were published in the *European Journal of Organic Chemistry*[2]:

D. Heerdegen, J. Junker, S. Dittrich, P. Mayer, F. Bracher, *Eur. J. Org. Chem.* **2020**, 3680-3687 (doi: 10.1002/ejoc.202000382).

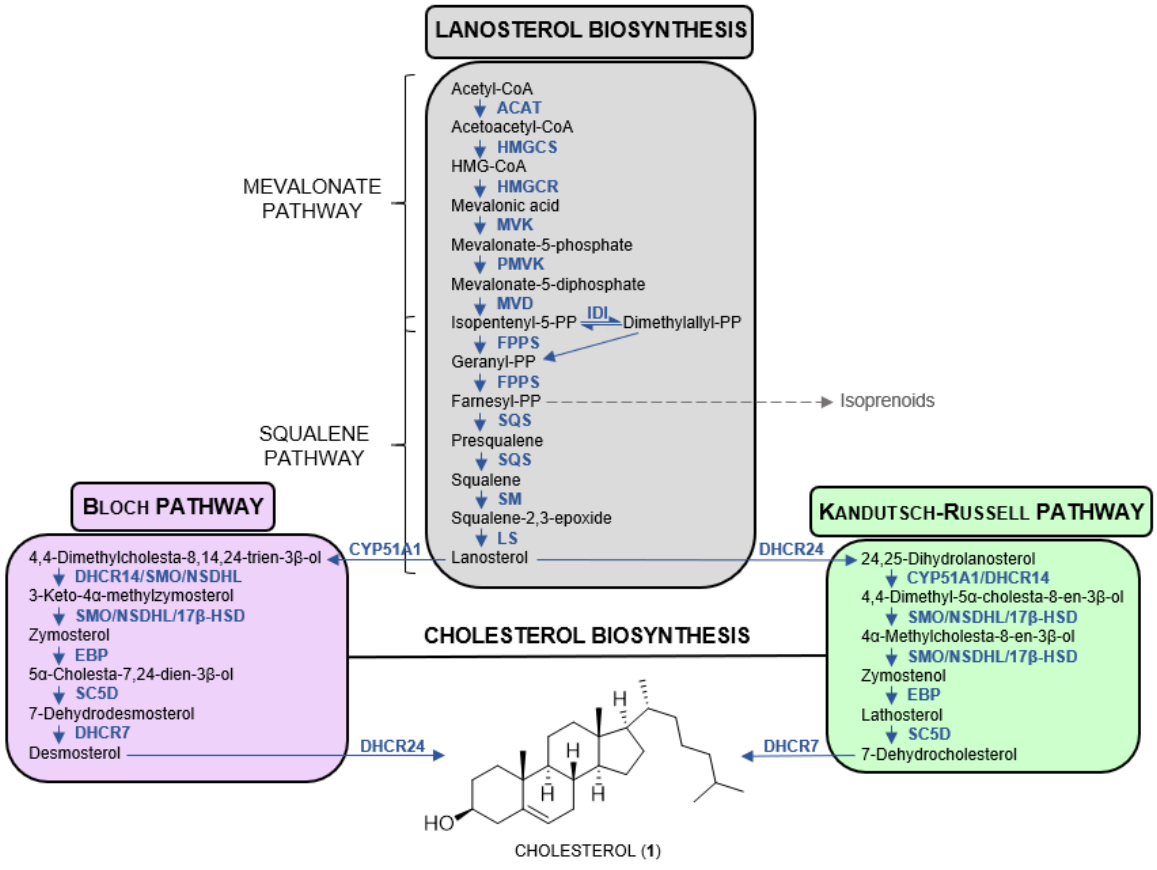
Chapter 1 - Synthesis of steroid-like analogues of cholesterol biosynthesis inhibitors

1. Introduction

Too much of a good thing: hypercholesterolaemia, the presence of high levels of cholesterol in the blood, is one of the major risk factors for several diseases, e.g. atherosclerotic cardiovascular diseases (CVD).[3-4] Thus, the development and synthesis of potent and selective inhibitors of cholesterol biosynthesis is continuously of great interest in pharmaceutical research and especially of high necessity worldwide.

1.1. Cholesterol biosynthesis and transport

The biomolecule cholesterol (**1**) plays an important role in the mammalian organism, since it is an essential component of cell membranes regulating the membrane rigidity and fluidity. Moreover, it acts as a precursor for steroid hormones and bile acids, which are crucial for further regulation of metabolic processes.[5-6] The biosynthesis of cholesterol (**1**) comprises two main stages: the lanosterol biosynthesis, followed by the actual cholesterol biosynthesis, which consists of the BLOCH and the KANDUTSCH-RUSSELL pathway (**Scheme 1**).



Scheme 1. Overview of the complete cholesterol biosynthesis, which is divided into the lanosterol biosynthesis (grey) and the actual cholesterol biosynthesis which proceeds *via* the BLOCH (lilac) and KANDUTSCH-RUSSELL (mint green) pathway. Enzymatic steps are marked in dark blue and the full names of the enzymes can be found in the abbreviation list (*cf.* [7-8]).

The mevalonate pathway is the first section of the lanosterol pathway (**Scheme 1**, marked in grey).[9] In the first steps acetyl-CoA is enzymatically converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) *via* acetyl-CoA-acetyltransferase (ACAT) and HMG-CoA synthase (HMGCS). Next, the irreversible reduction of HMG-CoA to mevalonic acid takes place, which is catalysed by HMG-CoA reductase (HMGCR). This step is described as the *committed step* in the cholesterol biosynthesis since this feedback regulatory effect is conveyed by changes in quantity and activity of HMGCR, depending on the available amount of cholesterol in cells. Then, mevalonic acid is converted to isopentenyl-5-pyrophosphate (IPP) in three steps. Reaching the squalene pathway, six units of IPP are needed to form one squalene. Geranyl-PP and farnesyl-PP are significant intermediates, whereby the latter is a precursor for the biosynthesis of isoprenoids. Lastly, the conversion of squalene to squalene-2,3-epoxide and subsequent cascade cyclisation generates lanosterol.[5] The post-squalene pathway, thus the cholesterol biosynthesis, can proceed *via* the BLOCH (**Scheme 1**, marked in lilac) or the KANDUTSCH-RUSSELL (**Scheme 1**, marked in mint green) pathway.[10] Using isotope labeling, MITSCHE *et al.* showed, that the relative use of both pathways is tissue and cell specific.[8] The BLOCH pathway can be found, for example in adrenal glands and testes, while brain and skin utilise the KANDUTSCH-RUSSELL pathway.[8, 11] Starting from lanosterol, cholesterol (**1**) is formed in both pathways *via* seven steps. All in all, both pathways seem to be related with the main difference between them being the point at which the reduction of the Δ^{24}-double bond in the side chain of the sterol intermediates takes place. The reduction is catalysed by the enzyme Δ^{24}-dehydrocholesterol reductase (DHCR24), which will be discussed in chapter 1.4. in more detail.

To understand the natural regulation and the impact of a disturbed cholesterol balance, it is important to understand the cholesterol transport. **Figure 1** shows a shortened overview of the lipoprotein metabolism and cholesterol transport, respectively.[5, 12] Due to the poor water solubility of cholesterol, it is packed into carrier particles, the so-called lipoproteins, which consists of lipids (triglycerides, cholesterol esters and free cholesterol) and apolipoproteins, whereby the latter are *inter alia* ligands for receptors. The lipoproteins are divided based on their density into VLDL (very low density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins) and the chylomicrons. Chylomicrons transport the dietary lipids (cholesterol and triglycerides) from the intestines to the liver *via* lymphatic tissues.[12-13] Triglycerides are lipolysed intro free fatty acids (FFA), which deposit in fatty and peripheral tissues and chylomicron remnants are taken up by the liver. The main location of cholesterol biosynthesis is the liver.[14] The cholesterol is enzymatically packed into VLDL (cholesterol esters and triglycerides), which is released to the blood system. After elimination of some triglycerides *via* hydrolysis, IDL is formed, whereby one part is absorbed by the liver and the

other part is formed to LDL *via* elimination of further triglycerides, which are lipolysed to FFA. LDL transports cholesterol to peripheral tissues and regulates the *de novo* cholesterol biosynthesis.[5, 15-16] Another important lipoprotein is HDL (high density lipoprotein). HDL transports surplus cholesterol from peripheral tissues back to the liver converting it into bile acids for excretion.[5, 12, 17]

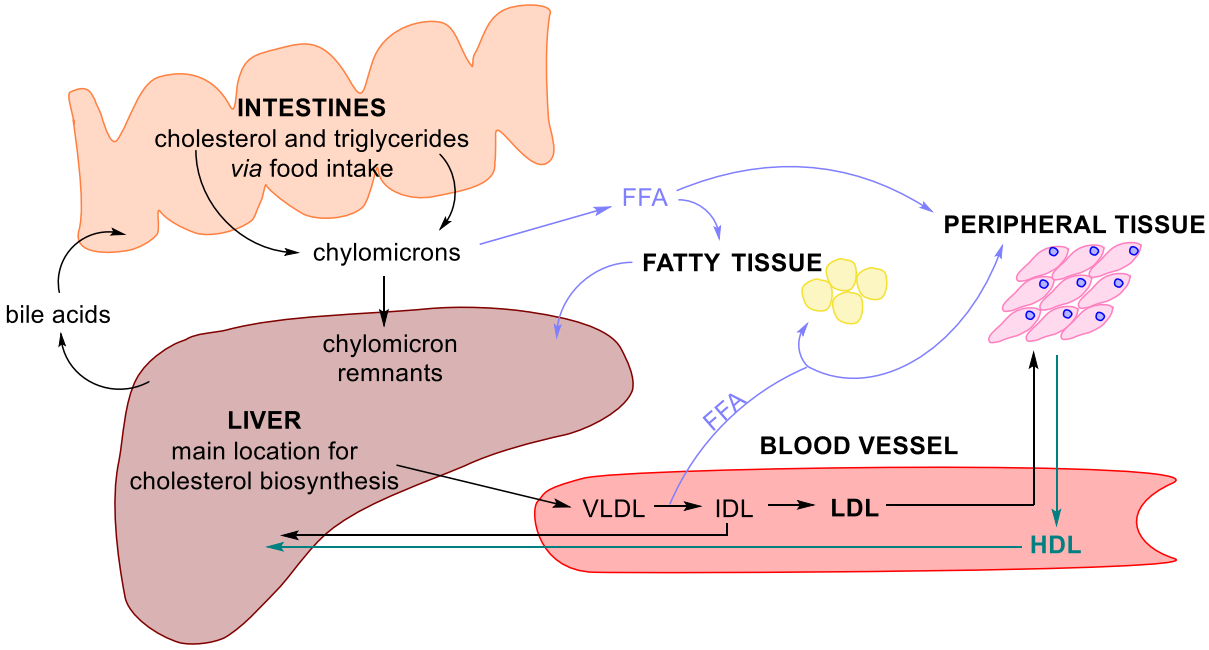


Figure 1. Shortened overview of the lipoprotein metabolism and *reverse cholesterol transport* (RCT) (*cf.* [5, 12]).

As a result, HDL is responsible for the so-called *reverse cholesterol transport* (RCT),[18-19] and therefore for the cholesterol balance.

1.2. Natural regulation and the impact of a disturbed cholesterol balance

The cholesterol biosynthesis is naturally regulated at the *committed step*, the reduction of HMG-CoA to mevalonic acid, catalysed by HMGCR.[5, 9] HMGCR can be controlled in several ways, e.g. by the sterol regulatory element-binding protein 2 (SREBP2), a transcription factor which is anchored in the endoplasmic reticulum and is bound to the integrated membrane protein SREBP-cleavage activating protein (SCAP), the cholesterol sensor. When the cholesterol concentration decreases, the SCAP-SREBP2 complex moves in small vesicles to the GOLGI apparatus where it is released from the membrane in two proteolytic cleavages. Consequently, the released protein binds to the sterol regulatory element (SRE) DNA sequence in the nucleus and the transcription of HMGCR is increased. When the cholesterol level is too high, the proteolytic release of SREBP2 is blocked and the protein is degraded in the nucleus and the transcription is stopped.[5, 16, 20] The HMGCR activity can further be regulated by phosphorylation. In the liver, HMGCR can be deactivated by an AMP-dependent

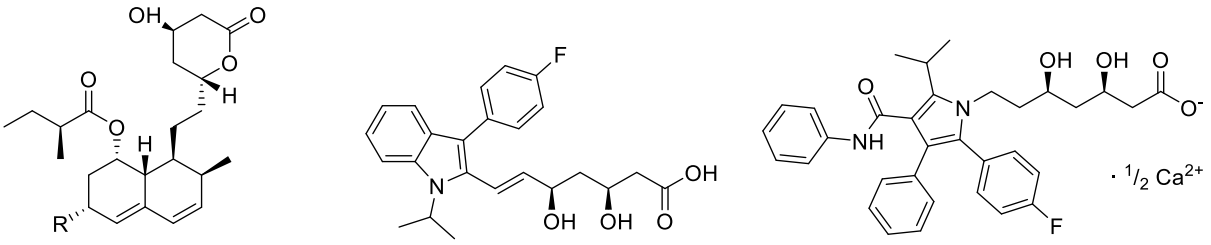
proteinkinase (AMPK). In case of a cellular energy deficiency, the AMP level is high and as a result HMGCR is phosphorylated by AMPK. As a result, HMGCR is deactivated, which means the cholesterol biosynthesis is shutting down.[5, 16, 21]

A genetically disturbed cholesterol balance can result in several diseases, e.g. NIEMANN-PICK type C disease, a neurodegenerative disease, whereby cholesterol accumulates with lysosomes. Besides neurodegeneration, an enlarged liver and spleen are typical symptoms.[16, 22] The SCHNYDER corneal dystrophy describes the accumulation of cholesterol in the cornea, resulting in opacification. Due to HMGCR stabilisation, the cholesterol production is enhanced.[16, 23] In contrast, the SMITH-LEMLI-OPITZ syndrome represents a cholesterol deficiency, due to decreased activity of the enzyme Δ^7-dehydrocholesterol reductase (DHCR7), leading to accumulation of 7-dehydrocholesterol. The consequence is mental and growth retardation.[16, 24] Another present health problem is hyperlipidaemia, which includes high levels of lipids like cholesterol, triglycerides and lipoproteins and is a risk factor for CVD.[4] A distinction is made here between primary (familial) and secondary (acquired) hyperlipidaemia. While the primary form has a genetic origin, the secondary form is caused by underlying reasons like diabetes mellitus or the use of certain drugs, such as diuretics or beta blockers.[25] Two subtypes of primary hyperlipidaemias are the common and the familial hypercholesterolaemia (FH), whereby both are induced by raised cholesterol levels due to LDL.[3] According to the World Health Organisation (WHO), raised cholesterol levels are a global health problem. Overall, a third of ischaemic heart disease cases result from hypercholesterolaemia and estimated to cause 2.6 million of global deaths.[26] The initial treatment of high cholesterol levels consists of a change of diet (reducing animal fats, increasing vegetables, dietary fibres, etc.) or lifestyle (limiting smoking and alcohol consumption, increasing physical activity).[27-28] If this does not lead to improvement, a medical treatment is required.

1.3. Inhibitors of cholesterol biosynthesis

Although inhibition of cholesterol biosynthesis is conceivable *via* interference in each enzymatic step, until now successful therapeutics only target the pre-squalene part. A clinically relevant class of inhibitors are statins,[29] which are used for the treatment of hyperlipidaemia and atherosclerosis. Statins reduce cholesterol synthesis by competitive inhibition of HMGCR. Consequently, the amount of cholesterol decreases, which results in an up regulation of hepatic LDL receptor expression. Therefore, more LDL can be taken up from the plasma into the cell, resulting in decreased LDL blood levels.[3] The first statin was Mevastatin (**2**), which was isolated from *Penicillium citrinum*, but due to side effects, **2** is not used therapeutically.

The first commercially introduced statin was Lovastatin (**3**), isolated from *Aspergillus terreus*.[30] Further synthetic statins are Fluvastatin (**4**) and Atorvastatin (**5**) (**Figure 2**).[31-32]



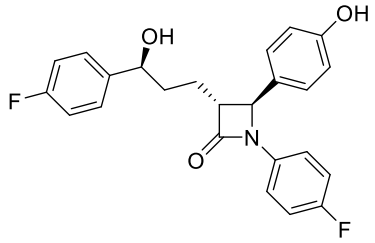
Mevastatin (**2**, R = H)
Lovastatin (**3**, R = CH_3)

Fluvastatin (**4**)

Atorvastatin (**5**)

Figure 2. Structures of isolated Mevastatin (**2**) and Lovastatin (**3**), and synthetic statins Fluvastatin (**4**) and Atorvastatin (**5**).

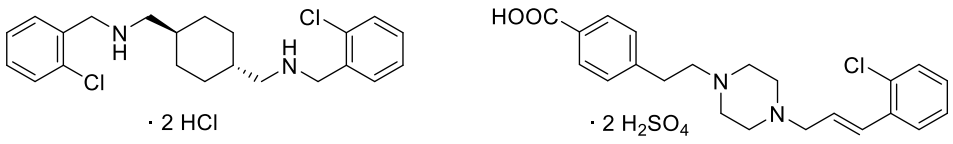
Unfortunately, statins cause few side effects such as muscle pains, including cramps and weakness.[33] Another cholesterol-lowering agent with a different mechanism of action is Ezetimibe (**6**, **Figure 3**), which is generally accepted, but less effective than statins. It binds to the NIEMANN-PICK C1-like 1 receptor and thus inhibits the intestinal dietary and biliary cholesterol absorption.[3] Various guidelines recommend to use Ezetimibe (**6**) in combination therapy together with statins or in case of statin intolerance solely as monotherapy.[34]



Ezetimibe (**6**)

Figure 3. Structure of Ezetimibe (**6**).

Nevertheless, there are inhibitors which target the post-squalene part, e.g. AY-9944 (**7**) and BM-15766 (**8**), which inhibit DHCR7, resulting in an accumulation of 7-dehydrocholesterol in tissues (**Figure 4**). However, both inhibitors show teratogenic effects and therefore the application of these inhibitors is limited to studies regarding the SMITH-LEMLI-OPTIZ syndrome.[35-36]



AY-9944 (**7**)

BM-15766 (**8**)

Figure 4. Structures of DHCR7 inhibitors AY-9944 (**7**) and BM-15766 (**8**).

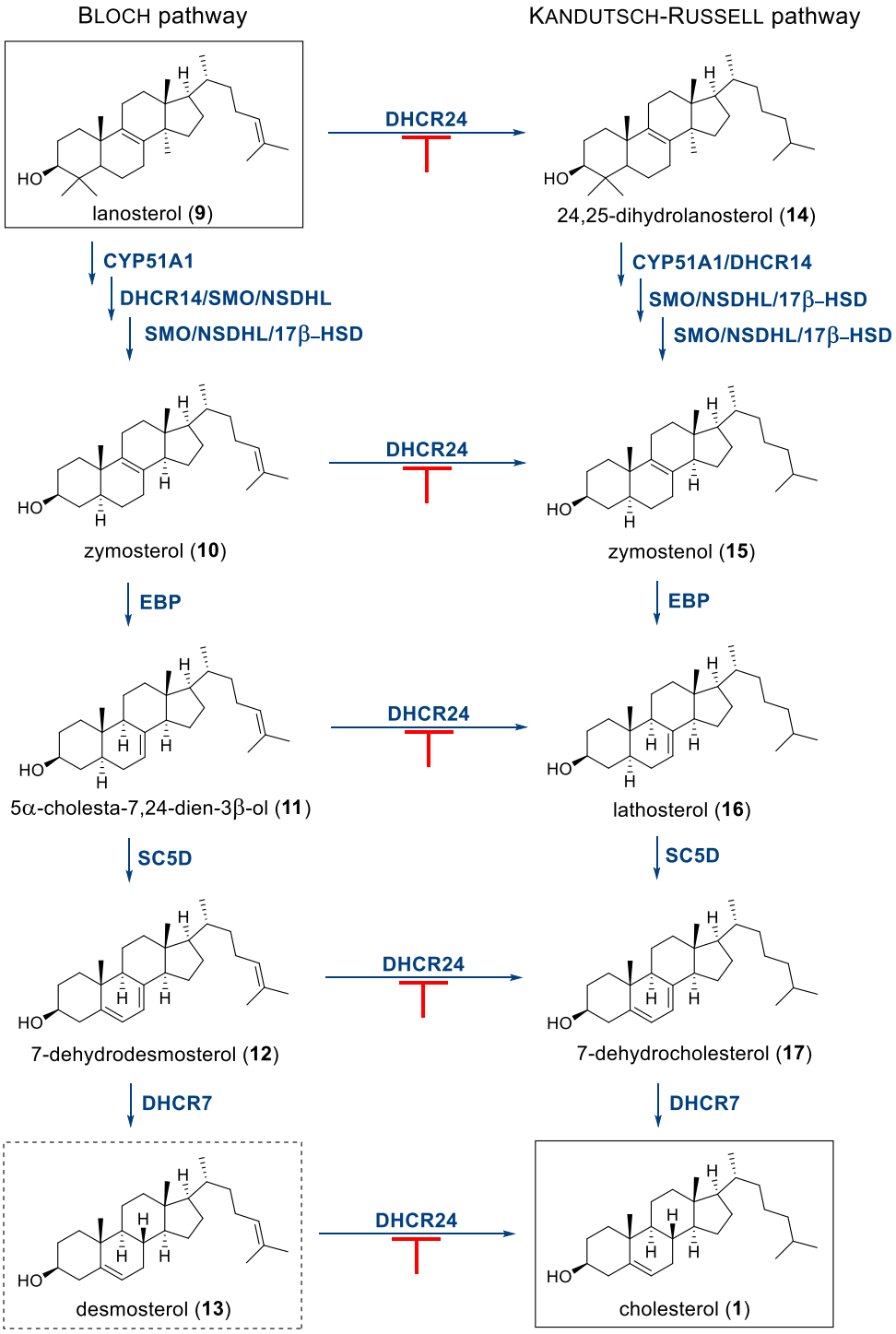
Another enzyme in the post-squalene part is DHCR24. It became a target of growing interest in the past years since it plays an integral role in research concerning cardiovascular diseases (CVD), ALZHEIMER'S disease (AD), hepatitis C virus (HCV) infections, certain types of cancer and desmosterolosis.[10, 37] GREEVE *et al.* showed that the Seladin-1 gene, that encodes for DHCR24, is down-regulated in neurons in vulnerable regions in AD.[38] HCV infection leads to increased DHCR24 expression in hepatocytes and plays a significant role in the viral replication, since treatment with DHCR24 inhibitor U18666A (**19**, structure shown in **Figure 6**) suppresses HCV replication. As a result, DHCR24 may act as a novel HCV drug target.[39] Desmosterolosis is a rare autosomal recessive disorder and describes the accumulation of desmosterol, due to defects on Seladin-1.[40] Psychomotor retardation, microcephaly, spasticity, development disorders, nystagmus or strabismus are consequences of this disease.[41] However, the relation between the phenotype of the disease and the accumulation of desmosterol is still unknown. Based on these diseases and the presumed strong involvement of cholesterol biosynthesis pathway, the importance of deeper understanding therof and in particular of the BLOCH and KANDUTSCH-RUSSELL pathway becomes clear.

1.4. Insight in the BLOCH and KANDUTSCH-RUSSELL pathway

To bring out why the BLOCH and KANDUTSCH-RUSSELL pathway are of special importance in cholesterol biosynthesis and related diseases **Scheme 2** provides a closer look on the important steps of these pathways. The first thing to be noticed is that both pathways are not strictly separated from each other. While in the KANDUTSCH-RUSSELL pathway, the reduction of the double bond, the conversion of lanosterol (**9**) to 24,25-dihydrolanosterol (**14**), occurs in the initial step, in the BLOCH pathway the reduction of the double bond can occur in any sterol intermediate, crossing-over to the KANDUTSCH-RUSSELL pathway. Overall, lanosterol (**9**), zymosterol (**10**) or desmosterol (**13**) are the major substrates of DHCR24.[8, 42-44] The enzymatic reduction is a two-step process utilising NADPH as reducing agent. Thus, C-24 is protonated, forming a carbocation at C-25 with subsequent addition of a hydride of NADPH to C-25, leading to the saturated form.[43]

Inhibition of DHCR24 (illustrated in **Scheme 2** in red) results in an accumulation of desmosterol (**13**). Desmosterol (**13**) has been proven to be a ligand for the liver X receptor (LXR),[45] which regulates the immune and inflammatory responses and plays also an important role in metabolic processes like glucose metabolism[46-47] and *inter alia* in the cholesterol homeostasis.[10, 45, 48] The LXR belongs to the nuclear receptor superfamily of DNA-binding transcription factors and exists in two isoforms: LXRα is highly expressed in metabolically active tissues, like liver and intestine, adipose tissues, kidney and macrophages, whereas LXRβ is ubiquitously expressed.[45-46, 49] LXR is ligand-depending and can be regulated by

endogenous ligands, like desmosterol (**13**), as well as by synthetic LXR agonists, e.g. benzenesulfonamine compound T0901317.[50] To fulfil the requirements of a transcription factor, LXR heterodimerises with retinoid X receptor (RXR) and binds to LXR-response elements (DR4).[49]



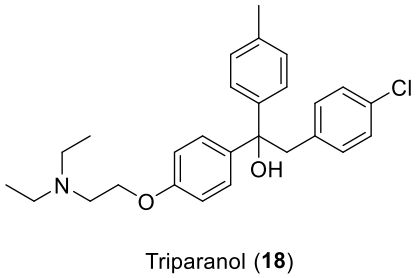
Scheme 2. Overview of the BLOCH and KANDUTSCH-RUSSEL pathway. Enzymes are written in dark blue. Possible inhibition of DHCR24 is marked in red (*cf.*[43])

With the binding of ligands, a conformational change of the heterodimer occurs, and the nuclear receptor coactivator, the so-called steroid receptor coactivator-1 (SRC-1), will be recruited, resulting in an activation of the gene transcription.[45, 51] LXR induces RCT,[52-53] whereby the cholesterol is secreted into bile or catabolised into bile acids, which results in an increase of bile acid production.[54-55] Nevertheless, there are also disadvantages of an increased LXR activation. LXR expression is correlated with an increased lipogenesis resulting in the so-called fatty livers.[56-57] As a consequence, fatty livers can lead to the non-alcoholic fatty liver disease (NAFLD),[58] a metabolic disorder which is not caused by excessive alcoholic drinking and become the most common chronic liver disease in industrial countries.[48] The non-alcoholic steatohepatitis (NASH) is the inflammatory and progressive form of NAFLD and can develop further into liver fibrosis and cirrhosis.[48, 59] Since an inhibition of LXR may lead to down regulation of lipogenesis resulting in a decrease of fatty livers which could progress to NASH, the development of LXR inhibitors became an important research topic.[37, 60]

Since desmosterol (**13**) is a good endogenous ligand for LXR, inhibition of DHCR24, leading to accumulated desmosterol can offer significant contribution to more detailed studies of the effect of desmosterol on LXR, e.g. studies towards inflammatory resolution.[37]

1.5. Development of DHCR24 inhibitors

Considering the broad involvement of DHCR24 and its substrates in biological processes, control and regulation of this enzyme are necessary for further advances in its research. Currently, there are several inhibitors, but most of them are known to be poorly selective or even toxic, which leads to an increasing demand in selective and potent inhibitors. The first drug, which was used clinically to lower cholesterol levels was the hypolipidemic Triparanol (**18**), also known as MER-29 (**Figure 5**).

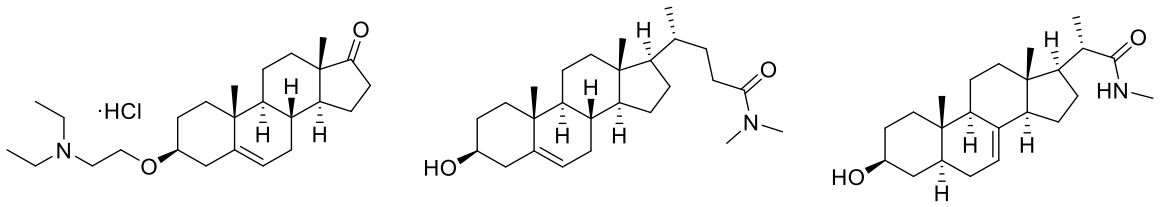


Triparanol (**18**)

Figure 5. Structure of the non-steroidal DHCR24 inhibitor Triparanol (**18**).

By inhibiting DHCR24, Triparanol (**18**) leads to decreased cholesterol and increased desmosterol levels.[61-62] However, Triparanol was withdrawn from commercial markets due to harmful side effects like hair loss, impotency or blindness from a form of cataracts.[63-64] Nevertheless, **18** is still used as reference substance in studies for novel DHCR24 inhibitors.

Figure 6 depicts steroidal DHCR24 inhibitors. U18666A (**19**) is not a selective DHCR24 inhibitor, since it also inhibits the enzymes 2,3-oxidosqualene synthase and $\Delta^{7,8}$-isomerase in the cholesterol biosynthesis.[53, 65] DMHCA (**20**) is a synthetic LXR agonist and showed inhibitory effect on DHCR24, but the selectivity over other enzymes is not yet fully established.[52-53] The last steroidal DHCR24 inhibitor in this set is MGI-21 (**21**). This compound was designed and synthesised in our group in the course of the development of a group of lathosterol side chain amides, the so-called chemotype I.[66]



U18666A (**19**) DMHCA (**20**) MGI-21 (**21**)

Figure 6. Established steroidal DHCR24 inhibitors: U18666A (**19**), DMHCA (**20**), and MGI-21 (**21**).

Compound MGI-21 (**21**), showed an inhibitory effect, but lacks in the necessary potency towards DHCR24 (IC_{50} = 823 nM for inhibition of overall cholesterol biosynthesis[43]). With the introduction of larger *N*-alkyl groups the selectivity was reduced and an additional undesired inhibitory effect on another enzyme in this pathway, lathosterol oxidase (sterol C5 desaturase), was observed.[43, 66] Based on these studies, our group recently developed new chemotypes of potent DHCR24 inhibitors. Besides chemotype I, inverse amides (chemotype II) and inverse esters (chemotype III) were synthesised.[43] Among these, synthesised inhibitors of chemotype III were identified as potent, selective and non-toxic inhibitors of DHCR24. In particular ester SH-42 (**22**) and the related free diols Δ^7-**23** and Δ^5-**24**, whereby **23** is the unesterified version of SH-42 (**22**), showed promising results (**Figure 7**).

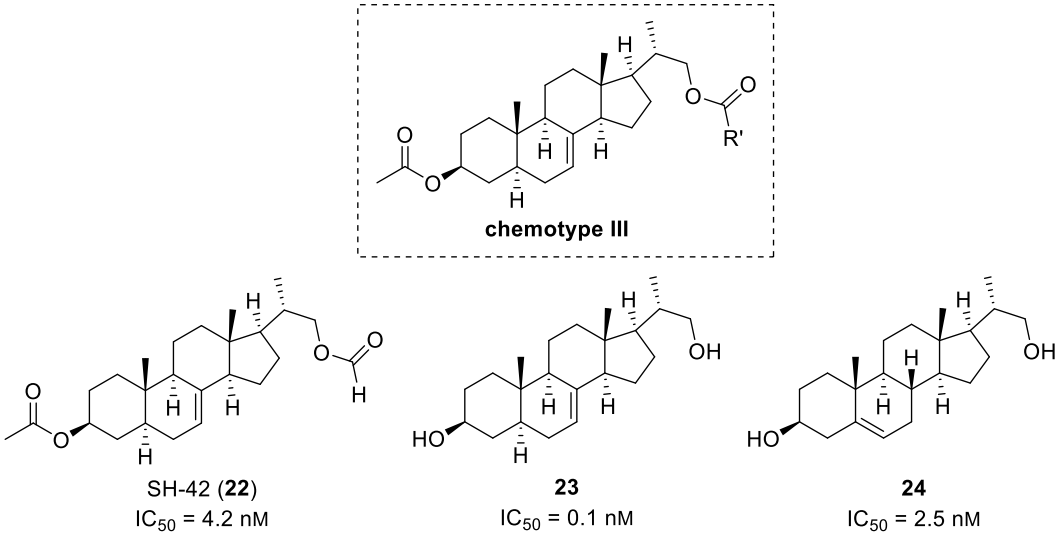
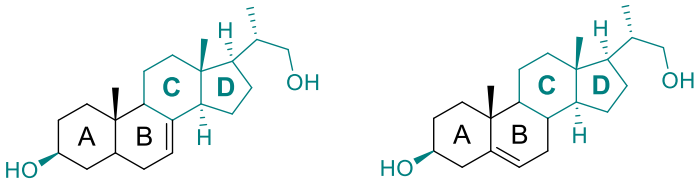


Figure 7. General structure of chemotype III (top), SH-42 (**22**) and related diols **23** and **24** and their IC_{50} values (bottom). The IC_{50} values refer to the inhibition of total cholesterol biosynthesis.[43]

Regarding the inhibition of the total cholesterol biosynthesis these compounds have IC_{50} values of 4.2 nM for SH-42 (**22**) and 0.1 nM and 2.5 nM for diols **23** and **24**, respectively. The slightly higher IC_{50} value of SH-42 (**22**) can be explained by the rather labile ester function in the side chain, which can be transformed into the free hydroxy groups *in vitro* – a characteristic for a possible pro-drug. When comparing both diols, it could be shown, that the exact position of the double bond in ring B is not significant for the inhibition, since the IC_{50} values of the free diols **23** (Δ^7-double bond) and **24** (Δ^5-double bond) are similar. With their high potency, selectivity and non-toxicity, SH-42 (**22**) and its related free diols **23** and **24** represent a new class of DHCR24 inhibitors.[43] Therefore, the development of further selective inhibitors is oriented towards their structures.

2. Objective

Recent research of our group showed, that inhibitors of chemotype III, especially diester SH-42 (**22**) and its related free diols **23** and **24** are inhibitors of DHCR24 with high efficacy.[43] These inhibitors are derived from natural sterols (cholesterol and others) by semi-synthesis. A couple of structural variations had been performed in previous projects, and structure-activity relationships of steroidal DHCR24 inhibitors accessible on the route are meanwhile well understood.[43] In order to get access to novel chemotypes with close structural relationships to the lead structures, syntheses starting from non-steroidal compounds were envisaged. Therefore, the aim of this part of the thesis is the synthesis of steroid-like analogues of diols **23** and **24**. The focus was not set on the synthesis of esterified steroid analogues, since we first wanted to study the inhibitory effect of the free hydroxylic analogues before heading to prodrug-like analogues. **Figure 8** shows both lead structures **23** and **24**, whereby the petrol marked structure motifs should be maintained.



23
IC_{50} = 0.1 nM

24
IC_{50} = 2.5 nM

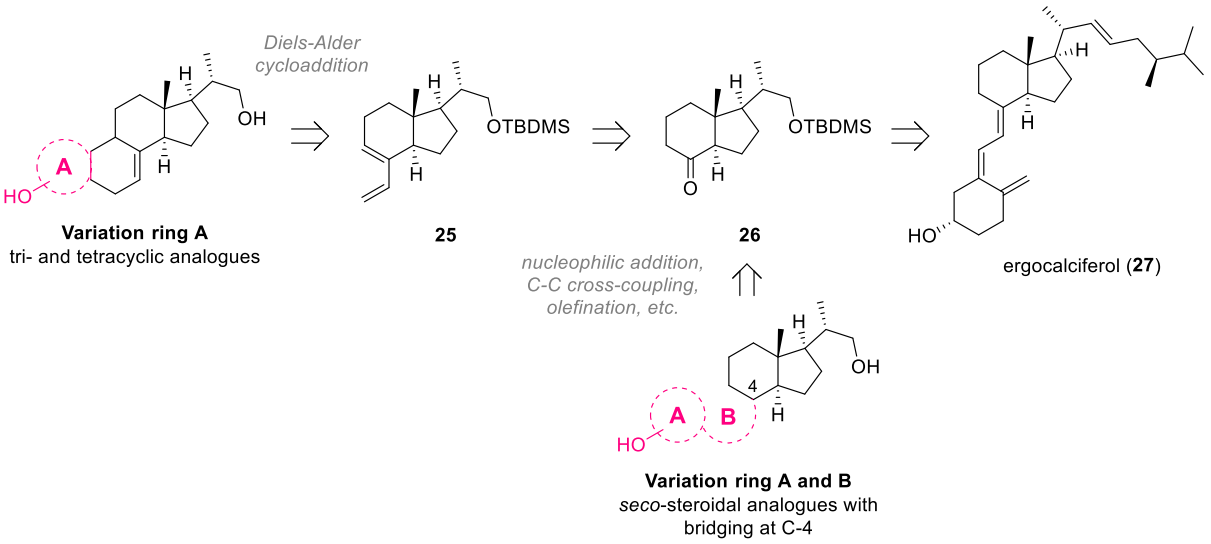
Figure 8. Lead structures **23** and **24**. The areas marked in petrol should be maintained in the target compounds.

Rings C and D, as well as the side chain containing the alcohol function and the hydroxyl group at C-3 of the molecule, should be retained. Consequently, ring A and B should be modified, resulting in tri- and tetracyclic compounds and *seco*-steroidal analogues. In the following, the retrosyntheses of the desired target structures are shown.

2.1. Tri- and tetracyclic compounds and *seco*-steroidal analogues with bridging at C-4 based on central building block **26** (bearing rings C and D)

The first retrosynthesis, which is shown in **Scheme 3**, shows *inter alia*, the formation of tri- and tetracyclic analogues. These should be obtained *via* DIELS-ALDER cycloaddition between various dienophiles and diene **25**. Diene **25** should be formed based on central building block **26** using cross-coupling reactions. Ketone **26** in turn should be obtained *via* ozonolysis of commercially available ergocalciferol (**27**), also known as vitamin D_2, with subsequent TBDMS protection of the primary alcohol group and oxidation of the remaining secondary hydroxyl group. It is important to maintain and thus protect the free primary hydroxyl group in the side chain since it is a necessary element to act as a selective DHCR24 inhibitor.[43] Further analogues, which should also be obtained based on central building block **26** are *seco*-

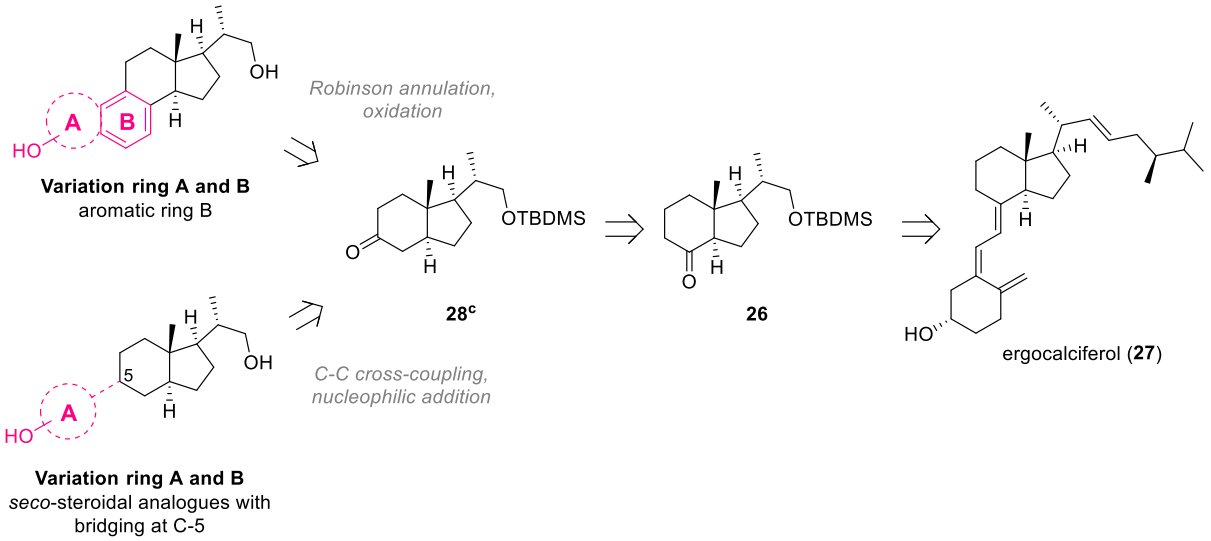
steroidal compounds with bridging at C-4 of the bicyclic building block **26**. In this process, various aliphatic and aromatic residues should be introduced at C-4 position of ketone **26** *via* C-C bond formation using organometallic chemistry, C-C cross-coupling reactions, e.g. SUZUKI-MIYAURA cross-coupling, or olefination methods like WITTIG olefination.



Scheme 3. Retrosynthesis of tri- and tetracyclic analogues based on diene **25** (top), and *seco*-steroidal analogues with bridging at C-4 based on the central building block **26** (bottom). Ketone **26** should be obtained from ergocalciferol (**27**). The moieties which should be introduced are marked in pink.

2.2. Aromatic ring B and *seco*-steroidal analogues based on central building block **28^{c}**

The first attempt of the second retrosynthesis, which is depicted in **Scheme 4**, shows the variation of ring A with concurrent formation of an aromatic ring B.



Scheme 4. Retrosynthesis of the formation of an aromatic ring B based on central building block **28^{c}** (top), and *seco*-steroidal analogues with bridging at C-5 (bottom). Ketone **28^{c}** should be obtained from regioisomer **26**, which in turn should be synthesised from ergocalciferol (**27**). The moieties which should be introduced are marked in pink.

The purpose of the formation of an aromatic ring B is, that both lead structures **23** and **24** showed high efficacy towards the inhibition of DHCR24 (IC_{50} = 0.1 nM (**23**) and 2.5 nM (**24**)), whereby the position of the double bond is probably negligible. With an aromatic ring B, this moiety would be fully planar, and the effect of this geometrical change of the inhibitor can be studied. The aromatic ring B should be obtained *via* ROBINSON annulation of central building block **28^{c}** with methyl vinyl ketone and subsequent copper catalysed oxidative aromatisation. Ketone **28^{c}** should be formed based on the regioisomer **26**, which was discussed in the first retrosynthesis (see chapter 2.1.) and should be synthesised from ergocalciferol (**27**). Another attempt based on central building block **28^{c}** is the synthesis of *seco*-steroidal analogues with bridging at C-5. Aliphatic and aromatic residues bearing hydroxyl groups should be attached *via* organometallic chemistry and C-C cross-coupling reactions like SONOGASHIRA cross-coupling.

3. Results and Discussion

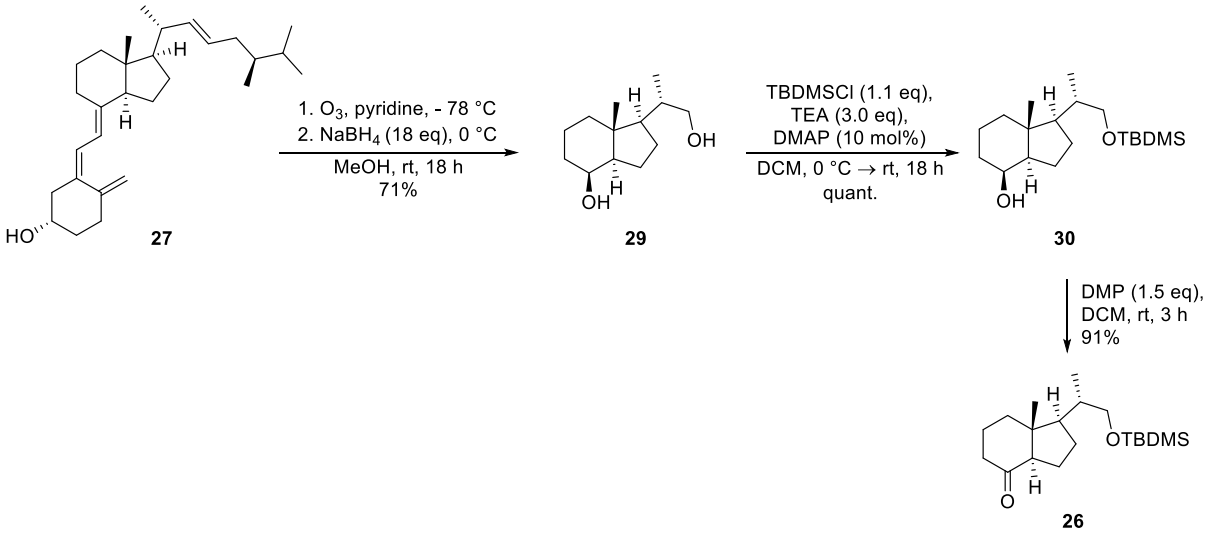
First, the syntheses of the central building blocks are shown followed by the studies towards the synthesis of tri- and tetracyclic compounds and the formation of various *seco*-steroidal analogues with bridging at C-4 and C-5, respectively. Furthermore, during the practical work, a *seco*-steroidal analogue, with an aromatic ring B and a "broken" ring C could be successfully synthesised (see chapter 3.4.).

3.1. Syntheses of the central building blocks **26** and **28c**

Based on ketone **26** and **28c** all analogues, except the studies towards the variation of ring C (chapter 3.4.), were synthesised.

3.1.1. Synthesis of ketone **26**

Central building block **26** was obtained in a three step synthesis (**Scheme 5**). Literature-known ozonolysis of ergocalciferol (**27**) with subsequent reduction using $NaBH_4$ led to the INHOFFEN-LYTHGOE diol **29** with 71% yield.[67-68] Since the primary hydroxyl group in the side chain is a necessary element in the structure of selective DHCR24 inhibitors,[43] it is crucial to selectively protect the alcohol function. Silyl groups are a common protecting group for alcohols, e.g. *tert*-butyldimethylsilyl (TBDMS). TBDMS has a high stability against a variety of influences, for example strong bases like LDA (pKa = 35.7[69]) or reducing agents like $LiAlH_4$,[70] which will be used in further syntheses. The desired *mono*-TBDMS-protected alcohol **30** was successfully obtained in quantitative yield.



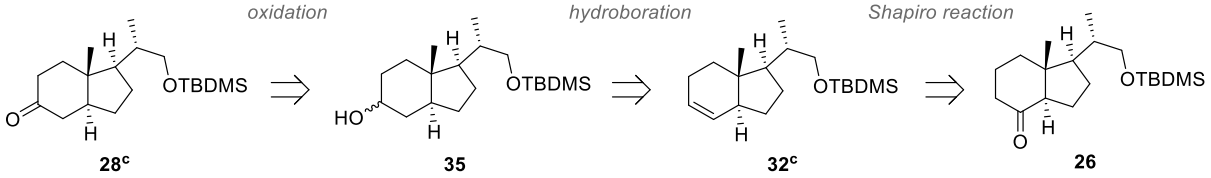
Scheme 5. Synthesis of ketone **26** starting from ergocalciferol (**27**) *via* ozonolysis, selective TBDMS protection and DESS-MARTIN oxidation.[68]

The last step was the oxidation of the remaining secondary alcohol group. As oxidising agent, the hypervalent iodine compound DESS-MARTIN periodinane (DMP) was chosen.[71] In contrast

to chromium reagents like pyridinium dichromate (PDC), which are often used in literature,[72] DMP is a mild and less-toxic alternative and is easy to handle. The desired ketone **26** was isolated with 91% yield.

3.1.2. Synthesis of ketone **28^{c}**

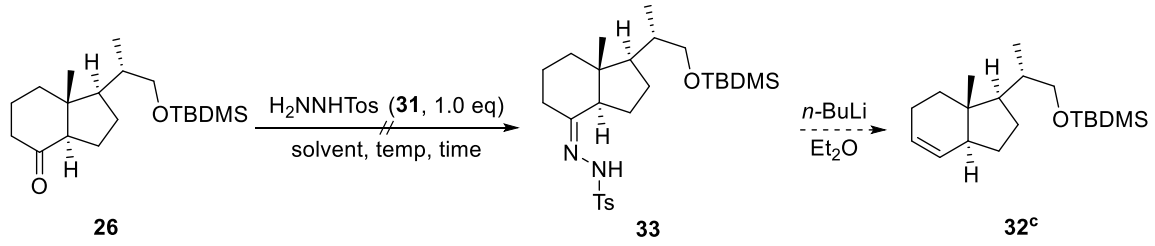
Besides ketone **26**, its regioisomer **28^{c}** is an important central building block for the following syntheses of various *seco*-steroids with bridging at C-5 and for the studies towards an aromatic ring B. This ketone was synthesised during the bachelor thesis of KATHARINA N. KRIEGLER under my supervision.[7] **Scheme 6** depicts the retrosynthesis of ketone **28^{c}**.



Scheme 6. Retrosynthesis of ketone **28^{c}**.

Ketone **28^{c}** should be obtained *via* oxidation of alcohol **35** which in turn should be synthesised from alkene **32^{c}** using hydroboration. Alkene **32^{c}** should be generated based on central building block **26**.

Based on ketone **26**, first, a SHAPIRO reaction,[73-74] which is a variation of the BAMFORD-STEVENS reaction,[75] was attempted (**Scheme 7**).

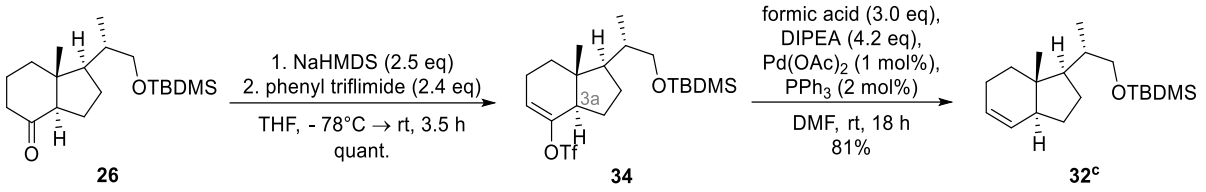


Scheme 7. Attempt for the synthesis of olefin **32^{c}** *via* SHAPIRO reaction.

In this two-step process the appropriate tosylhydrazone **33** should be formed in a condensation reaction of ketone **26** with toluenesulfonylhydrazide (**31**, NH_2NHTos). Deprotonation with *n*-BuLi should result in an elimination of the aryl sulfinate, liberating N_2 during aqueous work-up, leading to alkene **32^{c}**. Various reaction conditions for the formation of the tosylhydrazone **33** were tested. Nevertheless, the desired tosylhydrazone could not be synthesised. Therefore, an alternative approach for the synthesis of alkene **32^{c}** was made.

The idea was to convert ketone **26** into its enol triflate **34**, which then could be easily transformed into alkene **32^{c}** in a palladium-catalysed hydride transfer (**Scheme 8**). The

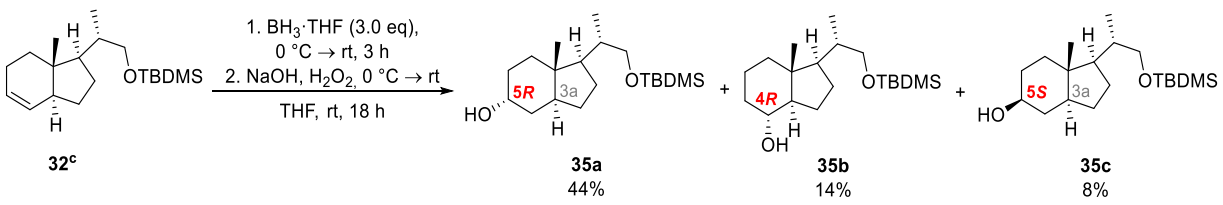
synthesis of enol triflate **34** proceeded in quantitative yield using *N*-phenylbistrifluoromethanesulfonimide (phenyl triflimide) as triflating agent and NaHMDS as base.



Scheme 8. Synthesis of alkene **32ᶜ** *via* enol triflate **34**.

Because of the chosen reaction conditions (strong base and low temperature), the formation of the enol triflate proceeds under kinetic control and the easier accessible proton is eliminated. Thus, only the lower substituted enolate is formed and the stereochemical information at C-3a is maintained. For the following palladium-catalysed hydride transfer two literature-known reaction conditions were tested. A STILLE-type hydride transfer using $Pd(PPh_3)_4$ as catalyst and tributyltin hydride as hydride source[76] did not result in the desired product. An alternative way described by LIU *et al.* uses $Pd(OAc)_2$ as catalyst and formic acid as hydride source.[77] A huge advantage of this reaction in contrast to the STILLE-type reaction is that there is no usage of toxic organotin reagents. The desired olefin was obtained with a high yield of 81%.

To generate the target ketone **28ᶜ**, a hydroxy group in C-5 position *via* hydroboration is introduced. Hereby the resulting stereochemistry of the secondary alcohol at C-5 is negligible since the desired compound has a ketone group at this position, resulting in the loss of stereoinformation. For hydroboration two boron reagents were tried. First, 9-borabicyclo-[3.3.1]nonane (9-BBN), one of the most sterically hindered commercial borane reagents, was used. Due to strong steric hindrance, the reaction to the appropriate alkylborane proceeded very slowly and after 48 h TLC showed no conversion to the desired alcohol. Thus, the reaction was tried using the smaller borane reagent BH_3·THF. After 24 h the formation of three products could be observed *via* TLC and isolated. NMR spectroscopy revealed that besides the epimer of alcohol **30** (see **Scheme 5**), compound **35b** with 14% yield, the 5-hydroxy products **35a** and **35c** were formed and isolated with yields of 44% and 8%, respectively (**Scheme 9**).



Scheme 9. Hydroboration of **32ᶜ** using BH_3·THF. Alcohols **35a**, **35b** and **35c** were isolated with yields of 44%, 14% and 8%. The generated stereocenters are marked in red.

The stereochemistry of the products was determined with NOESY spectroscopy. The NOESY spectrum of **35a** showed no spatial coupling between the 5-H and 3a-H, while the NOESY spectrum of **35c** showed a coupling between 5-H and 3a-H. Furthermore, the structure of **35a** was confirmed by X-ray crystallography (**Figure 9**).

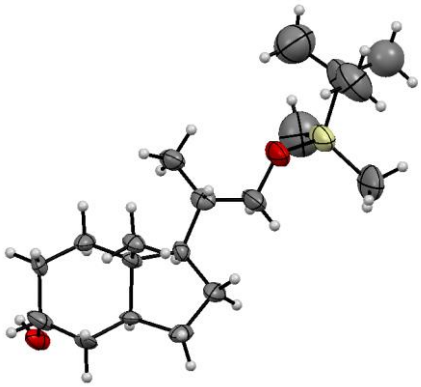
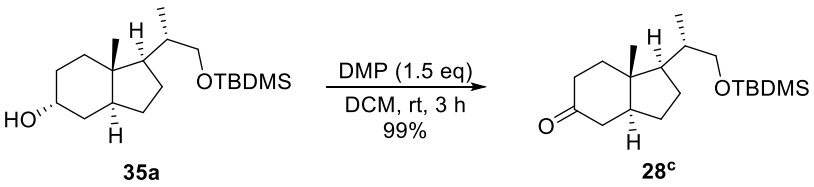


Figure 9. Mercury depiction of the structure of **35a** in the crystalline state. In this case, the hydroxyl group at C-5 is facing to the back, resulting in an *R* configuration.

Since the desired ketone **28^{c}** has the carbonyl group at C-5, only isomers **35a** and **35c** were of interest.



35a **28^{c}**

Scheme 10. Oxidation of **35a** to central building block **28^{a}** using DMP.

The alcohol function of **35a** was oxidised, using DMP and the desired ketone **28^{c}** was isolated in 99% yield (**Scheme 10**). Futhermore, **35c** was oxidised, resulting in **28^{c}** with 97% yield

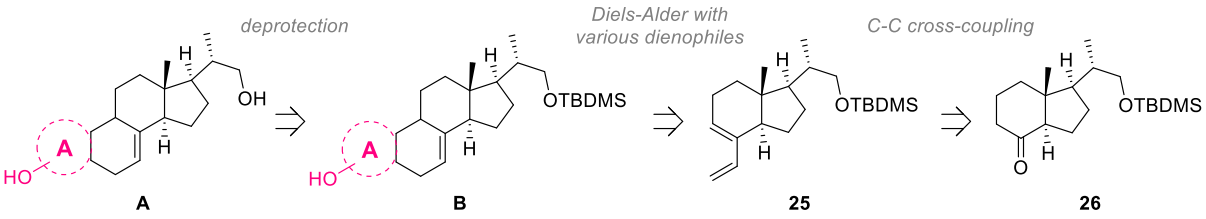
3.2. Variations of ring A and B – tri- and tetracyclic steroid-like analogues

After successful synthesis of the central building blocks **26** and **28^{c}**, variations of ring A and B could be synthesised. In this chapter the synthesis of tri- and tetracyclic steroid analogues is discussed, including the studies towards the formation of an aromatic ring B.

3.2.1. Variation of ring A – [4+2] cycloadditions

The first chapter of tri- and tetracyclic steroid analogues focuses on the variation of ring A with maintenance of ring B. For this purpose, [4+2] DIELS-ALDER cycloadditions are a suitable option for the simultaneous construction of rings A and B. **Scheme 11** shows the general retrosynthesis of the tri- and tetracyclic compounds. Tri- or tetracyclic compounds **A** should be formed after deprotection of DIELS-ALDER compounds **B** using diene **25**. A huge benefit of this

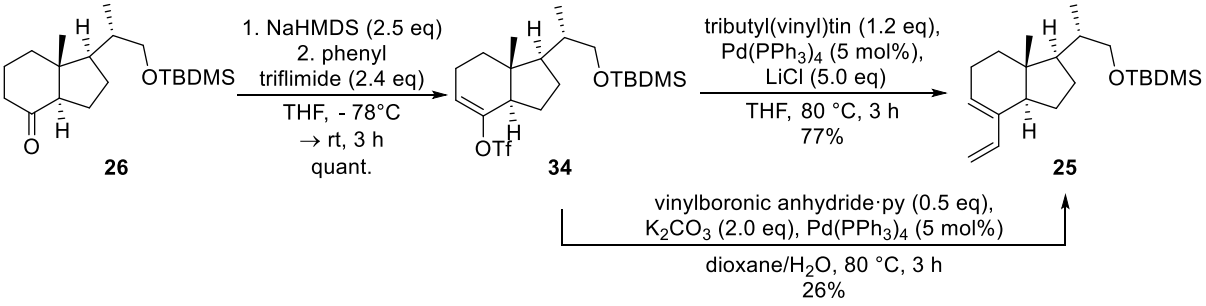
reactions is, that the cycloaddition products contain a Δ^7-double bond like lead structure **23**. Diene **25** should be obtained from central building block **26** *via* an enol triflate, followed by vinylation in a cross-coupling reaction.



Scheme 11. Retrosynthesis of tri- and tetracyclic compounds based on central building block ketone **26**. The new generated ring A is marked in pink, whereby the dashed line indicates cycles as well as chains.

3.2.1.1. Synthesis of diene **25**

For the synthesis of diene **25** a procedure from MAYER *et al.* was used, who synthesised tetracyclic compounds based on GRUNDMANN'S ketone, which is obtained *via* ozonolysis of cholecalciferol, also known as vitamin D_3.[78] Starting from building block **26** (for synthesis see chapter 3.1.1.), the first step was the formation of the appropriate enol triflate **34**, which was already discussed in chapter 3.1.2. (**Scheme 12**). Based on enol triflate **34**, cross-coupling attempts were made, to form the desired diene **25**.



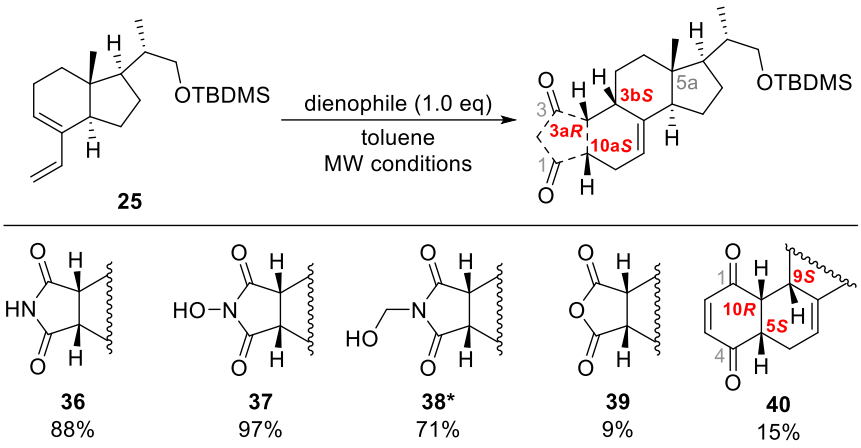
Scheme 12. Synthesis of diene **25**, based on ketone **26** *via* its enol triflate **34**, followed by STILLE or SUZUKI-MIYAURA cross-coupling.

SUZUKI-MIYAURA cross-coupling, using vinylboronic anhydride and K_2CO_3 as base, gave the desired diene **25** in moderate yield (26%). However, the yield could be increased to 77% with STILLE cross-coupling conditions, using tributyl(vinyl)tin and LiCl.

3.2.1.2. Tetracyclic compounds: cycloadditions using typical DIELS-ALDER dienophiles

To explore the scope of diene **25** towards [4+2] cycloadditions, first, typical DIELS-ALDER dienophiles were used. **Scheme 13** shows all performed cycloadditions using typical DIELS-ALDER dienophiles like maleimide and derivatives, maleic anhydride and benzoquinone, whereby a the procedure of MAYER *et al.* was used.[78] Instead of refluxing the reaction mixture, the reaction was performed using microwave irradiation to shorten the reaction time. DIELS-

ALDER reaction between diene **25** and maleimide gave tetracyclic **36** with a good yield of 88%, whereby the *N*-hydroxylated version of maleimide gave **37** in nearly quantitative yields. Dienophile 1-(hydroxymethyl)-1*H*-pyrrole-2,5-dione (**41**), which was used for the formation of DIELS-ALDER adduct **38**, was synthesised according to a procedure of TAWNEY *et al.* in 69% yield,[79] and the following cycloaddition went well with an isolated yield of 71%.



Scheme 13. General [4+2] DIELS-ALDER cycloaddition (top) and the isolated DIELS-ALDER adducts (bottom). The new stereocenters are marked in red. *Dienophile **41** was synthesised according to literature in 69% yield.[79]

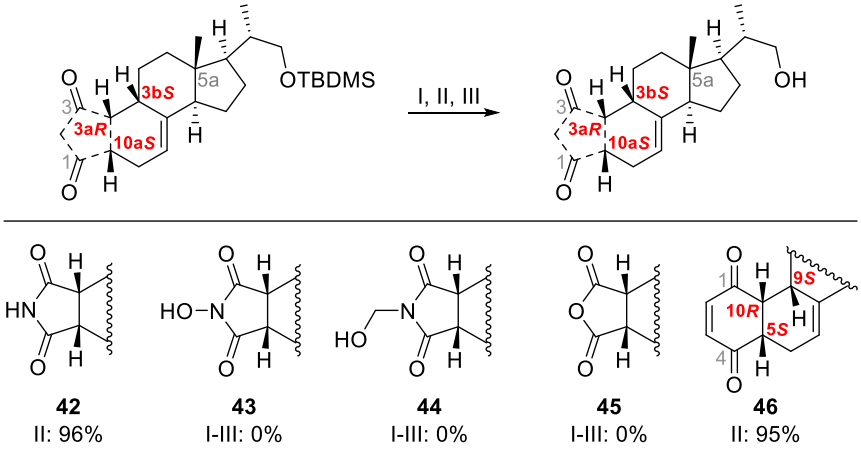
Cycloaddition of maleic anhydride and diene **25** showed a very good conversion on TLC. However, anhydride **39** decomposed immediately during the purification process on SiO_2. The replacement of the light acidic SiO_2 with basic Al_2O_3 was not successful and **39** decomposed again. Nevertheless, fast FCC with neutralised SiO_2 (using TEA) gave **39** in 9% isolated yield. Organic anhydrides are labile functional groups and can be hydrolysed easily, which explains the low yield after purification. However, purifcation was necessary after cycloaddition, since ^{1}H NMR spectrum of crude **39** showed some impurities. Cycloaddition of diene **25** and *p*-benzoquinone gave **40** in 15% isolated yield. A reason for the low yield could be, that the MICHAEL acceptor *p*-benzoquinone is a very reactive component in this reaction,[80-81] which can lead to several side products. Unidentifiable side products could also be observed on TLC. The stereoconfiguration of the new stereocenters were identified by NOESY spectroscopy. A strong coupling between 3b-H and 5a-CH_3 as well as a coupling between 3a-H/10a-H and 3b-H could be observed, resulting in 3a*R*, 3b*S* and 10a*S* configuration for all products (for tetracycle **40** 5*S*, 9*S* and 10*R* configuration according to IUPAC nomenclature).

The final step to the target compounds is the deprotection of the alcohol function in the side chain. For the TBDMS deprotection three methods were explored on the model compound **36** (**Scheme 14**). Fluoride sources are known to cleave silyl ethers. Therefore, the first attempt was the usage of TBAF/TEA (**Scheme 14**, I),[68] whereby the free primary alcohol could be isolated in 59% yield.

I: TBAF (1.5 eq), TEA (2.0 eq), dry THF, rt, 18 h, 59%
II: HF·py (2.2 eq), pyridine (2.3 eq), EtOAc, rt, 18 h, 96%
III: NIS (5 mol%), MeOH, rt, 18 h, 89% yield with 17% NIS impurity

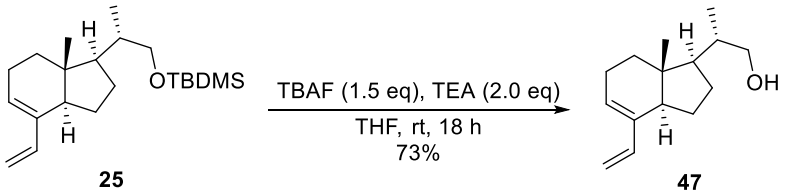
Scheme 14. Attempts for the TBDMS deprotection of model compound **36**.

In another attempt, the use of HF·py and pyridine was tested (**Scheme 14**, II).[82] The desired alcohol could be obtained in excellent yield (96%). Besides fluoride sources, catalytic amounts of *N*-iodosuccinimide (NIS) can cleave silyl ethers as well (**Scheme 14**, III).[83] The reaction proceeded very well, but even though the product was purified thrice with FCC, an NIS impurity of 17% (determined by ^{1}H NMR) could not be removed. Hence, the first two attempts were used. **Scheme 15** demonstrates the deprotected DIELS-ALDER adducts. Besides **42**, only dione **46** could be isolated in very good yields (95%).



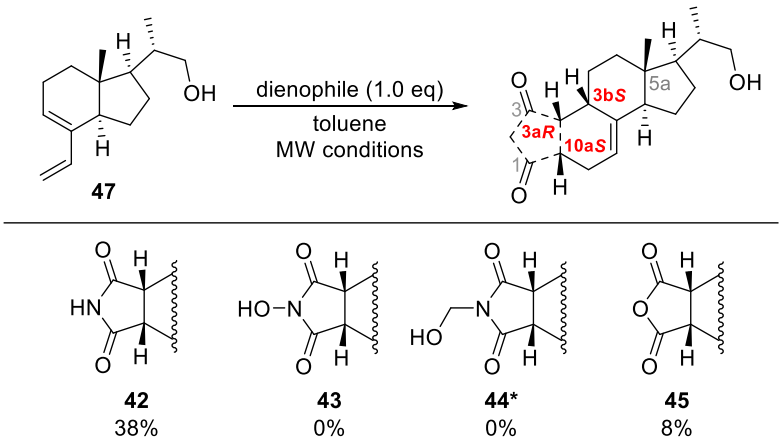
Scheme 15. Deprotection of the DIELS-ALDER adducts with methods I, II, III.

It is noteworthy, that TLC showed successful deprotection attempts, but products **43**, **44** and **45** decomposed during the purification process, although various stationary phases (Al_2O_3, (neutralised) SiO_2) were used for FCC. Due to decomposition during the chromatographic purification process, it was tried to deprotected diene **25** before the cycloaddition, to possibly forego the purification process (**Scheme 16**).



Scheme 16. Deprotection of **25** using TBAF/TEA, resulting in diene **47**.

Alcohol **47** could be synthesised in 73% yield under standard conditions. **Scheme 17** illustrates the cycloaddition of deprotected diene **47** with, *inter alia*, maleimide as model compound, whereby alcohol **42** could be isolated in moderate yield of 38%. Since deprotection after DIELS-ALDER reaction resulted in a very good yield of **42** (96%), the attempt using DIELS-ALDER reaction after deprotection showed a decrease in the yield. One possible reason can be the poor solubility of **47**, which means that **47** was not converted completely.



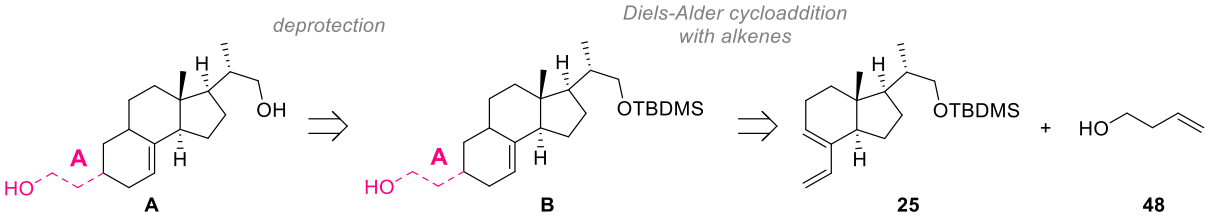
Scheme 17. Attempts for the DIELS-ALDER cycloaddition using deprotected diene **47** and maleimide, *N*-hydroxy maleimide, *N*-hydroxymethyl maleimide and maleic anhydride as dienophiles. The new stereocenters are marked in red. *Dienophile **41** was synthesised according to literature in 69% yield.[79]

As a result, purification by FCC was crucial in this step. Next to **42**, dione **45** could be isolated in this way, but only in a poor yield of 8%, probably due to fast hydrolysation. The stereocenters at C-3a, C-3b and C-10a could be again identified with NOESY spectroscopy as 3a*R*, 3b*S* and 10a*S* configurated. The *N*-hydroxylated imide **43**, as well as the *N*-hydroxymethylated imide **44** could not be isolated.

3.2.1.3. Tricyclic compounds: cycloadditions using MICHAEL systems

After several variations of ring A obtained by DIELS-ALDER cycloadditions with monocyclic dienophiles resulting in tetracyclic compounds, the aim was now to form tricyclic compounds, whereby these bear open chain fragments of ring A, especially a hydroxy group resembling 3-OH of the steroidal lead structures. **Scheme 18** shows the retrosynthesis of the target molecule diol **A**, which should be formed after deprotection of TBDMS-protected tricycle **B**. **B** should be

obtained by DIELS-ALDER cycloaddition of diene **25** and aliphatic alkenes bearing alcohol functions or precursors thereof, like alcohol **48**.

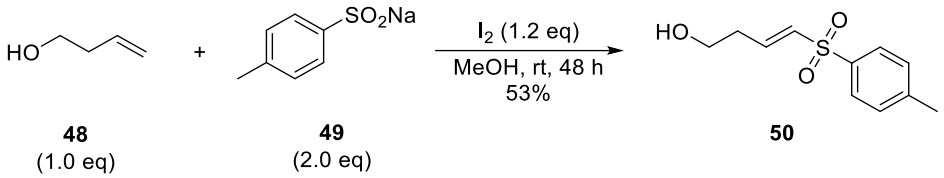


Scheme 18. Retrosynthesis of target compound diol **A**.

Since olefinic dienophiles typically need to bear conjugated electron withdrawing groups, e.g. carbonyl groups, to undergo successful cycloaddition, the use of an alcohol with a terminal olefin was a futile attempt. Therefore, we first tried to introduce an electron withdrawing group to transform a plain olefin into a reactive dienophile.

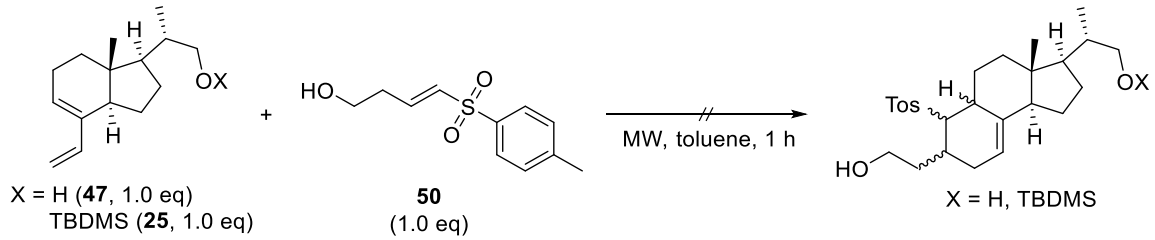
3.2.1.3.1. Introduction of electron withdrawing elements to obtain reactive dienophiles

An electron withdrawing group is for example the *p*-toluenesulfonyl group (tosyl). The introduction of the tosyl group to 3-buten-1-ol (**48**) resulting in the literature-known vinyl sulfone **50** was performed according to a procedure of CATURLA and NÁJERA.[84] In the presence of sodium 4-toluenesulfinate (**49**) and iodine the desired dienophile **50** could be obtained stereoselectively in *E*-configuration in a moderate yield of 53% (**Scheme 19**).



Scheme 19. Synthesis of the appropriate vinyl sulfone **50**, based on 3-buten-1-ol (**48**).

The *E*-configuration could be a problem for the following cycloaddition since the accessibility can be limited for the cycloaddition due to steric hindrance of the big tosyl group. The following cycloaddition was performed with the unprotected diene **47**, as well as with its TBDMS-protected version **25**, under microwave conditions (**Scheme 20**).

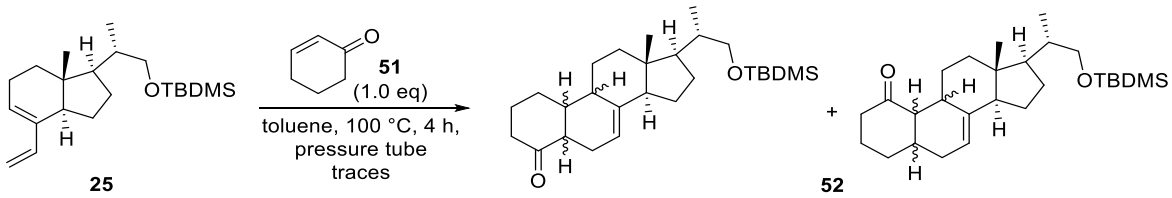


Scheme 20. Cycloaddition between unprotected diene **47** and TBDMS-protected diene **25**, respectively, with vinyl sulfone **50** under microwave conditions.

Unfortunately, no reaction occurred, and the starting material was left unreacted. There are some possible reasons for the failure of this reaction: The *E*-configuration of dienophile **50**, and consequently the sterically hindered sulfinate residue, or the introduction of just one electron withdrawing group was not enough. Therefore, in further reactions, other dienophiles, like MICHAEL systems, were tried, to obtain the target structures.

3.2.1.3.2 Cycloadditions using MICHAEL systems as dienophiles

In this chapter, DIELS-ALDER cycloadditions with "naked" MICHAEL systems as dienophiles are discussed. The first test reaction was perfomed with cyclohexenone **51** as dienophile (**Scheme 21**). Instead of microwave irradiation, the reaction mixture was heated to 100 °C in a pressure tube.

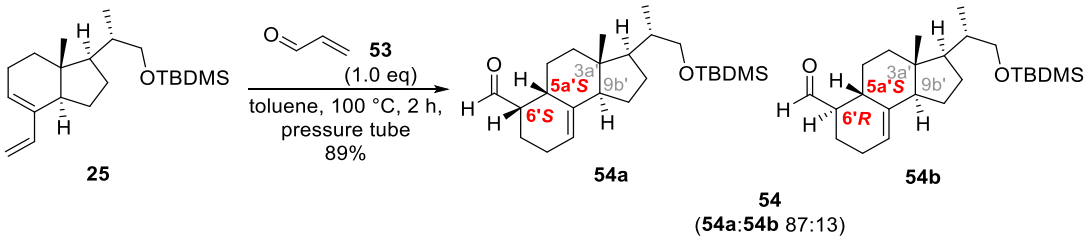


Scheme 21. DIELS-ALDER cycloaddition of diene **25** and cyclohexenone **51**.

The desired mass of *m*/*z* 430.3267 could be detected *via* GC/MS analysis, but TLC showed a smearing line of spots. After purification by FCC only unidentifiable products were obtained and target product **52** could not be isolated. Since these conditions were already too harsh for the starting materials, the reaction was not performed again with microwave irradiation.

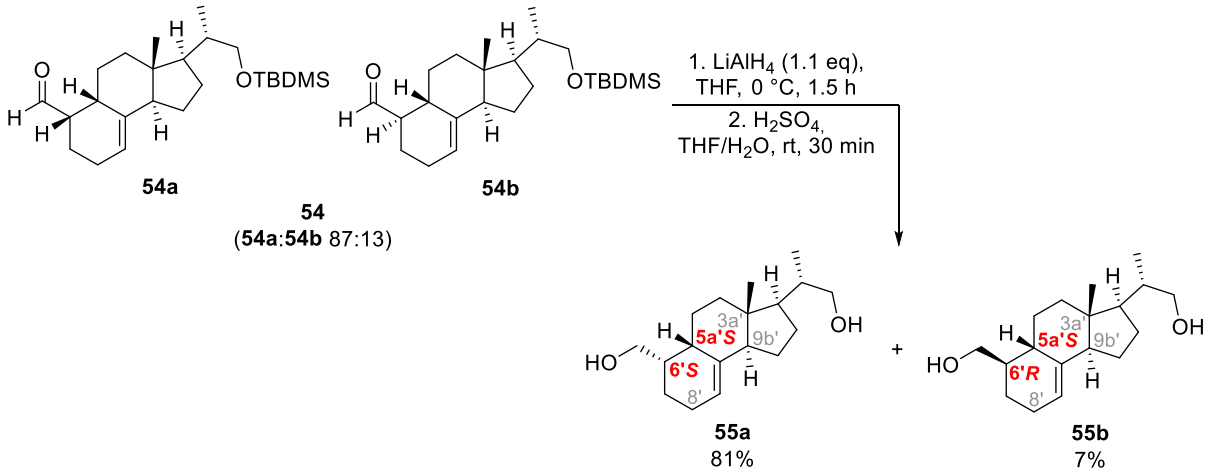
The next attempt was the usage of acrolein (**53**) as dienophile since it would result in the desired tricyclic target structure **A** (**Scheme 18**). Two diastereomers **54a** and **54b** were isolated with an isomeric ratio of 87:13 (determined *via* ^{1}H NMR) in a good yield of 89% (**Scheme 22**). It is noteworthy, that both isomers could not be separated by FCC, since they have the same R_f value (0.16 in hexanes/EtOAc 98:2). NMR analysis revealed that the wrong constitutional isomers were formed. Both isomers have the residue attached to C-6' and only differ in the newly built stereocenter at C-6'. Besides C-6', the stereocenter at C-5a' was built. The stereoconfiguration at C-5a' of both isomers could be identified as *S* configurated since both 5a'-H show a spatial coupling to the nearest proton of 3a'-CH_3. Moreover, no coupling can be seen between 5a'-H and 9b'-H.

The stereocenter at C-7' in **54a** has *S* configuration as well. 6'-H and 9b'-H form one multiplett, whereby this multiplett shows a coupling with 5a'-H. Since 9b'-H is definitely facing to the back, the observed coupling is between 5a'-H and 6'-H, resulting in S configuration of C-6' in **54a**. In **54b**, C-6' is *R* configurated since no coupling between 5a'-H and 6'-H can be observed. Moreover, a (weak) coupling between 6'-H and 9b'-H can be seen.



Scheme 22. DIELS-ALDER cycloaddition of diene **25** and acrolein (**53**), resulting in an inseparable mixture of **54a** and **54b** with an isomeric ratio of 87:13 (determined *via* ^{1}H NMR). The new stereocenters are marked in red.

To obtain the desired alcohol function in the western part of the molecule, reduction of **54** with $LiAlH_4$ was performed (**Scheme 23**). The alcohol chain is in this case two carbon atoms shorter than the lead **23**. But as the necessary dimensions of the molecule to be a potent inhibitor have not yet been explored these molecules could give further insight into the binding mode. During the work-up process of the reaction, $Al(OH)_3$ precipitated and was consequently dissolved with concentrated H_2SO_4. As a result, the hydroxyl group in the side chain was deprotected and diols **55a** and **55b** were obtained. The mixture was separated by FCC and diol **55a** was isolated in 81% yield and diol **55b** in 7% yield. The actual ratio between both isomers was not determined since mixed fractions were obtained and a crude ^{1}H NMR was not measured.

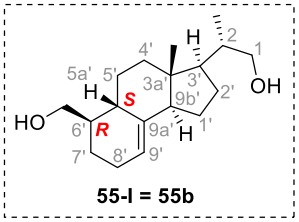


Scheme 23. Reduction of the aldehyde group of regioisomeric mixture **54** with subsequent TBDMS deprotection using conc. H_2SO_4, resulting in the separable compounds **55a** and **55b**. The stereocenters are marked in red.

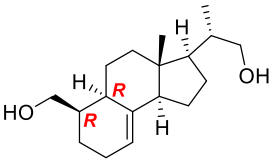
The stereoconfiguration at C-5a' and C-6' in both isomers could be identified with NOESY spectra and the calculated distances between characteristic protons (**Table 1**). Starting with isomer **55a**, a clear spatial coupling can be seen between 5a'-H and the nearest proton of 3a'-CH_3 (**Table 1**, marked in yellow), whereby no coupling is observable between 5a'-H and 9b'-H (**Table 1**, marked in green), which results in *S* configuration at C-5a' (**Table 1**, **55-I** or **55-III**). For the stereoconfiguration at C-6', first, the right position of 6'-H had to be identified in within the multiplett (2.03 – 1.82 ppm) *via* HMQC. A clear coupling can be observed between 6'-H

and 5a'-H (**Table 1**, marked in blue), resulting in isomer **55-III** with *S* configuration at C-6'. For isomer **55b**, 5a'-H shows a spatial coupling to 3a'-CH_3 (**Table 1**, marked in yellow), whereby no coupling can be seen between 5a'-H and 9b'-H (**Table 1**, marked in green), which results again in *S* configuration at C-5a' (**Table 1**, **55-I** or **55-III**). After identification of the location of 6'-H within the multiplett (1.40 – 1.17 ppm) *via* HMQC, a clear spatial coupling between 6'-H and 9b'-H can be observed. All calculated distances were too large for this strong coupling (**Table 1**, marked in pink), but **55-I** would be the likeliest. Moreover, no coupling can be observed between 6'-H and 5a'-H (**Table 1**, marked in blue).

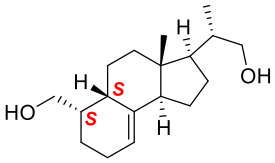
Table 1. Calculated distances between characteristic protons. For calculation details see chapter 6.1. Materials and methods. The distances are indicated in Å.



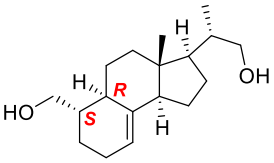
55-I = 55b



55-II



55-III = 55a

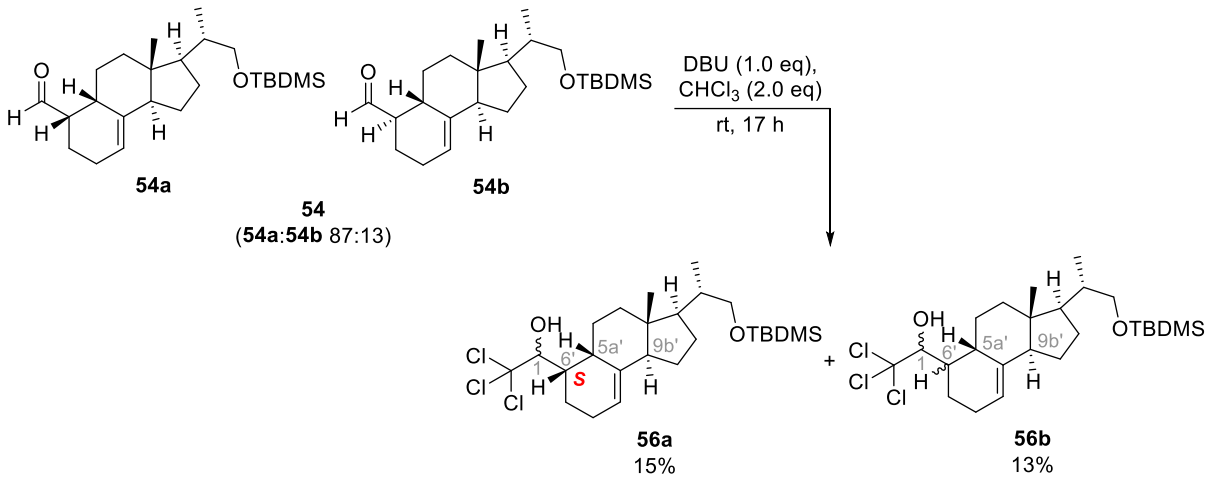


55-IV

Compound	Protons	5a'-H	6'-H	7'-H	9b'-H	6'-CH_2
55-I	**3a'-CH_3**	2.129	4.955	4.058	3.849	5.243
	5a'-H	-	3.062	2.506	3.687	3.235
	6'-H	-	-	2.522	3.845	2.453
	7'-H	-	-	-	5.252	2.448
	9b'-H	-	-	-	-	5.216
55-II	**3a'-CH_3**	4.217	5.061	3.346	3.844	4.809
	5a'-H	-	2.278	3.840	2.374	3.442
	6'-H	-	-	2.504	4.184	2.444
	7'-H	-	-	-	5.084	2.473
	9b'-H	-	-	-	-	5.495
55-III	**3a'-CH_3**	2.144	4.517	3.998	3.849	5.532
	5a'-H	-	2.375	2.461	3.665	3.782
	6'-H	-	-	2.406	4.861	2.464
	7'-H	-	-	-	5.240	3.184
	9b'-H	-	-	-	-	3.595
55-IV	**3a'-CH_3**	4.189	3.524	5.427	3.820	5.142
	5a'-H	-	3.063	2.735	2.542	2.523
	6'-H	-	-	2.485	4.767	2.510
	7'-H	-	-	-	4.459	2.585
	9b'-H	-	-	-	-	5.055

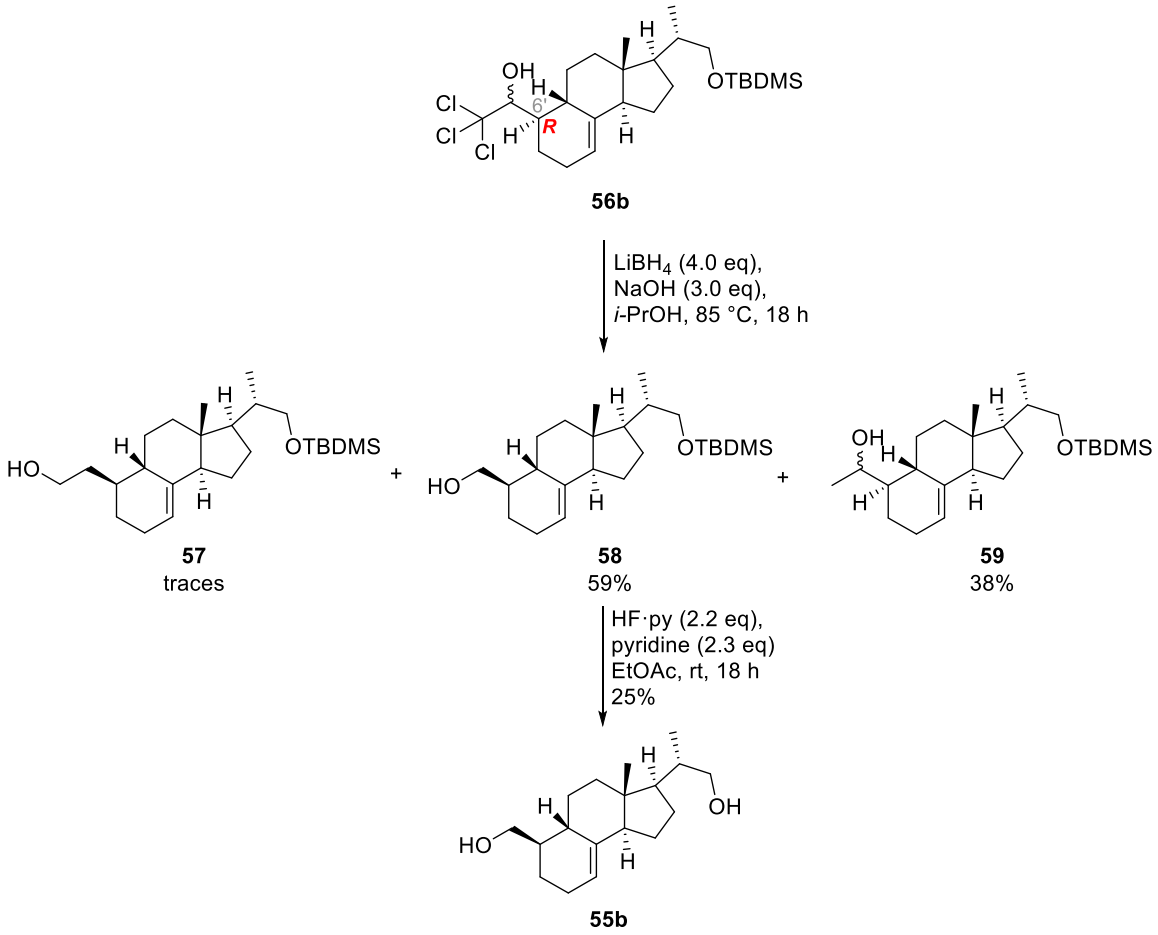
As a result, C-6' has *R* configuration (**Table 1**, **55-I**). The determined stereocenters C-6' and C-5a' in **55a** and **55b** are in accordance to the analysed stereocenters in the diastereomeric mixture of **54**.

Since the hydroxyl chain of **55a** and **55b** is two carbon atoms too short, the next attempt should lead to an extension of this chain, a so-called C-homologation. SNOWDEN and co-workers developed a one-carbon JOCIC-type homologation of aldehydes.[85] Based on the mixture of aldehydes **54**, first, the trichloromethylcarbinols were prepared using a method of AGGARWAL and MEREU.[86] In the presence of DBU and $CHCl_3$ the two trichloromethylcarbinols **56a** and **56b** could be synthesised and separated by FCC (**Scheme 24**). The stereocenter at C-6' in **56a** could be determined as *S* configurated since a clear coupling between 6'-H and 5a'-H could be observed. It could not be analysed which stereoconfiguration at C-1 was formed. The stereochemistry at position C-6' in **56b** could not be identified in this step since HMQC spectra did not allow the determination of the location of 5a'-H and 9b'-H in their small multiplett (2.44 – 2.32 ppm). Moreover, the configuration at C-1 could not be identified as in isomer **56a**. But as the stereoinformation at C-1 will be lost after this reaction, the stereoconfiguration at C-1 can be neglected.



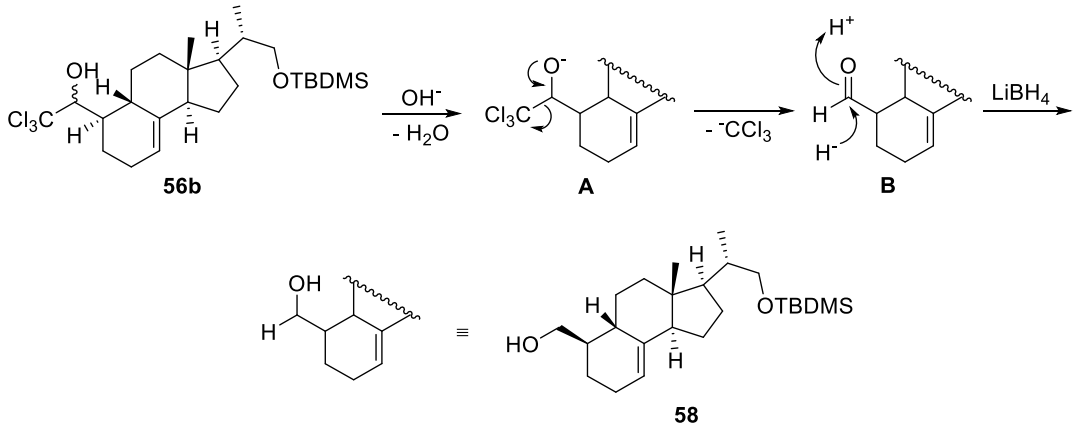
Scheme 24. Synthesis of trichloromethylcarbinols **56a** and **56b** starting from regioisomeric mixture **54**.

Now, based on **56a** and **56b**, C-homologation *via* a JOCIC-type reaction was attempted using $LiBH_4$ and NaOH (**Scheme 25**).[85] Due to low and with **56b** contaminated amount of **56a** the reaction was first carried out with pure **56b**. The desired mass could be detected *via* GC/MS but **57** could not be isolated. However, two related compounds were isolated: alcohol **58**, which is the protected version of **55b** and alcohol **59**, which is according to literature a typical side product in this reaction.[85]



Scheme 25. Results of the JOCIC-type C-homologation of **56b**.

Scheme 26 shows a possible mechanism for the formation of **58** from **56b** *via* a base-mediated inversion of the synthesis of the carbinols. With the presence of NaOH, the alcohol function of **56b** will be deprotonated and alcoholate **A** is formed. **A** can now undergo elimination of trichloromethylcarbanion ($^{-}CCl_3$) by generating aldehyde **B**. The aldehyde function will be reduced by $LiBH_4$ to alcohol **58**.

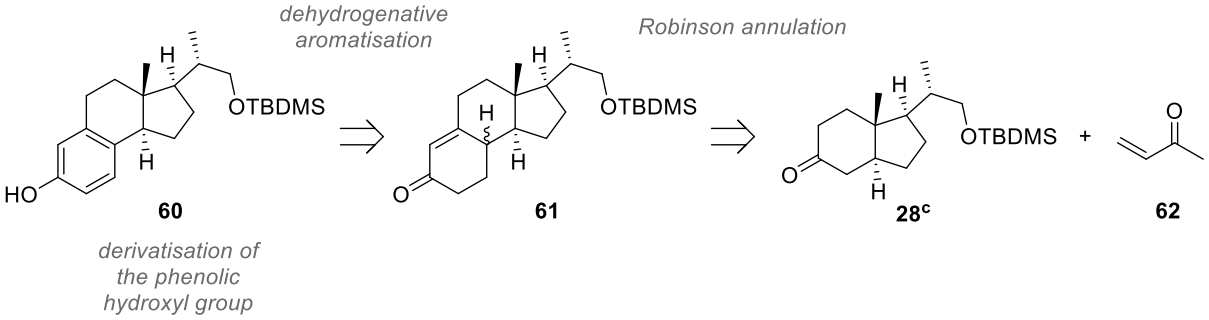


Scheme 26. Possible mechanism for formation of **58** from **56b**.

Deprotection of **58** using HF·py and pyridine resulted in **55b** in 25% yield, which confirms the formation of **58**. Unfortunately, a sufficent amount of **57** could not be isolated for full characterisation and for further reactions. With the formation of **55b** the stereochemistry at C-6' of **56b** could be determined retrospectively as *R* configurated (**Scheme 25**).

3.2.2. Variation of ring A and B – aromatic ring B

Since the IC_{50} values of lead structures **23** (Δ^7-sterol) and **24** (Δ^5-sterol) have shown, that the position of the double bond in ring B is negligible, aromatisation and planarisation of ring B and how this modification affects the inhibitory efficacy was of great interest. **Scheme 27** demonstrates the retrosynthesis of phenol **60**, bearing an aromatic ring B.



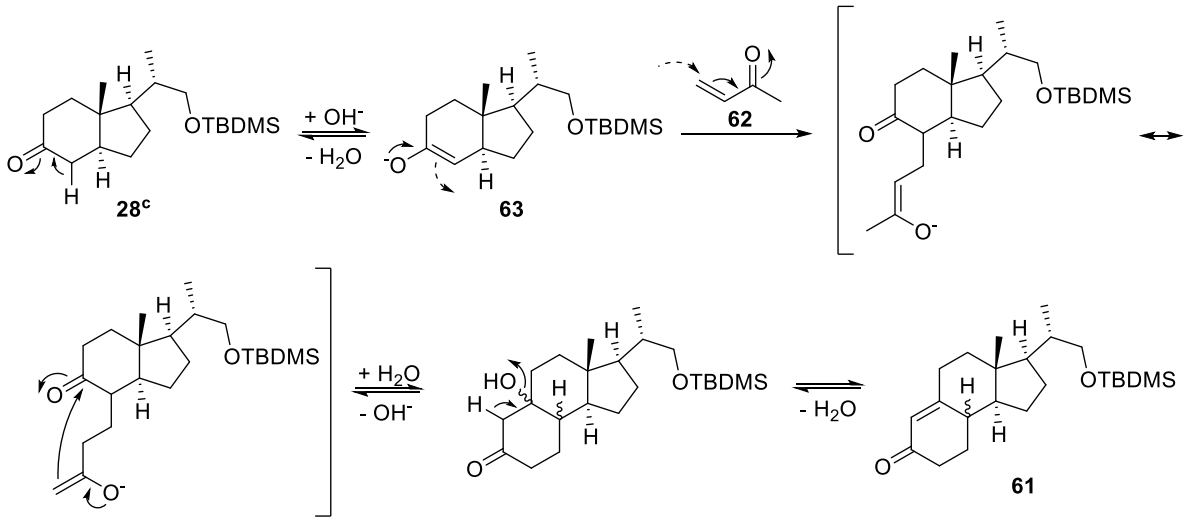
Scheme 27. Retrosynthesis of phenolic tricycle **60** based on central building block **28c**.

Based on phenol **60**, the reactivity of the phenolic hydroxyl group should be exploited, and various derivatives synthesised. Phenol **60** should be formed *via* dehydrogenative aromatisation of ketone **61**, which in turn should be generated *via* ROBINSON annulation out of central building block **28c** and methyl vinyl ketone (**62**). The following studies were part of the bachelor thesis of PATRICIA L. SKOWRONEK, which was performed under my supervision.[87]

3.2.2.1. ROBINSON annulation

A ROBINSON annulation comprises a MICHAEL addition with subsequent intramolecular Aldol condensation. In this case central building block **28c** (chapter 3.1.2.) should be added to methyl vinyl ketone (**62**) *via* 1,4-MICHAEL addition. **Scheme 28** shows the mechanism of this type of reaction with ketone **28c** under basic conditions.

In the first step, enolate **63** is formed by deprotonation of ketone **28c**. Due to the electron withdrawing keto group of **28c** the protons next to it are acidic, and therefore the deprotonation can occur on the left or right side of the ketone. This depends on various aspects, e.g. steric hindrance. However, for our purpose the deprotonation should occur at C-4. The formed enolate can now attack the MICHAEL system, in our case methyl vinyl ketone (**62**), in a 1,4-MICHAEL addition. Keto-enol-tautomerisation of the formed enolate enables the following Aldol addition, forming ring B. Dehydration should give ketone **61**.



Scheme 28. Mechanism of the ROBINSON annulation exemplified by central building block **28c** and methyl vinyl ketone (**62**) under basic conditions.

The ROBINSON annulation can be carried out under basic and acidic conditions. **Table 2** shows the explored conditions.

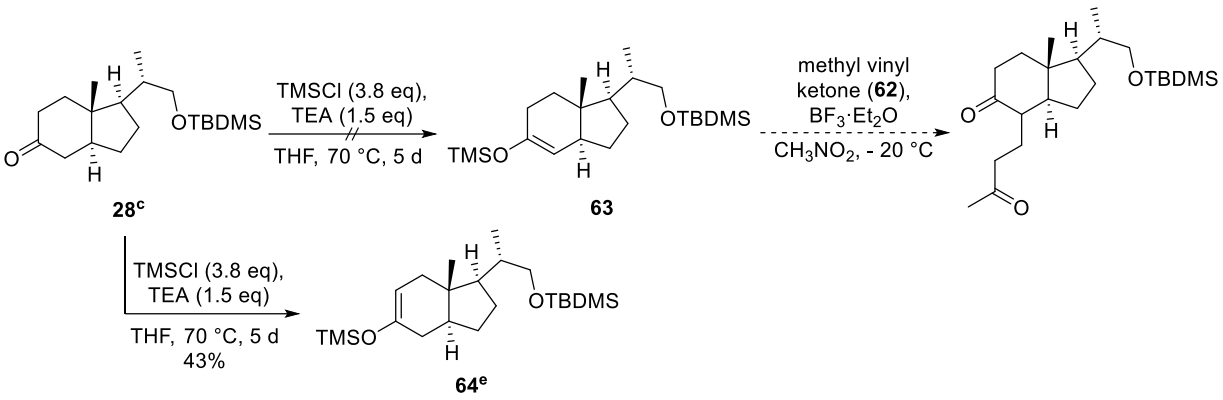
Table 2. Reaction conditions for the ROBINSON annulation between methyl vinyl ketone **62** and central building block **28c**. [e]Entries were perfomed by PATRICIA SKOWRONEK.[87]

entry	catalyst	solvent	T [°C]	t [h]	yield (**61**)
1	conc. H_2SO_4 (20 mol%)	toluene	115	17	-
2[e]	conc. H_2SO_4 (1.3 eq)	toluene	115	17	-
3[e]	KOH (2 mol%)	EtOH	42	18	-

Entry 1 and 2[e] follows a method of HEATHCOCK *et al.* using conc. H_2SO_4 as catalyst.[88] Catalytic amount as well as stochiometric amounts were tried, but both conditions did not result in any product. BERGMANN *et al.* described a method using KOH as catalyst,[89] but the product could not be identified in this approach either (entry 3[e]).

3.2.2.2. Trapping/imitating the enolate

A possible reason for the failed ROBINSON annulation, is the unsuccessful formation of the MICHAEL adduct, which could never be detected by GC/MS analysis. Hence, the idea was to trap the initial enolate as a silyl enol ether before the actual MICHAEL addition was performed. **Scheme 29** depicts the reaction. Based on a method of QUINIO *et al.*, ketone **28c** was converted to the appropriate silyl enol ether **63** using TMSCl and TEA.[90] The mass of the desired silyl enol ether was found by GC/MS, but NMR spectroscopy revealed that the constitutional isomer **64e** was obtained.



Scheme 29. Attempt for trapping the enolate as a silyl enol ether **63** resulting in the formation of isomer **64ᵉ**.

Figure 10 depicts the COSY spectrum of **64ᵉ**. The COSY spectrum shows a strong correlation between 6'-H and 7'-H and not between 4'-H and 3a'-H. The 7-H protons were assigned *via* $^{4}J_{H,H}$ coupling between 7'-H and 7a'-CH_3.

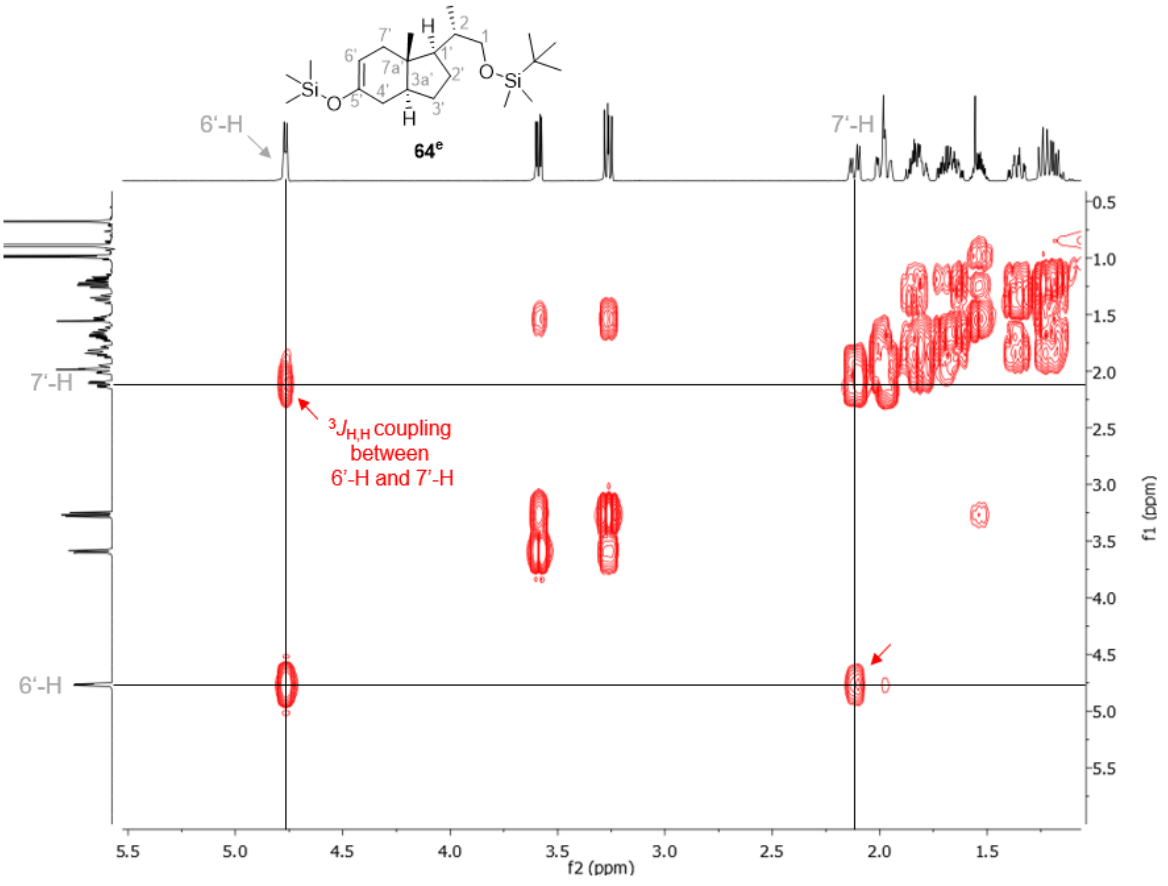


Figure 10. COSY spectrum of silyl enol ether **64ᵉ**.

Concerning acidity, both positions 4'-H and 6'-H should be equal, which means the only possible reason for the formation of this undesired constitutional isomer is steric hindrance. **Figure 11** shows a possible conformation of **28ᶜ**. In this case 6'-H is more accessible than 4'-H. Consequently, TEA cannot attack properly 4'-H.

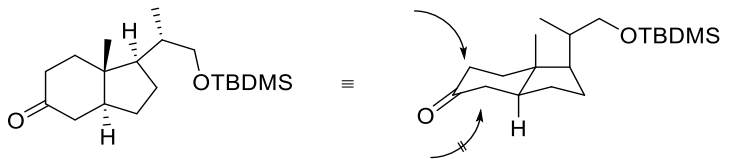
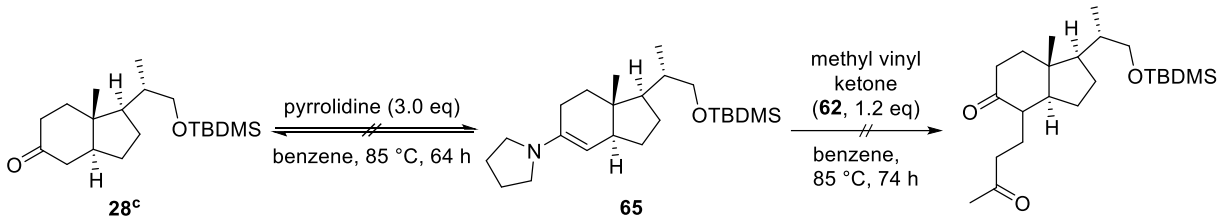


Figure 11. A possible conformation of central building block **28^{c}**.

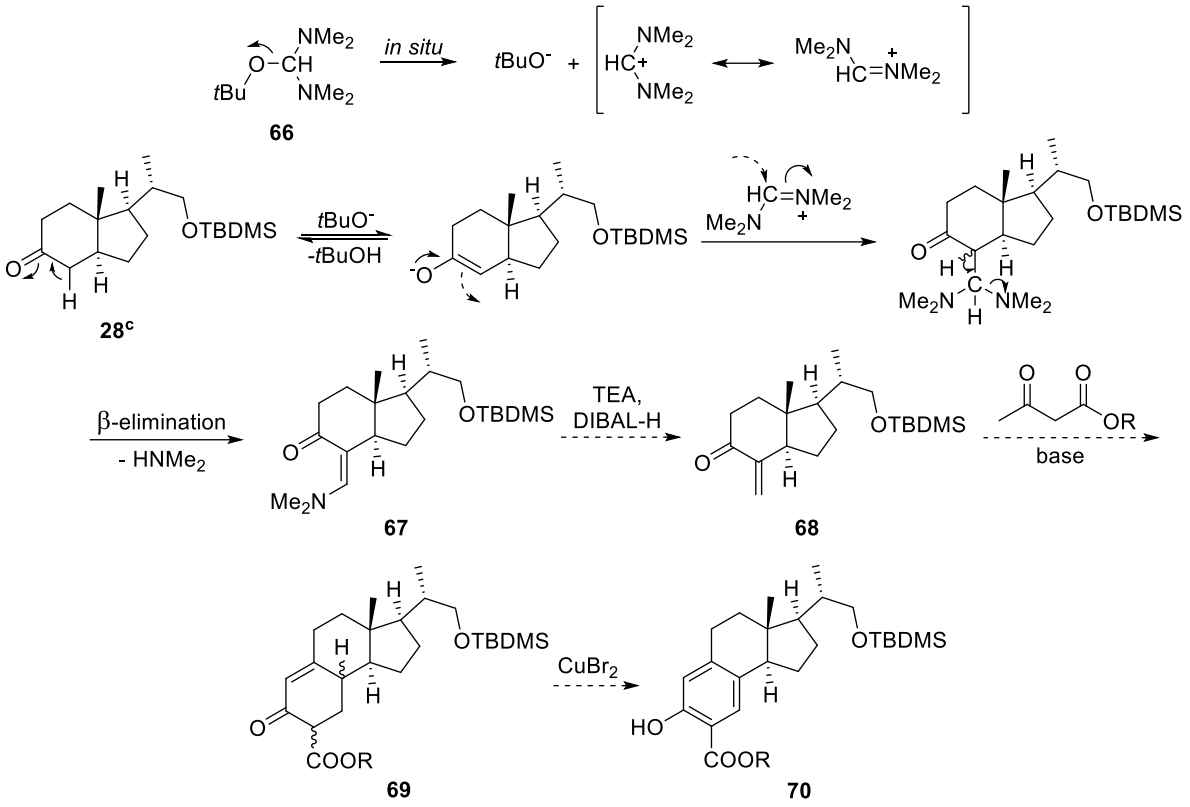
Due to the formation of the wrong constitutional isomer **64^{e}** the further planned steps could not be carried out.

Another idea was trapping the enolate as an enamine, which then can undergo the MICHAEL addition. This type of reaction is called STORK enamine reaction.[91] A benefit of this reaction is that no catalyst is needed, which means that this mild condition could reduce possible side reactions or decomposition. Using a method from YASUI *et al.*,[92] pyrrolidine was added to ketone **28^{c}** and the mixture was heated to reflux. TLC showed that the starting material was fully consumed, but crude ^{1}H NMR spectroscopy revealed more than one product. The crude product was not purified *via* FCC, since enamines are labile functional groups. Therefore, methyl vinyl ketone was added directly. Unfortunately, TLC showed no significant spots and GC/MS analysis revealed that the desired MICHAEL adduct could not be formed with this method (**Scheme 30**).



Scheme 30. Attempted STORK enamine reaction based on ketone **28^{c}**.

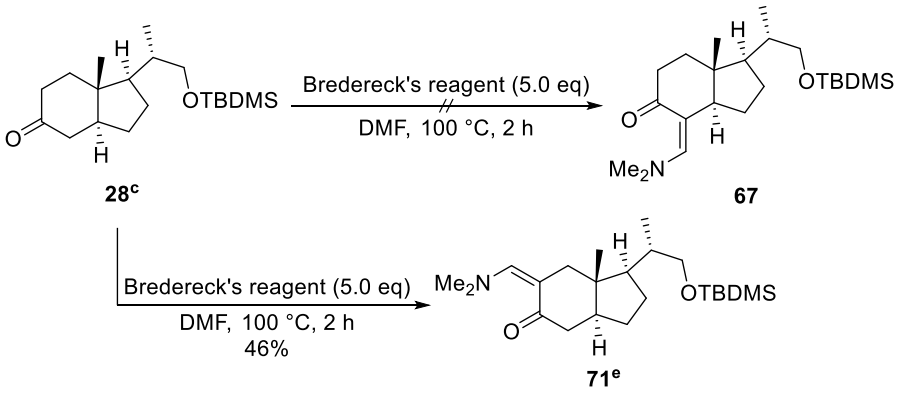
Neither a ROBINSON annulation nor attempts trapping or imitate enol **63** (**Scheme 28**) were successful. The fourth and last approach was developed using BREDERECK'S reagent. This reagent can be applied for α-aminomethylenation in molecules bearing an acidic methylene group. **Scheme 31** shows the mechanism. BREDERECK'S reagent has the property to generate *in situ* the strong basic *tert*-butoxide (*t*BuO^{-}) and the appropriate iminium ion. A MANNICH reaction takes places, whereby after keto-enol-tautomerism of **28^{c}** in the presence of *t*BuO^{-}, the corresponding enolate attacks the iminium ion. A β-elimination of dimethylamine leads to the enamino ketone **67**.[93]



Scheme 31. Mechanism using BREDERECK'S reagent giving an enamino ketone **67** and subsequent reactions to phenol **70**.

To form the desired aromatic ring B, enaminoketone **67** is converted to exomethylene compound **68** using TEA and DIBAL-H, which can now undergo a cyclisation with a β-ketoester to the appropriate ketone **69**. Oxidation with $CuBr_2$ should then result in phenol **70**.

Using a method of TANINO *et al.*,[94] BREDERECK'S reagent was added to ketone **28c**. After preservation of the enaminoketone **67**, 2D NMR spectra revealed that again the wrong constitutional isomer **71e** was synthesised in 46% yield (**Scheme 32**).



Scheme 32. Use of BREDERECK'S reagent results in the wrong constitutional isomer **71e**.

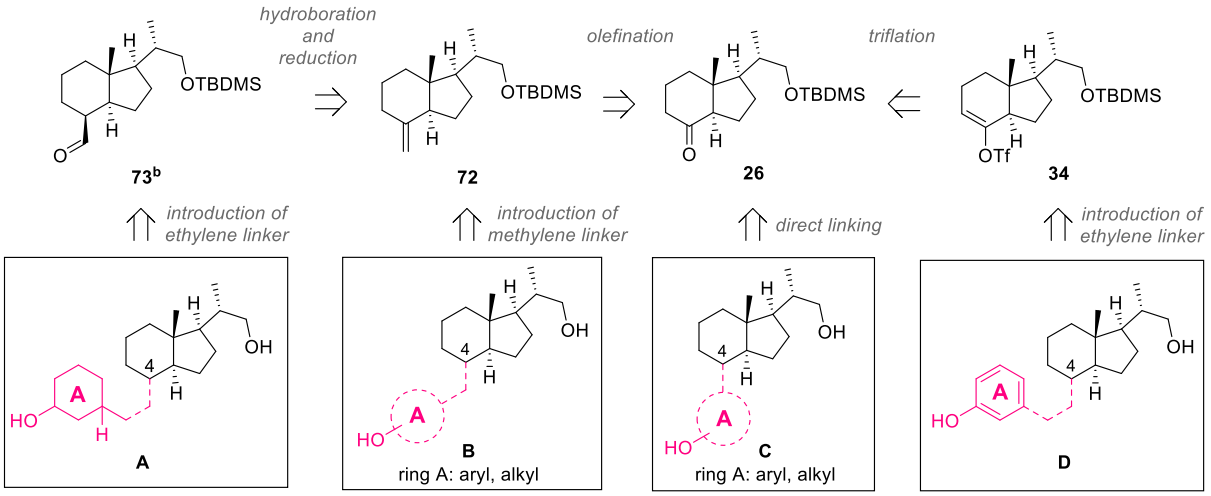
Four approaches were tried, but every attempt to synthesise phenols **60** and **70**, respectively failed. Due to the formation of the wrong constitutional isomers, the synthesis of the desired tricycle with ketone **28^{c}** is very difficult. These attempts also showed, that the C-6 position of ketone **28^{c}** is more reactive than C-4. In chapter 3.2.1. several variations of tri- and tetracyclic analogues of SH-42 (**22**) and diols **23** and **24**, respectively, were already successful. Therefore, the project of an aromatic ring B was closed, and the focus was set on synthesis of *seco*-steroidal analogues.

3.3. Variations of ring A and B – *seco*-steroidal analogues

Besides tri- and tetracyclic analogues derived from the lead structures **23** and **24**, *seco*-steroidal analogues are of high interest. With maintenance of rings C and D and a "broken" ring B, ring A should be varied using aromatic and aliphatic residues. These residues should be attachted to C-4 or C-5 position of the perhydroindane (rings C and D) unit.

3.3.1. *Seco*-steroidal analogues with bridging at C-4

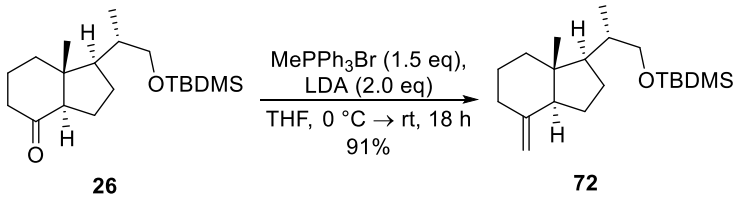
Starting with the attachment of residues at C-4, **Scheme 33** shows the general route to the desired *seco*-steroids. Based on central building block **26**, aryl and alkyl residues should be attached directly to C-4 using organometallic chemistry (**C**, **Scheme 33**, third column). The *seco*-steroids **B** containing an aryl or alkyl residue as ring A attached *via* methylene linker should be formed from exomethylene compound **72**, which should be synthesised from ketone **26** *via* methylenation using e.g. WITTIG olefination (**Scheme 33**, second column). *Seco*-steroid **D** bearing an aryl residue as ring A attached *via* an ethylene linker, should be formed from enol triflate **34** (for synthesis see chapter 3.1.2.) using SONOGASHIRA cross-coupling reaction (**Scheme 33**, fourth column). The saturated version *seco*-steroid **A** should be synthesised from aldehyde **73^{b}** *via* WITTIG olefination (**Scheme 33**, first column). Aldehyde **73^{b}** should be formed from alkene **72** using hydroboration and subsequent reduction.



Scheme 33. Planned routes for the synthesis of *seco*-steroidal analogues with bridging at C-4 with an aromatic or aliphatic ring A. The new generated ring A and the appropriate linkers are marked in pink.

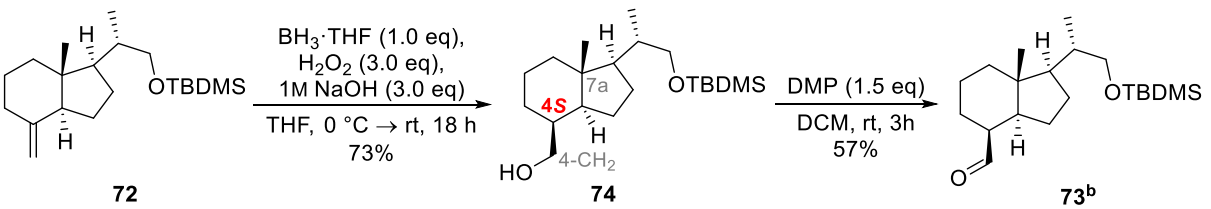
3.3.1.1. Synthesis of building blocks alkene **72** and aldehyde **73^{b}**

The two further required building blocks alkene **72** and aldehyde **73^{b}** were synthesised from central building block **26**. **Scheme 34** shows the synthesis of exomethylene compound **72** using WITTIG olefination. By the usage of methyltriphenylphosphonium bromide ($MePPh_3Br$) and LDA the appropriate ylide is formed, which reacts subsequently with ketone **26**. Next to triphenylphosphine oxide, the desired terminal olefin **72** is formed in a very good yield of 91%.



Scheme 34. Wittig olefination of **26** resulting in alkene **72**.

Aldehyde **73^{b}** was synthesised over two steps starting from terminal olefin **72** (**Scheme 35**). Hydroboration using BH_3·THF with subsequent addition of H_2O_2 and NaOH to form the hydroxyl group, gave selectively alcohol **74** with 73% yield. The stereochemistry at C-4 could be determined as *S* configurated since a strong coupling between 4-CH_2 and 7a-CH_3 could be observed in the NOESY spectrum.



Scheme 35. Synthesis of aldehyde **73^{b}** *via* hydroboration and reduction of **72**.

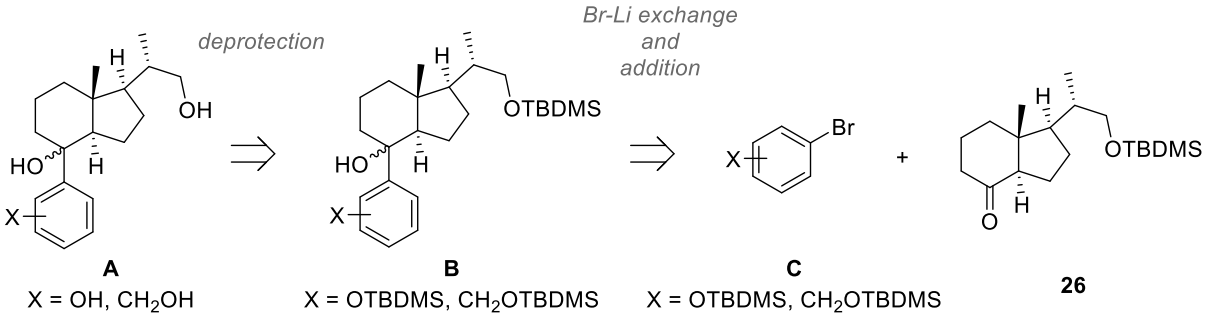
The final step to aldehyde **73^{b}** was performed during the bachelor thesis of DOREEN REUTER (née KREMER) based on alcohol **74**.[95] Oxidation with DMP gave the desired aldehyde **73^{b}** in 57% yield.

3.3.1.2. Aromatic residues

In this chapter all studies towards the introduction of aromatic residues with bridging at C-4 are discussed.

3.3.1.2.1. Directly attached aryl residues to C-4

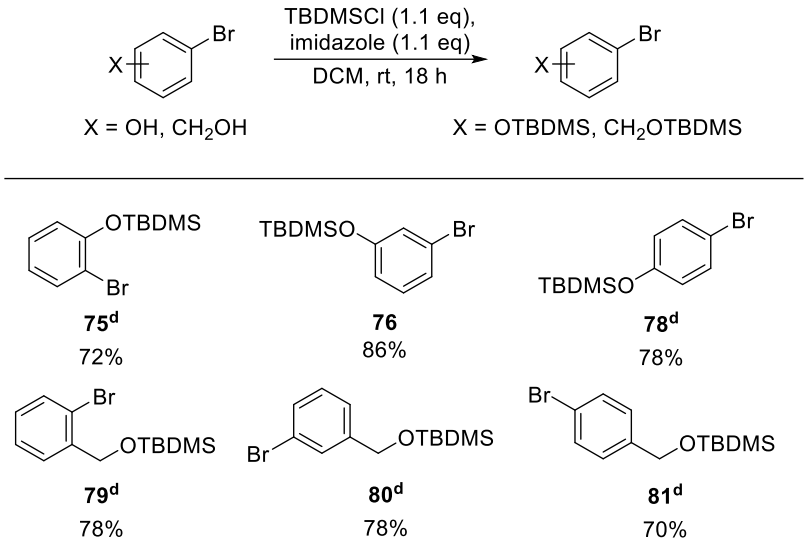
To study the effect of the length of the linker of *seco*-steroids, aromatic residues were directly attached to C-4, resulting in 4-arylperhydroindanes. Based on ketone **26** various hydroxyphenyl/(hydroxymethyl)phenyl residues were introduced. **Scheme 36** shows the general retrosynthesis of the target molecules.



Scheme 36. Retrosynthesis of triols with direct linking of the aromatic residues to C-4.

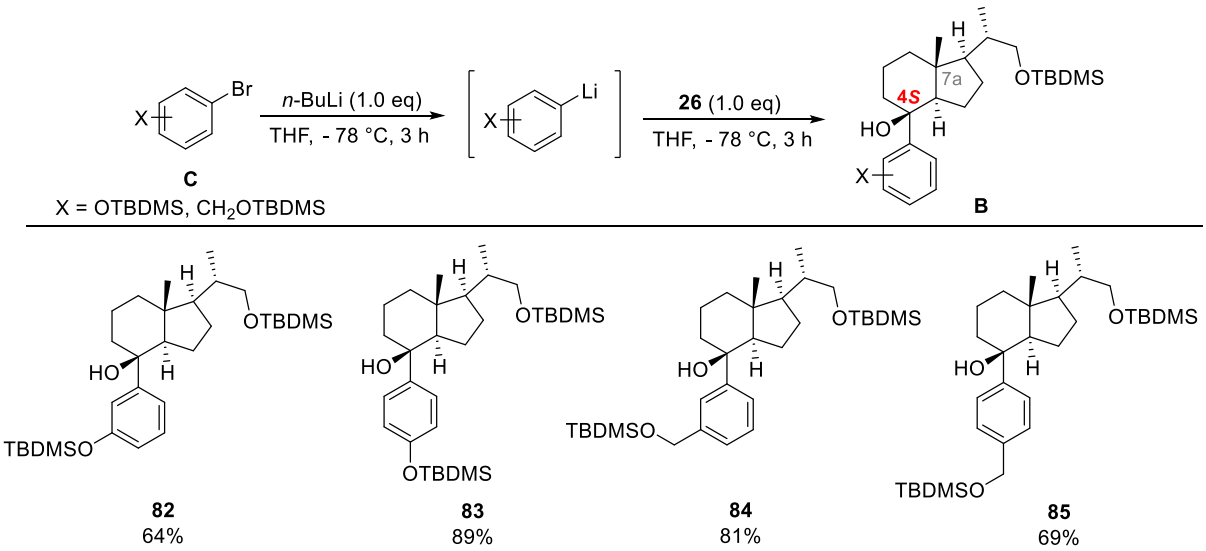
The desired triols **A** should be obtained after TBDMS deprotection. The (bis)silylethers **B** should be formed *via* Br-Li exchange of the TBDMS protected bromophenol/bromo-benzylalcohol **C** with subsequent addition to ketone **26**.

First, the phenols and benzyl alcohols were protected (**Scheme 37**). Six phenols and benzyl alcohols were protected using imidazole and TBDMSCl and all silylethers were isolated in good yields (70 – 86%), whereby five of them were synthesised during the bachelor thesis of MORITZ M. KORNMAYER.[96]



Scheme 37. TBDMS protection of phenols and benzylalcohols.

The following Br-Li exchange of the protected phenols and benzylalcohols using *n*-BuLi, with subsequent addition to ketone **26** are depicted in **Scheme 38**. The *meta* substituted bromide **76** was successfully added to ketone **26** and alcohol **82** was obtained in 64% yield. *Para* substituted bromide **78**[d] could be successfully converted to alcohol **83** in a very good yield of 89%. The addition of the protected benzyl alcohols **80**[d] (*meta* substituted) and **81**[d] (*para* substituted) took place in good yields of 81% for alcohol **84** and 69% for alcohol **85**. According to TLC, Br-Li exchange of the *ortho* substituted bromides **75**[d] and **79**[d] was successful, but the lithiated intermediate did not undergo addition to ketone **26**. A possible reason for the failed addition could be the steric hindrance between the large TBDMS group and the reactive site of the molecule.



Scheme 38. Resulting alcohols **82**, **83**, **84** and **85** from the addition of the TBDMS protected phenols and benzylalcohols. The new stereocenter is marked in red.

The configuration of the new stereocenter at C-4 was identified *via* NOESY. In all four cases a clear spatial coupling between the hydroxy group and 7a-CH_3 group could be observed, resulting in *S* configuration at C-4. As an example, **Figure 12** shows the NOESY spectrum of alcohol **83**.

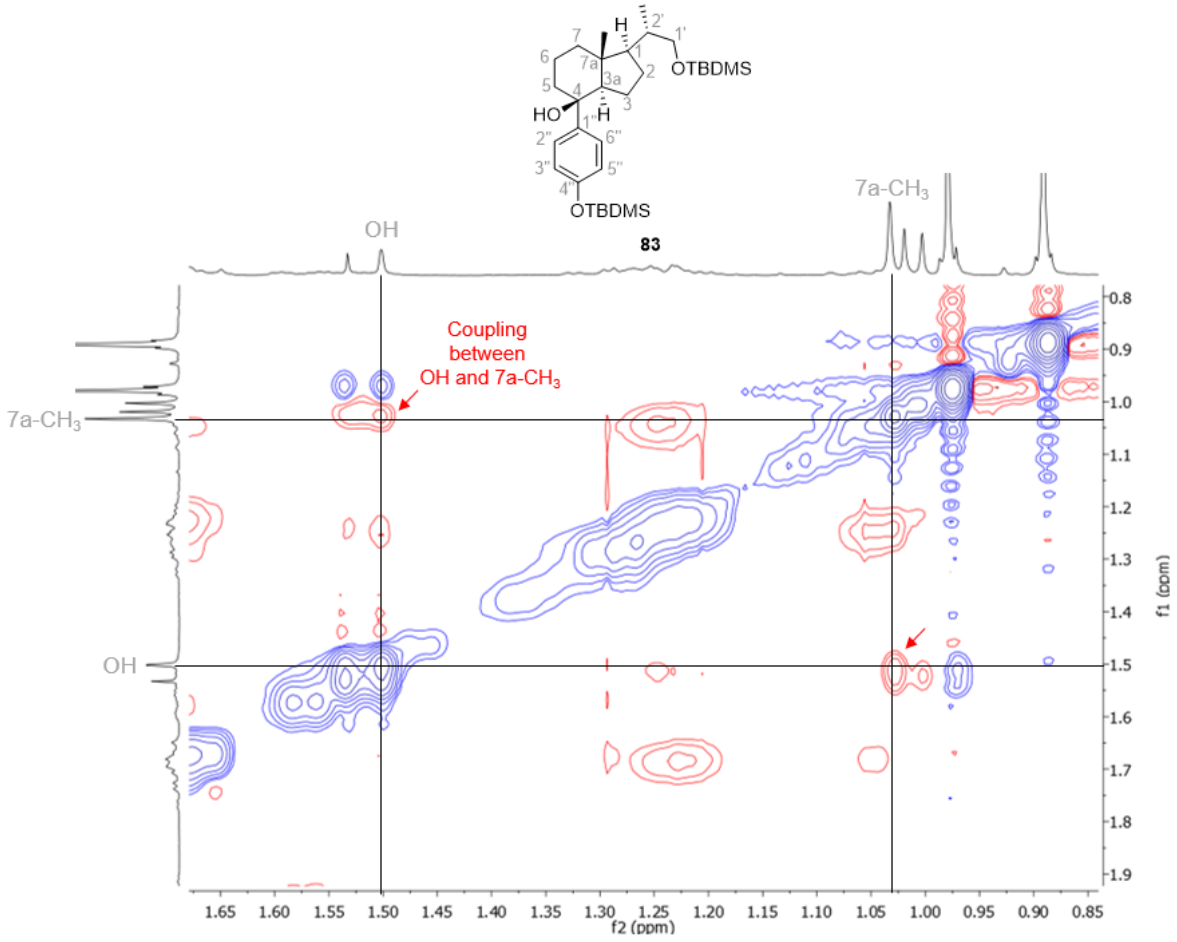
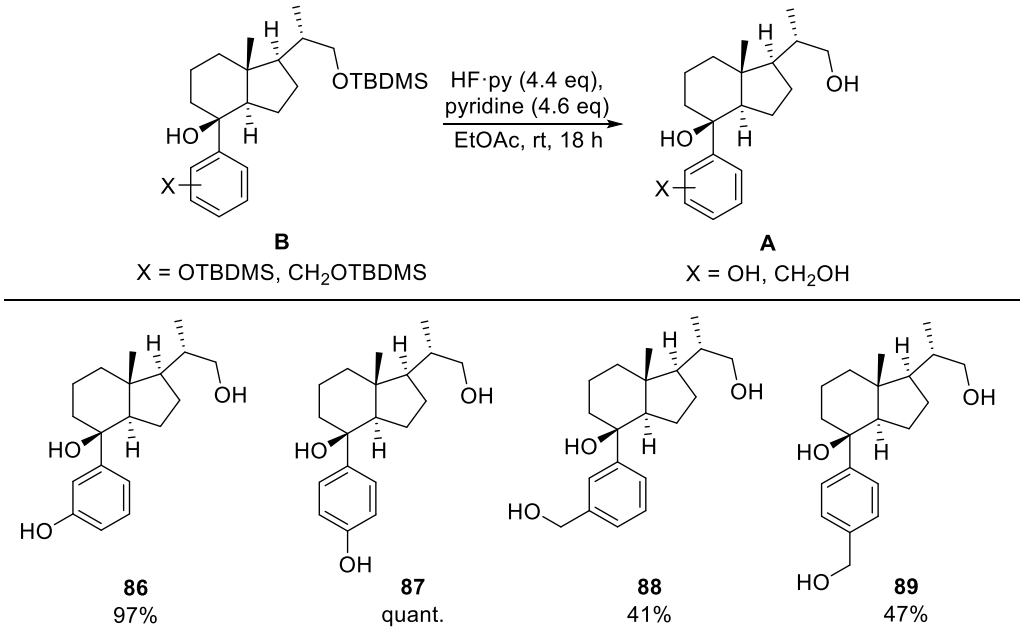


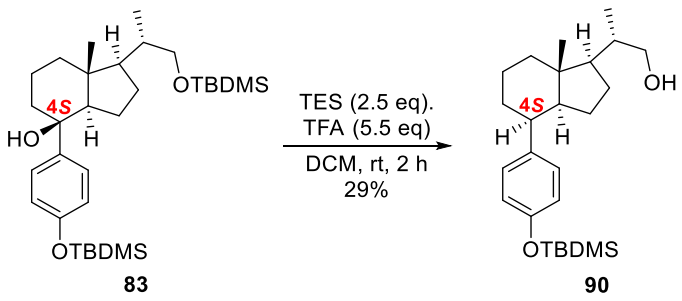
Figure 12. NOESY spectrum of alcohol **83**. The spatial coupling between 7a-CH_3 and OH are marked in red.

The last step was the deprotection of both TBDMS protected hydroxy groups using HF·py and pyridine (**Scheme 39**). Because of the presence of two TBDMS groups, twice the amount of HF·py and pyridine was required. In contrast to the deprotection of the benzyl alcohols **84** and **85**, the deprotection of the *meta* and *para* substituted phenols **82** and **83** went smoothly with very high yields (97% and quantitative). The deprotection of the benzyl alcohols only proceeded in moderate yields (41 and 47%).



Scheme 39. TBDMS cleavage of (bis)silylethers.

It was of chemical interest, which configuration at the former hydroxy stereocenter exists, after elimination of the hydroxyl group. Therefore, triethylsilane (TES) in combination with TFA was used, which leads to a dehydration of alcohols with subsequent hydrogenation of the formed alkene (ionic hydrogenation).[97] Alcohol **83** was used as a model compound for the elimination (**Scheme 40**).

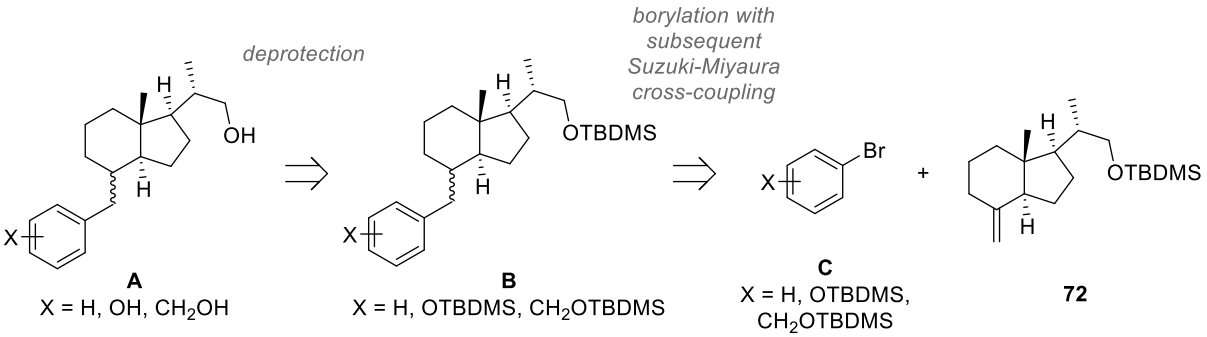


Scheme 40. Elimination of the hydroxyl group at C-4 resulting in arylperhydroindane **90**.

With the presence of TFA the hydroxy group is protonated, and water is eliminated, forming an alkene. Simultaneously, TES delivers a hydride, which attacks the double bond. During the reaction the stereoinformation at C-4 ist lost temporarily and the stereocenter is then rebuilt upon hydride transfer, resulting again in *S* configuration at C-4. In **83** the aryl residue is facing to the back, whereby in the case of **90** the residue is now facing to the front. Additionally, with the presence of 5.5 equivalents TFA the aliphatic side chain TBDMS ether was deprotected but the phenol remained protected.

3.3.1.2.2. *Seco*-steroids with methylene linker at C-4

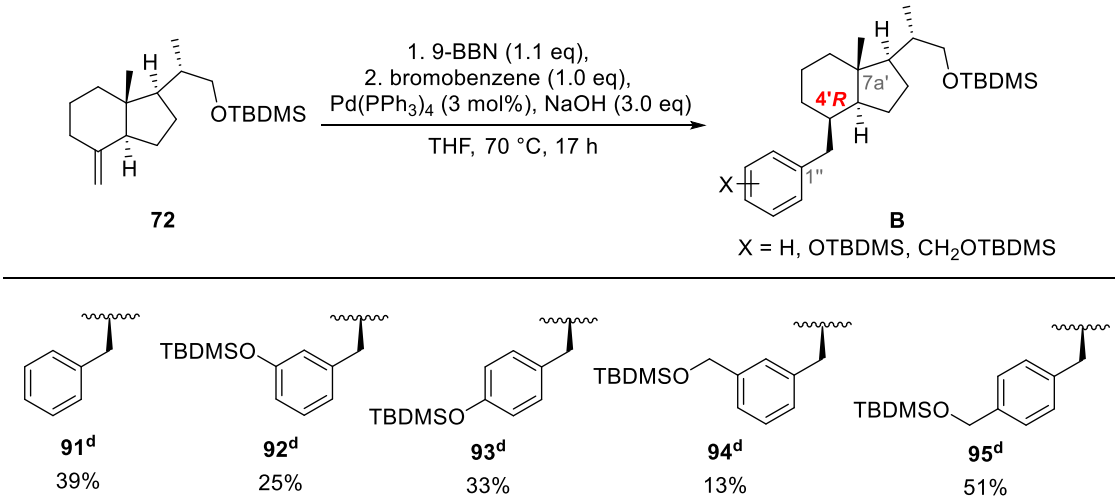
This chapter discusses the synthesis of 4-benzylperhydroindanes containing a methylene linker between the aromatic residue and C-4. This part of the project was carried out during the bachelor thesis of MORITZ M. KORNMAYER, under my supervision.[96] The idea was an extension of the directly linked aromatic residues (see chapter 3.3.1.2.1.) to a methylene group as linker. **Scheme 41** shows the retrosynthesis of the desired compounds.



Scheme 41. Retrosynthesis of 4-benzylperhydroindanes **A** bearing a methylene linker from alkene **72**.

The desired diols should be obtained *via* TBDMS deprotection, whereby the TBDMS protected alcohols should be synthesised using SUZUKI-MIYAURA cross-coupling conditions starting from exomethylene compound **72** (see chapter 3.3.1.1.) and various aryl bromides (see chapter 3.3.1.2.1.).

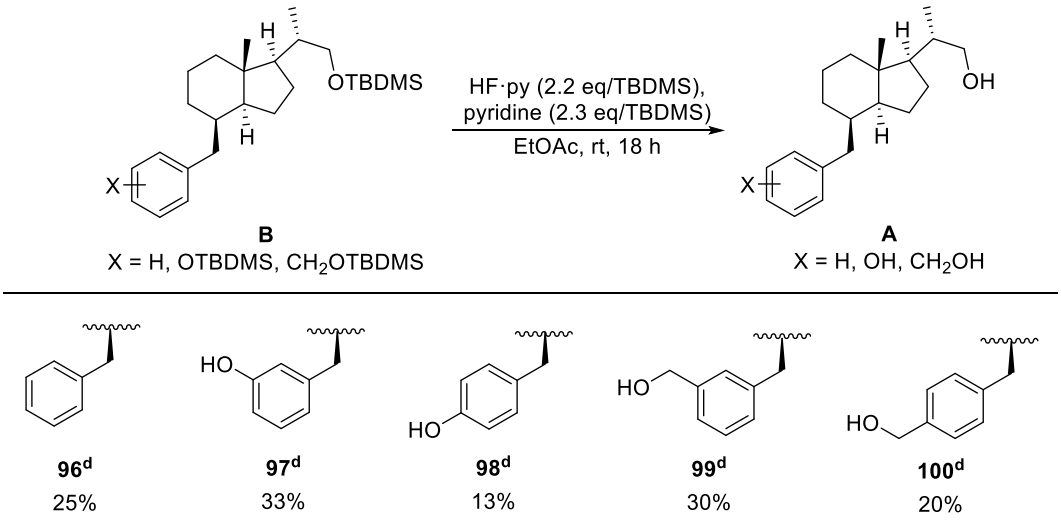
While in standard SUZUKI-MIYAURA procedures boronic acids as organoboron component are used, in this case 9-BBN was used, which should upon hydroboration of olefin **72** form the *B*-alkyl-9-BBN intermediate *in situ*. Due to the steric hindrance of 9-BBN, the anti-MARKOVNIKOV product is strongly preferred, and the chances of unwanted side reactions are reduced, *inter alia* because 9-BBN leads to 1:1 stoichiometry of the starting materials. Different catalysts ([1,1′-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) ($Pd(dppf)Cl_2$) and tetrakis-(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$)) and aryl halides (iodobenzene and bromobenzene) were tested, whereby the best result was achieved using bromobenzene with $Pd(dppf)Cl_2$ as catalyst. It was also examined, if the phenols and benzyl alcohols had to be protected and it became obvious that the use of the TBDMS protected derivatives led to higher yields, compared to the unprotected variant. **Scheme 42** depicts the isolated cross-coupling products.



Scheme 42. SUZUKI-MIYAURA cross-coupling products. The new stereocenter is marked in red.

The *ortho* substituted bromoarenes (see **Scheme 37**) did not undergo the cross-coupling. This observation is similar to the failed reactions for the introduction of a directly attached aromatic residue at C-4 (see chapter 3.3.1.2.1.). This means that the steric hindrance plays a huge role in this case as well. The model compound **91**^{d} was synthesised in moderate yield of 39%. The *meta* and *para* substituted TBDMS protected phenols **92**^{d} and **93**^{d} were synthesised in a similar yield (25% and 33%). TBDMS protected benzyl alcohols could be successfully coupled to **72** as well and (bis)silylethers **94**^{d} and **95**^{d} were isolated in 13% and 51% yield. The low yield of **94**^{d} can occur from not fully generated 9-alkyl-BNN, because amounts of alkene **72** were also isolated during the purification step. The stereocenter at C-4' was identified as *R* since a clear coupling between 1''-CH_2 and 7a'-CH_3 was observed in NOESY spectrum.

The last step to the final compound was deprotection of the hydroxy groups using HF·py and pyridine (**Scheme 43**).



Scheme 43. Formation of alcohol **96**^{d} and diols **97**^{d}, **98**^{d}, **99**^{d} and **100**^{d} *via* TBDMS cleavage.

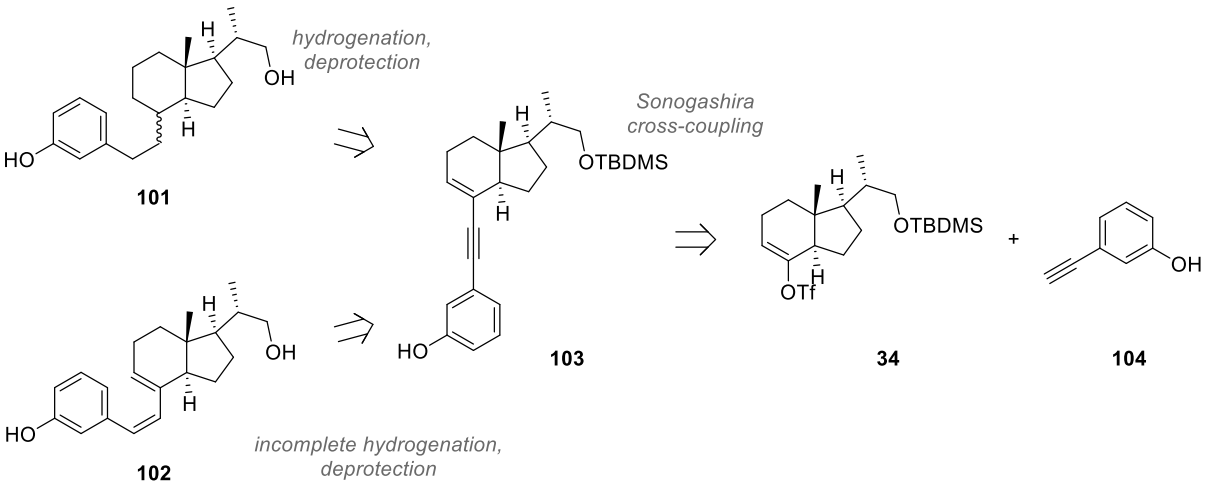
All synthesised cross-coupling products could be successfully TBDMS deprotected, although the yields are relatively low (13 – 33%). The alcohol and all diols can now be tested as potential inhibitors of DHCR24.

3.3.1.2.3. *Seco*-steroids with ethylene linker at C-4

In the last two chapters the synthesis of *seco*-steroids with direct linking of an aromatic ring at C-4, as well as the introduction of a methylene linker were discussed. To reach the concise length of the steroidal structure an ethylene linker is necessary, which results in 4-(arylethyl)perhydroindanes.

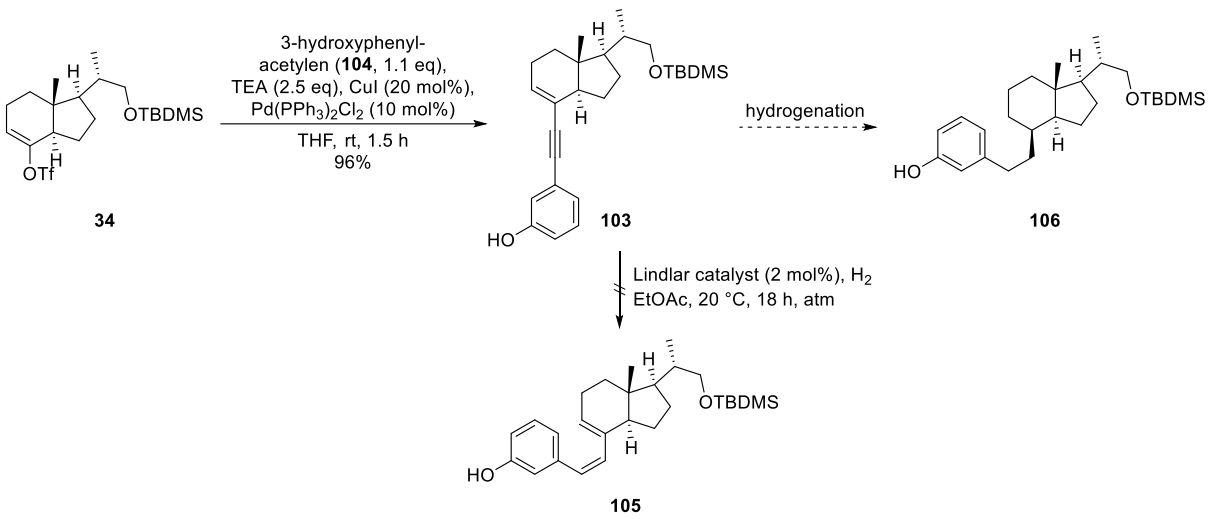
3.3.1.2.3.1. Introduction of an ethylene linker *via* SONOGASHIRA cross-coupling

First, it was tried to introduce an ethylene linker *via* Sonogashira cross-coupling. **Scheme 44** shows the retrosynthesis of the target compounds **101** and **102**. Diol **101** should be obtained after hydrogenation and TBDMS cleavage of cross-coupled product **103**, which should be formed from enol triflate **34** (see chapter 3.1.2.) and 3-hydroxyphenylacetylene (**104**). Diol **102** should also be synthesised from **103** by an incomplete hydrogenation of the acetylene using for example LINDLAR catalyst followed by deprotection.



Scheme 44. Retrosynthesis of target structures **101** and **102**.

SONOGASHIRA cross-coupling of enol triflate **34** and 3-hydroxyphenylacetylene (**104**) resulted in alkyne **103** in a very good yield of 96% (**Scheme 45**). It was tried to hydrogenate the triple bond without hydrogenating the double bond using LINDLAR catalyst, a lead poisoned Pd-catalyst, to preferably receive the *Z*-isomer but no reaction occurred (**Scheme 45**). Probably the catalyst was too mild for the extended conjugated system.



Scheme 45. SONOGASHIRA cross-coupling between enol triflate **34** and 3-hydroxyphenylacetylene (**104**) and subsequent hydrogenation attempts.

For the following simultaneous hydrogenation of double and triple bond, various attempts were made since the normal hydrogenation conditions (Pd/C, H_2) did not result in the desired hydrogenated phenol. The conditions are shown in **Table 3**.

Table 3. Hydrogenation conditions of alkyne **103**.

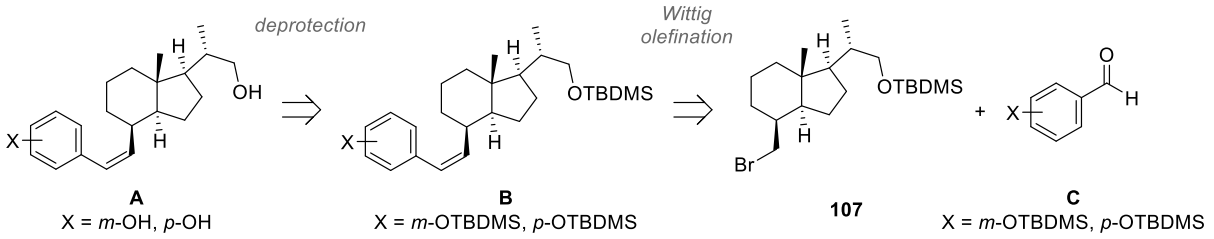
entry	catalyst	conditions	solvent	pressure	yield (**106**)
1	Pd/C (10 wt%)	1.5-18 h, 20 °C	EtOAc	atm	0%
2	Pd/C (10 wt%)	1.5-18 h, 23°C	EtOAc	20-30 bar	0%
3	PtO_2 (2 mol%)	18 h, 20 °C	EtOAc	atm	n.d.
4	PtO_2 (2 mol%)	18 h, 20 °C	EtOAc, AcOH	atm	n.d.
5	PtO_2 (2 mol%)	18 h, 23-30 °C	EtOAc	20-30 bar	n.d.
6	PtO_2 (2 mol%)	18 h, 23-30 °C	EtOAc, AcOH	20-30 bar	n.d.

Entries 1 and 2 show the hydrogenation using Pd/C at atmospheric pressure and at 20-30 bar. TLC monitoring revealed that no reaction at all took place and the starting material was left unreacted. For entries 3 and 4 platinum(IV)oxide (PtO_2) was used, whereby in entry 4 AcOH was added in addition, according to a method of SOBOTKA and CHANLEY.[98] In both reactions new spots could be detected on TLC, but GC/MS showed a lot of signals of unidentifiable, hydrogenated and partially hydrogenated products. The same reaction could be observed at 20-30 bar (entries 5 and 6) and only unidentifiable products were isolated.

3.3.1.2.3.2. Introduction of an ethylene linker *via* WITTIG olefination

Since the hydrogenation of the Sonogashira cross-coupled product **103** failed, another approach was made using WITTIG olefination. **Scheme 46** shows the planned route to the desired *seco*-steroidal compound **A** containing a *meta* or *para* substituted phenol. In the lead

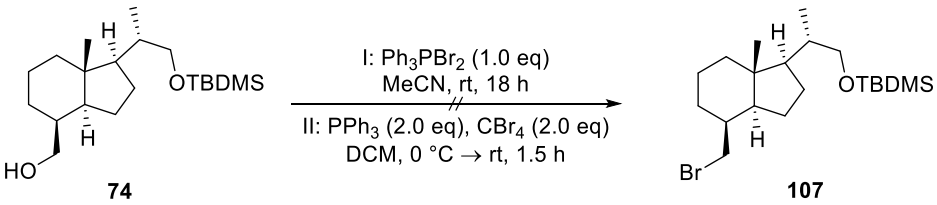
structures **23** and **24** the hydroxyl group is in *meta* position. However, by thermal rotation around the single bond connecting ring A, this position is not fixed anymore. Therefore, the phenolic residue bearing the hydroxyl group in *para* position was of interest as well as the hydroxyl group does not change its position by rotation. While in the SONOGASHIRA reaction (chapter 3.3.1.2.3.1.) the variation of starting material was limited, in this case *meta* and *para* substituted phenols were easily accessible.



Scheme 46. Planned route to diol **A** *via* WITTIG olefination between **107** and an appropriate aldehyde **C**.

The final compounds **A** should be formed from TBDMS deprotection, whereby the TBDMS protected compounds **B** should be generated from a WITTIG olefination between bromide **107** and substituted benzaldehydes **C**. In this step, the formation of the *Z*-olefin would be preferred since the configuration imitates the steroidal structure.

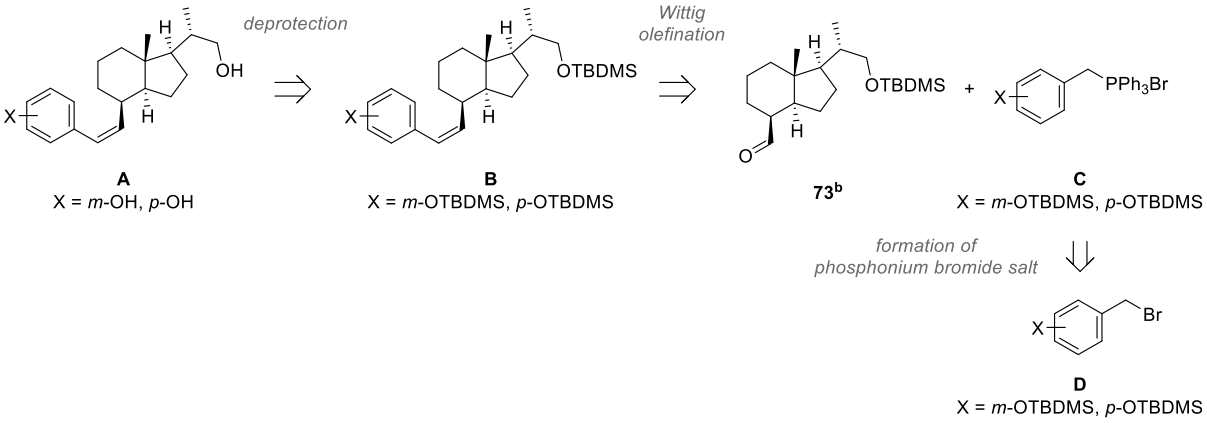
Two approaches for the synthesis of bromide **107** starting from primary alcohol **74** (for synthesis see chapter 3.3.1.1.) were tried (**Scheme 47**).



Scheme 47. Attempts for the synthesis of **107** from alcohol **74.**

In the first reaction (**Scheme 47**, I) a procedure from DANIELS *et al.*[99] was performed, using triphenylphosphine dibromide (Ph_3PBr_2). TLC showed a much more polar compound (R_f = 0.32, hexanes/EtOAc 6:4) than the starting material **74** (R_f = 0.76, hexanes/EtOAc 6:4), which rather not speaks for the desired bromide **107**, and after isolation and purification NMR analysis revealed that not the desired compound was synthesised, but that the silylether was substituted with bromine. Related substitutions of silylethers using Ph_3PBr_2 can be found in literature.[100] The second attempt was an APPEL reaction (**Scheme 47**, II), using triphenylphosphine (PPh_3) and carbon tetrabromide (CBr_4). During this reaction, more nonpolar compounds than **74** were observed on TLC, but only only unidentifiable aliphatic fragments were isolated.

Due to the unsuccessful attempts for the synthesis of **107**, it was decided to switch the substitution pattern and to perform the WITTIG olefination with aldehyde **73^{b}** (for synthesis see chapter 3.3.1.1.) and the appropriate benzyl bromides. **Scheme 48** shows the new route to the target structures.

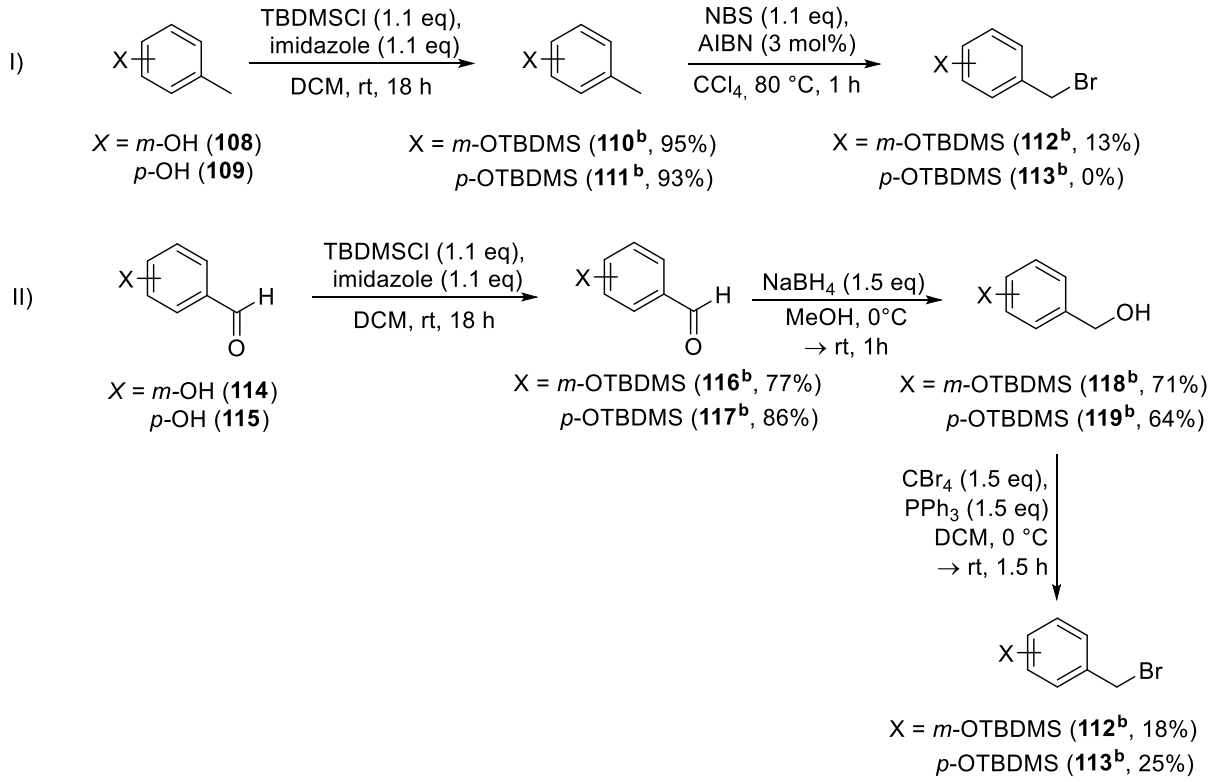


Scheme 48. Retrosynthesis of *seco*-steroid **A** based on aldehyde **73^{b}**.

Diols **A** should be formed *via* TBDMS deprotection. TBDMS protected olefins **B** should be synthesised *via* WITTIG olefination using previously described aldehyde **73^{b}** (for synthesis see chapter 3.3.1.1.) and ylides derived from TBDMS protected benzyl bromide. These studies were performed during the bachelor thesis of DOREEN REUTER (née KREMER) under my supervision.[95]

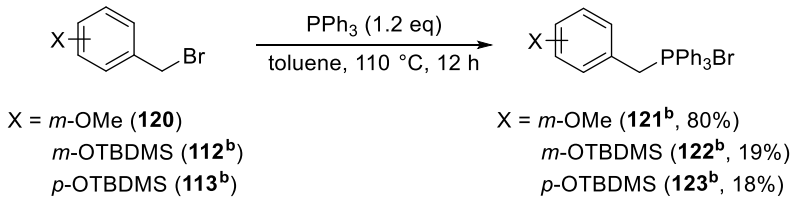
Scheme 49 depicts the synthesis of the desired *meta* and *para* hydroxy substituted benzyl bromides. Based on *m*-cresol (**108**) and *p*-cresol (**109**), a two-step synthesis was performed (**Scheme 49**, I) starting with the TBDMS protection of the phenolic function, which resulted in 95% *m*-OTBDMS protected **110^{b}** and 93% *p*-OTBDMS protected **111^{b}**. To generate the benzyl bromides from the protected cresols, radical WOHL-ZIEGLER bromination was used according to a published method.[101] Several test reactions were carried out, with variation of the radical starter solvent and reaction time, but the best results were obtained using AIBN in CCl_4 at 80 °C. While the *m*-substituted benzyl bromide **112^{b}** was isolated in a low yield of 13%, the *p*-substituted benzyl bromide **113^{b}** could not be synthesised by this way. A huge problem in this reaction was the fast multiple bromination of the protected cresols. Parallel to these reactions, a three step route based on 3- and 4-hydroxybenzaldehyde (**114** and **115**) was tried (**Scheme 49**, II). After successful TBDMS protection of the hydroxyl group, the aldehyde function was reduced using $NaBH_4$ and primary alcohols **118^{b}** and **119^{b}** were isolated in good yields of 71% and 64%. The last step was an APPEL reaction using PPh_3 and CBr_4, which resulted in the desired benzyl bromides (carried out according to Jones *et al.*[102]). The *m*-derivative **112^{b}** was obtained with 18% yield and the *p*-derivative **113^{b}** in 25% yield. All in all, in both attempts, the

bromination steps could only performed in low yields. Probably the conditions were too harsh for these molecules.



Scheme 49. Two routes for the synthesis of benzyl bromides **112^{b}** and **113^{b}**.

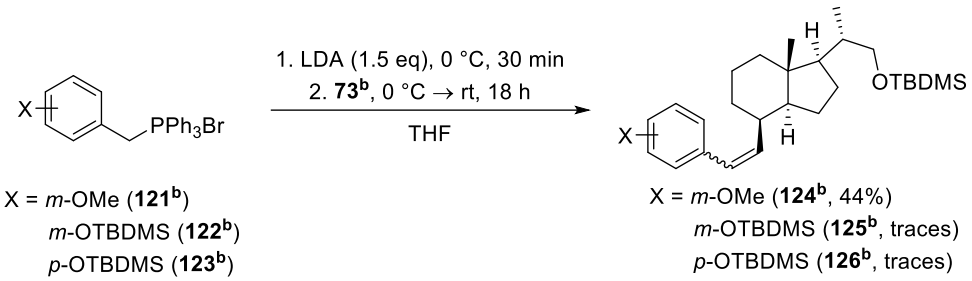
For the following WITTIG olefination, the triphenylphosphonium bromide salts were required. Therefore, the benzyl bromides were refluxed in the presence of PPh_3 (**Scheme 50**). Besides both benzyl bromides **112^{b}** and **113^{b}** the commercially available *m*-methoxy derivative **120** was used.



Scheme 50. Synthesis of the triphenylphosphonium bromide salts.

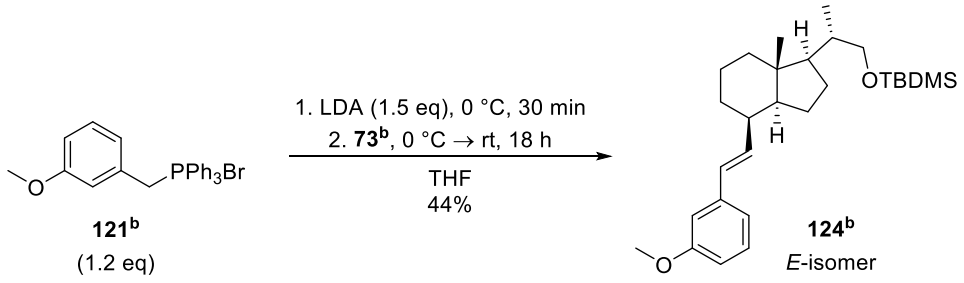
The triphenylphosponium bromide salt **121^{b}** bearing a methoxy group in *m*-position could be isolated with a good yield of 80%. The *m*-OTBDMS salt (**122^{b}**) as well as the *p*-OTBDMS salt (**123^{b}**) could be generated in only poor yields of 19% and 18%. A reason could be, that both reactions were performed with only 0.15 mmol due to low amount of isolated **112^{b}** and **113^{b}**, whereby the reaction with *m*-methoxy derivative was performed with 7.9 mmol.

The WITTIG olefination between aldehyde **73^{b}** and the synthesised phosphonium salts are depicted in **Scheme 51**. In all three reactions first the ylide was formed using LDA, which could be identified by a bright colour change. This visible approval was observed in all three reactions. After addition of aldehyde **73^{b}**, the colour slowly faded, and all three reactions showed a new spot on TLC and the desired mass was found with GC/MS analysis. However, purification *via* FCC gave only the *m*-methoxylated WITTIG product **124^{b}** in 44% isolated yield and the *m*-OTBDMS and *p*-OTBDMS WITTIG products (**125^{b}** and **126^{b}**) could not be isolated.



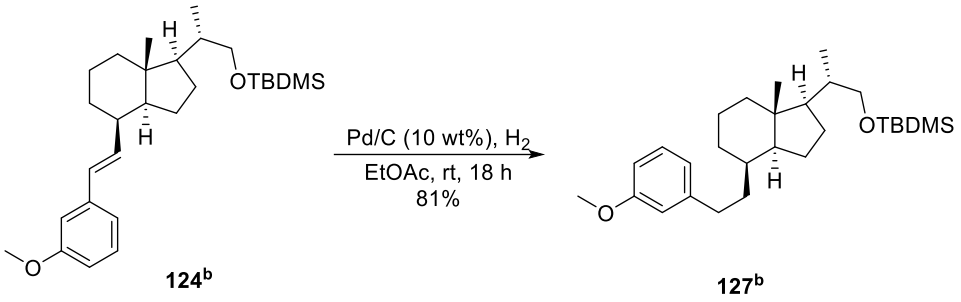
Scheme 51. WITTIG olefination of aldehyde **73^{b}** and the appropriate benzyl phosphonium bromides.

Due to lack of time in the bachelor thesis, we focused on the *m*-methoxylated compound. After the successful WITTIG olefination, it was important to identify whether the *E*- and/or *Z*- isomer was formed. Only one new spot was observed on TLC and the ^{1}H NMR spectrum also showed only one set of signals. With the coupling constant 15.8 Hz of the olefinic protons the *E*-isomer was identified (*E*-isomer: range 11 – 18 Hz, typically 16 Hz; *Z*-isomers: range: 6 – 14 Hz, typically 10 Hz).[103] All in all it was possible to synthesise the *seco*-steroid **124^{b}** in moderate yield (44%) (**Scheme 52**). The stereochemistry was also verified *via* NOESY spectroscopy.



Scheme 52. Formation of *E*-isomer **124^{b}** *via* WITTIG olefination.

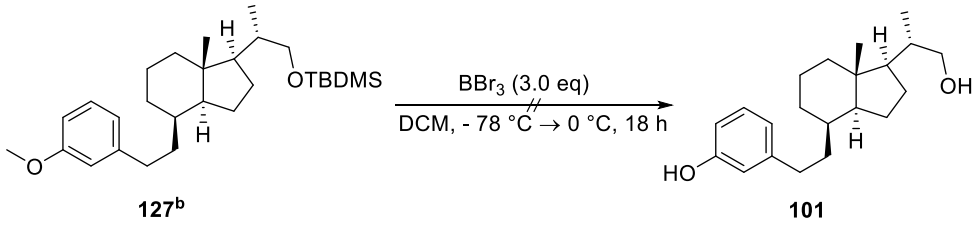
Since only the *Z*-isomer of **124^{b}** would mimic the steroidal structure of the lead structures **23** and **24**, it was not necessary to deprotect the *E*-isomer. Therefore, the next step was hydrogenation of the double bond. Hydrogenation was performed in the presence of Pd/C and H_2 (**Scheme 53**). The desired hydrogenated *seco*-steroid **127^{b}** was obtained with 81% yield.



124[b] **127[b]**

Scheme 53. Hydrogenation of **124[b]** resulting in **127[b]**.

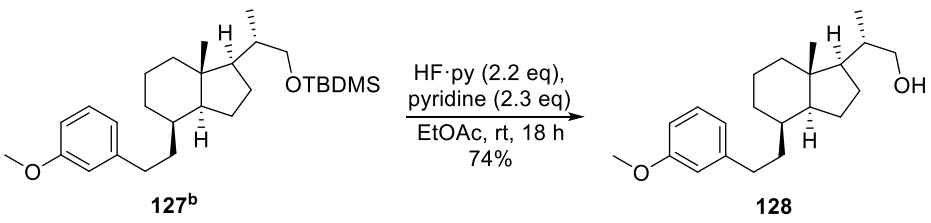
The last steps to the desired diol were TBDMS deprotection and methyl ether cleavage. SINGH *et al.* showed, that BBr_3 can cleave methyl ethers, as well as trimethylsilyl (TMS) ethers in one step.[104] Although compound **127[b]** contains a TBDMS instead of TMS group, this procedure was tried (**Scheme 54**). The starting material (R_f = 0.96, hexanes/EtOAc 9:1) was fully consumed and a new polar spot (R_f = 0.42, hexanes/EtOAc 9:1) appeared, which theoretically could be the desired diol regarding the polarity. After purification, ^{1}H NMR spectroscopy showed that the diol was not formed, but that the starting material **127[b]** decomposed. No aromatic signals could be observed in the ^{1}H NMR spectrum and only aliphatic signals of ring C and D as well as the characteristic side chain signals could be seen. A possible reason for the decomposition can be the warm-up to 0 °C.



127[b] **101**

Scheme 54. Attempt for methyl ether and TBDMS cleavage using BBr_3.

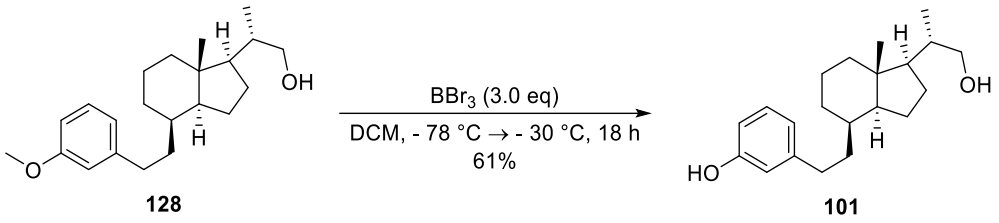
Due to limited amount of *seco*-steroid **127[b]** TBDMS deprotection was now tried first. Methoxy groups can act as prodrugs, so if the methyl ether cleavage will fail again, the methoxylated compound could be tested. **Scheme 55** shows the TBDMS deprotection using HF·py and pyridine. The desired alcohol could be obtained in a good yield of 74%.



127[b] **128**

Scheme 55. TBDMS cleavage of **127[b]**.

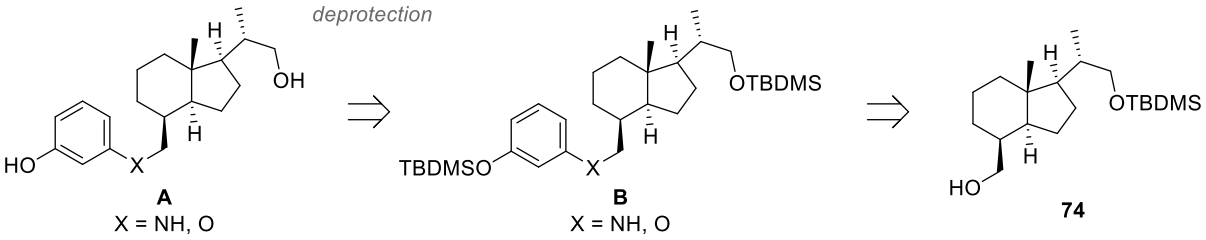
The following methyl ether cleavage was performed again with BBr_3. After addition of BBr_3 the reaction mixture was first slowly warmed to - 30 °C. At this temperature, a slow progression of the reaction could be monitored on TLC. That confirms the consideration why the starting material decomposed and that the reagent was too reactive at 0 °C. **Scheme 56** shows the methyl ether cleavage. The desired diol could be isolated with a yield of 61%.



Scheme 56. Methyl ether cleavage using BBr_3, resulting in diol **101**.

3.3.1.2.4. Studies towards the introduction of an amine and ether linker

A side project of *seco*-steroidal analogues with bridging at C-4 was the introduction of an amine or ether linker. **Scheme 57** shows the retrosynthesis of the desired compounds.

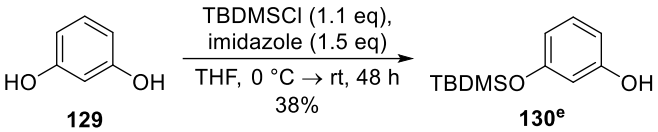


Scheme 57. Retrosynthesis of target diols **A**, bearing an amine or ether linker.

The target diols **A** should be formed *via* deprotection of the phenol and aliphatic side chain. *Seco*-steroids **B** bearing an amine and ether linker, respectively, should be synthesised from alcohol **74** using standard amine and ether synthesis protocols.

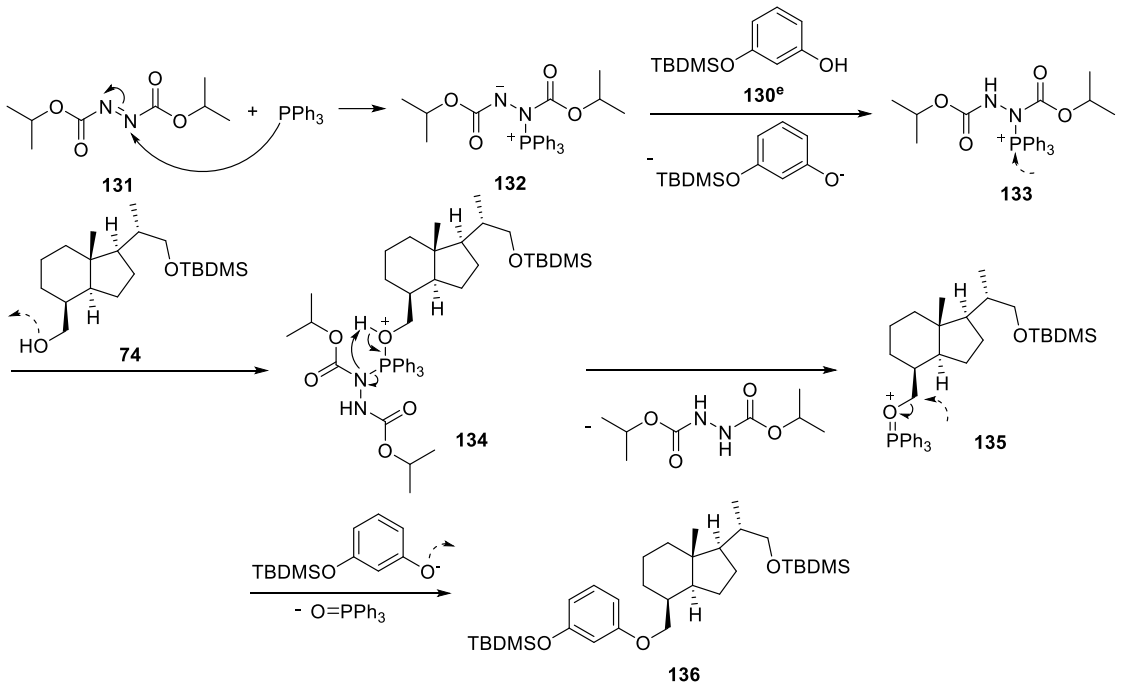
3.3.1.2.4.1. Attempts for the introduction of an ether linker

Starting with the introduction of an ether linker, first, the aromatic building blocks had to be synthesised. For the aromatic building block TBDMS-protected phenyl bromide **76** (for synthesis see chapter 3.3.1.2.1.) and mono-TBDMS-protected resorcinol (**130^{e}**) were used. The TBDMS protection was performed according to a procedure of WU *et al.*,[105] and was conducted during PATRICIA SKOWRONEK'S bachelor thesis[87] (**Scheme 58**).



Scheme 58. Mono-TBDMS protection of resorcinol (**129**).

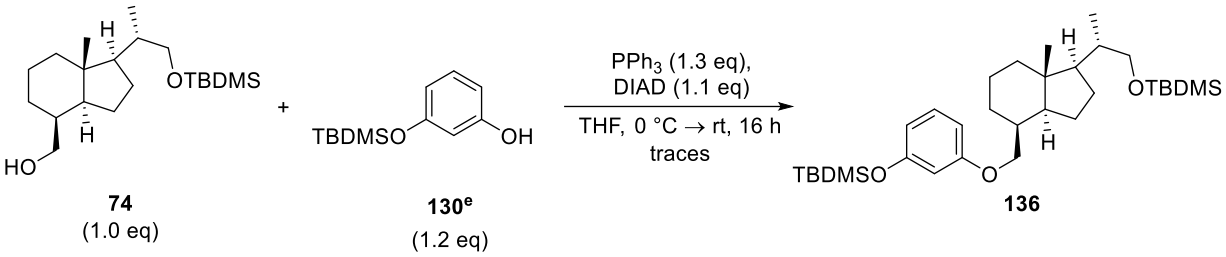
Phenol **130^{e}** was synthesised with a moderate yield of 38%. A popular method for, *inter alia*, etherification is the MITSUNOBU reaction. **Scheme 59** shows the mechanism of the MITSUNOBU reaction on the example of protected resorcinol **130^{e}** and alcohol **74**, using the standard MITSUNOBU reagents PPh_3 and diisopropyl azodicarboxylate (DIAD, **131**).



Scheme 59. Mechanism of MITSUNOBU reaction[106] by the example of **130^{e}** and **74**.

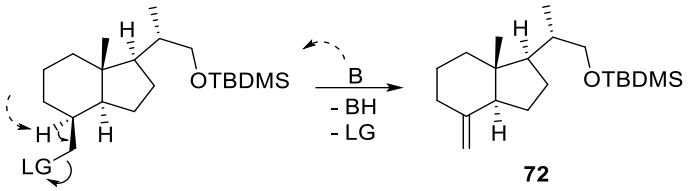
Nucleophilic attack of PPh_3 to DIAD (**131**) lead to intermediate **132**, whereby the negatively charged nitrogen acts as base and deprotonates the present phenol **130^{e}**. The resulting intermediate **133** with the positively charged phosphorus is now attacked by alcohol **74** and intermediate **134** is formed. Subsequent elimination of the hydrazine derivative gives **135** carrying a good leaving group. The lately formed phenolate of **130^{e}** attacks the alcohol in α-position in a S_N2 reaction, triphenylphosphine oxide is eliminated and the desired ether **136** is formed.[106-107]

For the etherification, a method of BOXHALL *et al.* was used.[108] The mass of the desired ether **136** was obtained by GC/MS analysis, but TLC showed a smearing line and as a consequence ether **136** could not be isolated by FCC (**Scheme 60**).



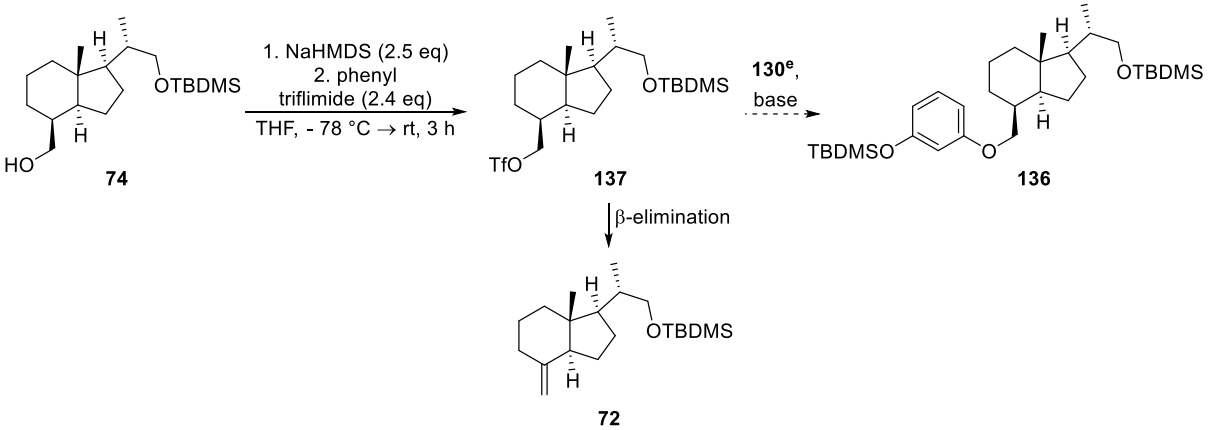
Scheme 60. Result of the MITSUNOBU reaction of **74** and **130^{e}**.

Certainly, a β-elimination led to isolation of alkene **72**. A β-elimination can occur in three different types: E1, E2 or E1cB reaction, whereby in this case, the mechanism follows the E2 mechanism. Due to the formation of the good leaving group (LG; here: triphenylphosphine oxide in **135**, see **Scheme 59**) and the presence of a base (B), which is in this case the formed phenolate of **130^{e}**, the E2 elimination takes place and alkene **72** is formed (**Scheme 61**).



Scheme 61. Example of the E2 elimination.

Another attempt for the synthesis of **136** was an S_N2 reaction *via* triflate **137** (**Scheme 62**). A method of NAGASAKA *et al.* was used,[109] but the reaction failed already with the isolation of triflate **137** and again, alkene **72** was obtained after β-elimination.

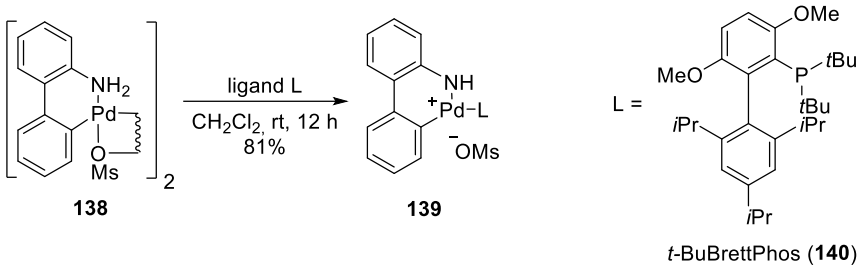


Scheme 62. Attempt towards the synthesis of **137** results in E2 elimination, receiving alkene **72**.

With the formation of **137**, a good leaving group was built and consequently the β-elimination took place.

Another approach using Pd-catalysed C-O cross-coupling was tried. This method was developed by BUCHWALD and co-workers for the C-O cross-coupling on primary alcohols.[110]

In this publication they describe catalytic systems, which provide general and mild conditions for a Pd-catalysed C-O cross-coupling. In a previous publication of BUCHWALD and coworkers, the synthesis of a methanesulfonate precatalyst **138** is described.[111] As ligand, *t*-BuBrettPhos (**140**) was used and the catalyst **139** was isolated with 81% yield (**Scheme 63**).



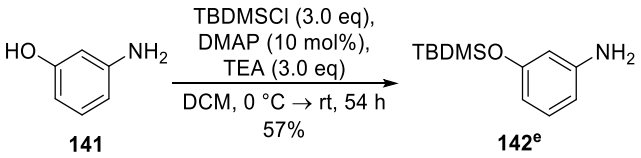
Scheme 63. Synthesis of catalyst **139** for BUCHWALD-HARTWIG cross-coupling.[111]

In the presence of catalyst **139**, a C-O cross-coupling approach was made, using TBDMS protected phenyl bromide **76** and alcohol **74** (**Scheme 64**). TLC showed no new spot and both starting materials were also still visible, but the desired mass could be detected by GC/MS. BUCHWALD described a few cases, in which the alcohol and the product had the same R_f value. Therefore, the reaction mixture was treated with DMAP, TEA and acetic anhydride to acetylate the remaining alcohol **74**. However, only the acetylated alcohol was obtained, and no product was formed in a sufficient amount for an isolation. After all attempts to synthesise ether **136** failed, this project was closed at this stage.

Scheme 64. Attempted BUCHWALD-HARTWIG C-O cross-coupling of **76** and **74**.

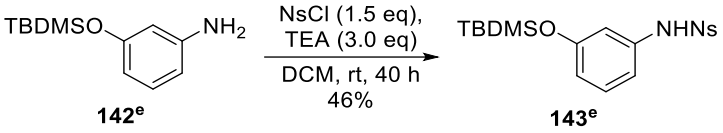
3.3.1.2.4.2. Attempts for the introduction of an amine linker

For the formation of an amine linker, TBDMS protected 3-aminophenol **142^{e}** had to be synthesised (**Scheme 65**).[112] The protected amine **142^{e}** was obtained in a good yield of 57%.



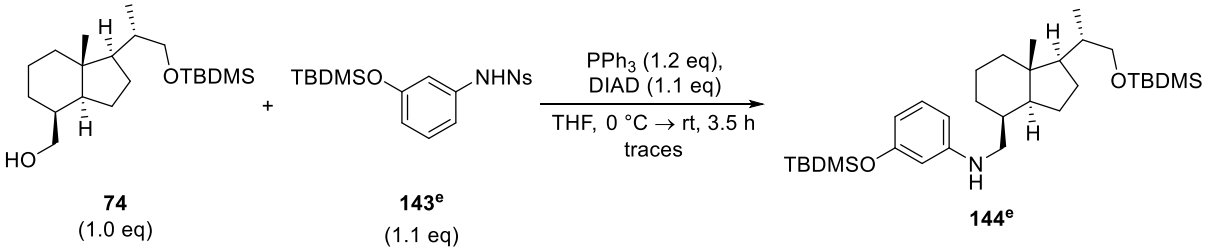
Scheme 65. TBDMS protection of 3-aminophenol (**141**).

For the introduction of an amine linker, a MITSUNOBU reaction was tried. Earlier research in our group showed that a primary amine is too inactive to react in this type of reaction.[113] Therefore, a strong electron withdrawing group, e.g. 2-nitrobenzenesulfonyl (nosyl, Ns) group, was introduced (**Scheme 66**). A method of MIYAUCHI *et al.* was used for the activation of amine **142^{e}**.[114] The desired activated amine **143^{e}** was obtained with 46% yield.



Scheme 66. Introduction of a nosyl group.

For the MITSUNOBU reaction of primary alcohol **74** with activated amine **143^{e}**, a procedure of LEPORE and HE was used (**Scheme 67**).[115] The reaction proceeded in a similar way to the unsuccessful MITSUNOBU etherification. TLC showed a lot of new spots and with GC/MS analysis the desired mass was detected, but the product could not be isolated by FCC. Probably the amount of the formed secondary amine was too low for isolation. As main side product alkene **72** was isolated, which means that a β-elimination took place again and prevented the formation of amine **144^{e}**.



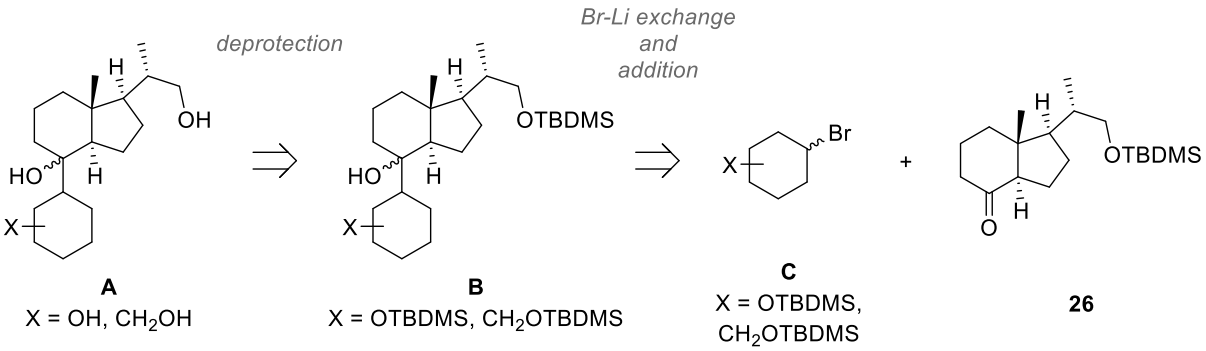
Scheme 67. Introduction of an amine linker *via* MITSUNOBU reaction.

3.3.1.3. Aliphatic residues

Besides aromatic residues, aliphatic residues should be attached at C-4. These studies are discussed in the following chapters.

3.3.1.3.1. Direct attachted aliphatic residue at C-4

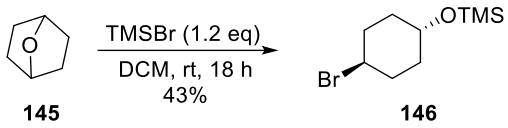
Starting with the introduction of aliphatic residues, which should be attached directly to C-4, **Scheme 68** shows the retrosynthesis of the desired triols **A**. Triols **A** should be obtained *via* deprotection of the protected alcohols **B**, which should be generated from cyclohexyl bromides **C** *via* Br-Li exchange with subsequent addition to central building block ketone **26**.



Scheme 68. Retrosynthesis of desired triols **A** based on central building block **26**.

3.3.1.3.1.1. Synthesis of building block **146**

Besides central building block **26**, the cyclohexyl bromide building block had to be synthesised. For the test reaction, *para* substituted cyclohexyl bromide **146** was synthesised in one step. Starting from 7-oxabicyclo[2.2.1]heptane (**145**), cyclohexyl bromide **146** was synthesised according to a patent in 43% yield (**Scheme 69**).[116]

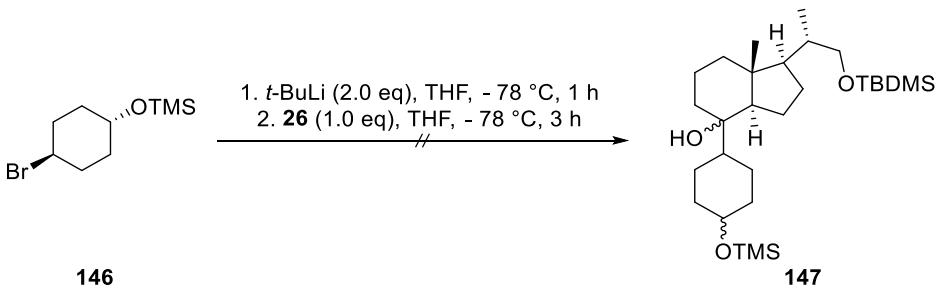


Scheme 69. Synthesis of cyclohexyl bromide **146**.

The addition of TMSBr leads to ether cleavage by the attack of the bromide from the less hindered side and while the bromide is formed, the alcohol is TMS protected.

3.3.1.3.1.2. Br-Li exchange of **146** and addition to ketone **26**

For the formation of the *seco*-steroid, Br-Li exchange of **146** with subsequent addition of the lithiated compound to ketone **26** was performed (**Scheme 70**).



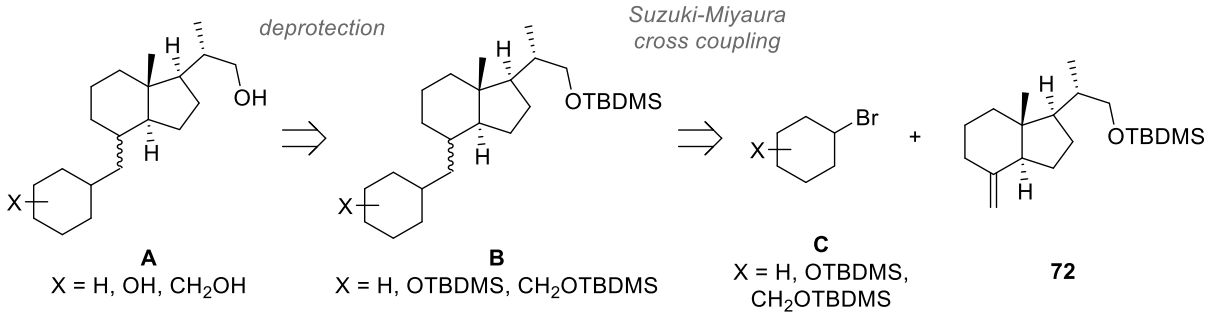
Scheme 70. Br-Li exchange of **146** with subsequent addition to **26**.

TLC of the Br-Li exchange showed that no starting material was left, but more than one spot was observed. Nevertheless, ketone **26** was added and after 4 h the reaction was stopped. TLC showed again a lot of new spots but no characteristic spot. The desired mass of alcohol **147** could not be detected *via* GC/MS analysis. Other approaches for the synthesis of *seco*-

steroids with direct attachment of the residue to C-4, were not performed since the *seco*-steroids bearing an aromatic residue directly linked to C-4, showed no inhibitory effect on DHCR24.

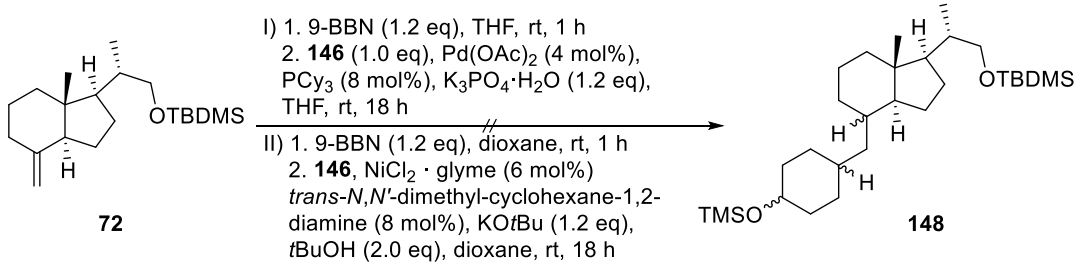
3.3.1.3.2. *Seco*-steroids with methylene linker at C-4

In this chapter the approaches towards the introduction of an aliphatic residue to C-4 connected with a methylene linker is discussed. **Scheme 71** depicts the retrosynthesis of the desired alcohols **A**, which should be generated from TBDMS protected compounds **B** *via* deprotection. The TBDMS protected *seco*-steroids should be synthesised using SUZUKI-MIYAURA cross-coupling of bromocyclohexanes **C** and terminal alkene **72** (as discussed in chapter 3.3.1.2.2.).



Scheme 71. Retrosynthesis of *seco*-steroids **A** based on alkene **72**.

For the test reaction, bromide **146** was used. First, a Pd-catalysed method of FU and co-workers was tried, using $Pd(OAc)_2$ as catalyst, $K_3PO_4 \cdot H_2O$ as base and PCy_3 as ligand (**Scheme 72**, I).[117] In the first stage of the reaction, terminal alkene **72** was borylated using 9-BBN, whereby formation of the *B*-alkyl-9-BBN intermediate could be observed with TLC. The actual cross-coupling reaction showed a lot of new spots on TLC, but the desired mass could not be detected *via* GC/MS analysis. The reaction was repeated, with the difference, that the particular reaction mixtures were degassed longer. Nevertheless, the desired mass could not be found *via* GC/MS and separation of the spots revealed that no product was formed. Moreover, alkene **72** was isolated, which means that the borylation did not proceed quantitatively.

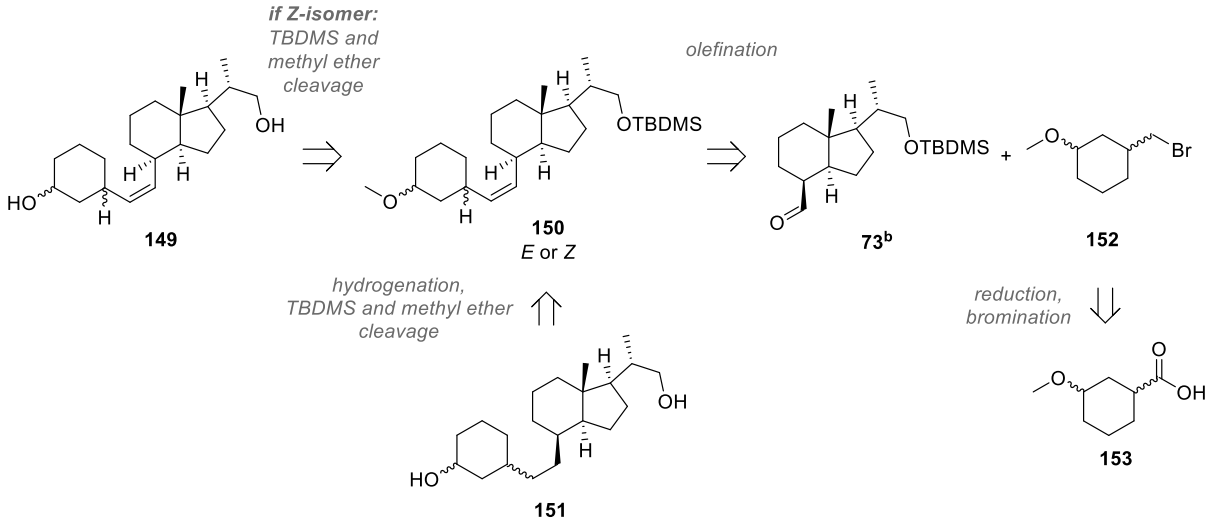


Scheme 72. SUZUKI-MIYAURA cross-coupling of alkene **72** with cyclohexyl bromide **146**.

For the next approach, a procedure of SAITO and FU was used, whereby in this procedure, unactivated secondary alkyl halides were cross coupled, using $NiCl_2$·glyme as catalyst and *trans*-*N*,*N'*-dimethylcyclohexane-1,2-diamine as ligand (**Scheme 72**, II).[118] In this case solid 9-BBN was used, which resulted in a faster borylation, but the following alkyl-alkyl cross-coupling was not successful. Although the desired mass was detected by GC/MS, TLC showed a smearing line of spots and the desired product **148** could not be obtained *via* FCC purification. Alkene **72** was recovered under these conditions as well, which means, that the formation of the *B*-alkyl-9-BBN adduct did not proceed quantitatively, although TLC showed no leftover starting material **72**. After these attempts, the synthesis of *seco*-steroids bearing a cyclohexyl residue attached *via* a methylene linker at C-4 were no longer pursued.

3.3.1.3.3. *Seco*-steroids with ethylene linker at C-4

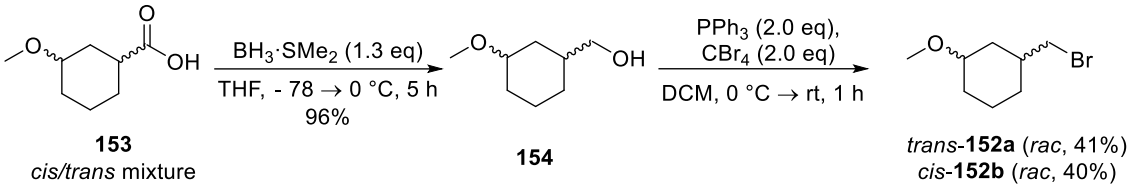
The last chapter of the introduction of aliphatic residues discusses the introduction of cyclohexyl residues *via* an ethylene linker. With this linker, the correct dimension of the steroidal structure will be achieved. **Scheme 73** demonstrates the retrosynthesis of the desired target diols **149** and **151**. *Z*-Olefin **149** should be synthesised *via* TBDMS and methyl ether cleavage of **150** if the *Z*-isomer of **150** was formed. Olefin **150** should be synthesised using an olefination method like WITTIG olefination from aldehyde **73^{b}** and bromide **152**. The latter should be synthesised from of 3-methoxycyclohexane-carboxylic acid (**153**) in two steps. Since the synthesis of building block **107** was not successful (see chapter 3.3.1.2.3.), the reaction should be performed with aldehyde **73^{b}**. Besides the *Z*-configurated diol **149**, its saturated form **151** should be generated *via* hydrogenation and subsequent TBDMS and methyl ether cleavage of **150**, whereby the *E*/*Z* configuration of the starting olefin is negligible in this step.



Scheme 73. Retrosynthesis of target diols **149** and **151**, which should be synthesised from aldehyde **73^{b}** and 3-methoxycyclohexanecarboxylic acid (**153**).

3.3.1.3.3.1. Synthesis of building blocks **152a** and **152b**

The synthesis of the required aliphatic building block **152** is shown in **Scheme 74**. Based on commercially available *cis*/*trans* mixture of 3-methoxycyclohexanecarboxylic acid (**153**), the first step was the reduction of the carboxylic acid group to an alcohol function using dimethylsulfide borane according to a patent.[119] The reaction should occur at - 78 °C, but at this temperature no reaction was monitored on TLC. Therefore, the reaction was slowly warmed to 0 °C and gas evolution could be observed. With the ceasing of gas evolution, TLC showed that the starting material was fully consumed, and the reduction was finished. Next, the crude *cis*/*trans* mixture of alcohol **154** was brominated under APPEL conditions.[99]



153
cis/trans mixture

154

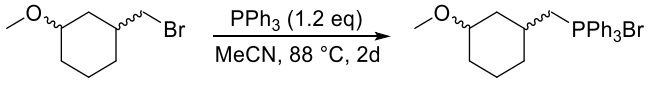
trans-**152a** (*rac*, 41%)
cis-**152b** (*rac*, 40%)

Scheme 74. Two step synthesis of cyclohexylmethyl bromide *trans*-**152a** and *cis*-**152b** from 3-methoxycyclohexanecarboxylic acid (**153**) (*cis*/*trans* assignment was performed retrospectively from *trans*-**158** and *cis*-**160**).

With the formation of the bromides **152**, the *cis*/*trans* isomers could be separated *via* FCC and racemic *trans*-isomer **152a** was obtained in a moderate yield of 41% and racemic *cis*-isomer **152b** with 40%. It is noteworthy, that at this stage the *cis*/*trans* assignment was not possible and could only be performed retrospectively.

3.3.1.3.3.2. WITTIG olefination

The first attempt for the olefination was a WITTIG olefination, whereby *E* and *Z* isomers can be formed. For the synthesis of the appropriate phosphonium bromide salts, the racemic bromides *trans*-**152a** and *cis*-**152b** and PPh_3 were dissolved in toluene and heated to reflux. When only triphenylphosphine oxide and the starting material could be isolated, toluene was replaced by acetonitrile. For *trans*-**152a** the desired phosphonium bromide *trans*-**155** could be isolated, but in the case of isomer *cis*-**152b** only the mass of the phosphonium bromide salt *cis*-**156** could be found, but the product could not be isolated and only triphenylphosphine oxide was obtained (**Scheme 75**).

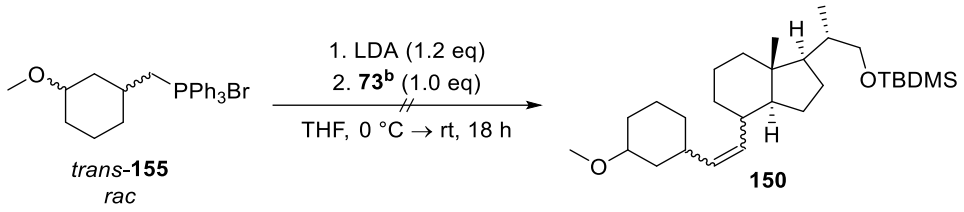


trans-**152a** (*rac*)
cis-**152b** (*rac*)

trans-**155** (*rac*, 24%)
cis-**156** (traces)

Scheme 75. Formation of the triphenylphosphonium bromide salts from cyclohexylmethyl bromides *trans*-**152a** and *cis*-**152b** (*cis*/*trans* assignment was performed retrospectively from *trans*-**158** and *cis*-**160**).

Consequently, the following WITTIG olefination was only performed with phosphonium bromide *trans*-**155** (**Scheme 76**). The reaction was performed with LDA as base to generate the appropriate ylide.

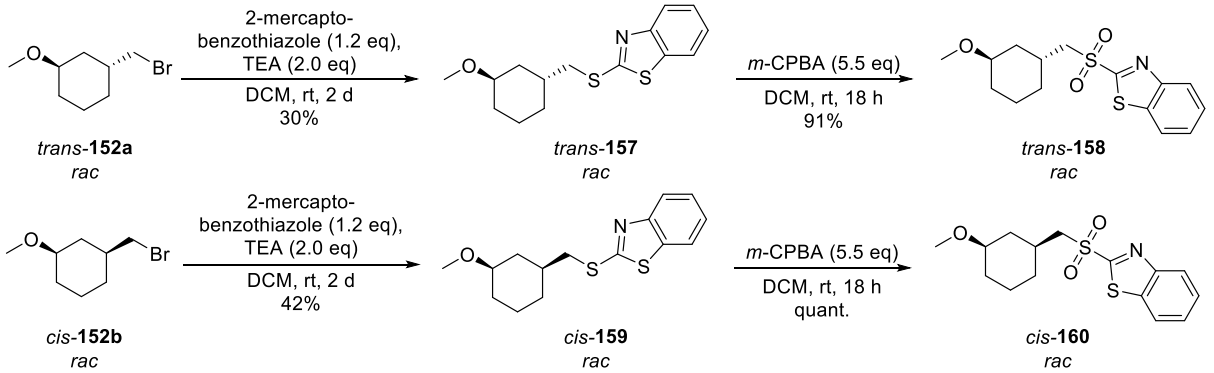


Scheme 76. Attempted WITTIG olefination of **73**^{b} and *trans*-**155**.

The formation of the ylide was confirmed by the colour change from colourless to deep orange. However, the desired olefin **150** could not be synthesised using WITTIG conditions and only unidentifiable products were isolated.

3.3.1.3.3.3. JULIA-KOCIENSKI olefination

An alternative to WITTIG olefination is the JULIA-KOCIENSKI olefination, a modified version of the JULIA olefination in which alkenes can be generated from alkylsulfonyl benzothiazole and aldehydes. The JULIA-KOCIENSKI olefination predicts a high *E* selectivity which is in this case not the favoured configuration. Nevertheless, this type of olefination was tried. Starting from racemic bromides *trans*-**152a** and *cis*-**152b**, the bromide was substituted with mercaptobenzothiazole in an S_N2 reaction, resulting in *trans*-**157** and *cis*-**159** (stereoconfiguration determined retrospectively), followed by oxidation of the thioether moiety using *m*-CPBA to receive the racemic JULIA-KOCIENSKI reagents *trans*-**158** and *cis*-**160** in 91% and quantitative yield, respectively (**Scheme 77**).



Scheme 77. Synthesis of JULIA-KOCIENSKI reagents *trans*-**158** and *cis*-**160** from *trans*-**152a** and *cis*-**152b** (*cis*/*trans* assignment was performed retrospectively from *trans*-**158** and *cis*-**160**).

In this stage, both stereocenters of the methoxycyclohexylmethyl residue could be clearly identified *via* NOESY spectroscopy. **Figure 13** shows the NOESY spectrum of sulfonyl *trans*-**158**. At 400 MHz 3'-H and 1'-CH_2 appear together as one multiplett, but measurement with

600 MHz resulted in a split up of the signals and the couplings could be analysed separately. No spatial coupling between 3'-H and 1'-H could be seen, which means that both protons are *trans* to one another. Consequently, both residues, the methoxy group and the methyl sulfonyl group are in *trans* position to each other as well.

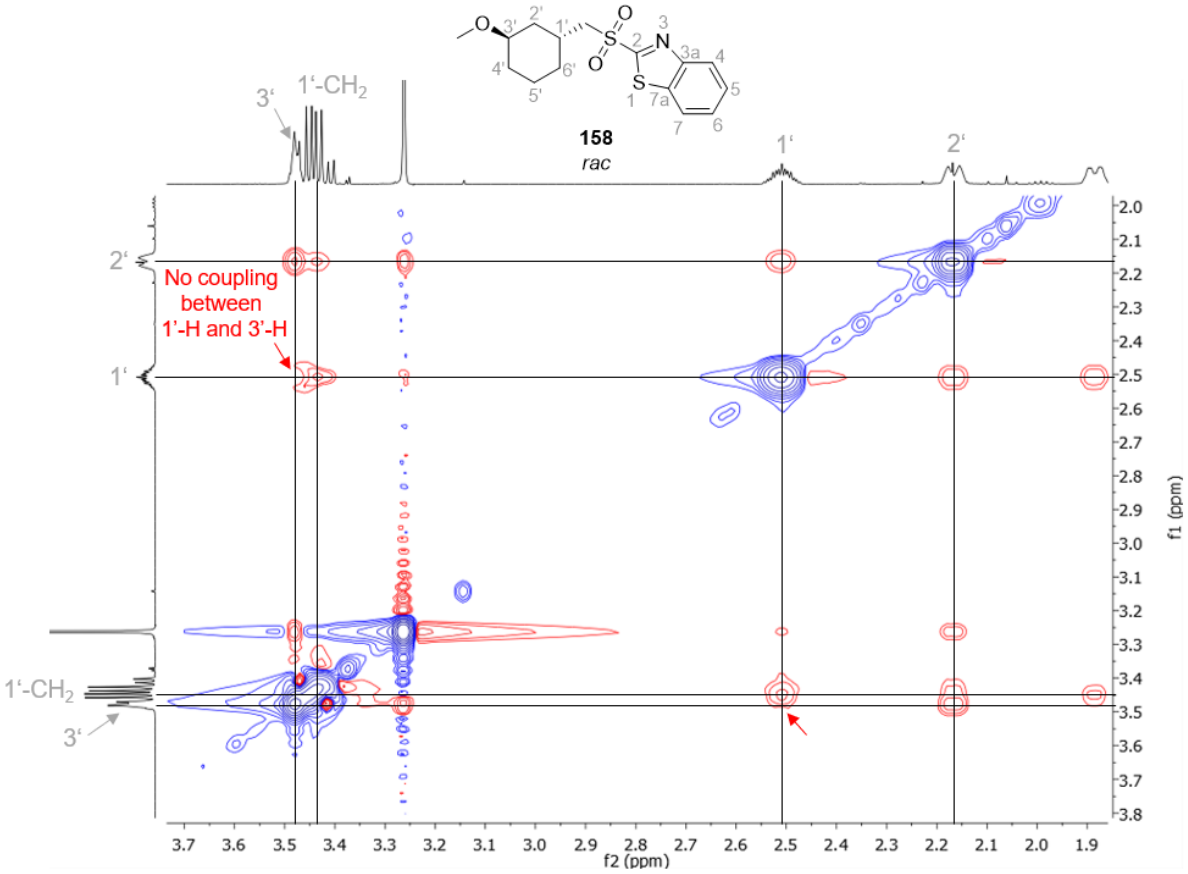


Figure 13. NOESY spectrum of racemic *trans*-**158**.

Figure 14 shows the NOESY spectrum of sulfonyl *cis*-**160**. Upon the measurement at 400 MHz, one proton of C-2' and 1'-H appeared together in a multiplett. Therefore, the NOESY was measured again with 800 MHz and the signals split up to a duplet for 2'-H and a multiplett for 1'-H. A coupling between 3'-H and 1'-H can be clearly seen. As a result, the methoxy group and the methyl sulfonyl residue are in *cis* position to each other.

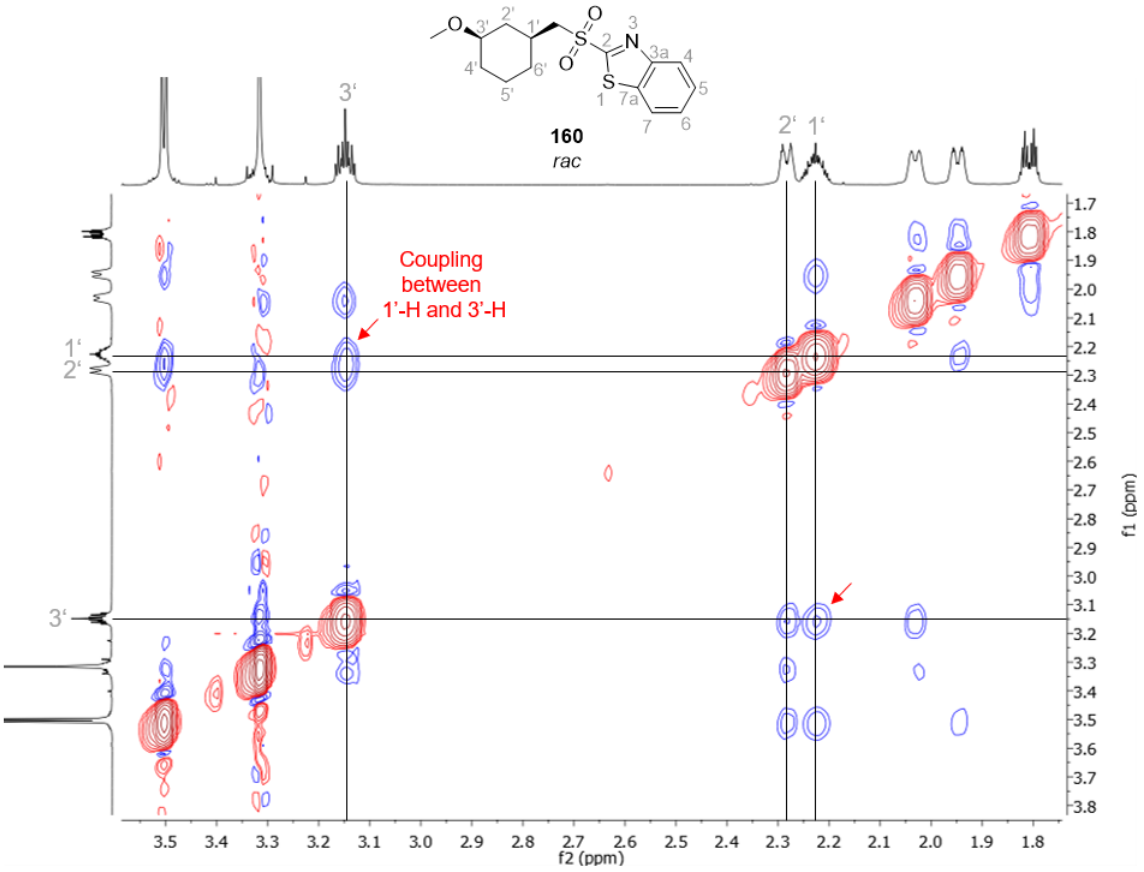
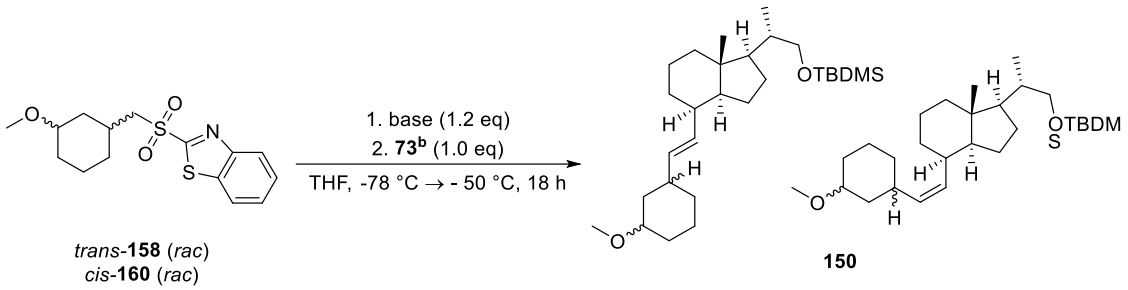


Figure 14. NOESY spectrum of racemic *cis*-**160**.

After successful synthesis of both JULIA-KOCIENSKI reagents, the olefination was performed, using aldehyde **73ᵇ**. **Table 4** shows the used conditions and results towards the olefination. The first two entries show the attempts using sulfonyl compound *cis*-**160**. In entry 1 NaHMDS (pKa = 29.5[69]) was used as base. The desired mass could not be detected by GC/MS and no characteristic spot was observed on TLC. Consequently, FCC did not result in the desired olefin. The exchange of NaHMDS with the stronger base LDA (pKa = 35.7[69]) did also not result in the desired olefin **150** (entry 2). Entries 3 and 4 shows the results using sulfonyl compound *trans*-**158**. With the use of NaHMDS the desired mass was detected by GC/MS and TLC showed a new characteristic spot, but the product could not be isolated (entry 3). NMR spectroscopy showed olefinic peaks, but also aromatic peaks, which could be derived from sulfonyl reagent *trans*-**158**. The exchange of NaHMDS with LDA gave the desired product with 69% yield (entry 4).

Table 4. Attempts for the JULIA-KOCIENSKI olefination of *trans*-**158** and *cis*-**160**, respectively, with aldehyde **73**[b].



trans-**158** (*rac*)
cis-**160** (*rac*)

150

entry	reagent	base	yield (**150**)
1	*cis*-**160**	NaHMDS	0%
2	*cis*-**160**	LDA	0%
3	*trans*-**158**	NaHMDS	traces
4	*trans*-**158**	LDA	69%

NMR spectroscopy showed only aliphatic signals as well as the characteristic olefinic signals, which split of as *E*/*Z* isomers in a ratio of 56:44 (determined *via* ^{1}H NMR spectroscopy). Due to the racemic mixture of *trans*-**158**, four diastereomers can be generated in total. A closer look at the ^{1}H NMR showed that four methoxy groups are present, which means that all four isomers were formed. Also, ^{13}C NMR shows, that more than two isomers were isolated. GC/MS chromatogram of **150** confirmed the assumption of the formation of all four diastereomers (**Figure 15**).

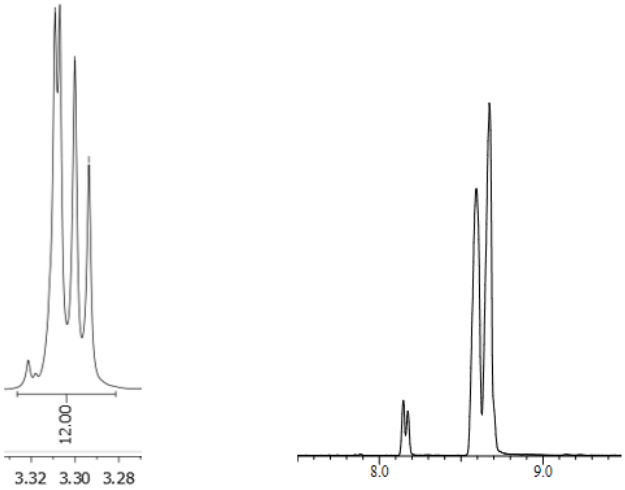
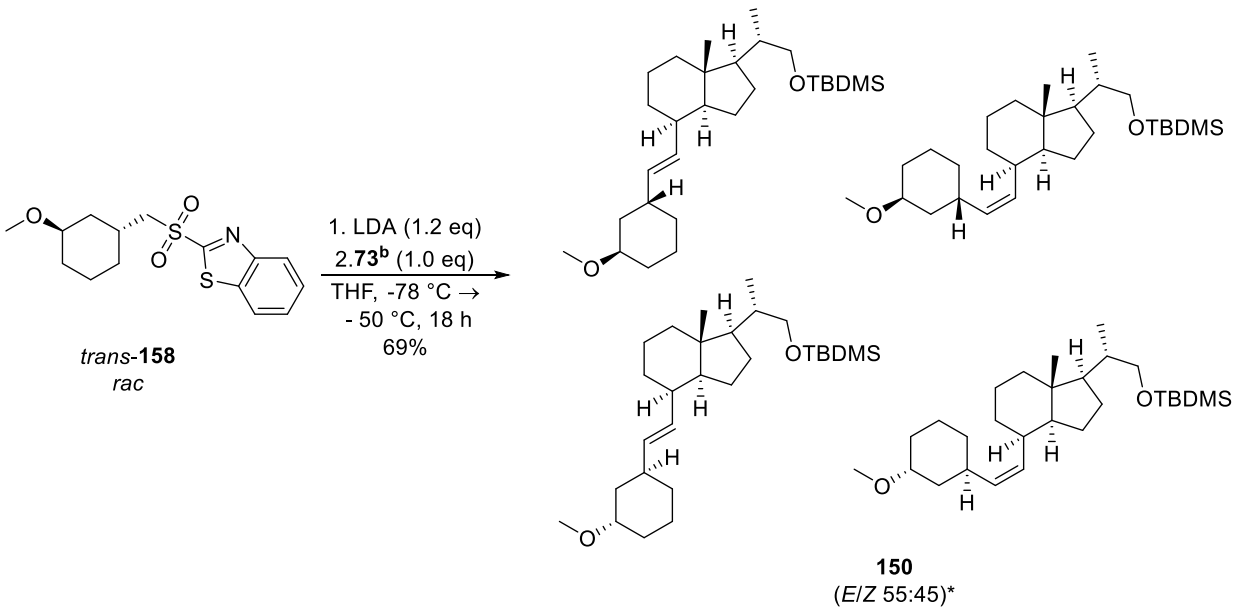


Figure 15. Left: Methoxy group signals in the ^{1}H NMR spectrum of **150**. Right: section of the GC/MS chromatogram detecting the four isomeric signals of **150**.

Based on the ^{1}H NMR, the *E*/*Z* ratio is 55:45, but the ratio between the four isomers could not be determined, since a lot of signals come together in a multiplett. Integration of the chromatogram revealed a ratio of 4:5:43:48 of the four isomers. Due to the identical mass of

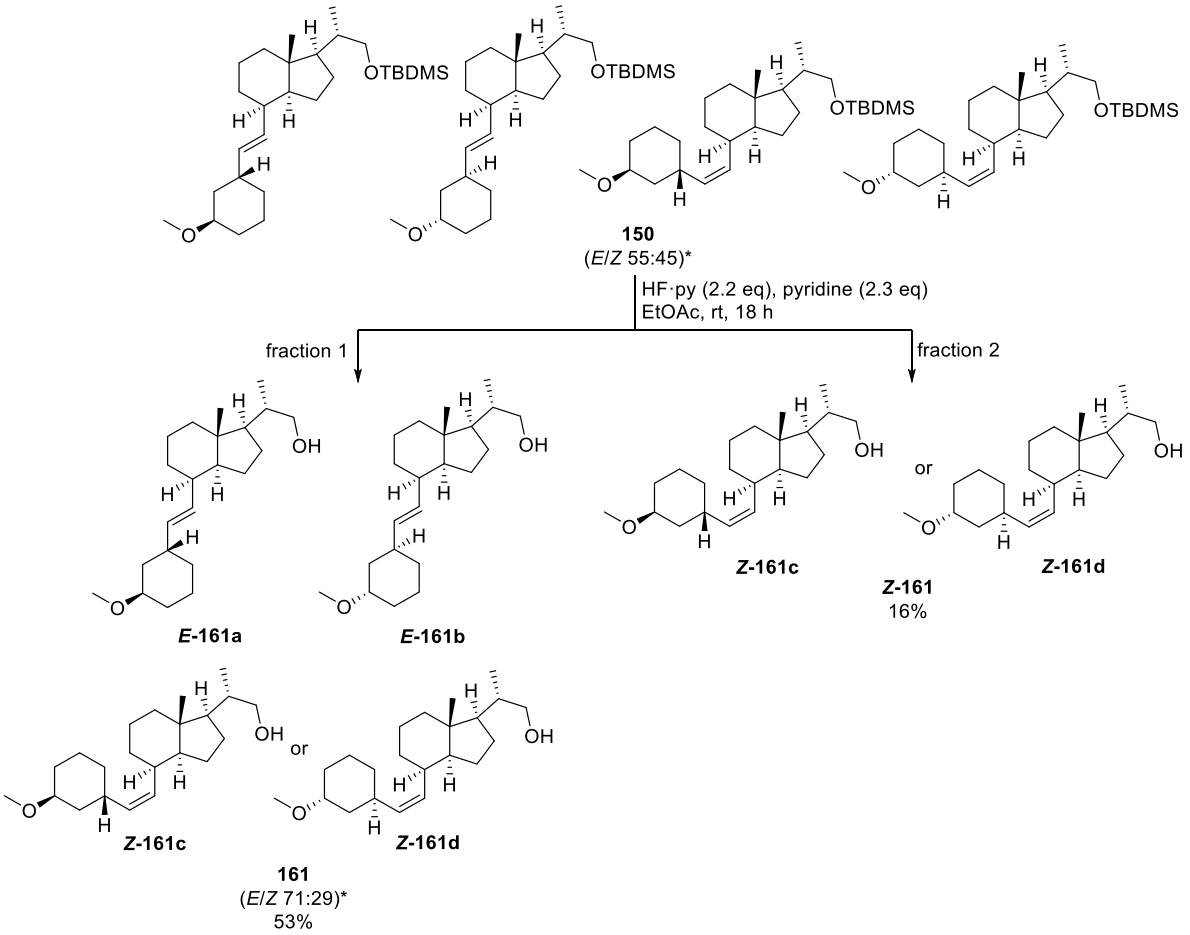
the isomers, it cannot be specified which diastereomere belongs to which signals. However, with the *E*/*Z* ratio and the ratio of the four isomers detected *via* GC/MS analysis, it is clear, that one *E*- and one *Z*-isomer were preferably formed than the diastereomeric version of them. The four isomers could not be separated and therefore the mixture was used for the next steps (**Scheme 78**).



Scheme 78. JULIA-KOCIENSKI olefination of **73b** and racemic mixture of sulfonyl *trans*-**158** resulted in the four diastereomers. **E*/*Z* ratio determined *via* ^{1}H NMR.

For biological testing, the *Z*-isomers were preferred, since they mimic the steroidal structure best. Due to impossible separation of the four diastereomeres with our options the mixture was used. First, the TBDMS group was cleaved using HF·py and pyridine. Using FCC, two fractions were isolated, whereby the first fraction showed only three methoxy groups signal in the ^{1}H NMR spectrum and moreover the *E*/*Z* ratio had changed to 71:29 (**Scheme 79**).

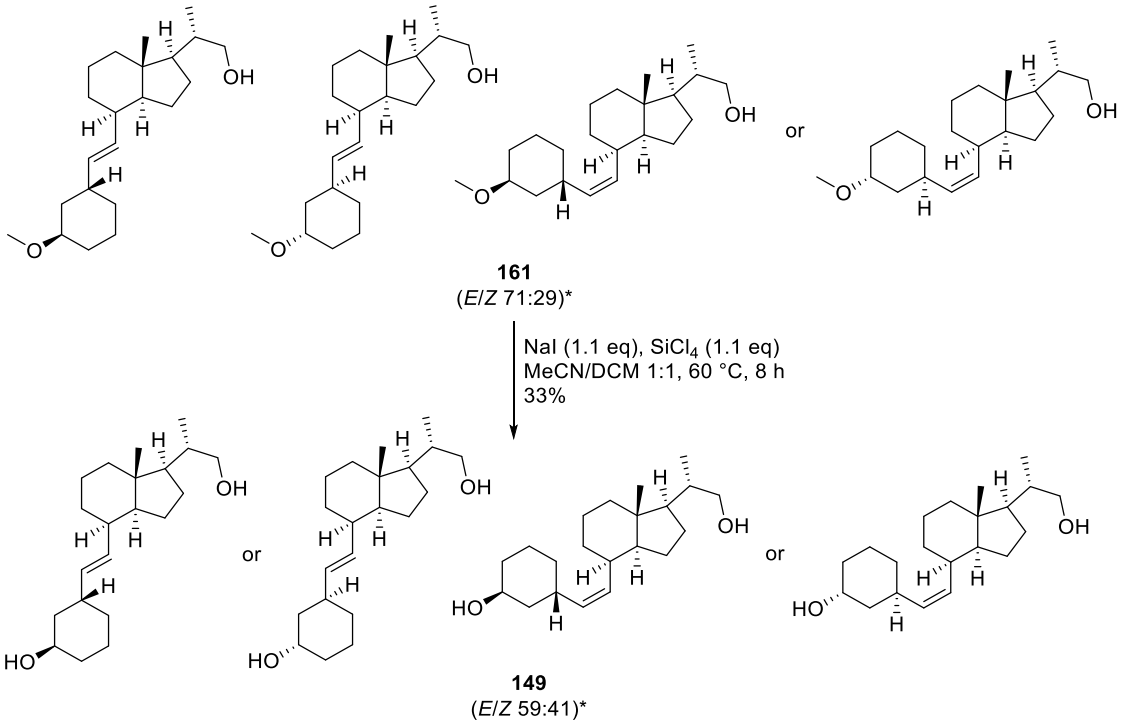
The second fraction exposed to be one *Z*-isomer, which is in accordance to the observation of the ^{1}H NMR spectrum of the first fraction. Since the residue can rotate, the distances of the sterecenters' protons cannot be measured and consequently the stereoconfiguration of the isomer cannot be determined. The mixture of the three isomers was isolated in 53% yield and the *Z*-isomer in 16% yield.



Scheme 79. TBDMS cleavage of **150** resulting in two fractions. *E/Z ratio determined *via* ^{1}H NMR.

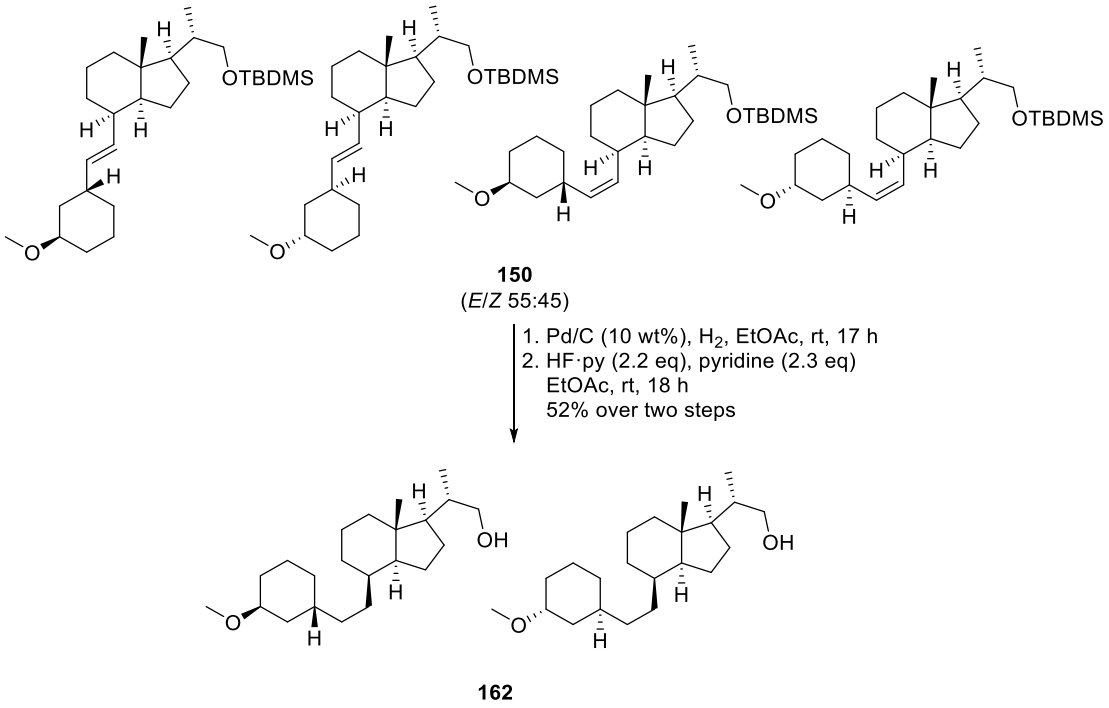
To cleave the methyl ether, a procedure from BHATT *et al.* was used.[120] In the presence of NaI and $SiCl_4$ the phenol of *E*/*Z* mixture **161** was deprotected and *E*/*Z* mixture **149** could be obtained in 33% yield (**Scheme 80**). Unfortunately, the amount of *Z*-**161** was too low to perform methyl ether cleavage.

After methyl ether cleavage, the *E*/*Z* ratio was 59:41 (determined *via* ^{1}H NMR) and NMR spectra showed only two sets of signals, which means that one *E*-isomer was separated. Nevertheless, the amount of **149** was so low, that the fraction with the separated *E*-isomer could not be isolated. However, this isomer is not desired anyway, as the *E*-isomer does not mimic the orginal steroidal scaffold. Nevertheless, the inhibitory effect on the cholesterol biosynthesis of the diastereomeric *E*/*Z* mixture **161** and the separated *Z*-isomer of **161** as well as diastereomeric *E*/*Z* mixture of diol **149** was analysed.



Scheme 80. Methylether cleavage of diastereomeric mixture **161**. *E/Z ratio determined *via* ^{1}H NMR.

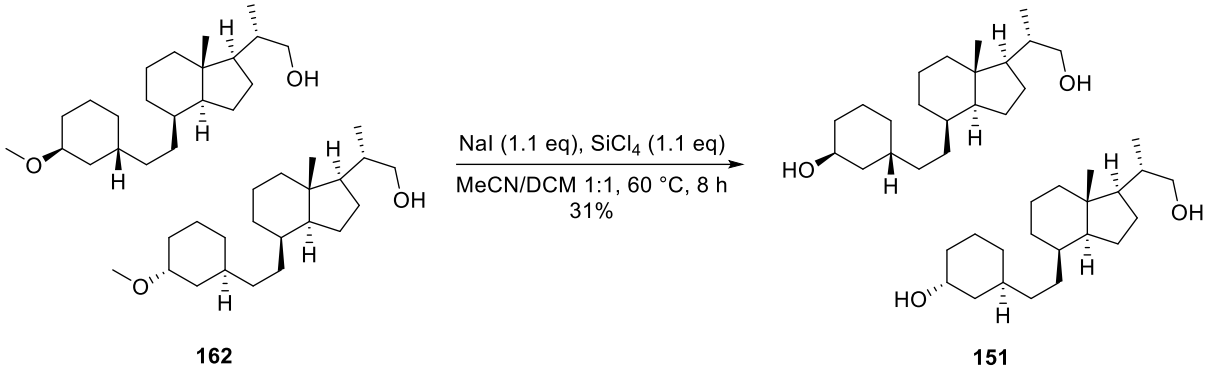
For the removal of the double bond, the diastereomeric *E*/*Z* mixture of **150** was hydrogenated using Pd/C and H_2, followed by TBDMS cleavage with HF·py and pyridine, resulting in the diastereomeric mixture **162** in 52% yield over two steps (**Scheme 81**).



Scheme 81. Hydrogenation and TBDMS cleavage of diastereomeric mixture **150**.

NMR spectra show two products, but the ratio could not be determined since the signals of each diastereomer appear together in a multiplett.

Methylether cleavage using NaI and $SiCl_4$ led to the final compound **151** as inseparable diastereomeric mixture in 31% yield. The inhibitory effect of **151** was also tested on the cholesterol biosynthesis (**Scheme 82**).



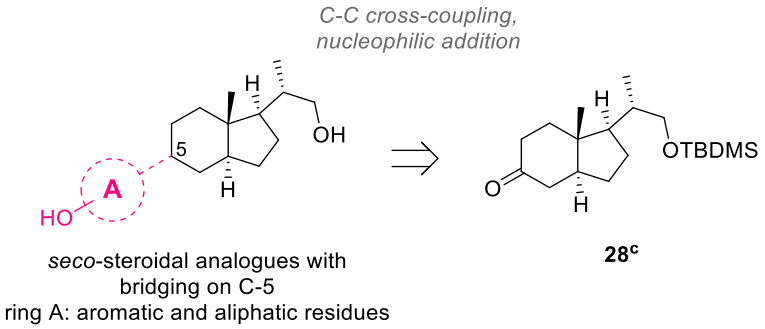
162 **151**

Scheme 82. Methylether cleavage of diastereomeric mixture **162**.

The ratio between both products could not be determined in this step as well, since the signals of each diastereomer comes in a multiplett.

3.3.2. *Seco*-steroidal analogues with bridging at C-5

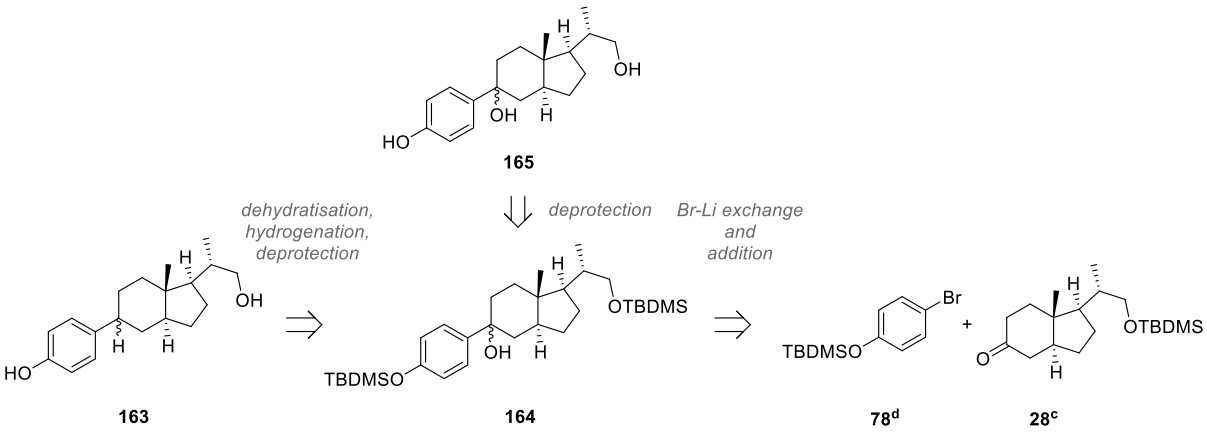
Besides bridging at C-4, *seco*-steroids with bridging on C-5 were of high interest. Therefore, central building block **28^{c}**, which was already discussed in chapter 3.1.2., was required (**Scheme 83**).



Scheme 83. Planned route for the synthesis of *seco*-steroidal analogues with bridging at C-5. Ring A should be aromatic or aliphatic (marked in pink).

3.3.2.1. Aromatic residue

In this chapter, the introduction of a phenol is discussed. **Scheme 84** shows the retrosynthesis of the target compounds **163** and **165**.

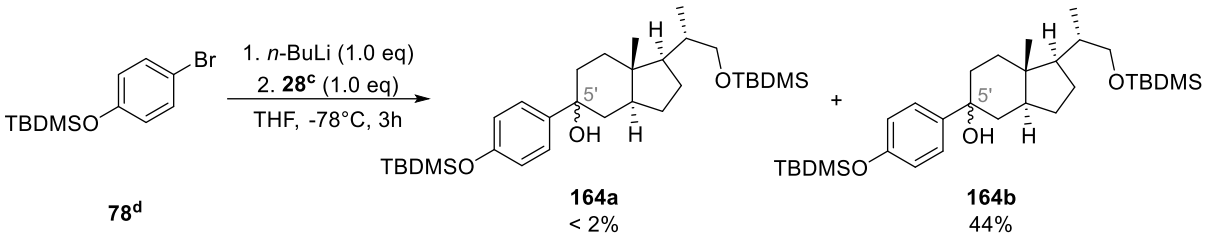


Scheme 84. Retrosynthesis of *seco*-steroid **163**, based on central building block **28^{c}**.

Diol **163** should be obtained after dehydration with subsequent hydrogenation and double TBDMS cleavage. The protected alcohol **164** should be generate *via* Br-Li exchange of **78^{d}** (for synthesis see chapter 3.3.1.2.1.) with subsequent addition to ketone **28^{c}**. Moreover, triol **165** should be obtained *via* deprotection of **164**.

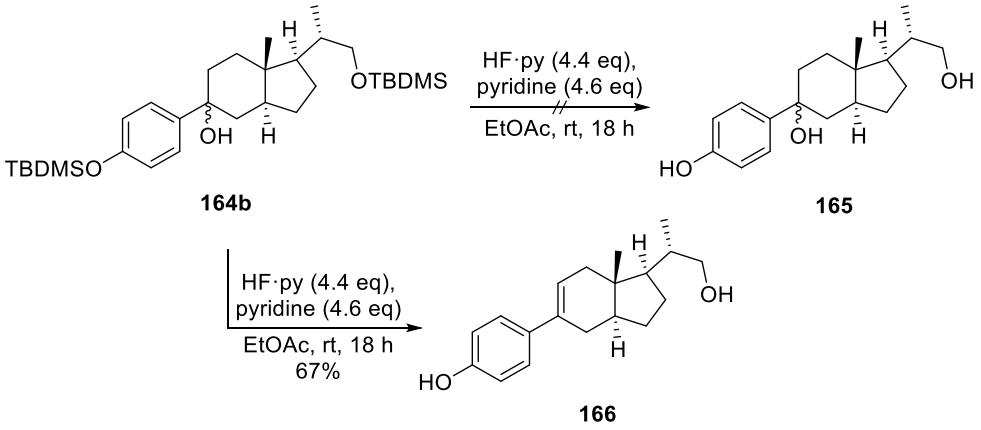
Starting with the Br-Li exchange of **78^{d}** and the following addition to ketone **28^{c}**, this reaction proceeds identical to the addition shown in chapter 3.3.1.2.1. (**Scheme 85**). TLC showed two new spots. Alcohol **164a** (R_f = 0.55, hexanes/EtOAc 9:1) and its diastereomer **164b** (R_f = 0.26, hexanes/EtOAc 9:1) were separated and isolated by FCC in < 2% and 44% yield, respectively. In solution, both diastereomers undergo dehydration very fast, which can be observed during

the NMR measurement. Consequently, it was not possible to determine the stereoconfiguration at C-5.



Scheme 85. Br-Li exchange of **78**[d] and following nucleophilic addition of ketone **28**[c].

Alcohols **164a** and **164b** should be deprotected in order to get the desired triol **165**. Starting with **164b**, the phenol and the primary alcohol were deprotected, using HF·py and pyridine. TLC showed a clear new polar spot, but ^{1}H NMR did not show the desired compound **165**. Besides the deprotection, an elimination took place and compound **166**, bearing a Δ^5 double bond, was obtained in 67% yield (**Scheme 86**).



Scheme 86. Results of the attempt to deprotect **164b**, resulting in **166**.

In the ^{1}H NMR spectrum the characteristic olefinic signal of 6'-H around 5.92 – 5.85 ppm can be seen. 4'-H and 7'-H appear as a multiplett, which makes the determination of the double bond position difficult. The position of the 7'-H protons in the multiplett were assigned *via* 2D HMBC spectrum, observing a $^{4}J_{H,H}$ coupling between 7a-CH_3 and 7'-H. Thus, COSY spectrum revelead, that 6'-H shows a clear $^{3}J_{H,H}$ coupling to one of the 7'-H protons (**Figure 16**). The position of the double bond is in accordance to the attempts of trapping and imitating the enol in chapter 3.2.2.2. describing the attempts of the formation of an aromatic ring B.

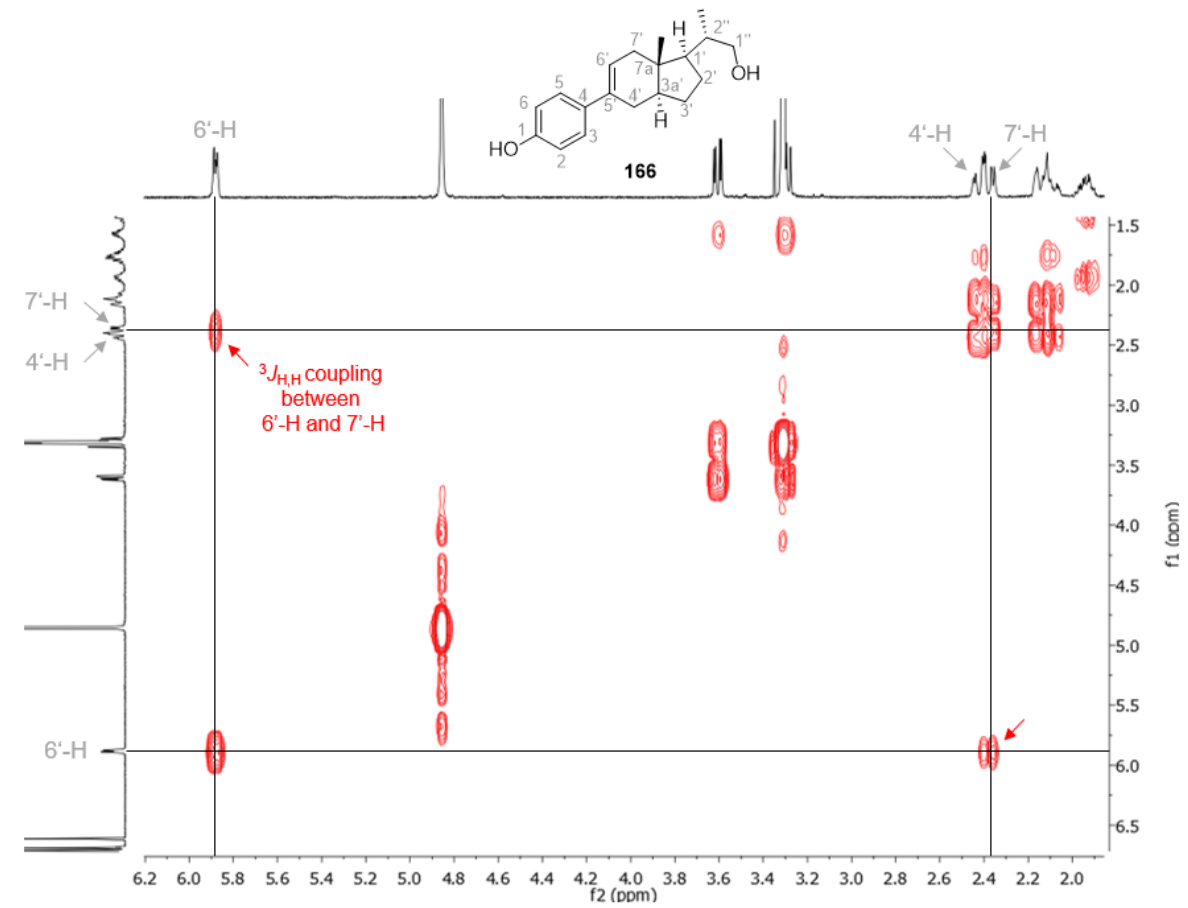
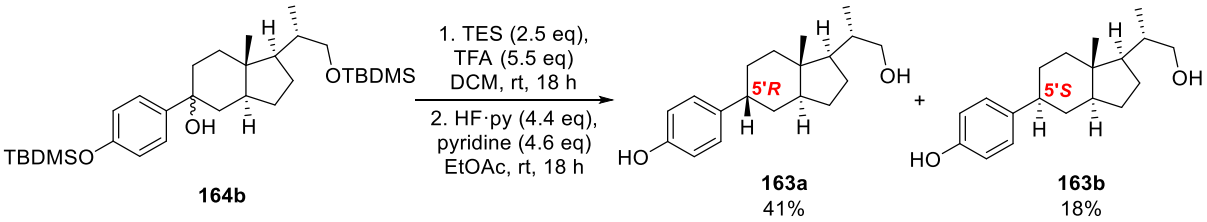


Figure 16. COSY spectrum of **166**.

Based on **164a** and **164b** the hydroxy group at C-5' should be eliminated to get the desired diol. During dehydration, loss of the stereoinformation at C-5' occurs, which means, that it does not matter if the reaction is performed with **164a** or **164b** (**Scheme 87**).



Scheme 87. Dehydration, ionic hydrogenation and TBDMS cleavage of **164b** resulting in diastereomers **163a** and **163b**.

Successful dehydration with subsequent hydrogenation using TES/TFA was confirmed by GC/MS analysis and the product was used without further purification. The crude (bis)silylether was then TBDMS deprotected using HF·py and pyridine. TLC showed two new spots and **163a** (R_f = 0.63, hexanes/EtOAc 7:3) and **163b** (R_f = 0.30, hexanes/EtOAc 7:3) could be separated and isolated by FCC. The stereocenter at C-5' in **163a** could be determined as *R* configurated, since a clear spatial coupling between 5'-H and 7a'-CH_3 could be observed in the NOESY

spectrum. The formed stereocenter in **163b** could not be identified *via* NOESY spectroscopy since important signals like 3a'-H are located under a multiplett, but crystals of diastereomer **163b** could be obtained and the structure in the solid state was determined by X-ray structure analysis (**Figure 17**).

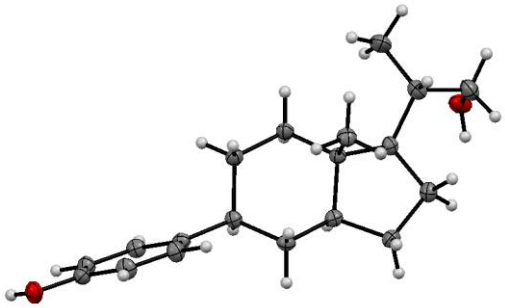


Figure 17. Mercury depiction of the structure of **163b** in the crystalline state.

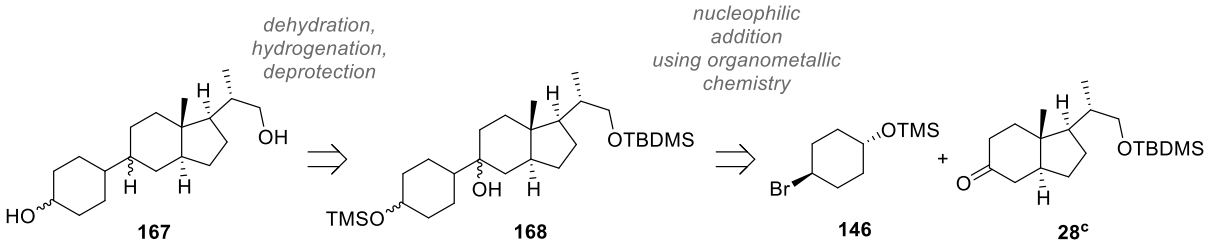
The phenol at C-5 is facing to the front and consequently 5-H to the back, resulting in *S* configuration.

3.3.2.2. Aliphatic and open chained residues

In this chapter the introduction of cyclohexanol and open chained residue at C-5 is discussed.

3.3.2.2.1. Introduction of a cyclohexanol

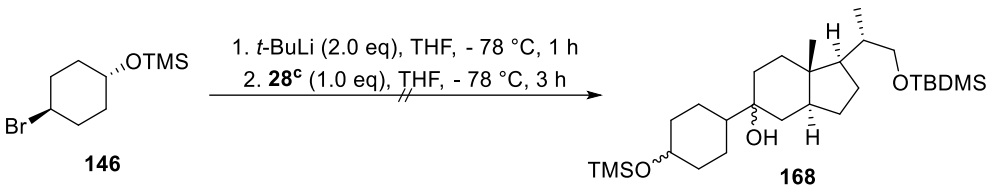
For the introduction of a cyclohexanol at C-5 position organometallic chemistry was used. **Scheme 88** shows the retrosynthesis of the desired *seco*-steroidal diol **167**.



Scheme 88. Retrosynthesis of *seco*-steroid **167** based on central building block **28^{c}**.

The desired diol **167** should be formed *via* dehydration and hydrogenation, followed by deprotection of alcohol **168**. Alcohol **168** should be obtained *via* nucleophilic addition of bromide **146** (for synthesis see chapter 3.3.1.3.1.1.) and ketone **28^{c}**, using organometallic chemistry.

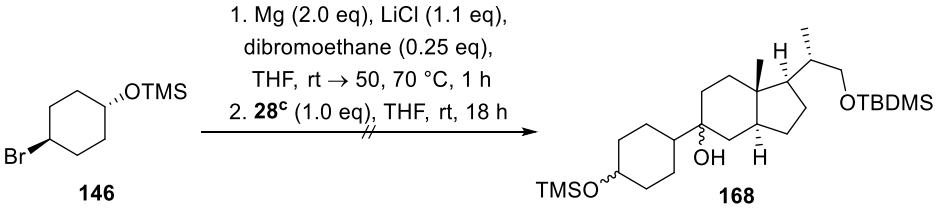
The first approach was a Br-Li exchange of the bromide followed by addition of the lithiated intermediate to ketone **28^{c}**, which is depicted in **Scheme 89**.



Scheme 89. Results of Br-Li exchange of **146** with subsequent nucleophilic addition to **28c**.

Br-Li exchange showed a lot of new spots on TLC and the starting material was consumed completely. Therefore, ketone **28c** was added and after 1 h TLC showed already a lot of spots. After, in total, 3 h, nothing has changed according to TLC and GC/MS analysis showed not the desired mass. Probably the desired Br-Li exchange did not take place. A possible reason can be, that the silyl ether was cleaved. The reaction was performed again, now using 3 equivalents of *t*-BuLi, but the reaction proceeded in the same way.

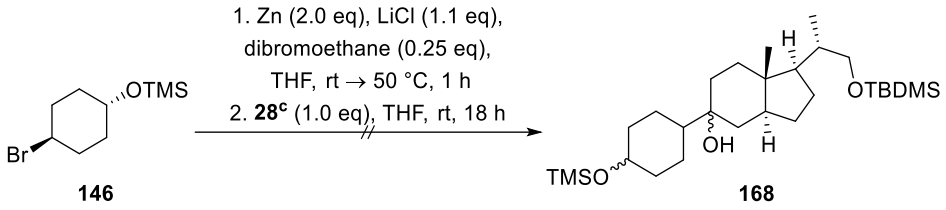
Therefore, another approach was tried. GRIGNARD reagents (RMgX) are a central tool for the formation of a C-C bond in the organic chemistry.[121] **Scheme 90** depicts the attempted GRIGNARD reaction of **146** and ketone **28c**.



Scheme 90. Attempted GRIGNARD reaction of **146** with **28c**.

To activate Mg, dibromoethane was added,[122] since a layer of unreactive $Mg(OH)_2$ or MgO_2 can lead to the inactivation of the magnesium metal. The use of LiCl has an accelerating effect on the Br-Mg exchange.[123] Nevertheless, the GRIGNARD formation showed no reaction on TLC. The starting material **146** seems to be untouched at room temperature. Therefore, the reaction was heated to 50 °C, but no reaction occurred. Ketone **28c** was added and the reaction mixture was stirred overnight, but both starting materials left unreacted. The reaction was repeated, and heated to 70 °C, but nothing happened.

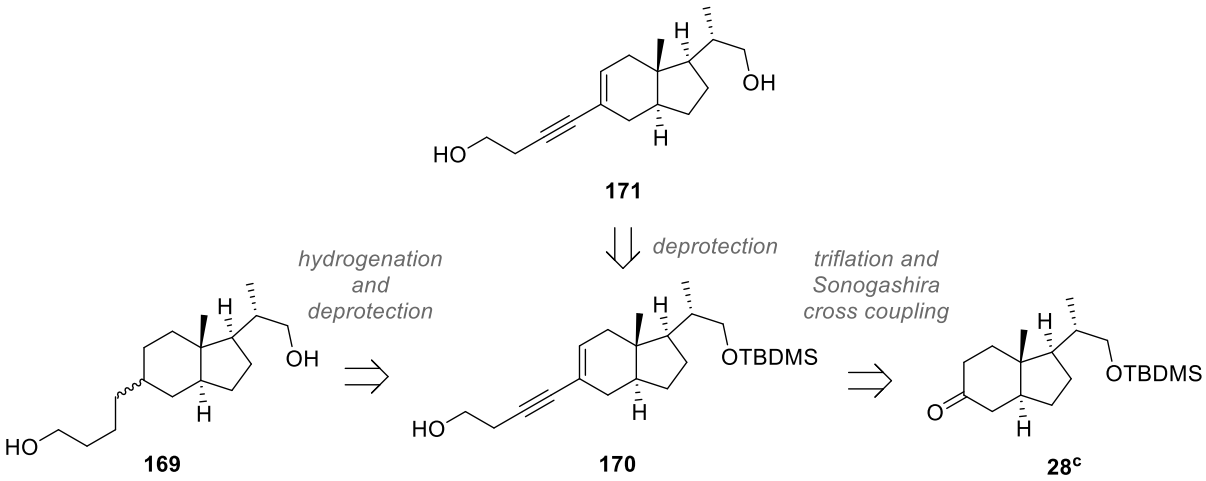
Besides GRIGNARD reagents, organozinc reagents have become a powerful tool in organometal chemistry.[124] In this case, Zn was used instead of Mg (**Scheme 91**). Unfortunately, the reaction was not successful and desired *seco*-steroid **168** could not be obtained. As in the attempt of the GRIGNARD reaction, the organozinc reagent could not be formed. A possible reason can be, that bromide **146** is too inactive for this reaction. After these unsuccessful attempts, the introduction of cyclohexanol to C-5 was no longer pursued.



Scheme 91. Attempted organozinc reaction of **146** with **28c**.

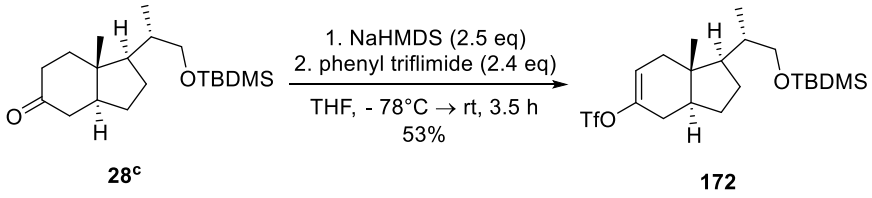
3.3.2.2.2. Introduction of an open chained residue

Scheme 92 illustrates the retrosynthesis of the open chained residue. Desired diol **169** should be formed *via* hydrogenation and subsequent TBDMS deprotection of alkyne **170**. Alkyne **170** should be generated from central building block **28c** *via* triflation, followed by SONOGASHIRA cross-coupling. Furthermore, diol **171** should be generated *via* deprotection of **170** since the rigid alkyne structure mimics the length of the lead structures.



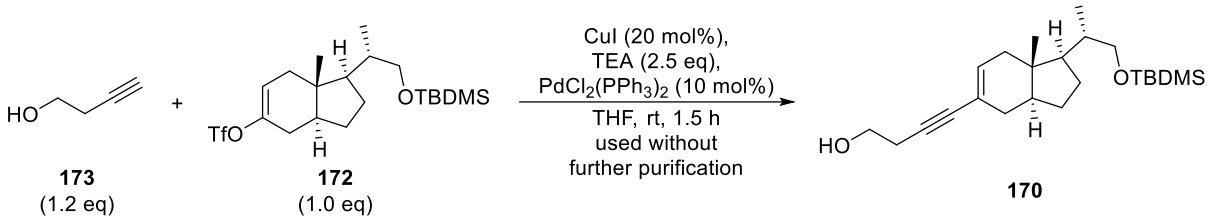
Scheme 92. Retrosynthesis of diols **169** and **171**.

Starting from ketone **28c**, enol triflate **172** was synthesised, using phenyltriflimide and NaHMDS, in 53% yield (**Scheme 93**). The double bond was formed selectively in Δ^5-position, which is in accordance to the studies towards the synthesis of an aromatic ring B (see chapter 3.2.2.).



Scheme 93. Synthesis of enol triflate **172**.

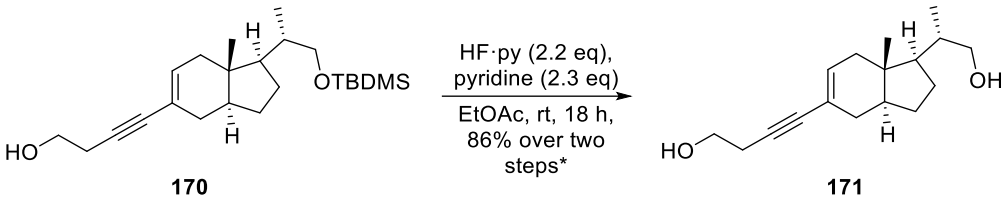
With enol triflate **172**, SONOGASHIRA cross-coupling with but-3-yn-1-ol (**173**) was performed (**Scheme 94**). The resulting alkyne **170** was used without further purification.



173 (1.2 eq) **172** (1.0 eq) **170**

Scheme 94. SONOGASHIRA cross-coupling between **172** and but-3-yn-1-ol (**173**).

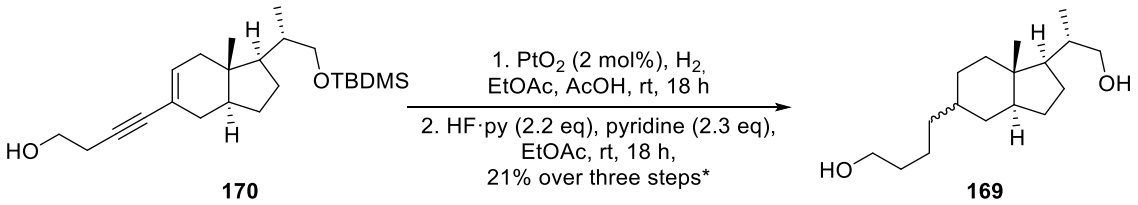
Scheme 95 depicts the deprotection of the alcohol group using HF·py and pyridine. Diol **171** was obtained in a good yield of 86% over both steps.



170 **171**

Scheme 95. TBDMS cleavage of **170** using HF·py and pyridine, resulting in diol **171**. *Yield is based on starting material **172** over two steps.

In the next step, hydrogenation of **170** was performed to receive the saturated version of **171**. **Scheme 96** shows the hydrogenation with subsequent deprotection.



170 **169**

Scheme 96. Hydrogenation of **170** with subsequent TBDMS cleavage resulting in **169**. *Yield is based on starting material **172** over three steps.

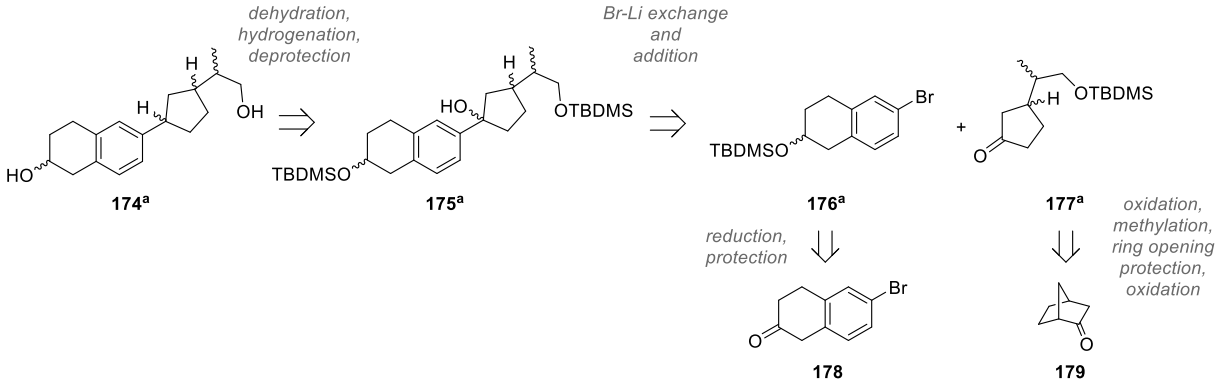
Diol **169** could be obtained in 21% over three steps. Unfortunately, the stereocenter at C-5 could not be determined since the 5-H split up in a multiplett with other protons. Moreover, various crystallisation attempts of the oil did not result in measurable crystals.

3.4. Studies towards *seco*-steroids with a “broken” ring C

A side project of this thesis was the study towards the variation of ring C for the synthesis of further *seco*-steroidal structures. This chapter was developed in the bachelor thesis of ANNA J. STEINMETZ, which was carried out under my supervision.[125]

3.4.1. Retrosynthesis of *seco*-steroidal diol **174ᵃ**

In **Scheme 97** the retrosynthesis of diol **174ᵃ** is shown. Diol **174ᵃ** should be obtained *via* TBDMS cleavage and dehydration with subsequent hydrogenation of alcohol **175ᵃ**, which should be formed *via* Br-Li exchange of bromotetralin **176ᵃ**, with subsequent addition to ketone **177ᵃ**.

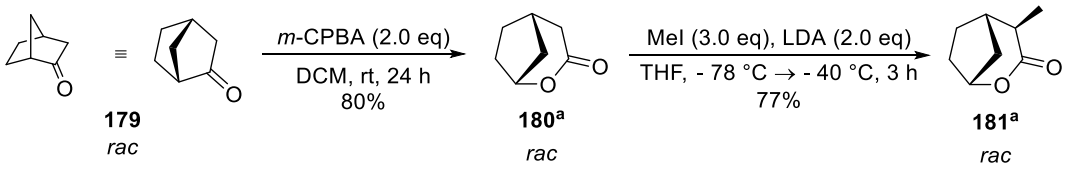


Scheme 97. Retrosynthesis of **174ᵃ**, based on bromotetralone **178** and norcamphor (**179**).

Bromide **176ᵃ** should be formed *via* reduction of the keto group of bromotetralone **178** and TBDMS protection of the formed alcohol group. Building block **177ᵃ** should be synthesised over five steps from norcamphor (**179**).

3.4.2. Synthesis of building block **177ᵃ**

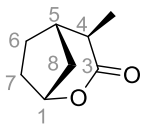
The first two steps of the five-step synthesis of ketone **177ᵃ** are literature-known and followed a procedure of BURNELL AND WU.[126] The steps are depicted in **Scheme 98**. The first step is a BAYER-VILLIGER oxidation of racemic norcamphor (**179**) to lactone **180ᵃ**, using *m*-CPBA as oxidising agent. Lactone **180ᵃ** could be isolated in a good yield of 80%.



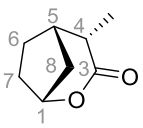
Scheme 98. BAYER-VILLIGER oxidation of racemic norcamphor (**179**), followed by C-methylation resulting in racemic **181ᵃ**.

Diastereoselective mono-methylation of **180ª** using methyl iodide (MeI) and LDA gave methylated lactone **181ª** in a good yield of 77%. Instead of the highly toxic solvent HMPA, THF was used. With the methylation a new stereocenter was built. Using NOESY spectroscopy as identification method for the new stereocenter, a coupling between 4-H and 5-H was very weak and would therefore speak for the *trans* derivative. The distances of the methyl group to 4-H, 5-H, 6-H and 8-H were determined (**Table 5**).

Table 5. Distances of the methyl group 4-CH_3 to certain protons in **DH-AS-2ª**. 8-H shows the distances to the nearest proton of the CH_2 group.



cis, rac
181ª



trans, rac
181ª

Configuration	4-H	5-H	6-H	8-H
cis	2.431 Å	2.505 Å	4.885 Å	2.059 Å
trans	2.448 Å	2.496 Å	2.113 Å	4.752 Å

Figure 18 shows the NOESY spectrum of **181ª**. Looking at the measured distances, it makes no difference looking at their spatial coupling, since the distance in the cis isomer (2.431 Å) is nearly the same as in the *trans* isomer (2.448 Å). The crucial factor of the determination of the stereoconfiguration are the couplings between the methyl group and 6-H and the methyl group and 8-H since the distances in *cis* and *trans* are completely different. There is no spatial coupling between the methyl group and 6-H, but a strong coupling between methyl group and 8-H, resulting in the *cis* isomer.

This is in accordance to the study of FUKUMOTO *et al.*, saying that the methylation takes place from the less hindered side, resulting in this isomer.[127] Additionally the specific rotation was measured, resulting in racemic *cis* methylated lactone **181ª** was obtained.

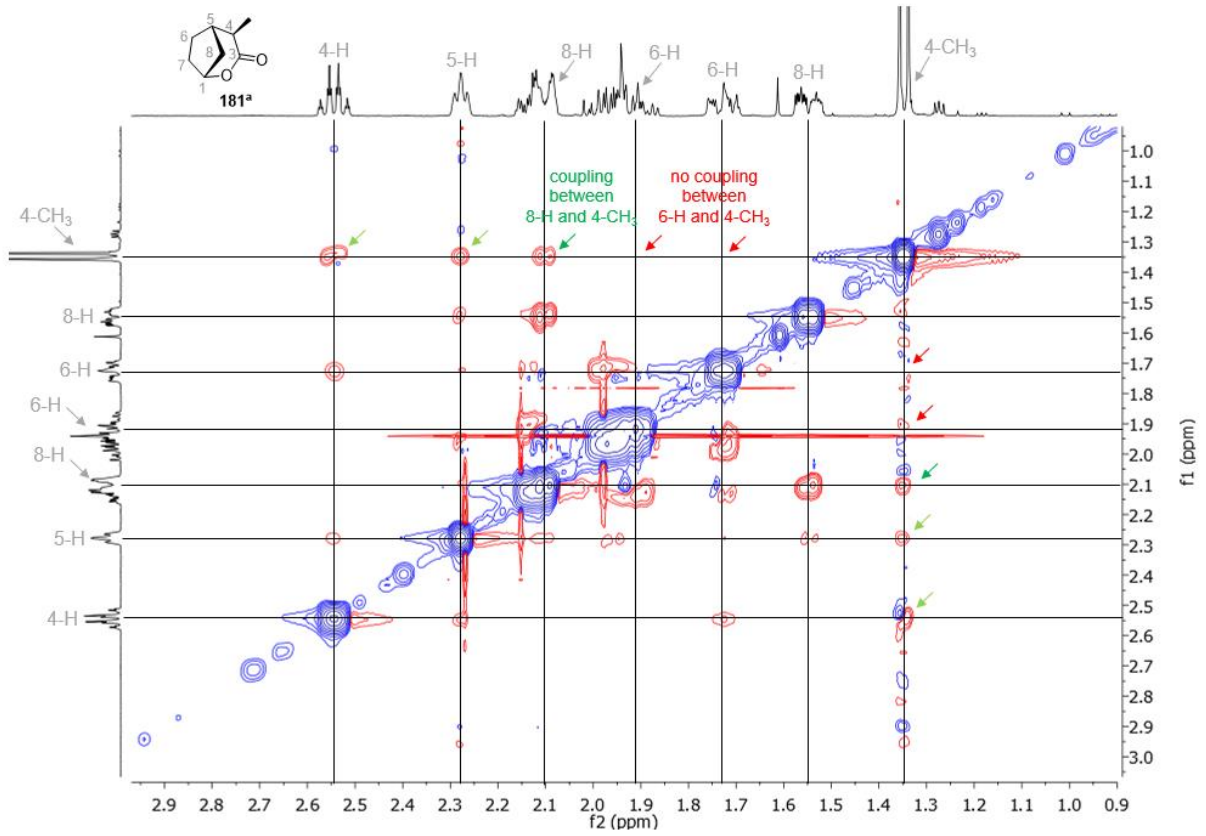
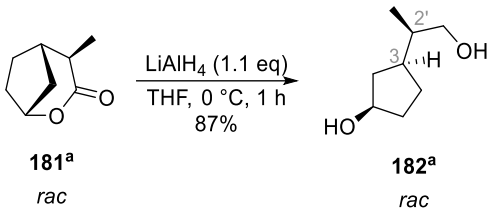


Figure 18. NOESY spectrum of **181ª**.

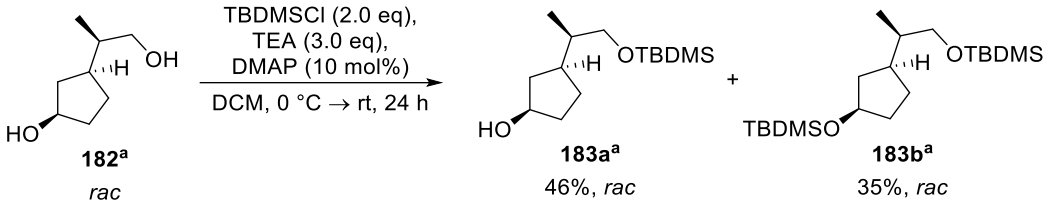
According to FUKUMOTO *et al.*, the reduction of the ester of lactone **181ª** was performed, using $LiAlH_4$. A strong reducing agent is needed here, because of the stable ester. Reduction resulted in ring opening of the lactone, obtaining diol **182ª** (**Scheme 99**).



Scheme 99. Reductive ring opening of **181ª**.

Since the stereochemistry is not affected by the ring opening and reduction, the relative configuration is maintained and the racemic mixture of **182ª** was obtained. A clear coupling between 3-H and 2'-H could be observed *via* NOESY spectroscopy. Unfortunately, the stereochemistry at C-3 and C-2' is not the same as in the lead structures, but since the aim of this project was to find a route to this type of *seco*-steroid with variation on ring C, the stereoconfiguration was initially neglected.

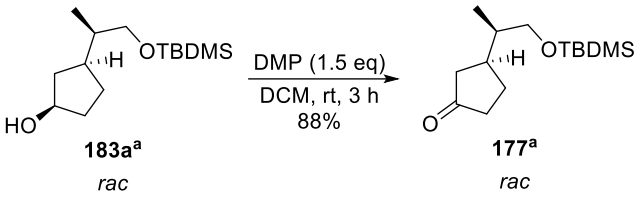
The following mono-TBDMS protection is depicted in **Scheme 100**. Two products were isolated, the mono-protected silyl ether **183a[a]** and the double-protected silyl ether **183b[a]**.



Scheme 100. TBDMS protection of primary hydroxyl group of **182[a]**.

A possible reason for the double TBDMS protection can be the used amount of 2 equivalents of TBDMSCl. Lowering the amount could lead to more mono-deprotected product. Nevertheless, the formation of both isomers is in accordance with the literature.[128]

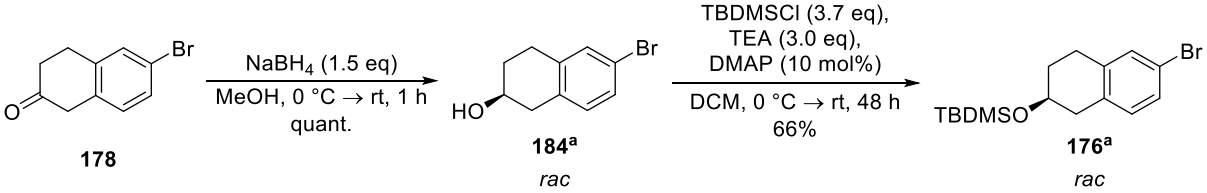
For the final step to building block **177[a]**, the secondary alcohol group was oxidised using DMP (**Scheme 101**). The desired ketone could be isolated in a very good yield of 88% as a racemic mixture.



Scheme 101. Oxidation of remaining hydroxyl group of **183a[a]** using DMP.

3.4.3. Synthesis of building block **176[a]**

The second building block **176[a]** was synthesised from bromotetralone **178**, following a procedure of TSCHAEN *et al.* for the reduction of the keto group.[129] **Scheme 102** depicts the reduction, followed by the protection of the formed alcohol group.

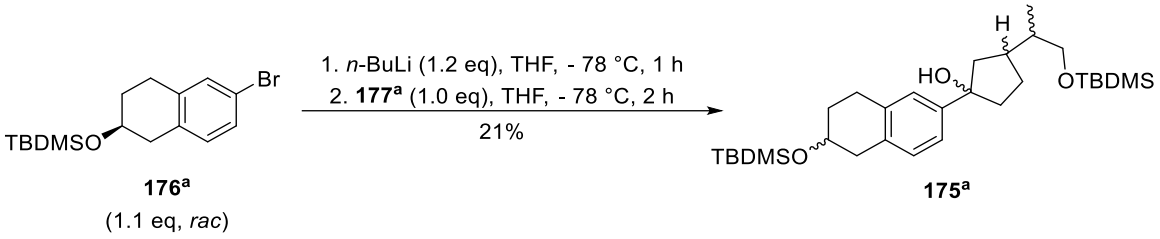


Scheme 102. Reduction of bromotetralone **178**, followed by TBDMS protection of the hydroxyl group.

The reduction using $NaBH_4$ gave racemate **184[a]** in quantitative yield. The TBDMS protection of the resulting alcohol group gave racemic **176[a]** in a good yield of 66%.

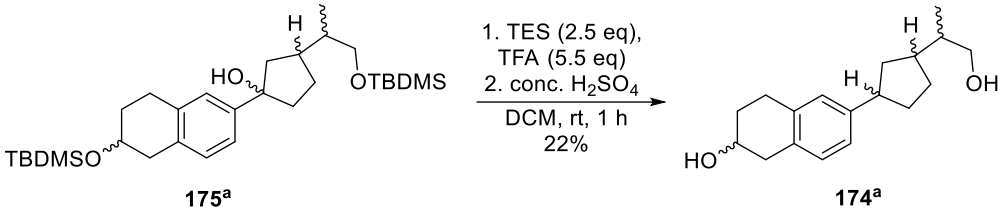
3.4.4. Nucleophilic addition of metalated **176[a]** to **177[a]**

To receive the *seco*-steroidal structure, building block **176[a]** should be attached to **177[a]**. Therefore, a Br-Li exchange of **176[a]** using *n*-BuLi, followed by addition to ketone **177[a]** was performed (**Scheme 103**).



Scheme 103. Nucleophilic addition of lithiated **176[a]** to **177[a]**.

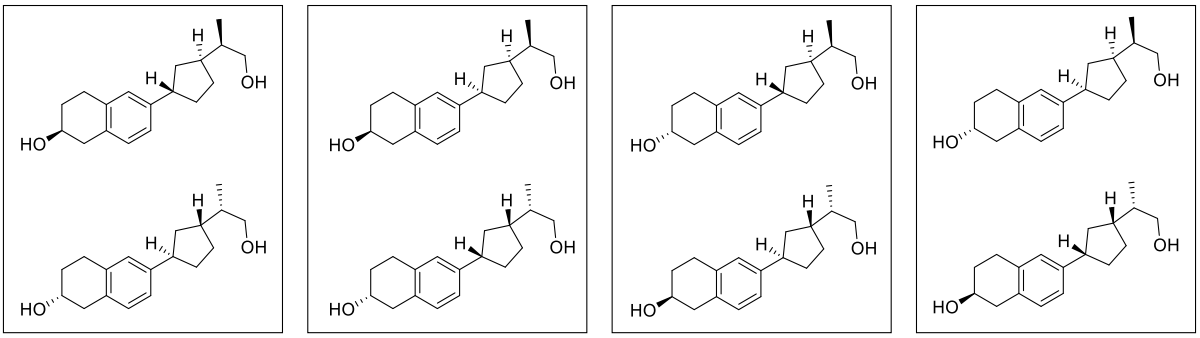
The Br-Li exchange was monitored *via* TLC and a complete exchange could not be observed, although more *n*-BuLi was added. Nevertheless, the crude lithiated product was directly reacted with ketone **177[a]** and the desired product **175[a]** was isolated with a low yield of 21%. Thereby a new stereocenter was built, but the stereocenters could not be identified in this step. The final step was the dehydration (TFA) of the tertiary alcohol of **175[a]** with subsequent ionic hydrogenation (TES) of the double bond[97] and deprotection of both TBDMS groups (**Scheme 104**).



Scheme 104. Synthesis of **174[a]** *via* dehydration with subsequent hydrogenation of **175[a]**.

The usage of TFA also leads to the deprotection of both alcohols. For a complete deprotection, the reaction mixture was treated with conc. H_2SO_4 before workup. The desired diol **174[a]** could be isolated, but only in a poor yield of 22%. TLC showed a lot of other spots, which speaks for still incomplete deprotection or decomposed fragments.

Unfortunately, the stereochemistry could not be determined with NOESY spectroscopy and no X-ray crystal structure could be measured, due to the oily aggregate condition of the product. **Scheme 105** shows the eight possible formed isomers and the four racemates, respectively.



Scheme 105. Eight possible isomers of **174[a]**.

With the knowledge of the stereochemistry of both racemic building blocks **177[a]** and **176[a]**, obviously the final product occurs as a racemate as well. Certainly, which diastereomers, where formed could not be determined. The racemic character was confirmed by the measurement of the optical rotation. HPLC chromatogram showed four signals in a ratio of 2:3:12:83, but an assignment to individual isomers was not possible.

4. Biological Testing

The herein synthesised test compounds and some intermediates were tested regarding to their microbial effect using agar diffusion assay and cytotoxicity using MTT assay. Furthermore, their activity towards cholesterol biosynthesis was examined with the usage of a developed assay from our group.[130]

4.1. Agar diffusion assay

In the agar diffusion assay, the antimicrobial effect of the test compounds was analysed on various model germs, which are listed in **Table 6**. Compounds which inhibit the growth of microorganisms impede the growth of various germs on medium containing agar resulting in inhibition zones. Their diameters give a statement about the qualitative existence of a microbial effect. A quantitative assertion cannot be made, since the sizes of the inhibition zones are dependent on the diffusion of every single compound on the aqueous medium. Clotrimazole was used for the antimycotic effect and tetracycline·HCl for the antibacterial effect as reference substances. In chapter 6.4.1. the detailed procedure for the agar diffusion assay is described.

Table 6. Used model germs in agar diffusion tests.

Model germ	DSM number	species
Escherichia coli	426	gram-negative bacteria
Pseudomonas marginalis	7527	gram-negative bacteria
Straphylococcus equorum	20675	gram-positive bacteria
Streptococcus entericus	14446	gram-positive bacteria
Yarrowia lipolytica	1345	yeast
Saccharomyces cerevisiae	1333	yeast

Table 7 shows the results of the agar diffusion test. The diameters of the inhibition zones were measured in mm and are indicated as “total inhibition” (t.i.) or “growth inhibition” (g.i.). If no antimicrobial activity is shown, the field is marked with a dash (-) and not tested substances are labelled with “not tested” (n.t.).

None of the herein tested compounds showed an antimicrobial effect towards the model germs.

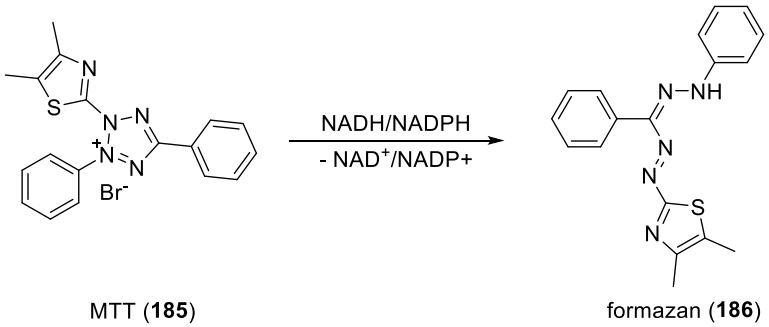
Table 7. Results of the agar diffusion test.

compound	gram-negative bacteria		gram-positive bacteria		yeast	
	Escherichia coli	*Pseudomonas marginalis*	*Straphylococcus equorum*	*Streptococcus entericus*	*Yarrowia lipolytica*	*Saccharomyces cerevisiae*
reference substances						
clotrimazole	n.t.	n.t.	n.t.	n.t.	30 TH	27 TH
tetracycline·HCl	34 TH	35 TH	38 TH	34 TH	n.t.	n.t.
tri- and tetracyclic compounds						
55a	-	-	-	-	-	-
55b	-	-	-	-	-	-
42	-	-	-	-	-	-
45	-	-	-	-	-	-
46	-	-	-	-	-	-
seco-steroids						
86	-	-	-	-	-	-
87	-	-	-	-	-	-
88	-	-	-	-	-	-
89	-	-	-	-	-	-
96[d]	-	-	-	-	-	-
97[d]	-	-	-	-	-	-
98[d]	-	-	-	-	-	-
99[d]	-	-	-	-	-	-
100[d]	-	-	-	-	-	-
129	-	-	-	-	-	-
101	-	-	-	-	-	-
161	-	-	-	-	-	-
***Z*-161**	-	-	-	-	-	-
149	-	-	-	-	-	-
162	-	-	-	-	-	-
151	-	-	-	-	-	-
166	-	-	-	-	-	-

163a	-	-	-	-	-	-
163b	-	-	-	-	-	-
174[a]	-	-	-	-	-	-
other compounds / intermediates						
171	-	-	-	-	-	-
169	-	-	-	-	-	-
39	-	-	-	-	-	-
37	-	-	-	-	-	-
38	-	-	-	-	-	-

4.2. MTT assay

Besides the antimicrobial aspect, the cytotoxic activity of these compounds was tested, using a standard MTT method of MOSMANN (for procedure see chapter 6.4.2.).[131] This assay is based on the reduction of the soluble yellow coloured tetrazolium salt 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT, **185**) to the insoluble blue coloured formazan (**186**) (**Scheme 106**).



Scheme 106. Reduction of MTT (**185**) to formazan (**186**).

This reduction can only occur *in vivo*, since the reducing agents are NADH and NADPH, respectively. Photometric measurement can determine the amount of the formed formazan (**186**), which correlates with the cell viability. HL-60 cells were used, and Triton X-100 was included as positive control. With this assay, potential cytotoxic substances can be identified *via* determined IC_{50} values, but no statement about the underlying mode of action can be made.

The IC_{50} value of cisplatin was determined with this assay resulting in 5 µM and is used as reference for the interpretation of the test results. Compounds with a comparable or lower value are considered as toxic (for example compound **166** with an IC_{50} value of 7.3 µM). It is noteworthy, that the IC_{50} values can vary depending on the cell line. **Table 8** shows the results.

Table 8. Results of the MTT assay.

Compound	IC_{50} [µM]
tri and tetracycles	
55a	33
55b	14
42	> 50
45	10
46	> 50
other compounds / intermediates	
171	> 50
169	19
39	> 50
37	12
38	17

Compound	IC_{50} [µM]
seco-steroids	
86	45
87	> 50
88	> 50
89	> 50
96[d]	29
97[d]	20
98[d]	20
99[d]	11
100[d]	27
129	30
101	39
161	29
Z-**161**	28
149	19
162	38
151	> 50
166	7.3
163a	42
163b	19
174[a]	46

Ten compounds resulted in IC_{50} values above 50 µM and thus, they are considered as non-toxic. All other tested compounds showed IC_{50} values greater than 5 µM and are therefore also considered as not significantly toxic (compared to reference substance cisplatin). A huge difference in cytotoxicity was noticed between the tetracycles **42** and **45**. The exchange of the nitrogen atom in **42** with an oxygen atom in **45** shows an increase in toxicity. The introduction of an aliphatic chain at C-5 showed that the unsaturated diol **171**, bearing a double and a triple bond, has a higher IC_{50} value (> 50 µM) than its saturated version **169** with an IC_{50} value of 19 µM. The opposite could be observed in the *seco*-steroids bearing an aromatic residue at C-5. The unsaturated *seco*-steroid **166**, bearing a double bond in Δ^5 position has a very low IC_{50} value of 7.3 µM and is therefore considered as toxic. Its saturated versions diastereomers **163a**

and **163b** show higher IC_{50} values than **166**, whereby **163a** has the highest with 42 µM (**Figure 19**).

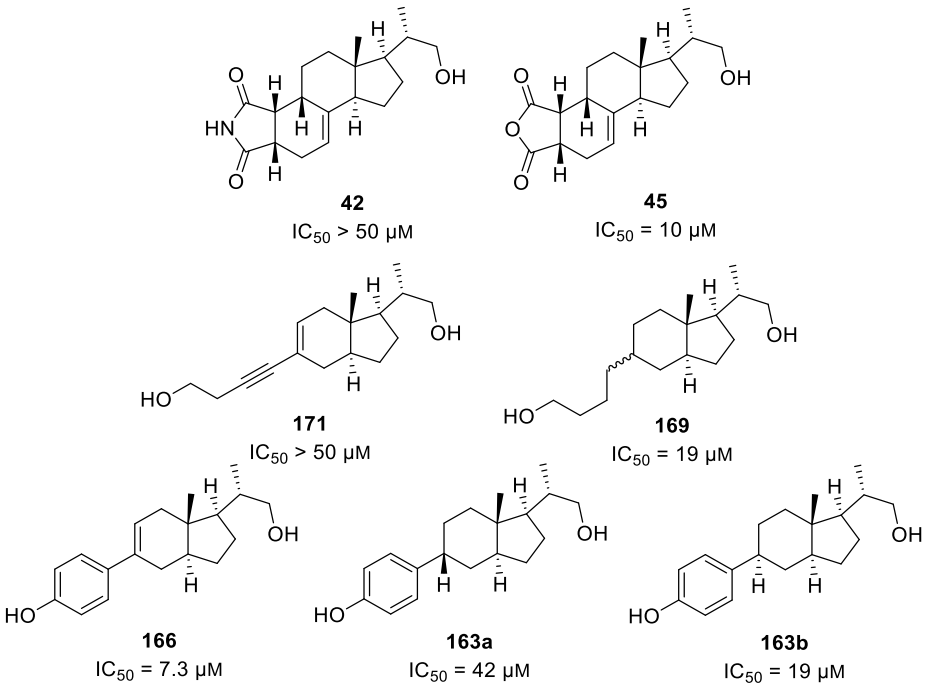


Figure 19. Structures and IC_{50} values of tetracycles **42** and **45** (top), diols **171** and **169** (middle) and *seco*-steroids **166**, **163a** and **163b** (bottom).

Moreover, it is interesting to see, that **86**, **87**, **88**, **89** bearing a directly linked aromatic residue at C-4 are all non-toxic with IC_{50} values of ≥ 45 µM, and with the introduction of a methylene or ethylene linker cytotoxicity of the compounds increases up to 11 µM (**99^{d}**) (**Figure 20**).

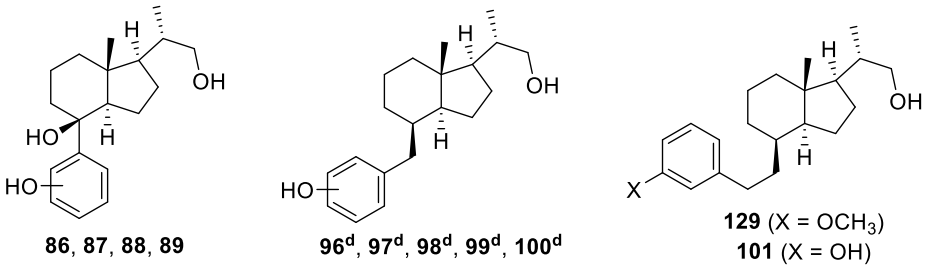


Figure 20. Structure of *seco*-steroids with attachment of aromatic residues at C-4.

Regarding to the cholesterol biosynthesis, the application as inhibitors can be positively evaluated, since the compounds are considered as not (significantly) toxic (except s*eco*-steroid **166**, IC_{50} = 7.3 µM).

4.3. Cholesterol biosynthesis assay

The inhibitory effect of the synthesised steroid-like analogues towards the cholesterol biosynthesis was analysed using an assay developed in our group, whereby inhibitors of the

post sqalene part can be identified and classified (for more details see chapter 6.4.3.).[130, 132] **Table 9** shows the tested compounds and the inhibited enzyme in the cholesterol biosynthesis.

Table 9. Qualitative results towards the efficacy of the synthesised compounds as inhibitor of cholesterol biosynthesis.

Compound	inhibited enzyme
tri and tetracycles	
55a	-
55b	DHCR24 (low)
42	-
45	-
46	-
other compounds / intermediates	
171	-
169	C5 desaturase
39	-
37	-
38	-

Compound	inhibited enzyme
seco-steroids	
86	-
87	-
88	-
89	-
96[d]	-
97[d]	C5 desaturase
98[d]	-
99[d]	-
100[d]	-
129	-
101	-
161	-
***Z*-161**	-
149	-
162	-
151	-
166	-
163a	-
163b	-
174[a]	-

Only three of the compounds showed an inhibitory effect on cholesterol biosynthesis (**Figure 21**). Tricycle **55b** showed a weak inhibition of DHCR24. Compared to lead structures **23** and **24**, ring A is eliminated and replaced with CH_2-OH at C-7'. **55b** has a structure similar to chemotype III inhibitors, like the lead structures of this thesis. Although, the chain is two carbon atoms too short and also attached at C-6' instead of C-7', it showed a slight inhibitory effect towards DHCR24.

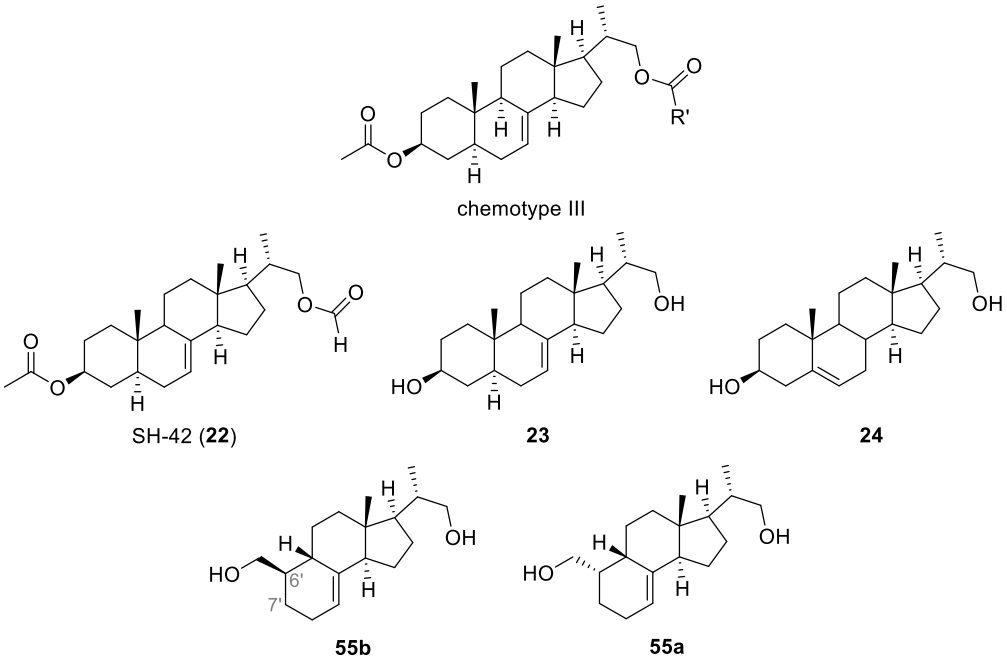


Figure 21. Top: Structure of chemotype III. Middle: Lead structures **SH-42** (**22**) and its related diols **23** and **24**.[43] Bottom: Structures of **55b** and its diastereomer **55a**.

Its diastereomer **55a**, in which the chain is attached to C-7', showed no effect on cholesterol biosynthesis.

Furthermore, diols **169** and **97^{d}** inhibited the enzyme lathosterol oxidase (sterol C5 desaturase, SC5D) (**Figure 22**). This enzyme catalyses the conversion of lathosterol to 7-dehydrocholesterol.[133] Known inhibitors of lathosterol oxidase belong to chemotype I, e.g. lathosterol side chain amides like MGI-21 (**21**).[66]

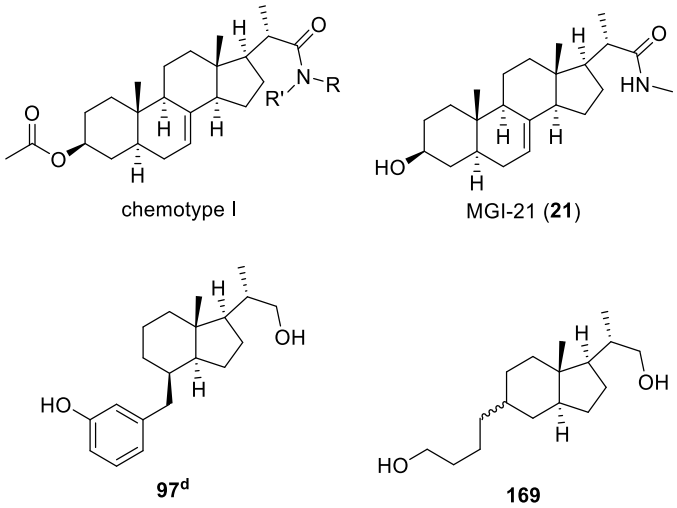


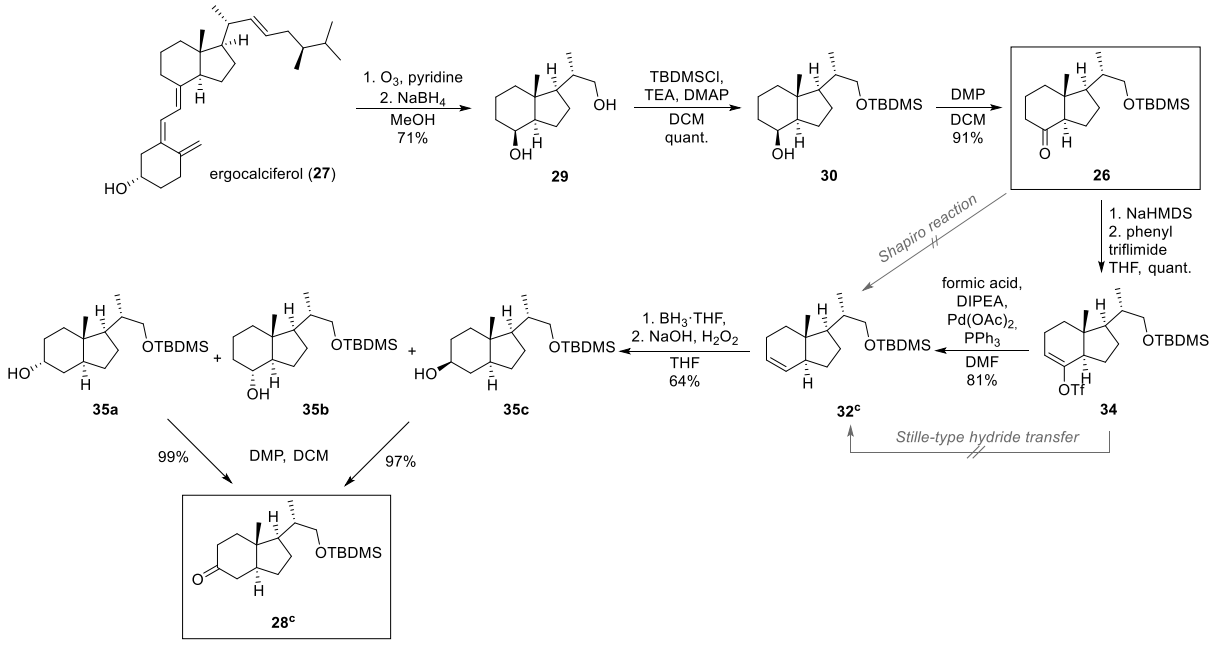
Figure 22. Top: Lathosterol oxidase inhibitors: Lathosterol side chain amides (chemotype I) and MGI-21 (**21**).[66] Bottom: Structures of **97^{d}** and **169**.

No similarity between the chemotype I structure, and the structures of **97^{d}** / **169** can be observed. Instead of the amide in the side chain, these structures carry a hydroxyl chain, which is present in chemotype III structures like lead structures **23** and **24** and its esterified version SH-42 (**22**), which are DHCR24 inhibitors.[43]

5. Summary and Conclusion

The aim of this thesis was to synthesise steroid analogues, based on lead structures **23** and **24**, which are very potent and selective inhibitors of the enzyme DHCR24 in cholesterol biosynthesis with IC_{50} values of 0.1 nM and 2.5 nM, respectively. Structure variations of these compounds were, *hitherto*, exclusively performed regarding the side chain of ring D starting from steroidal building blocks. In order to learn more about structure-activity relationships in this class of DHCR24 inhibitors, and possibly improve activity, the synthesis of tri- and tetracylic steroid-like compounds, as well as *seco*-steroidal compounds was the focus of this project.

Scheme 107 depicts an overview of the synthesis of central building blocks **26** and **28^c**. The literature-known synthesis of **26** started with the ozonolysis of ergocalciferol (**27**) with subsequent reductive work-up leading to INHOFFEN-LYTHGOE diol (**29**) in 71% yield.[67] To maintain the primary hydroxy group in the side chain, which is a crucial functional group for the DHCR24 inhibitors, it was TBDMS protected and the remaining secondary hydroxyl group was oxidised using DMP to receive central building block **26** in 91% yield.

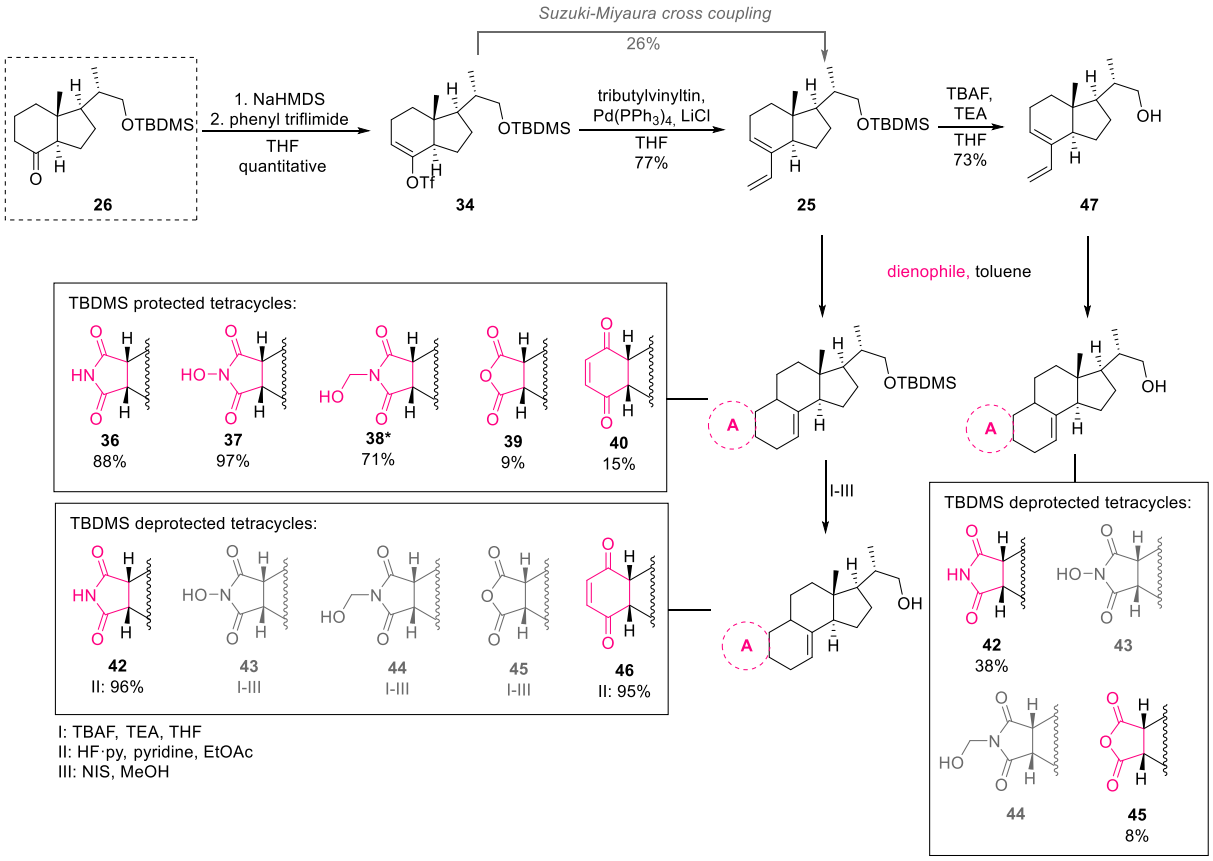


Scheme 107. Overview of the synthesis of central building blocks **26** and **28^c**. The failed attempts are marked in grey.

Based on ketone **26** its constitutional isomer **28^c** was synthesised. Due to the failed attempt of a SHAPIRO reaction (**Scheme 107**, marked in grey), which should provide alkene **32^c** *via* a tosylhydrazone with subsequent deprotonation, alkene **32^c** was obtained *via* enol triflate **34**. STILLE-type hydride transfer of **34** with tributylvinyltin did not result in the desired alkene (**Scheme 107**, marked in grey), but Pd-catalysed hydride transfer using formic acid gave alkene **32^c** in a very good yield of 81%. After regioselective hydroboration of alkene **34^c**, the

three isomers **35a**, **35b** and **35c** were isolated. Only isomers **35a** and **35c** were of interest, since these have the required hydroxyl group attached at C-5. After oxidation using DMP, the desired central building block **28c** could be isolated in very good yields of 97% and 99%, respectively.

Scheme 108 depicts an overview of the syntheses of tetracyclic steroid-like analogues of the lead structures containing a modified ring A. Based on central building block **26**, the desired diene **25** was synthesised *via* the appropriate enol triflate **34**, which is already known from the synthesis of ketone **28c**. SUZUKI-MIYAURA cross-coupling between enol triflate **34** and vinylboronic acid did result in the desired diene **25** in only 26% yield (**Scheme 108**, marked in grey), but the usage of STILLE cross-coupling conditions increased the yield to 77%.

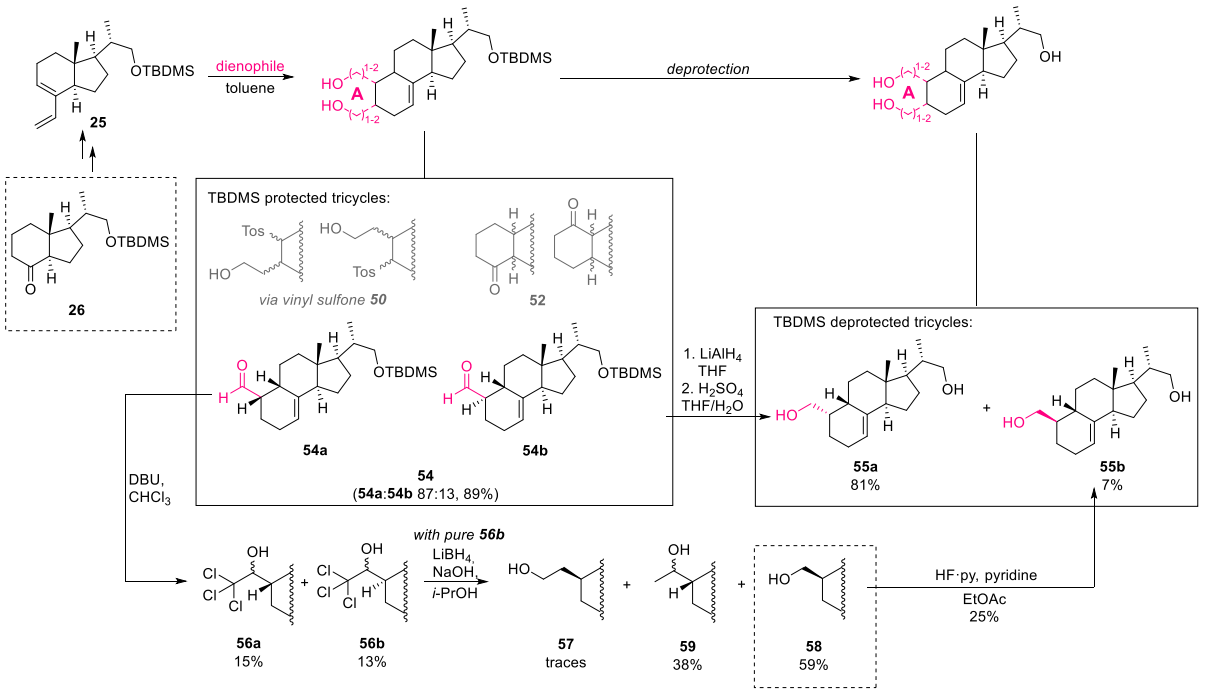


Scheme 108. Overview of the syntheses of tetracyclic steroid analogues based on central building block **26**. Failed attempts are marked grey. The newly built ring A is marked in pink. *Dienophile **41** was synthesised according to literature in 69% yield.[79]

Diene **25** smoothly underwent DIELS-ALDER cycloaddition with various dienophiles, e.g. maleimide and derivatives, maleic anhydride, and benzoquinone, and resulted in tetracycles **36**, **37**, **38**, **39** and **40** in 9 – 97% yield. The low yields of **39** (9%) and **40** (15%) can be explained by decomposition during the chromatographic purification step, although various stationary phases, e.g. SiO_2, Al_2O_3 or neutralised SiO_2 were tested. For the final TBDMS deprotection,

three methods (I – III) were explored, whereby method II turned out as the best deprotection method, but overall, only tetracycles **42** and **46** could be isolated in very good yields (95 and 96%). Even though the other desired deprotected products could be confirmed *via* GC/MS, the purification step led again to decomposition of the product. Purification was necessary in this step, since the reagents could not be removed in another way. A different option, to evade the purification step was deprotecting diene **25** before cycloaddition. In the presence of TBAF and TEA diene **47** was obtained in 73% yield. Subsequent cycloaddition with maleimide led to the tetracycle **42** in 38% yield, which is much lower than *via* the other pathway (96%). However, dione **45** could now be isolated, even if only in a poor yield of 8%. Hydroxylated diones **43** and **44** could not be obtained *via* this route, too. One possible reason for the low yields using already deprotected diene **47** could be its bad solubility, which resulted in an incomplete cycloaddition.

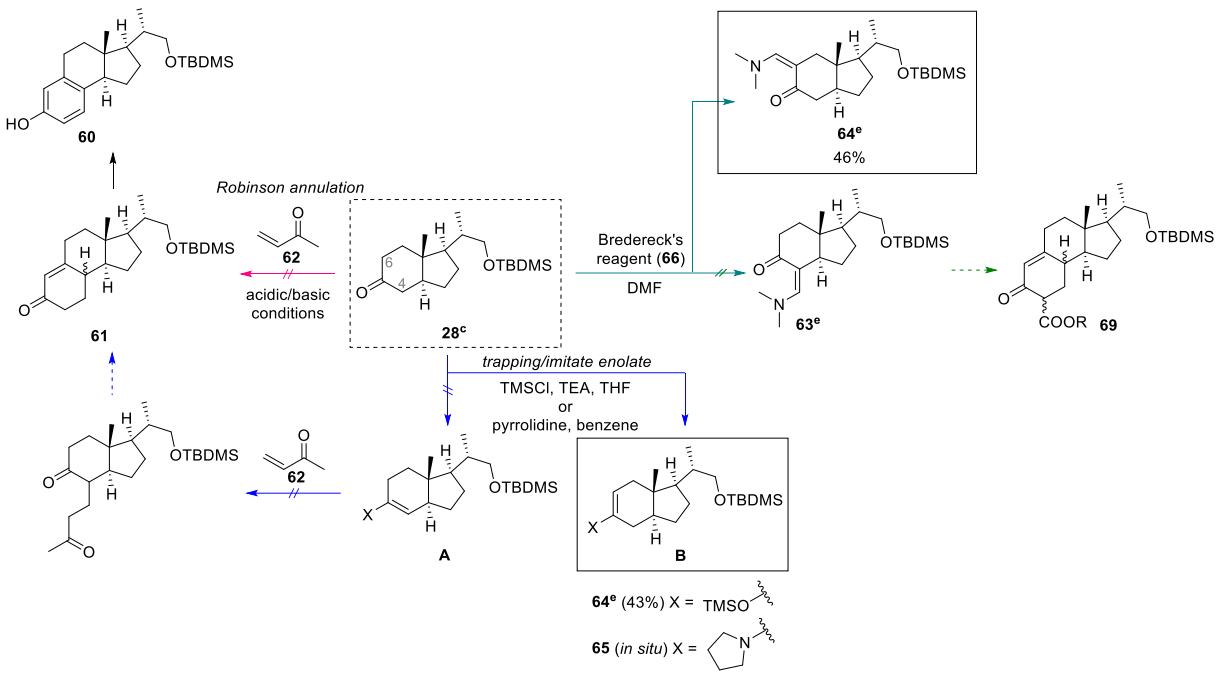
Scheme 109 shows the attempts for the synthesis of tricycles. Vinyl sulfone **50** was synthesised according to literature in 53% yield.[84] Unfortunately, the target tricycle could not be isolated. The use of cyclohexenone as dienophile did also not lead to the desired tricycle **52**. Cycloaddition between diene **25** and acrolein (**53**) resulted in an inseparable mixture of isomers **54a** and **54b** in 87:13 ratio. The configuration of the newly built stereocenters at C-5a' and C-6' could be defined in this step (for **54a**: 5a'*S*, 6'*S*; **54b**: 5a'*S*, 6'*R*). The aldehyde function was reduced to the hydroxyl group using $LiAlH_4$, and the TBDMS group was cleaved using conc. H_2SO_4. Diols **55a** and **55b** were isolated in 81% and 7% yield.



Scheme 109. Overview of the synthesis of tricyclic compounds *via* DIELS-ALDER cycloaddition. The failed attempts are marked in grey. The attached aliphatic residue is marked in pink.

Since the hydroxymethyl chain in **55a**/**55b** is two carbon atoms too short to fit with the geometry of the lead compounds, C-homologation was performed using DBU and $CHCl_3$. Instead of a regioisomeric mixture of two trichloromethylcarbinols, diastereomers **56a** with 15% and **56b** with 13% yield were isolated, whereby both residues are attached to the C-6' position. The following JOCIC-type reaction was performed only with pure **56b**, as only a low amount of pure **56a** could be obtained by FCC. The desired C-homologated product **57** could be detected *via* GC/MS, but not isolated. Instead, **59** and **58** were isolated, whereby **59** is a typical side product in this reaction, and **58** is the protected version of **55b**. Probably **58** was formed *via* a base-mediated inversion of the synthesis of the carbinols. Deprotection also led to **55b**.

Another aim of the synthesis of tricyclic compounds was the formation of an aromatic ring B (**60**) (**Scheme 110**), since in the lead structures Δ^7-sterol **23** and Δ^5-sterol **24** the exact position of the double bond in ring B seems to be less important for the potenty of enzyme inhibitory potency. Based on central building block **28^c**, the first approach was a ROBINSON annulation with methyl vinyl ketone using acidic or basic conditions (**Scheme 110**, marked in pink).

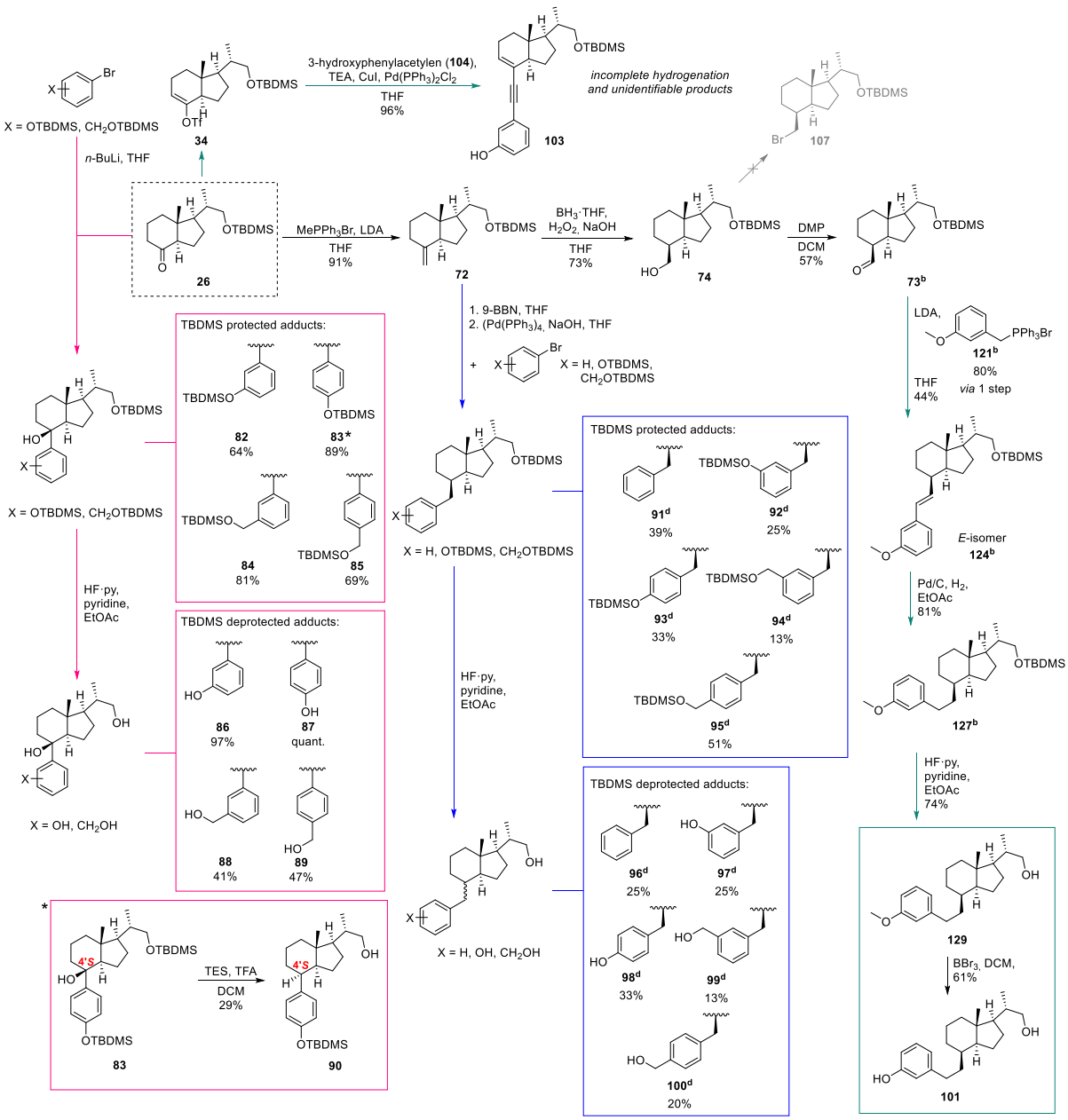


Scheme 110. Overview of the attempts for the formation of an aromatic ring B. Attempted ROBINSON annulation is marked in pink. Attempts of trapping/imitating the enolate is marked in blue and the use of BREDERECK'S reagent is marked in petrol.

Unfortunately, these attempts did not result in the desired product **61** and only decomposition products were obtained. It was assumed that the MICHAEL adduct was not formed and the idea was to trap or imitate the enolate which should attack the methyl vinyl ketone (**62**) (**Scheme 110**, marked in blue). Silyl enol ether **64^{e}** and pyrrolidine enamine **65** should be synthesised to receive the desired structure **A**. Nevertheless, the products **B**, bearing the double bond at the wrong position were obtained (only **64^{e}** was isolated), which means that the following MICHAEL addition to methyl vinyl ketone will not lead to the desired MICHAEL adduct.

Another approach was the usage of BREDERECK'S reagent (**66**) (**Scheme 110**, marked in petrol). This can be applied for α-aminomethylenation in molecules bearing an acidic methylene group to receive, after subsequent treatment with TEA and DIBAL-H, **69** as a precursor of a phenolic ring. However, instead of enaminoketone **63^{e}**, its regioisomer **64^{e}** was isolated in 46% yield. After these attempts, it became clear, that the C-6 position of ketone **28^{c}** is more acidic and accessible than position C-4. At this point, the project of the formation of an aromatic ring B based on central building block **28^{c}**, was stopped.

Besides tri- and tetracyclic analogues of the steroidal lead structures, also *seco*-steroidal analogues were of high interest. **Scheme 111** depicts an overview of the syntheses of *seco*-steroids consisting of rings C and D and an aromatic residue at C-4.



Scheme 111. Overview of the introduction of an aromatic residue at C-4 position of building blocks consisting of ring C and D: Direct linking is marked in pink, introduction of a methylene linker is marked in blue and introduction of an ethylene linker is marked in petrol. Failed attempts are marked in grey.

Starting with the directly linked residues (**Scheme 111**, marked in pink), Br-Li exchange of TBDMS protected phenol and benzylalcohol units with subsequent addition to central building block **26** resulted in 4-arylperhydroindanes. While *meta*- and *para*-substituted aryllithium compounds did undergo the addition, *ortho*-substituted residues left unreacted, probably due to steric hindrance. Tertiary alcohols **82**, **83**, **84** and **85** could be isolated in good yields of 64 – 89%, whereby the new stereocenter at C-4' is *S* configurated. The following double TBDMS deprotection using HF·py and pyridine resulted in the desired structures, triols **86**, **87**, **88** and **89**. It was of interest which stereoconfiguration at C-4' is formed after deoxygenation. This was

examined by the example of **83** using TFA and TES. The resulting compound **90** had *S* configuration at C-4, like **83**, but this time the aryl residue is facing to the front.

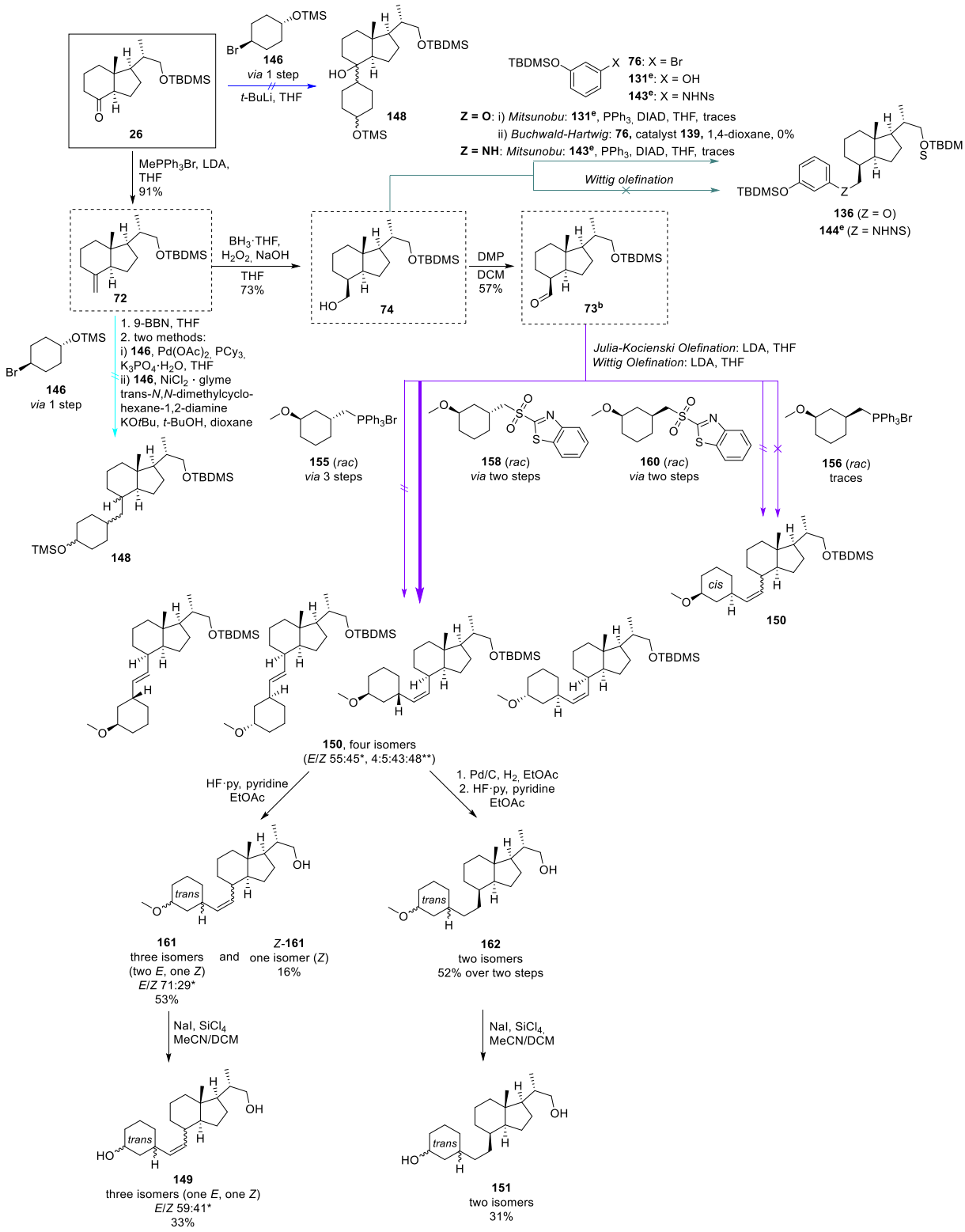
The studies towards *seco*-steroids with a methylene linker giving 4-benzylperhydroindanes (**Scheme 111**, marked in blue) were performed with exomethylene compound **72**, which was synthesised from central building block **26** *via* WITTIG olefination. To generate the borylated compound for cross-coupling, **72** was treated with 9-BBN to form the *B*-alkyl-9-BBN intermediate. Various TBDMS protected bromophenols/-benzylalcohols were coupled *via* SUZUKI-MIYAURA-type cross-coupling. Besides the "naked" phenyl **91[d]**, the *meta*- and *para*-substituted phenyls/benzyls **92[d]**, **93[d]**, **94[d]** and **95[d]** were isolated in yields ranging from 13 to 51%. *Ortho*-substituted phenol and benzylalcohol could not be obtained with this procedure, probably due to steric hindrance. The low yields are the results of incomplete formation of the *B*-alkyl-9-BBN intermediate. The following deprotection gave the target compounds **96[d]**, **97[d]**, **98[d]**, **99[d]** and **100[d]** in 13 – 33 %.

To receive ring B *seco*-analogues of the lead structures with correct distance betweens rings A and C, an ethylene linker resulting in 4-arylethylperhydroindanes was introduced (**Scheme 111**, marked in green). First, a SONOGASHIRA cross-coupling between enol triflate **34**, which is formed from ketone **26**, and 3-hydroxyphenylacetylene (**104**) was performed, resulting in alkyne **103**. Hydrogenation attempts did not give the desired *seco*-steroid and only unidentifiable and (half)hydrogenated compounds were isolated. Therefore, another attempt was tried based on aldehyde **73[b]**, which was synthesised from alkene **72** *via* hydroboration and subsequent oxidation with DMP. Besides phosphonium bromide **121[b]**, *m*-OTBDMS and *p*-OTBDMS protected phosphonium bromides were synthesised, but only **121[b]** gave the desired *seco*-steroid **124[b]** as *E*-isomer in 44% yield *via* WITTIG olefination. It was also tried to convert alcohol **74** to **107**, but the attempts were unsuccessful (**Scheme 111**, marked in grey). Nevertheless, the isolated *E*-isomer **124[b]** was hydrogenated to *seco*-steroid **127[b]**, since the *E*-isomer would not comply with the shape of the lead structures. The last steps were the deprotections of the alcohol functions. After TBDMS deprotection using HF·py and pyridine and subsequent methyl ether cleavage with BBr_3, the desired *seco*-steroid **101** was obtained.

Besides an ethylene linker, attempts for the synthesis of isosteric ether and amine linkers were made (**Scheme 112**, marked in petrol). For the preparation of an ether linker starting from alcohol **74** MITSUNOBU as well as BUCHWALD-HARTWIG reaction was tried. The mass of the desired ether **136** was found in the MITSUNOBU reaction, but the BUCHWALD-HARTWIG reaction was unsuccessful. Unfortunately, the product could not be isolated in a sufficent amount. For the amine linker, MITSUNOBU reaction with *N*-nosyl derivative **143[e]** was tried as well, but also in this case, only traces of the desired product **144[e]** were found by GC/MS.

Besides aromatic residues, aliphatic residues bearing hydroxyl groups were attached to the C-4 position of central building block **26** (**Scheme 112**). The introduction of a cyclohexanol unit with direct attachment to C-4 (**Scheme 112**, marked in blue), was attempted *via* Br-Li exchange of **146** and subsequent addition to ketone **26**. Unfortunately, this did not result in the desired product **148**. Other attempts were not tried, as the corresponding directly linked compounds bearing aromatic residues did not show any effect on cholesterol biosynthesis. For the introduction of a methylene linker (**Scheme 112**, marked in turquoise), two methods based on alkene **72** were tried. First, bromide **146** was tried to couple to exomethylene compound **72** *via* *B*-alkyl-9-BBN derivative in a SUZUKI-MIYAURA cross-coupling, but the desired product **148** could not be obtained. The second approach was for inactivated secondary alkyl halides using $NiCl_2$, but also this attempt did not lead to the desired product.

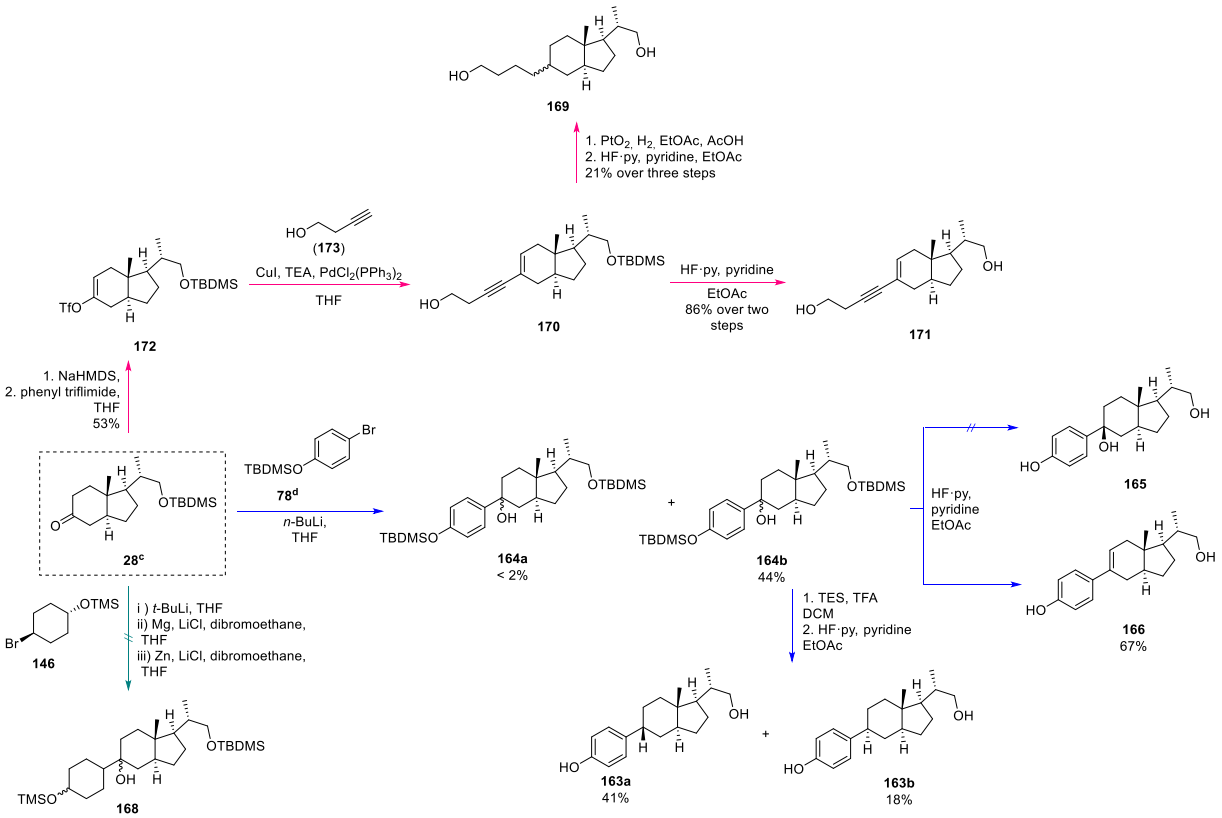
For the introduction of a cyclohexanol unit (resembling ring A) with an ethylene linker (**Scheme 112**, marked in purple) aldehyde **73[b]** was used. The WITTIG reagents **155** and **156** were synthesised *via* three steps, whereby **156** was only obtained in traces and therefore the following WITTIG olefination could not be performed. Olefination using **155** did not result in the desired product **150**. The next attempt was a JULIA-KOCIENSKI olefination. The racemic JULIA reagents **158** and **160** were synthesised from the *cis*/*trans* mixture of 3-methoxycyclohexanecarboxylic acid *via* four steps. Only **158** underwent the JULIA-KOCIENSKI olefination and *seco*-steroid **150** was obtained as an *E*/*Z* mixture (ratio 55:45, determined *via* ^{1}H NMR) of four isomers (ratio 4:5:43:38, determined *via* GC/MS) in 69% yield. The four isomers could not be separated by FCC. The *E*/*Z* mixture of the four isomers was TBDMS deprotected using HF·py and pyridine, whereby after this step one *Z*-isomer (**161**) could be separated from the mixture of two *E*-isomers and one Z-isomer (ratio 71:29, determined *via* ^{1}H NMR). Unfortunately, it could not be identified which *Z*-isomer was isolated. Since the isolated amount of *Z*-**161** was too low for methyl ether cleavage, its biological activity was tested as a potential prodrug. Methyl ether cleavage of the *E*/*Z* mixture **161** was performed using NaI and $SiCl_4$ and **149** was isolated in 33% yield with an *E*/*Z* ratio of 59:41, which means, that one *E*-isomer was not deprotected or isolated.



Scheme 112. Overview of the introduction of aliphatic residues at C-4. Introduction of an amine/ether linker is marked in petrol. Attempts for direct linking are marked in blue and introduction of a methylene linker is marked in turquois. Introduction of an ethylene linker is marked in lilac.

Additionally, the *E*/*Z* mixture **150** was hydrogenated and TBDMS deprotected to receive **162**, a mixture of two diastereomers, in 52% yield after two steps. Methyl ether cleavage resulted in the mixture of two diols **151** in 31% yield.

Besides *seco*-steroids with bridging at C-4, residues resembling ring A of the steroidal lead compounds were attached at C-5 of ring C and D building blocks. For this purpose, the 5-ketoperhydroindane **28^{c}** was used (**Scheme 113**).



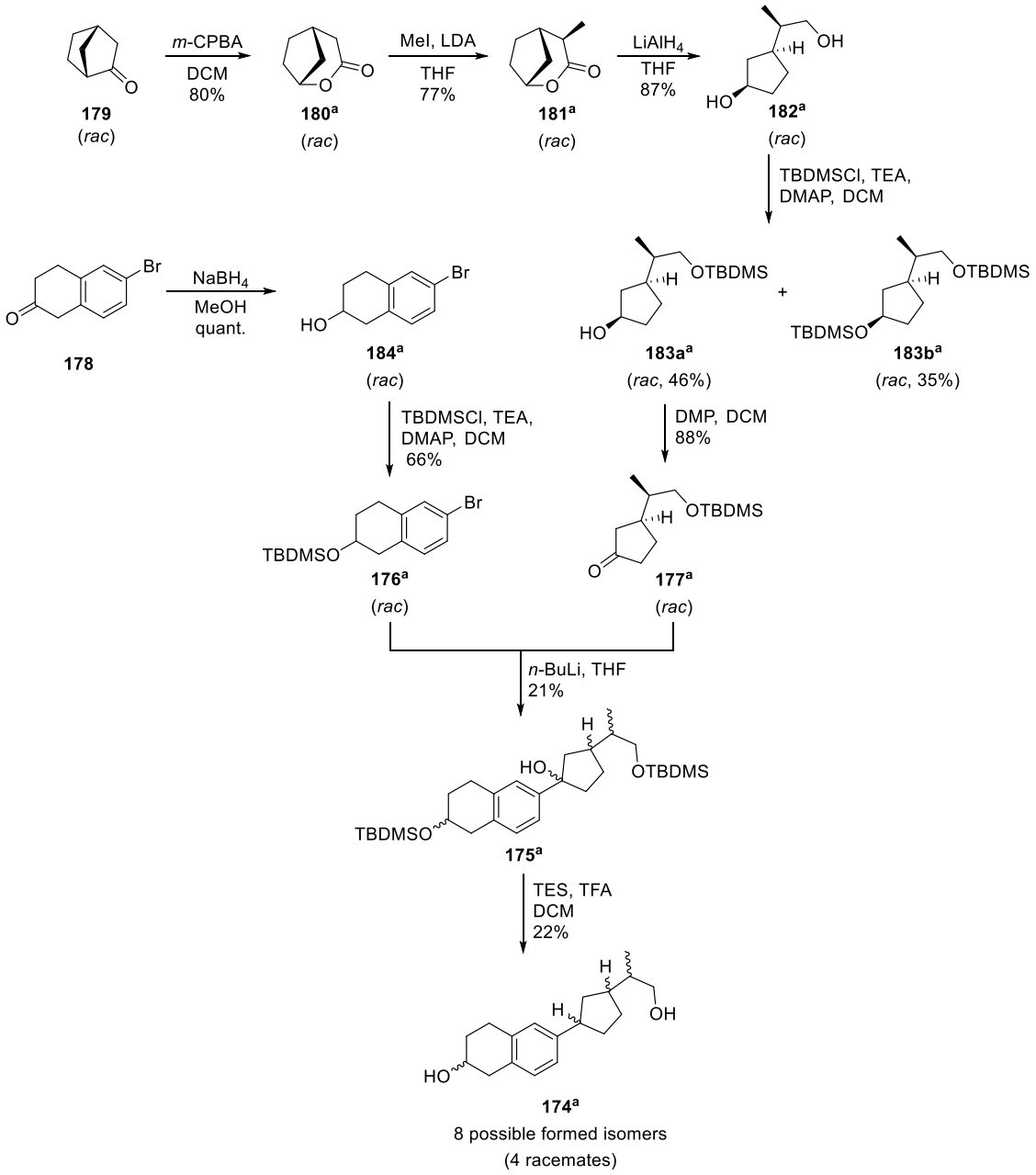
Scheme 113. Overview of the syntheses of *seco*-steroids with ring A equivalents attached to C-5. Introduction of an aliphatic chain is marked in pink. Introduction of an aryl residue is marked in blue and the attempts of attaching a cyclohexyl residue to C-5 is marked in petrol.

An aliphatic chain was introduced *via* SONOGASHIRA cross-coupling (**Scheme 113**, marked in pink). The appropriate enol triflate **172** of ketone **28^{c}** was cross coupled with but-3-yn-1-ol (**173**) to give alkyne **170**. Since the presence of the alkyne group lead to an overall molecule geometry similar to the lead structures, the alkyne was TBDMS deprotected to give diol **171** in 86% yield over two steps. Additionally, the triple and double bond in **170** were hydrogenated using PtO_2 and after TBDMS deprotection, diol **169** was obtained in 11% yield over three steps based on **172**. The introduction of a cyclohexanol residue, which would mimic the complete ring A of steroids, faced some difficulties (**Scheme 113**, marked in petrol). Organometallic reactions were tried, e.g. Br-Li exchange with subsequent addition to ketone **28^{c}**, GRIGNARD reaction using Mg/LiCl and organozinc reaction. However, all three approaches did not result

in the desired *seco*-steroid **168**, whereby it is noteworthy that already the formation of the alkyl-Li/MgX/ZnX was not successful and ketone **28[c]** was recovered.

The attachment of a phenol unit as ring A equivalent was performed using bromoarene **78[d]** (**Scheme 113**, marked in blue). Br-Li exchange with subsequent addition to **28[c]** resulted in a separable mixture of alcohols **164a** and **164b** in < 2% and 44% yield, respectively, whereby the stereoconfiguration at C-5 could not be determined. Since in further reactions removal of the generated tertiary hydroxyl group under loss of stereoinformation at C-5 was intended, this isomeric mixture can in principle be used for the next step. But as isomer **164b** was isolated with 44% yield, the following reactions were performed only with this isomer. First, we tried to isolate the TBDMS deprotected version of **164b** to obtain the triol **165**. However, the isolated product turned out to be the dehydrated version **166** in a good yield of 67%. To get rid of the olefinic double bond, **164b** was dehydrated and hydrogenated simultaneously with TES/TFA, and subsequent TBDMS deprotection gave the separable mixture of diols **163a** and **163b** in 41% and 18% yield, respectively.

Scheme 114 depicts the studies towards *seco*-steroids with an open ring C and an aromatic ring B. The ring D building block **177[a]** was synthesised in a five step synthesis. Starting from racemic norcamphor (**179**), BAYER-VILLIGER oxidation led to lactone **180[a]** in 80% yield. C-monomethylation gave pure **181[a]** in 77% yield. Reductive ring opening gave racemic diol **182[a]** in 87% yield, and the following TBDMS protection gave a mixture of mono-protected **183a[a]** and double-protected **183b[a]**. The mono-protected alcohol was oxidised with DMP to ketone **177[a]** in 88% yield. The ring A and B building block **176[a]** was synthesised from 6-bromo-2-tetralone (**178**), which was first reduced to racemic tetralol **184[a]** in quantitative yield. The following TBDMS protection gave **176[a]** in 66% yield. The bromoarene **176[a]** was added to the ketone **177[a]** *via* Br-Li exchange and *seco*-steroid **175[a]** could be isolated in 21% yield. The tertiary alcohol and TBDMS groups were removed simultaneously with TES and an excess TFA and **174[a]** was obtained in 22% yield as a racemic mixture of stereoisomers. The configuration of the single components of **174[a]** could not be identified with our methods, but all in all eight possible isomers (4 racemates) can be formed. This mixture was subjected to testing as potential inhibitor of DHCR24.



Scheme 114. Overview of the studies towards *seco*-steroidal analogues with an open ring C and an aromatic ring B.

All test compounds were tested regarding their antimicrobial/antibiotic effect in an agar diffusion assay, as well as their cytotoxicity using an MTT assay. None of the compounds showed an antimicrobial/antibiotic effect or were considered as strong cytotoxic (except **166** with an IC_{50} = 7.3 µM). The biological activity towards cholesterol biosynthesis was tested as well, whereby **55b** showed a low inhibitory effect on DHCR24, and **169** and **97d** on lathosterol oxidase. Tricycle **55b** has a related structure to lead structures **23** and **24**, which are in the class of chemotype III inhibitors. Diols **169** and **97d** have no structural similarities to lathosterol oxidase inhibitors like MGI-21 (**21**), since their side chains do not contain an amide function.

Unfortunately, the other synthesised tri/tetracyclic and *seco*-steroid analogues of lead structures **23** and **24** did not lead to an inhibitory effect on the cholesterol biosynthesis.

6. Experimental Part

6.1. Materials and methods

General conditions

All oxygen- and moisture-sensitive reactions were carried out in oven-dried glassware under nitrogen atmosphere using Schlenk-technique. Anhydrous solvents and reagents were transferred through syringes under nitrogen.

Reagents and solvents

Solvents used for anhydrous reactions were dried by standard methods of distillation over drying agents. DCM was dried over molecular sieve (3 Å) after distillation. THF was distilled over sodium and benzophenone. All other solvents and reagents were obtained from commercial sources (abcr, Acros, Fluka, Merck, Sigma-Aldrich or TCI in the qualities puriss., p.a., or purum) and used without further purification.

Chromatography

Thin layer chromatography (TLC) for qualitative reaction and fraction controls was performed using pre-coated polyester sheets polygram SIL G/UV254 with SiO_2 coating (0.2 mm, 40 x 80 mm) by Macherey-Nagel. As visualisation method CAM stain (ceric ammonium molybdate) with subsequent heating was used. Flash column chromatography (FCC) was carried out using SiO_2 60 (particle size 40 – 63 µm) by Merck.

Analytical data

Melting points were measured in single determination on a Büchi Melting Point B-540 device and are stated in °C.

Values for specific rotation [α] were measured at 23 °C at a wavelength of λ = 589 nm (Na-D-line) using a Perkin Elmer 241 Polarimeter instrument. All samples were dissolved in chloroform (layer thickness l = 10 cm), the concentration is stated in g/100 mL.

All NMR spectra were recorded at room temperature using JNM-Eclipse 400 (400 MHz), JNM-Eclipse 500 (500 MHz), Avance III HD 400 MHz Bruker Biospin (400 MHz) and Avance III HD 500 MHz Bruker Biospin (500 MHz) mit CryoProbe™ Prodigy through the NMR-division of the Department of Pharmacy of the LMU. Chemical shifts δ are reported as δ-values in ppm (parts per million) and refer to the deuterated solvent peak. Coupling constants (J) of protons are stated in Hz. The signal multiplicities are defined using the following abbreviations: s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), q (quartet), p (pentet), ddd (doublet of doublet of doublets), tdd (triplet of doublet of doublets), dtd (doublet of triplet of doublets) and m (multiplet). The signal assignment was carried out using HMQC, HMBC,

COSY and DEPT spectra. All spectra were evaluated using MestReNova by Mestrelab Research S.L.

Infrared spectra were measured on a JASCO FT/IR-4100 infrared spectrometer, using a Smiths Detection DuraSamp IR II Diamond ATR sensor for detection. The measured wavenumbers $\tilde{\nu}$ are reported in cm^{-1}.

High resolution mass spectra (HRMS) were recorded on a Jeol Mstation 700 or JMS GCmate II Jeol instrument for electron ionisation (EI). Electrospray ionisation (ESI) was measured on a Thermo Finnigan LTQ-FT. All measurements were performed by the mass spectroscopy service of the LMU. The mass is reported in *m*/*z* units with the mass of the molecular ion.

Gas chromatography (GC) for the determination of purities was performed on a Varian 3800 gas chromatograph coupled to a Saturn 2200 ion trap from Varian (Darmstadt, Germany). The auto sampler was from CTC Analytics (Zwingen, Switzerland) and the split/splitless injector was a Varian 1177 (Darmstadt, Germany). Instrument control and data analysis were carried out with Varian Workstation 6.9 SP1 software. A VF-5-ms capillary column of 30 m length, 0.25 mm i.d. and 0.25 µm film thickness was used at a constant flow rate of 1.4 mL/min. Carrier gas was helium 99.999% from Air Liquide (Düsseldorf, Germany). The inlet temperature was kept at 300 °C and injection volume was 1 µL with splitless time 1.0 min. The initial column temperature was 50 °C and was held for 1.0 min. Then temperature was ramped up to 250 °C with 50 °C/min. Then the sterols were eluted at a rate of 5 °C/min until 310 °C (hold time 3 min). Total run time was 20 min. Transfer line temperature was 300 °C and the ion trap temperature was 150 °C. The ion trap was operated with electron ionization (EI) at 70 eV in scan mode (*m*/*z* 50 - 650) with a solvent delay of 6.3 min.

HPLC analytical measurements for determination of the purities of the products were carried out detecting at 191 nm, 210 nm, 250 nm and 254 nm using the following methods:

Method a:

Column: Agilent Poroshell 120®, EC-C18 2.7µm (3.0 x 100 mm)

Flow rate: 0.5 mL/min

Eluent: MeCN/H_2O 40:60 + 0.1% formic acid

Method b:

Column: InfinityLab Poroshell 120®, EC-C18 2.7 µm (3.0 x 100 mm)

Flow rate: 0.5 mL/min

Eluent: MeCN/H_2O 50:50 + 0.1% formic acid

Method c:

Column: Zorbax Eclipse Plus®, C18 5.0 µm (4.6 x 150 mm)

Flow rate: 0.5 mL/min

Eluent: MeCN/H_2O 70:30 + 0.1% formic acid

Method d:

Column: Agilent Poroshell 120®, EC-C18 2.7 µm (3.0 x 100 mm)

Flow rate: 1.0 mL/min

Eluent: MeCN/H_2O 90:10

Method e:

Column: InfinityLab Poroshell 120®, EC-C18 2.7 µm (3.0 x 100 mm)

Flow rate: 0.5 mL/min

Eluent: MeCN/MeOH 90:10

Method f:

Column: Zorbax Eclipse Plus®, C18 5.0 µm (4.6 x 150 mm)

Flow rate: 0.5 mL/min

Eluent: MeCN/H_2O 95:5

The X-ray intensity data were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror monochromator and a Mo Kα rotating anode X-ray tube (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The structure was solved and refined using the Bruker SHELXTL Software Package.

To explore the minima of the ground state potential energy surface of **55a** and **55b** the program package “Conformational Search” of Macro Model (S. Schrödinger Release 2019-2: MacroModel, Schrödinger, LLC, New York, NY, 2019) was used. The conformational search was conducted from a guessed structure with the “Torsional Sampling MCMM” method with 100 steps per rotatable bond and a maximum atom deviation cutoff of 0.5 Å in the MMFF force field. In total 100 structures within a window of a maximum of 5 kcal/mol from the lowest found MMFF energy were saved. The distances between characteristic atoms of the lowest energy structure are shown in **Table 1**. All other found structures are only single bond rotamers, showing that the presented ring conformation is the only stable conformation in a range of 5 kcal/mol.

6.2. Synthetic procedures and analytical data

6.2.1. General procedures for synthesis

General procedure 1 (GP1): TBDMS protection (1)

In an oven-dried two-necked Schlenk flask the appropriate alcohol/phenol (1.00 eq) was dissolved in dry DCM to receive a concentration of 0.1 mmol/mL. The solution was cooled to 0 °C and TBDMSCl (1.10 eq), DMAP (10 mol%) and TEA (3.00 eq) were sequentially added. The reaction mixture was slowly warmed to rt and stirred for 13 h. The reaction mixture was quenched with water and extracted with DCM (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (SiO_2).

General procedure 2 (GP2): TBDMS protection (2)

In an oven-dried flask the appropriate alcohol/phenol (1.00 eq) was dissolved in dry DCM to receive a concentration of 0.1 mmol/mL and imidazole (1.10 eq) and TBDMSCl (1.10 eq) were sequentially added. The reaction mixture was stirred at rt for 18 h. The reaction was stopped with water and extracted with DCM (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (SiO_2).

General procedure 3 (GP3): DESS-MARTIN oxidation

In an oven-dried flask the appropriate alcohol (1.00 eq) was dissolved in dry DCM to receive a concentration of 0.1 mmol/mL. DMP (1.50 eq) was added and the reaction mixture was stirred at rt for 3 h. The reaction mixture was diluted with Et_2O (13.0 mL pro 1.00 mmol alcohol), water (13.0 mL pro 1.00 mmol alcohol) and an excess of $Na_2S_2O_3$ and the suspension was stirred for additional 30 min. The two layers were separated, and the aq. phase was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The product was purified *via* FCC (SiO_2).

General procedure 4 (GP4): Hydroboration with BH_3·THF and oxidation

In an oven-dried two-necked Schlenk flask the appropriate alkene (1.00 eq) was dissolved in dry THF to receive a concentration of 0.1 mmol/mL and the solution was cooled to 0 °C. BH_3·THF (1M in THF, 3.00 eq) was added dropwise and the reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was cooled to 0 °C and aq. 1M NaOH (12.0 mL per 1.00 mmol alkene) and 30% (*w*/*w*) H_2O_2 (12.0 mL per 1.00 mmol alkene) were added and the resulting mixture was stirred at rt for 18 h. The two layers were separated, and the aq. phase

was extracted with DCM (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (SiO_2).

General procedure 5 (GP5): DIELS-ALDER cycloaddition

The DIELS-ALDER reactions were carried out in the microwave or in a pressure tube. In an oven-dried pressure/microwave tube diene **25** (1.00 eq) was dissolved in dry toluene to receive a concentration of 0.1 mmol/mL and the appropriate dienophile (1.00 eq) was added. When using a pressure tube, reaction mixture was heated to 100 °C for 2 h. When using microwave conditions, the used parameters are indicated in the appropriate approach. The solvent was removed *in vacuo* and the crude product was purified *via* FCC (SiO_2).

General procedure 6 (GP6): Br-Li exchange and nucleophilic addition

In an oven-dried two-necked Schlenk flask the appropriate aryl bromide (1.10 eq) was dissolved in dry THF to receive a concentration of 0.3 mmol/mL. The solution was cooled to - 78 °C and *n*-BuLi (1.20 eq) was added. The reaction mixture was stirred for 1 h at - 78 °C. The organolithium species was used without further purification.

Ketone **26/28^c** (1.00 eq) was dissolved in dry THF to receive a concentration of 0.3 mmol/mL and this solution was added to the solution of the organolithium species at - 78 °C and stirred for additional 1 h. The reaction was stopped with sat. aq. NH_4Cl solution, allowed to warm to rt and the layers were separated. The aq. layer was extracted with EtOAc (3 x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (SiO_2).

General procedure 7 (GP7): SUZUKI-MIYAURA cross-coupling

In an oven-dried two-necked Schlenk flask alkene **72** (1.00 eq) was dissolved in dry THF to receive a concentration of 0.3 mmol/mL and cooled to 0 °C. 9-BBN (0.5M in THF, 1.10 eq) was added and the mixture was warmed up slowly to rt and then stirred for 2 h to give a solution of the appropriate *B*-alkyl-9-BBN.

The aryl bromide (1.00 eq) and $Pd(PPh_3)_4$ (3 mol%) were dissolved in dry THF to receive a concentration of 0.3M and added to the degassed *B*-alkyl-9-BBN solution and aq. 2M NaOH (40.0 µL per 1.00 mmol alkene) was added. The mixture was refluxed for 12 h. The reaction mixture was diluted with water and the aq. phase was extracted with hexanes (3 x), washed with brine, dried over Na_2SO_4, filtered and the crude product was purified *via* FCC (SiO_2).

General procedure 8 (GP8): Dehydration and ionic hydrogenation

In an oven-dried flask the appropriate tertiary alcohol (1.00 eq), TFA (5.50 eq) and TES (2.50 eq) were dissolved in dry DCM to receive a concentration of 0.1 mmol of tertiary alcohol

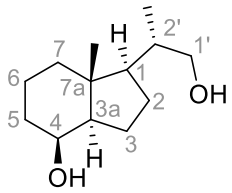
per mL and stirred for 2 h at rt. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and the aq. phase was extracted with DCM (3 x). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The compounds were used without further purification.

General procedure 9 (GP9): TBDMS deprotection

In an oven-dried flask the appropriate TBDMS-protected alcohol/phenol (1.00 eq), HF·pyr (~30% pyridine, ~70% HF, 2.20 eq per TBDMS group), pyridine (2.30 eq per TBDMS group) were dissolved in EtOAc to receive a concentration of 0.1 mmol/mL. The reaction mixture was stirred at rt for 18 h. The reaction was stopped with methoxytrimethylsilane (35.0 eq) and stirred for additional 40 min. The solvent was removed *in vacuo* and the crude product was purfied *via* FCC (SiO_2).

6.2.2. Procedures and data for building blocks bearing ring C and D

(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (Inhoffen-Lythgoe-Diol, 29)[67-68]



29

$C_{13}H_{24}O_2$

M = 212.33 g/mol

Ergocalciferol (**27**, 5.00 g, 13.0 mmol, 1.00 eq) was dissolved in methanol p.a. (500 mL) and dry pyridine (5.00 mL) was added. The reaction mixture was cooled to - 78 °C. Ozone was passed through the reaction mixture (flow rate 60 L/h, 50 Hz). After 2 h a grey-blue colour appeared, and the ozone flow was discontinued, and the reaction mixture was purged with N_2 to remove the remaining dissolved ozone for 10 min. The solution was warmed to 0 °C and $NaBH_4$ (8.50 g, 225 mmol, 18.0 eq) was added portionwise over a period of 1 h. The reaction mixture was allowed to warm up to rt overnight. The reaction was quenched with 1M aq. HCl (100 mL), concentrated *in vacuo* (~ 100 mL) and the residue was extracted with EtOAc (3 x 200 mL). The organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as white crystalline solid (1.73 g, 8.15 mmol, 65%).

R_f = 0.21 (hexanes/EtOAc 7:3).

mp: 113 °C.

$[\alpha]_D^{23}$: + 36.3 (c = 0.11, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.08 (t, *J* = 2.8 Hz, 1H, 4-H), 3.63 (dt, *J* = 10.4, 3.8 Hz, 1H, 1'-H), 3.40 – 3.34 (m, 1H, 1'-H), 2.01 – 1.95 (m, 1H, 7-H), 1.88 – 1.76 (m, 3H, 2, 5, 6-H), 1.60 – 1.51 (m, 2H, 3, 2'-H), 1.51 – 1.40 (m, 3H, 3, 5, 6-H), 1.38 – 1.29 (m, 4H, 2, 3a, 4-OH, 1'-OH), 1.21 – 1.12 (m, 2H, 1, 7-H), 1.02 (d, *J* = 6.7 Hz, 3H, 2'-CH_3), 0.95 (s, 3H, 7a-CH_3).

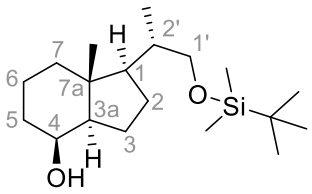
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 69.4 (C-4), 67.9 (C-2'), 53.1 (C-1), 52.51 (C-3a), 42.0 (C-7a), 40.4 (C-7), 38.4 (C-1'), 33.7 (C-5), 26.8 (C-2), 22.7 (C-3), 17.6 (C-6), 16.8 (1'-CH_3), 13.7 (7a-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3957, 3809, 3792, 3348, 3271, 3271, 2930, 2864, 2359, 1714, 1699, 1473, 1458, 1439, 1382, 1358, 1181, 1161, 1066, 1030, 987, 957, 940, 727, 626, 603, 571.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{21}O_2$ $[M\text{-}CH_3]^{\bullet+}$ 197.1542; found 197.1532.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV))

(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (30)



30

$C_{19}H_{38}O_2Si$

M = 326.59 g/mol

Alcohol **30** was synthesised according to **GP1**, using diol **29** (200 mg, 0.942 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as colourless oil (309 mg, 0.946 mmol, quantitative).

R_f = 0.51 (hexanes/EtOAc 8:2).

$[\alpha]_D^{23}$: + 29.8 (c = 0.12, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.07 (d, *J* = 3.1 Hz, 1H, 4-OH), 3.57 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.26 (dd, *J* = 9.6, 7.3 Hz, 1H, 1'-H), 1.99 (dt, *J* = 12.7, 3.1 Hz, 1H, 7-H), 1.87 – 1.74 (m, 3H, 2, 5, 6-H), 1.61 – 1.38 (m, 5H, 3, 5, 6, 2'-H), 1.36 – 1.25 (m, 3H, 2, 3a-H, 4-OH), 1.19 – 1.07 (m, 2H 1, 7-H), 0.96 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.93 (s, 3H, 7a-CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.02 (s, 6H, $Si(CH_3)_2$).

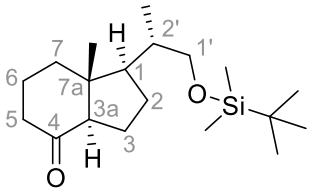
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 69.4 (C-4), 67.9 (C-2'), 53.3 (C-1), 52.5 (C-3a), 42.0 (C-7a), 40.4 (C-7), 38.7 (C-1'), 33.8 (C-5), 26.8 (C-2), 26.11 ($SiC(\underline{C}H_3)_3$), 22.8(C-3), 18.5 ($Si\underline{C}(CH_3)_3$), 17.6 (C-6), 16.9 (1'-CH_3), 13.8 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3769, 3677, 3414, 2928, 2856, 1471, 1388, 1360, 1251, 1091, 1061, 1033, 1005, 989, 942, 833, 812, 773, 723, 692, 664, 620.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{38}O_2Si$ $[M]^{\cdot+}$ 326.2636; found 326.2628.

Purity (GC): 94% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3a*R*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-4*H*-inden-4-one (26)



26

$C_{19}H_{36}O_2Si$

M = 324.58 g/mol

Ketone **26** was synthesised according to **GP3**, using alcohol **30** (1.12 g, 3.43 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (1.01 g, 3.11 mmol, 91%).

R_f = 0.40 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 1.0 (c = 0.11, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 3.56 (dd, *J* = 9.6, 2.7 Hz, 1H, 1'-H), 3.35 – 3.28 (m, 1H, 1'-H), 2.48 – 2.39 (m, 1H, 3a-H), 2.32 – 2.17 (m, 2H, 5-H), 2.11 (ddd, *J* = 13.1, 4.7, 2.4 Hz, 1H, 7-H), 2.01 (dddt, *J* = 14.4, 7.3, 4.8, 2.3 Hz, 1H, 6-H), 1.95 – 1.81 (m, 2H, 2, 6-H), 1.74 (dtd, *J* = 13.3, 11.8, 6.2 Hz, 1H, 3-H), 1.64 – 1.46 (m, 4H, 1, 3, 7, 2'-H), 1.39 – 1.29 (m, 1H, 2-H), 1.02 (d, *J* = 6.0 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.64 (s, 3H, 7a-CH_3), 0.03 (s, 6H, $Si(CH_3)_2$).

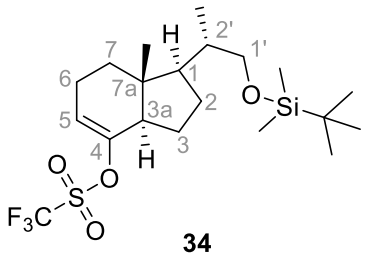
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 212.1 (C-4), 67.7 (C-2'), 61.9 (C-3a), 53.3 (C-1), 50.1 (C-7a), 41.1 (C-5), 39.0 (C-7), 38.8 (C-1'), 27.1 (C-2), 26.1 ($SiC(\underline{C}H_3)_3$), 24.2 (C-6), 19.4 (C-3), 18.5 ($Si\underline{C}(CH_3)_3$), 17.2 (1'-CH_3), 12.7 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3892, 3803, 2954, 2929, 2889, 2856, 1715, 1471, 1458, 1384, 1361, 1307, 1250, 1218, 1186, 1091, 1057, 1038, 1005, 940, 834, 773, 679, 662, 563.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{36}O_2Si$ $[M]^{\cdot+}$ 324.2479; found 324.2464.

Purity (HPLC): > 95 % (λ = 191 nm) (method d).

(1*R*,3a*R*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl trifluoromethanesulfonate (34)



34

$C_{20}H_{35}F_3O_4SSi$

M = 456.64 g/mol

A solution of ketone **26** (106 mg, 0.327 mmol, 1.00 eq) in dry THF (15.0 mL) was added dropwise to NaHMDS (2M in THF, 0.410 mL, 0.820 mmol, 2.50 eq) at - 78 °C. After 1 h *N*-phenyl-bis(trifluoromethansulfonimide) (280 mg, 0.784 mmol, 2.40 eq) was added and stirred for additonal 20 min. The reaction mixture was warmed up to rt and stirred for additional 2 h. The reaction was stopped with water (15.0 mL) and the organic solvent was removed *in vacuo*. The aq. residue was extracted with hexanes (3 x 20.0 mL). The combined organic layers were washed with water (30.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (135 mg, 0.297 mmol, 91%).

R_f = 0.81 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 16.8 (c = 0.10, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.58 (q, *J* = 3.6 Hz, 1H, 5-H), 3.56 (dd, *J* = 9.7, 3.3 Hz, 1H, 1'-H), 3.31 (dd, *J* = 9.7, 6.9 Hz, 1H, 1'-H), 2.51 – 2.44 (m, 1H, 3a-H), 2.34 – 2.28 (m, 2H, 6-H), 2.02 – 1.91 (m, 2H, 2-H, 2, 7-H), 1.82 – 1.75 (m, 1H, 3-H), 1.62 – 1.34 (m, 5H, 1, 2, 3, 7, 2'-H), 1.01 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.77 (s, 3H, 7a-CH_3), 0.03 (s, 6H, $Si(CH_3)_2$).

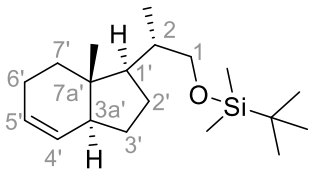
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 150.0 (C-4), 118.7 (q, $J_{C\text{-}F}$ = 320.3 Hz, CF_3) 116.3 (C-5), 67.7 (C-1'), 50.9 (C-1), 50.1 (C-3a), 45.5 (C-7a), 39.2 (C-2'), 34.9 (C-7), 27.9 (C-2), 26.1 ($SiC(\underline{C}H_3)_3$), 24.0 (C-6), 21.8 (C-3), 18.5 ($Si\underline{C}(CH_3)_3$), 17.2 (2'-CH_3), 11.6 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3909, 3861, 2954, 2929, 2857, 1676, 1471, 1445, 1417, 1361, 1314, 1246, 1205, 1142, 1099, 1002, 899, 870, 857, 834, 812, 774, 631, 604, 567.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{35}F_3O_4SSi$ $[M]^{\bullet+}$ 456.1972; found 456.1970.

Purity (HPLC): > 95 % (λ = 210 nm) (method d).

tert-Butyldimethyl((*S*)-2-((1*R*,3a*S*,7a*S*)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl)propoxy)silane (32^{c})



32^{c}

$C_{19}H_{36}OSi$

M = 308.58 g/mol

To a solution of enol triflate **34** (3.04 g, 6.69 mmol, 1.0 eq) in dry THF (50.0 mL) DIPEA (4.83 mL, 27.7 mmol, 4.15 eq) and formic acid (0.78 mL, 20.1 mmol, 3.00 eq) were added and the solution was degassed before $Pd(OAc)_2$ (15.0 mg, 0.067 mmol, 1.00 mol%) and PPh_3 (35.0 mg, 0.134 mmol, 2.00 mol%) were added. The reaction mixture was stirred at rt for 18 h. EtOAc (50.0 mL) was added and the organic phase was washed with brine (40.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (hexanes/EtOAc 99:1) and olefin **32^{c}** was obtained as colourless oil (1.81 g, 5.61 mmol, 84%).

R_f = 0.88 (hexanes/EtOAc 99:1).

$[\alpha]_D^{23}$: + 60.8 (c = 0.12, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.66 – 5.52 (m, 2H, 4'-H, 5'-H), 3.60 (dd, *J* = 9.6, 3.4 Hz, 1H, 1-H), 3.30 – 3.23 (m, 1H, 1-H), 2.13 – 1.94 (m, 3H, 3a', 6'-H), 1.99 (dt, *J* = 12.7, 4.1 Hz, 1H, 7'-H), 1.86 (dtd, *J* = 13.0, 9.4, 6.5 Hz, 1H, 2'-H), 1.68 – 1.53 (m, 2H, 3', 2-H), 1.51 – 1.32 (m, 2H, 2', 7'-H), 1.30 – 1.14 (m, 2H, 1', 3'-H), 1.02 (d, *J* = 6.5 Hz, 3H, 2-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.70 (s, 3H, 7a'-CH_3), 0.03 (s, 6H, $Si(CH_3)_2$).

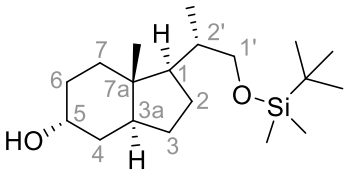
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 128.5 (C-4'), 126.7 (C-5'), 68.1 (C-1), 51.2 (C-1'), 48.5 (C-3a'), 42.0 (C-7a'), 39.6 (C-2), 36.7 (C-7'), 28.1 (C-2'), 26.2 ($SiC(\underline{C}H_3)_3$), 25.2 (C-3'), 24.6 (C-6'), 18.6 ($Si\underline{C}(CH_3)_3$), 17.2 (2-CH_3), 11.2 (7a'-CH_3) -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3825, 3742, 3689, 3019, 2950, 2928, 2875, 2857, 1639, 1471, 1458, 1388, 1361, 1251, 1127, 1085, 1030, 1005, 939, 833, 812, 772, 702, 675, 620, 562.

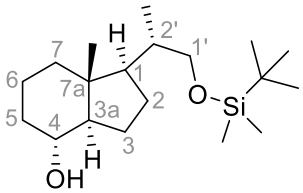
HRMS (EI): *m*/*z* calculated for $C_{18}H_{33}OSi$ $[M]^{\cdot+}$ 293.2301; found 293.2295.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 191 nm) (method f).

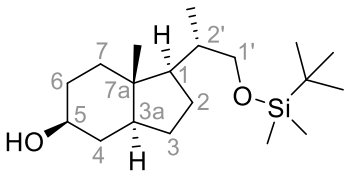
(1*R*,3a*S*,5*R*,7a*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-5-ol (35a), (1*R*,3a*R*,4*R*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (35b) and (1*R*,3a*S*,5*S*,7a*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)-oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-5-ol (35c)



35a



35b



35c

$C_{19}H_{38}O_2Si$

M = 326.59 g/mol

The title compounds were synthesised according to **GP4**, using olefin **32[c]** (1.80 g, 5.80 mmol, 1.00 eq). The alcohols were purified and separated *via* FCC (hexanes/EtOAc 8:2) and alcohol **35a** was obtained as white solid (831 mg, 2.55 mmol, 44%), alcohol **35b** as white solid (273 mg, 0.838 mmol, 14%) and alcohol **35c** as white solid (150.3 mg, 0.460 mmol, 8%).

Analytical data of alcohol **35a**:

R_f = 0.39 (hexanes/EtOAc 8:2).

mp: 98 °C.

$[\alpha]_D^{23}$: + 32.6 (c = 0.10, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.06 (p, *J* = 2.9 Hz, 1H, 5-H), 3.58 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.26 (dd, *J* = 9.6, 7.5 Hz, 1H, 1'-H), 1.83 – 1.45 (m, 10H, 2, 3, 3a, 4, 6, 7, 2'-H), 1.37 (bs, 1H, 5-OH), 1.31 – 1.20 (m, 2H, 1, 2-H), 1.16 – 1.04 (m, 1H, 3-H), 0.99 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.66 (s, 3H, 7a-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 68.1 (C-1'), 66.7 (C-5), 52.6 (C-1), 42.4 (C-7a), 42.2 (C-3a), 39.3 (C-2'), 34.6 (C-7), 33.5 (C-4), 29.3 (C-6), 27.4 (C-2), 26.6 (C-3), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 17.1 (2'-CH_3), 10.3 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3882, 3626, 3286, 2928, 2889, 2855, 2364, 2345, 1473, 1460, 1407, 1352, 1333, 1252, 1197, 1093, 1022, 997, 976, 937, 920, 833, 812, 770, 742, 700, 656, 585, 566.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{37}O_2Si$ $[M-H]^{\cdot+}$ 325.2557; found 325.2572.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

Analytical data of alcohol **35b**:

R_f = 0.33 (hexanes/EtOAc 8:2).

mp: 77 °C.

$[\alpha]_D^{23}$: + 9.4 (c = 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 3.57 (ddd, *J* = 10.8, 6.7, 4.0 Hz, 2H, 4, 1'-H), 3.26 (dd, *J* = 9.6, 7.4 Hz, 1H, 1'-H), 2.04 – 1.95 (m, 1H, 5-H), 1.91 – 1.76 (m, 3H, 2, 3, 7-H), 1.67 – 1.46 (m, 3H, 6, 2'-H), 1.38 – 1.17 (m, 5H, 1, 2, 3, 3a, OH), 1.15 – 1.03 (m, 2H, 5, 7-H), 0.98 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.68 (s, 3H, 7a-CH_3), 0.02 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 71.3 (C-4), 67.9 (C-1'), 57.1 (C-3a), 53.2 (C-1), 44.9 (C-7a), 39.2 (C-7), 38.8 (C-2'), 36.1 (C-5), 27.5 (C-2), 26.1 ($SiC(\underline{C}H_3)_3$), 23.8 (C-3), 21.9 (C-6), 18.5 ($Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), 12.2 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3293, 2927, 2855, 1471, 1459, 1386, 1360, 1251, 1097, 1069, 1030, 1017, 1005, 954, 832, 812, 769, 719, 667.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{37}O_2Si$ $[M]^{\cdot+}$ 326.2636; found 326.2641.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

Analytical data of alcohol **35c**:

R_f = 0.28 (hexanes/EtOAc 8:2).

mp: 83 °C.

$[\alpha]_D^{23}$: + 38.1 (c = 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 3.68 – 3.53 (m, 2H, 5, 1'-H), 3.25 (dd, *J* = 9.6, 7.3 Hz, 1H, 1'-H), 1.92 (dt, *J* = 13.1, 3.6 Hz, 1H, 7-H), 1.86 – 1.73 (m, 3H, 3, 6-H), 1.57 – 1.43 (m, 3H, 4, 2'-H, OH), 1.37 – 1.08 (m, 7H, 1, 2, 3a, 4, 6, 7-H), 0.98 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.72 (s, 3H, 7a-CH_3), 0.02 (s, 6H, $Si(CH_3)_2$).

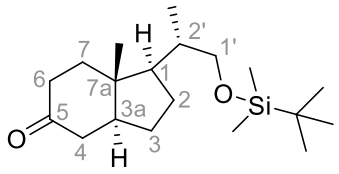
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 76.8 (C-5), 71.9 (C-1'), 67.9 (C-1), 52.0 (C-3a), 48.6 (C-7a), 42.1 (C-2'), 39.2 (C-7), 37.5 (C-6), 35.3 (C-3), 31.7 (C-2), 28.3 ($SiC(\underline{C}H_3)_3$), 26.1 (C-4), 18.5 ($Si\underline{C}(CH_3)_3$), 17.0 (2'-CH_3), 11.4 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3304, 2928, 2856, 1471, 1359, 1249, 1104, 1088, 1056, 1027, 1004, 957, 883, 858, 833, 812, 772, 702, 665.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{38}O_2Si$ $[M]^{\cdot+}$ 326.2636; found 326.2630.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3a*S*,7a*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-5*H*-inden-5-one (28^{c})



28^{c}

$C_{19}H_{36}O_2Si$

M = 324.58 g/mol

Ketone **28^{c}** was synthesised according to **GP3**, using alcohol **35a** (888 mg, 2.72 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white solid (872 mg, 2.69 mmol, 99%).

R_f = 0.63 (hexanes/EtOAc 9:1).

mp: 60 °C.

$[\alpha]_D^{23}$: + 41.8 (c = 0.11, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 3.58 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.30 (dd, *J* = 9.6, 7.1 Hz, 1H, 1'-H), 2.45 – 2.37 (m, 1H, 6-H), 2.35 – 2.23 (m, 3H, 4, 7-H), 2.16 (ddd, *J* = 13.1, 7.0, 2.0 Hz, 1H, 4-H), 1.93 (dtd, *J* = 13.3, 9.5, 6.3 Hz, 1H, 3-H), 1.85 – 1.76 (m, 1H, 3a-H), 1.67 – 1.52 (m, 3H, 2, 6, 2'-H), 1.50 – 1.41 (m, 1H, 3-H), 1.31 – 1.21 (m, 2H, 1, 2-H), 1.01 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.92 (s, 3H, 7a-CH_3), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.03 (s, 6H, Si(CH_3)$_2$).

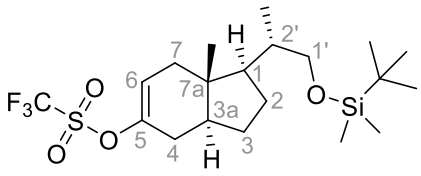
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 212.4 (C-5), 67.7 (C-1'), 51.5 (C-1), 49.9 (C-3a), 42.9 (C-7), 42.0 (C-7a), 39.0 (C-2'), 37.7 (C-4 or C-6), 37.7 (C-4 or C-6), 28.7 (C-3), 26.7 (C-2), 26.1 (SiC(CH_3)$_3$), 18.5 (SiC(CH_3)$_3$), 17.1 (2'-CH_3), 10.8 (7a-CH_3), -5.2 (Si(CH_3)$_2$), -5.3 (Si(CH_3)$_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3384, 2946, 2928, 2896, 2857, 1717, 1470, 1412, 1361, 1250, 1226, 1200, 1144, 1081, 1045, 1017, 1005, 992, 962, 939, 915, 856, 835, 813, 772, 749, 701, 681, 664, 619, 574.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{27}O_2Si$ $[M]^{\cdot+}$ 267.1780; found 267.1773.

Purity (HPLC): 83% (λ = 191 nm), > 95% (λ = 210 nm) (method f).

1*R*,3a*S*,7a*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl trifluoromethanesulfonate (172)



172

$C_{20}H_{35}F_3O_4SSi$

M = 456.64 g/mol

A solution of **28**[c] (350 mg, 1.08 mmol, 1.0 eq) in dry THF (20.0 mL) was added dropwise to NaHMDS (1M in THF, 2.70 mL, 2.70 mmol, 2.50 eq) at - 78 °C. After 1 h *N*-phenyl-bis(trifluoromethansulfonimide) (925 mg, 2.59 mmol, 2.40 eq) was added and stirred for additonal 20 min. The reaction mixture was warmed up to rt and stirred for 2 h. The reaction was stopped with water (25.0 mL) and the organic solvent was removed *in vacuo*. The aq. residue was extracted with hexanes (3 x 25.0 mL). The combined organic layers were washed with water (30.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title product was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (260 mg, 0.569 mmol, 53%).

R_f = 0.54 (hexanes/EtOAc 95:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 34.1 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.66 (dt, *J* = 5.7, 2.1 Hz, 1H, 6-H), 3.57 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.31 (dd, *J* = 9.7, 6.8 Hz, 1H, 1'-H), 2.40 – 2.25 (m, 2H, 4, 7-H), 2.23 – 2.06 (m, 2H, 4, 7-H), 1.99 – 1.68 (m, 3H, 2, 3, 3a-H), 1.60 – 1.51 (m, 1H, 2'-H), 1.47 – 1.18 (m, 3H, 1, 2, 3 -H), 0.99 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.72 (d, *J* = 0.7 Hz, 3H, 7a-CH_3), 0.03 (s, 6H, $Si(CH_3)_2$).

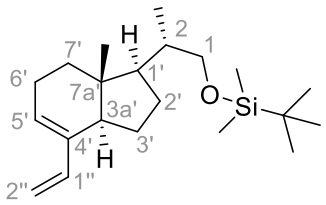
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 148.8 (C-5), 120.3 (q, $J_{C\text{-}F}$ = 320.2 Hz, CF_3), 118.5 (C-6), 67.7 (C-1'), 51.6 (C-1), 46.3 (C-3a), 41.1 (C-7a), 38.8 (C-2'), 38.7 (C-7), 30.8 (C-4), 28.4 (C-2 or 3), 26.1 (C-2 or 3), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 16.8 (2'-CH_3), 11.2 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2955, 2929, 2886, 2857, 1472, 1416, 1245, 1206, 1142, 1078, 1044, 1017, 968, 906, 886, 854, 833, 774, 733, 665.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{35}O_4F_3SSi$ $[M]^{\cdot+}$ 456.1972; found 456.1978.

Purity (HPLC): 90% (λ = 210 nm), 81% (λ = 250 nm) (method e).

tert-Butyldimethyl((*S*)-2-((1*R*,3a*R*,7a*R*)-7a-methyl-4-vinyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl)propoxy)silane (25)



25

$C_{21}H_{38}OSi$

M = 334.62 g/mol

Enol triflate **34** (1.00 g, 2.20 mmol, 1.00 eq) was dissolved in dry THF (20.0 mL) and tributyl(vinyl)tin (0.770 mL, 2.60 mmol, 1.20 eq) and LiCl (466 mg, 11.0 mmol, 5.00 eq) were added. The suspension was degassed before $Pd(PPh_3)_4$ (127 mg, 0.110 mmol, 5.00 mol%) was added and the reaction mixture was stirred at 80 °C for 3 h. The reaction was stopped with water (10.0 mL) and the organic solvent was removed *in vacuo*. The aq. residue was extracted with hexanes (3 x 30.0 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 99:1) and isolated as colourless oil (591 mg, 1.70 mmol, 77%).

R_f = 0.40 (hexanes/EtOAc 99:1).

$[\alpha]_D^{23}$: + 31.9 (c = 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.20 (ddt, *J* = 17.7, 11.2, 0.9 Hz, 1H, 1''-H), 5.70 – 5.67 (m, 1H, 5'-H), 5.22 – 5.17 (m, 1H, 2''-H), 4.87 – 4.82 (m, 1H, 2''-H), 3.61 (dd, *J* = 9.6, 3.4 Hz, 1H, 1-H), 3.28 (dd, *J* = 9.6, 7.4 Hz, 1H, 1-H), 2.28 – 2.18 (m, 3H, 3a', 6'-H), 2.04 – 1.86 (m, 3H, 2', 3', 7'-H), 1.62 – 1.52 (m, 1H, 2-H), 1.46 – 1.35 (m, 3H, 2', 3', 7'-H), 1.30 – 1.21 (m, 1H, 1'-H), 1.04 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.70 (s, 3H, 7a'-CH_3), 0.04 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$).

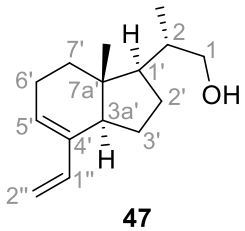
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 138.9 (C-1''), 138.2 (C-4'), 126.1 (C-5'), 111.6 (C-2''), 68.0 (C-1), 50.7 (C-1'), 49.7 (C-3a'), 43.02 (C-7a'), 39.5 (C-2), 35.9 (C-7'), 28.3 (C-2'), 26.1 ($SiC(\underline{C}H_3)_3$), 24.9 (C-6'), 24.3 (C-3'), 18.6 ($Si\underline{C}(CH_3)_3$), 17.3 (2-CH_3), 11.5 (7a'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952, 2926, 2857, 1471, 1385, 1361, 1251, 1127, 1085, 1032, 1024, 1004, 833, 808, 773, 664, 586.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{38}OSi$ $[M]^{\cdot+}$ 334.2686; found 334.2689.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(*S*)-2-((1*R*,3a*R*,7a*R*)-7a-Methyl-4-vinyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-1-yl)propan-1-ol (47)



47

$C_{15}H_{24}O$

M = 220.36 g/mol

In an oven-dried flask diene **25** (630 mg, 1.88 mmol, 1.00 eq) was dissolved in dry THF (5.00 mL). TBAF (1M in THF, 2.82 mL, 2.82 mmol, 1.50 eq) and TEA (0.525 mL, 3.77 mmol, 2.00 eq) were added and the resulting reaction mixture was stirred at rt for 18 h. The reaction was stopped with water (5.00 mL) and the aq. phase was extracted with EtOAc (3 x 7.00 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purfied *via* FCC (hexanes/EtOAc 7:3) and isolated as viscous, colourless oil (303 mg, 1.38 mmol, 73%).

R_f = 0.48 (hexanes/EtOAc 7:3).

$[\alpha]_D^{23}$: + 16.7 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.19 (ddt, *J* = 17.7, 11.2, 1.0 Hz, 1H, 1''-H), 5.69 (q, *J* = 3.5 Hz, 1H, 5'-H), 5.19 (dd, *J* = 17.7, 1.6 Hz, 1H, 2''-H), 4.84 (dd, *J* = 11.2, 1.6 Hz, 1H, 2''-H), 3.66 (dd, *J* = 10.6, 3.2 Hz, 1H, 1'-H), 3.40 (dd, *J* = 10.5, 6.9 Hz, 1H, 1'-H), 2.31 – 2.13 (m, 3H, 3a', 6'-H), 2.04 – 1.91 (m, 3H, 2', 3', 7'-H), 1.67 – 1.55 (m, 1H, 2-H), 1.48 – 1.36 (m, 3H, 2', 3', 7'-H), 1.34 – 1.26 (m, 2H, 1'-H, OH), 1.09 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 0.71 (s, 3H, 7a'-CH_3).

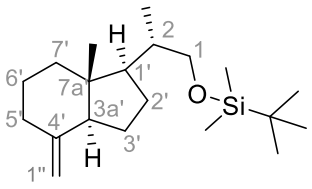
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 138.9 (C-1''), 138.1 (C-4'), 126.0 (C-5'), 111.7 (C-2''), 68.1 (C-1), 50.4 (C-1'), 49.7 (C-3a'), 42.9 (C-7a'), 39.2 (C-2), 35.9 (C-7'), 28.3 (C-2' or 3'), 24.9 (C-6'), 24.2 (C-2' or 3'), 17.1 (2-CH_3), 11.4 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3324, 2949, 2874, 1445, 1378, 1038, 983, 889.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{24}O$ $[M]^{\bullet+}$ 220.1822; found 220.1820.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

tert-Butyldimethyl((*S*)-2-((1*R*,3a*S*,7a*R*)-7a-methyl-4-methyleneoctahydro-1*H*-inden-1-yl)propoxy)silane (72)



72

$C_{20}H_{38}OSi$

M = 322.61 g/mol

Methyltriphenylphosphonium bromide (2.41 g, 6.75 mmol, 1.50 eq) was dissolved in dry THF (30.0 mL) and the solution was cooled to 0 °C. LDA (2M in THF, 4.50 mL, 9.00 mmol, 2.00 eq) was added and the mixture was stirred for 30 min. A solution of ketone **26** (1.46 g, 4.50 mmol, 1.00 eq) in dry THF (10.0 mL) was added and the reaction mixture was slowly warmed up to rt and stirred for 18 h. The reaction was diluted with water (20.0 mL) and the mixture was extracted with EtOAc (3 x 40.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/toluene 9:1) and obtained as colourless oil (980 mg, 3.04 mmol, 68%).

R_f = 0.30 (hexanes/toluene 9:1).

$[\alpha]_D^{23}$: + 59.8 (c = 0.11, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 4.74 (q, *J* = 1.9 Hz, 1H, 1''-H), 4.46 (q, *J* = 2.0 Hz, 1H, 1''-H), 3.60 (dd, *J* = 9.6, 3.4 Hz, 1H, 1-H), 3.27 (dd, *J* = 9.6, 7.4 Hz, 1H, 1-H), 2.30 – 2.23 (m, 1H, 5'-H), 2.04 – 1.97 (m, 1H, 7'-H), 1.96 – 1.89 (m, 2H, 3a', 5'-H), 1.88 – 1.81 (m, 1H, 3'-H), 1.66 – 1.47 (m, 5H, 2, 2', 6'-H), 1.37 – 1.23 (m, 3H, 1', 3', 7'-H), 1.01 (d, *J* = 6.5 Hz, 3H, 2-CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.57 (d, *J* = 0.6 Hz, 3H, 7a'-CH_3), 0.04 (s, 3H, $Si(CH_3)_2$), 0.04 (s, 3H, $Si(CH_3)_2$).

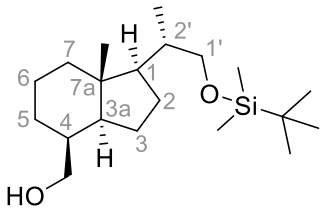
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 149.7 (C-4'), 105.2 (C-1''), 68.0 (C-1), 55.2 (C-3a'), 53.1 (C-1'), 45.3 (C-7a'), 40.2 (C-7'), 39.5 (C-2), 35.6 (C-5'), 27.3 (C-3'), 26.1 ($SiC(\underline{C}H_3)_3$), 23.9 (C-6'), 22.6 (C-2'), 18.6 ($Si\underline{C}(CH_3)_3$), 17.2 (2-CH_3), 12.0 (7a'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3076, 2950, 2927, 2855, 1650, 1471, 1252, 1088, 1030, 1004, 884, 833, 773, 665.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{38}OSi$ $[M]^{\cdot+}$ 322.2686; found 322.2689.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

((1*R*,3a*S*,4*S*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)methanol (74)



74

$C_{20}H_{40}O_2Si$

M = 340.62 g/mol

Alcohol **74** was synthesised according to **GP4**, using olefin **72** (688 mg, 2.13 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as white solid (526 mg, 1.54 mmol, 72%).

R_f = 0.37 (hexanes/EtOAc 8:2).

mp: 86°C.

$[\alpha]_D^{23}$: + 64.4 (c = 0.11, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 3.72 (ddd, *J* = 10.3, 3.1, 1.2 Hz, 1H, 4-CH_2), 3.66 (t, *J* = 10.0 Hz, 1H, 4-CH_2), 3.57 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.25 (dd, *J* = 9.6, 7.4 Hz, 1H, 1'-H), 1.96 – 1.90 (m, 2H, 4, 6-H), 1.90 – 1.85 (m, 1H, 5-H), 1.82 – 1.74 (m, 1H, 3-H), 1.58 – 1.41 (m, 5H, 2, 3a, 7, 2'-H), 1.37 – 1.29 (m, 1H, 5-H), 1.27 – 1.19 (m, 2H, 3-H, OH), 1.17 – 1.08 (m, 2H, 1, 6-H), 0.95 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.64 (s, 3H, 7a-CH_3), 0.02 (s, 3H, $Si(CH_3)_2$), 0.02 (s, 3H, $Si(CH_3)_2$).

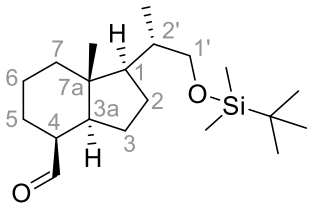
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 67.9 (C-1'), 61.7 (4-CH_2), 53.5 (C-1), 51.6 (C-3a), 42.2 (C-7a), 40.9 (C-4), 40.7 (C-6), 39.2 (C-2'), 28.1 (C-5), 26.9 (C-3), 26.1 ($SiC(\underline{C}H_3)_3$), 23.8 (C-2), 18.5 ($Si\underline{C}(CH_3)_3$), 18.3 (C-7), 16.9 (2'-CH_3), 13.6 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3298, 2945, 2928, 2854, 1471, 1250, 1087, 1019, 908, 859, 844, 833, 733, 734, 663.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{40}O_2Si$ $[M]^{\cdot+}$ 340.2792; found 340.2791.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3a*S*,4*S*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-indene-4-carbaldehyde (73^{b})



73^{b}

$C_{20}H_{38}O_2Si$

M = 338.60 g/mol

Aldehyde **73^{b}** was synthesised according to **GP3** using alcohol **74** (465 mg, 1.37 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 85:15) and isolated as a colourless oil (265 mg, 0.783 mmol, 57%).

R_f = 0.90 (hexanes/EtOAc 85:15).

$[\alpha]_D^{23}$**:** + 94.9 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 10.03 (s, 1H, CHO), 3.57 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.29 (dd, *J* = 9.6, 7.0 Hz, 1H, 1'-H), 2.52 – 2.46 (m, 1H, 4-H), 2.28 (dd, *J* = 13.7, 3.3 Hz, 1H, 2-H or 5-H), 1.96 (dt, *J* = 13.3, 3.5 Hz, 1H, 7-H), 1.93 – 1.87 (m, 1H, 2-H or 5-H), 1.87 – 1.80 (m, 1H, 1-H), 1.80 – 1.69 (m, 2H, 3-H or 6-H), 1.48 (ddq, *J* = 13.5, 6.7, 3.7 Hz, 3H, 2´´-H, 3-H or 6-H), 1.38 – 1.30 (m, 1H, 2-H or 5-H), 1.30 – 1.09 (m, 3H, 3a-H, 7-H), 0.97 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.63 (s, 3H, 7a-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 205.0 (CHO), 67.9 (C-1'), 52.9 (C-3a), 51.2 (C-1), 48.7 (C-4), 42.9 (C-7a), 40.1 (C-7), 39.1 (C-2'), 26.9 (C-2 or C-5), 26.1 ($SiC(\underline{C}H_3)_3$), 25.2 (C-2 or C-5), 23.2 (C-3 or C-6), 19.1 (C-3 or C-6), 18.5 ($Si\underline{C}(CH_3)_3$), 17.1 (2'-CH_3), 12.7 (7a-CH_3), -5.2 ($Si(CH_3)_2$) , -5.3 ($Si(CH_3)_2$).

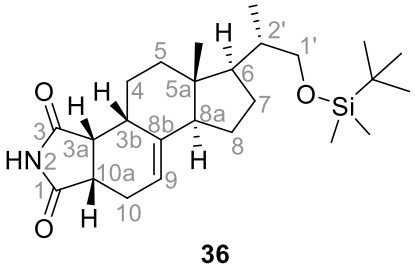
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2951, 2930, 2855, 2736, 2363, 1716, 1472, 1462, 1388, 1361, 1250, 1187, 1124, 1088, 1058, 1035, 1006, 981, 938, 915, 894, 833, 814, 773, 733, 705, 666.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{38}O_2Si$ $[M]^{\cdot+}$ 338.2641; found 338.2632.

Purity (GC): 86% (scan mode *m*/*z* 50-650 (EI 70 eV)).

6.2.3. Procedures and data for tri/tetracycles (chapter 3.2.)

(3a*R*,3b*S*,5a*R*,6*R*,8a*R*,10a*S*)-6-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydroindeno[5,4-e]isoindole-1,3(2*H*,3a*H*)-dione (36)



36

$C_{25}H_{41}NO_3Si$

M = 431.69 g/mol

Tetracycle **36** was synthesised according to **GP5** (microwave conditions: 125 °C, 5 min, 6 bar, 300 W), using diene **25** (52.7 mg, 0.157 mmol, 1.00 eq) and maleimide (15.3 mg, 0.157 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as white crystalline solid (60.0 mg, 0.139 mmol, 89%).

R_f = 0.26 (hexanes/EtOAc 8:2).

mp: 205 °C.

$[\alpha]_D^{23}$: + 105.5 (c = 0.08, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 8.21 (s, 1H, NH), 5.46 – 5.40 (m, 1H, 9-H), 3.57 (dd, *J* = 9.7, 2.7 Hz, 1H, 1'-H), 3.28 (dd, *J* = 9.6, 6.6 Hz, 1H, 1'-H), 3.13 (ddd, *J* = 8.7, 7.2, 1.5 Hz, 1H, 10a-H), 3.08 (dd, *J* = 8.8, 6.0 Hz, 1H, 3a-H), 2.70 (ddt, *J* = 15.1, 7.2, 1.1 Hz, 1H, 10-H), 2.41 – 2.25 (m, 3H, 3b, 4, 8a-H), 2.16 – 2.08 (m, 1H, 10-H), 2.01 – 1.94 (m, 1H, 5-H), 1.94 – 1.86 (m, 1H, 7-H or 8-H), 1.79 – 1.71 (m, 1H, 4-H), 1.61 – 1.53 (m, 1H, 7-H or 8-H), 1.50 – 1.27 (m, 5H, 5, 6, 7, 8, 2'-H), 0.98 (d, *J* = 5.9 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.52 (s, 3H, 5a-CH_3), 0.02 (s, 6H, $Si(CH_3)_2$).

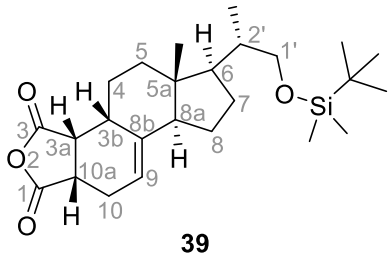
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 180.5 (C-1), 178.6 (C-3), 144.9 (C-8b), 116.5 (C-9), 67.8 (C-1'), 52.7 (C-6), 48.8 (C-8a), 44.7 (C-3a), 42.9 (C-5a), 41.7 (C-10a), 39.6 (C-2'), 36.4 (C-5), 34.8 (C-3b), 28.6 (C-7 or C-8), 26.1 ($SiC(\underline{C}H_3)_3$), 23.9 (C-10), 23.2 (C-4), 21.9 (C-7 or C-8), 18.5 (5a-CH_3 or $Si\underline{C}(CH_3)_3$), 18.5 (5a-CH_3 or $Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3837, 3801, 3225, 2956, 2928, 2855, 1747, 1699, 1461, 1441, 1378, 1354, 1328, 1254, 1198, 1184, 1163, 1093, 999, 938, 858, 833, 812, 773, 742, 687, 665, 635, 559.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{41}NO_3Si$ $[M]^{\cdot+}$ 431.2850; found 431.2853.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(3a*R*,3b*S*,5a*R*,6*R*,8a*R*,10a*S*)-6-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydro-1*H*-cyclopenta[5,6]naphtho[1,2-c]furan-1,3(3a*H*)-dione (39)



39

$C_{25}H_{40}O_4Si$

M = 432.68 g/mol

Tetracycle **39** was synthesised according to **GP5** (microwave conditions: 125 °C, 5 min, 6 bar, 300 W), using diene **25** (109 mg, 0.326 mmol, 1.00 eq) and maleic anhydride (31.9 mg, 0.326 mmol, 1.00 eq). The title compound was purified *via* FCC (SiO_2, neutralised with TEA, hexanes/EtOAc 8:2) and isolated as white crystalline solid (12.9 mg, 0.029 mmol, 9%).

R_f = 0.50 (hexanes/EtOAc 8:2).

mp: 207 °C.

$[\alpha]_D^{23}$: + 104.9 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.51 (dd, *J* = 7.1, 2.9 Hz, 1H, 9-H), 3.57 (dd, *J* = 9.7, 2.6 Hz, 1H, 1'-H), 3.40 (ddd, *J* = 9.7, 7.1, 1.7 Hz, 1H, 10a-H), 3.30 (td, *J* = 9.4, 6.4 Hz, 2H, 3a, 1'-H), 2.80 – 2.67 (m, 1H, 10-H), 2.44 – 2.15 (m, 3H, 3b, 8a, 10-H), 2.05 – 1.97 (m, 1H, 5-H), 1.96 – 1.86 (m, 1H, 4, 7 or 8-H), 1.77 (dt, *J* = 12.8, 5.7 Hz, 1H, 4, 7 or 8-H), 1.65 – 1.27 (m, 6H, 4, 5, 6, 7, 8, 2'-H), 0.98 (d, *J* = 5.9 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.53 (s, 3H, 5a-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

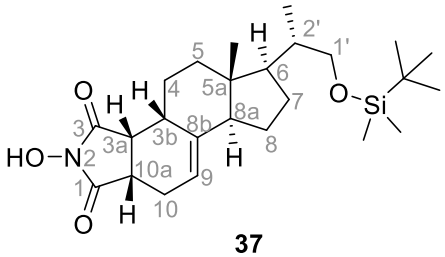
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 174.7 (C-1), 171.9 (C-3), 145.6 (C-8b), 117.0 (C-9), 67.7 (C-1'), 52.8 (C-6), 48.8 (C-8a), 44.4 (C-3a), 42.9 (C-5a), 41.1 (C-10a), 39.5 (C-2'), 36.1 (C-5), 34.4 (C-3b), 28.5 (C-4, 7 or 8), 26.1 ($SiC(\underline{C}H_3)_3$), 24.1 (C-10), 23.1 (C-4, 7 or 8), 21.9 (C-4, 7 or 8), 18.6 (5a-CH_3), 18.5 ($Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3348, 2954, 2854, 1765, 1632, 1413, 1247, 1187, 1092, 1024, 954, 923, 832, 773, 699.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{40}O_4Si$ $[M]^{\cdot+}$ 432.2696; found 432.2694.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm) (method f).

(5a*R*,6*R*,8a*R*)-6-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-2-hydroxy-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydroindeno[5,4-e]isoindole-1,3(2*H*,3a*H*)-dione (37)



37

$C_{25}H_{41}NO_4Si$

M = 447.69 g/mol

Tetracycle **37** was synthesised according to **GP5** (microwave conditions: 125 °C, 5 min, 6 bar, 300 W), using diene **25** (150 mg, 0.448 mmol, 1.00 eq) and *N*-hydroxy maleimide (50.7 mg, 0.448 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as white solid (196 mg, 0.438 mmol, 97%).

R_f = 0.48 (hexanes/EtOAc 5:5).

mp: 167 °C.

$[\alpha]_D^{23}$: + 95.0 (c = 0.03, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.38 (dq, *J* = 7.4, 2.4 Hz, 1H, H-9), 3.57 (dd, *J* = 9.7, 2.9 Hz, 1H, 1'-H), 3.28 (dd, *J* = 9.6, 6.7 Hz, 1H, 1'-H), 3.11 – 3.02 (m, 2H, 3a, 10a-H), 2.71 (ddd, *J* = 16.0, 7.0, 1.5 Hz, 1H, 10-H), 2.38 – 2.27 (m, 3H, 8a, 3b-H, 4, 7 or 8-H), 2.18 – 2.11 (m, 1H, 10-H), 1.97 (dd, *J* = 13.9, 6.8 Hz, 1H, 5-H), 1.93 – 1.86 (m, 1H, 4, 7 or 8-H), 1.76 (dt, *J* = 12.5, 4.6 Hz, 1H, 4, 7 or 8-H), 1.59 – 1.52 (m, 1H, 4, 7 or 8-H), 1.50 – 1.40 (m, 3H, 5, 6, 2'-H), 1.40 – 1.24 (m, 3H, OH, 4, 7 or 8-H), 0.98 (d, *J* = 6.0 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.51 (s, 3H, 5a-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

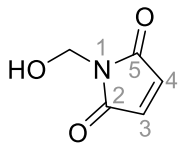
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 174.6 (C-1), 172.9 (C-3), 144.8 (C-8b), 116.2 (C-9), 67.8 (C-1'), 52.7 (C-6), 48.7 (C-8a), 42.9 (C-5a), 41.0 (C-3a), 39.6 (C-2'), 37.7 (C-10a), 36.3 (C-5), 34.8 (C-3b), 28.5 (C-4, 7 or 8), 26.1 ($SiC(\underline{C}H_3)_3$), 23.8 (C-10), 23.2 (C-4, 7 or 8), 21.9 (C-4, 7 or 8), 18.5 ($Si\underline{C}(CH_3)_3$), 18.5 (5a-CH_3), 16.9 (2'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2929, 2855, 1770, 1699, 1681, 1515, 1469, 1436, 1362, 1315, 1256, 1218, 1182, 1093, 1076, 1060, 1019, 1005, 938, 852, 835, 812, 773, 714, 663, 603, 577, 567.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{41}NO_3Si$ $[M]^{\cdot+}$ 431.2850; found 431.2832.

Purity (HPLC): 93% (λ = 191 nm), > 95% (λ = 210 nm) (method f).

1-(Hydroxymethyl)-1*H*-pyrrole-2,5-dione (41)[79]



41

$C_5H_5NO_3$

M = 127.09 g/mol

Maleimide (200 mg, 2.06 mmol, 1.00 eq) was added to a mixture of formaldehyde (37% solution, 500 µL) and 5% aq. NaOH solution (0.010 mL) was added. Maleimide had dissolved within a few seconds and an exothermic reaction proceeded. After 30 sec a white solid has formed, which was filtrated and washed with ice cold EtOH (10.0 mL) and Et_2O (10.0 mL). The title compound was obtained as white solid (181 mg, 1.43 mmol, 69%).

R_f = 0.32 (hexanes/EtOAc 6:4).

mp: 99 °C.

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.77 (s, 2H, 3, 4-H), 5.08 (d, *J* = 7.8 Hz, 2H, N-CH_2), 3.18 (t, *J* = 7.9 Hz, 1H, OH).

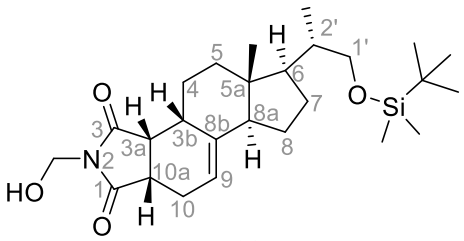
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 170.3 (C-2, 5), 134.8 (C-3, 4), 61.2 (N-CH_2).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3092, 1698, 1357, 1325, 1165, 1036, 911, 840, 757, 694, 657.

HRMS (EI): *m*/*z* calculated for $C_5H_4NO_3$ $[M]^{\cdot+}$ 126.0191; found 126.0176.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

(5a*R*,6*R*,8a*R*)-6-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-2-(hydroxymethyl)-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydroindeno[5,4-e]isoindole-1,3(2*H*,3a*H*)-dione (38)



38

$C_{26}H_{43}NO_4Si$

M = 461.72 g/mol

Tetracycle **38** was synthesised according to **GP5** (microwave conditions: 125 °C, 5 min, 6 bar, 300 W), using diene **25** (123 mg, 0.368 mmol, 1.00 eq) and **41** (46.7 mg, 0.368 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 6:4) and isolated as white oily solid (121 mg, 0.262 mmol, 71%).

R_f = 0.46 (hexanes/EtOAc 6:4).

$[\alpha]_D^{23}$: + 102.0 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.43 – 5.34 (m, 1H, 9-H), 4.95 (d, *J* = 8.2 Hz, 2H, N-CH_2), 3.56 (dd, *J* = 9.6, 2.6 Hz, 1H, 1'-H), 3.28 (dd, *J* = 9.6, 6.5 Hz, 1H, 1'-H), 3.21 (t, *J* = 8.1 Hz, 1H, OH), 3.15 – 3.04 (m, 2H, 3a, 10a-H), 2.76 – 2.68 (m, 1H, 10-H), 2.40 – 2.28 (m, 3H, 4, 8a, 3b-H), 2.19 – 2.10 (m, 1H, 10-H), 1.97 (dd, *J* = 15.0, 6.5 Hz, 1H, 5-H), 1.92 – 1.84 (m, 1H, 8-H), 1.82 – 1.74 (m, 1H, 4-H), 1.59 – 1.23 (m, 6H, 5, 6, 7, 8, 2'-H), 0.98 (d, *J* = 5.9 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, Si-C(CH_3)$_3$), 0.51 (s, 3H, 5a-CH_3), 0.02 (s, 6H, Si(CH_3)$_2$).

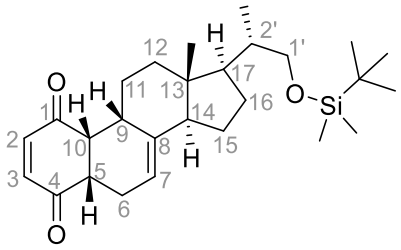
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 179.9 (C-1), 178.1 (C-3), 144.9 (C-8b), 116.4 (C-9), 67.8 (C-1'), 62.6 (N-CH_2), 52.7 (C-6), 48.7 (C-8a), 43.7 (C-3a), 42.9 (C-5a), 40.5 (C-10a), 39.6 (C-2'), 36.4 (C-5), 34.8 (C-3b), 28.5 (C-8), 26.1 (Si-C($\underline{C}H_3$)$_3$), 23.9 (C-10), 23.3 (C-4), 21.9 (C-7), 18.5 (Si-$\underline{C}$(CH_3)$_3$), 18.5 (5a-CH_3), 16.9 (1'-CH_3), -5.2 (Si(CH_3)$_2$), -5.2 (Si(CH_3)$_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2927, 2854, 1766, 1719, 1695, 1468, 1425, 1358, 1253, 1205, 1091, 1069, 1048, 1005, 977, 852, 834, 773, 639, 591.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{41}NO_3Si$ [M-CH_2OH]$^{\cdot+}$ 431.2850; found 431.2853.

Purity (HPLC): > 95% (λ = 210 nm) (method c).

(5*S*,9*S*,10*R*,13*R*,14*R*,17*R*)-17-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-13-methyl-6,9,10,11,12,13,14,15,16,17-decahydro-1*H*-cyclopenta[a]phenanthrene-1,4(5*H*)-dione (40)



40

$C_{27}H_{42}O_3Si$

M = 442.72 g/mol

Tetracycle **40** was synthesised according to **GP5** (microwave conditions: 125 °C, 2.5 h, 6 bar, 300 W), using diene **25** (303 mg, 0.906 mmol, 1.0 eq) and *p*-benzochinone (98 mg, 0.91 mmol, 1.0 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as orange solid (62 mg, 0.14 mmol, 15%).

R_f = 0.17 (hexanes/EtOAc 95:5).

mp: 147 °C.

$[\alpha]_D^{23}$: + 170.4 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.57 (d, *J* = 10.2 Hz, 1H, 3-H), 6.50 (dd, *J* = 10.3, 1.3 Hz, 1H, 2-H), 5.07 (t, *J* = 3.1 Hz, 1H, 7-H), 3.59 (dd, *J* = 9.7, 3.1 Hz, 1H, 1'-H), 3.29 (dd, *J* = 9.6, 6.8 Hz, 1H, 1'-H), 3.25 – 3.20 (m, 2H, 5, 10-H), 2.63 – 2.51 (m, 2H, 11, 14-H), 2.50 – 2.37 (m, 2H, 6, 9-H), 2.21 – 2.08 (m, 1H, 6-H), 1.90 (ddt, *J* = 21.0, 14.3, 9.1 Hz, 2H, 12, 15-H), 1.77 – 1.67 (m, 1H, 16-H), 1.58 – 1.24 (m, 6H, 11, 12, 15, 16, 17, 2'-H), 0.98 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.69 (s, 3H, 13-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

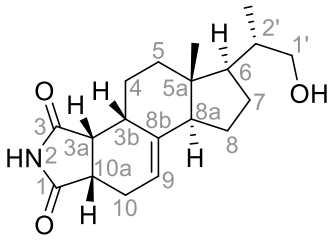
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 201.7 (C-1), 199.7 (C-4), 141.9 (C-8), 141.1 (C-3), 137.2 (C-2), 114.6 (C-7), 67.8 (C-1'), 53.6 (C-17), 50.9 (C-5), 50.2 (C-10), 48.9 (C-14), 41.9 (C-13), 39.5 (C-2'), 37.5 (C-12), 36.4 (C-9), 28.4 (C-15), 27.3 (C-6), 26.1 ($SiC(\underline{C}H_3)_3$), 24.2 (C-11), 23.0 (C-16), 18.9 (13-CH_3), 18.5 ($Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954, 2929, 2879, 2856, 2358, 1681, 1600, 1471, 1438, 1382, 1360, 1341, 1251, 1184, 1091, 1006, 977, 939, 858, 834, 816, 774, 691, 667.

HRMS (EI): *m*/*z* calculated for $C_{27}H_{42}O_3Si$ $[M]^{\cdot+}$ 442.2897; found 442.2901.

Purity (HPLC): 93% (λ = 210 nm) (method e).

(3a*R*,3b*S*,5a*R*,6*R*,8a*R*,10a*S*)-6-((*S*)-1-Hydroxypropan-2-yl)-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydroindeno[5,4-*e*]isoindole-1,3(2*H*,3a*H*)-dione (42)



42

$C_{19}H_{27}NO_3$

M = 317.43 g/mol

Alcohol **42** was synthesised according to **GP9**, using tetracycle **36** (45.3 mg, 0.105 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and obtained as white solid (32 mg, 0.101 mmol, 96%).

R_f = 0.34 (hexanes/EtOAc 5:5).

mp: 170 °C.

$[\alpha]_D^{23}$: + 126.1 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.22 (s, 1H, NH), 5.44 (dq, *J* = 7.7, 2.7 Hz, 1H, 9-H), 3.64 (dd, *J* = 10.5, 2.8 Hz, 1H, 1'-H), 3.37 (dd, *J* = 10.5, 6.3 Hz, 1H, 1'-H), 3.18 – 3.05 (m, 2H, 3a, 10a-H), 2.70 (ddt, *J* = 15.1, 7.2, 1.2 Hz, 1H, 10-H), 2.44 – 2.25 (m, 3H, 3b, 4, 8a-H), 2.17 – 2.06 (m, 1H, 10-H), 2.03 – 1.87 (m, 2H, 5-H), 1.82 – 1.71 (m, 1H, 4-H), 1.64 – 1.27 (m, 5H, 6, 7, 8, 2'-H), 1.03 (d, *J* = 6.1 Hz, 3H, 2'-CH_3), 0.53 (s, 3H, 5a-CH_3).

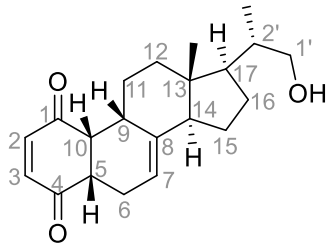
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 180.4 (C-1), 178.5 (C-2), 144.7 (C-8b), 116.6 (C-9), 67.8 (C-1'), 52.6 (C-6), 48.8 (C-8a), 44.7 (C-3a), 43.0 (C-5a), 41.7 (C-10a), 39.3 (C-2'), 36.4 (C-5), 34.8 (C-3b), 28.6 (C-7 or C-8), 23.9 (C-10), 23.2 (C-4), 21.9 (C-7 or C-8), 18.4 (5a-CH_3), 16.7 (2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2924, 1770, 1702, 1467, 1436, 1354, 1199, 1103, 1044, 1031, 985, 824, 793, 638, 564.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{27}NO_3$ $[M]^{\bullet+}$ 317.1986; found 317.1988.

Purity (HPLC): > 95% (λ = 191 nm), 92% (λ = 210 nm) (method f).

(5*S*,9*S*,10*R*,13*R*,14*R*,17*R*)-17-((*S*)-1-Hydroxypropan-2-yl)-13-methyl-6,9,10,11,12,13,14,15,16,17-decahydro-1*H*-cyclopenta[*a*]phenanthrene-1,4(5*H*)-dione (46)



46

$C_{21}H_{28}O_3$

M = 328.45 g/mol

Alcohol **46** was synthesised according to **GP9**, using tetracycle **40** (53.0 mg, 0.120 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 4:6) and isolated as orange oily solid (37.4 mg, 0.114 mmol, 95%).

R_f = 0.52 (hexanes/EtOAc 5:5).

$[\alpha]_D^{23}$: + 246.6 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.57 (d, *J* = 10.3 Hz, 1H, 2 or 3-H), 6.51 (dd, *J* = 10.3, 1.3 Hz, 1H, 2 or 3-H), 5.08 (t, *J* = 3.1 Hz, 1H, 7-H), 3.66 (dd, *J* = 10.5, 3.1 Hz, 1H, 1'-H), 3.39 (dd, *J* = 10.5, 6.6 Hz, 1H, 1'-H), 3.28 – 3.21 (m, 2H, 5, 10-H), 2.64 – 2.51 (m, 2H, 14-H, 11, 15 or 16-H), 2.50 – 2.38 (m, 2H, 6, 9-H), 2.23 – 2.10 (m, 1H, 6-H), 2.00 – 1.89 (m, 3H, 12-H, 11, 15 or 16-H), 1.80 – 1.69 (m, 1H, 11, 15 or 16-H), 1.60 – 1.25 (m, 5H, 11, 15, 16, 17, 2'-H), 1.05 (d, *J* = 6.4 Hz, 3H, 2'-CH_3), 0.71 (s, 3H, 13-CH_3).

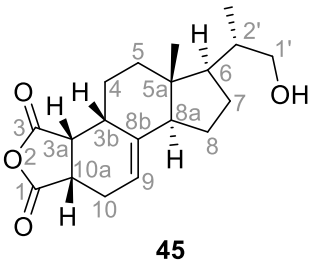
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 201.7 (C-1 or 4), 199.7 (C-1 or 4), 141.7 (C-8), 141.1 (C-2 or 3), 137.2 (C-2 or 3), 114.8 (C-7), 67.9 (C-1'), 53.4 (C-17), 50.9 (C-5 or 10), 50.2 (C-5 or 10), 48.9 (C-14), 41.9 (C-13), 39.3 (C-2'), 37.5 (C-12), 36.4 (C-9), 28.4 (C-11, 15 or 16), 27.3 (C-6), 24.2 (C-11, 15 or 16), 22.9 (C-11, 15 or 16), 18.9 (13-CH_3), 16.6 (2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2940, 2875, 2361, 1682, 1600, 1468, 1441, 1379, 1341, 1262, 1179, 1088, 1072, 1039, 997, 982, 948, 901, 873, 848, 749, 728.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{28}O_3$ $[M]^{\cdot+}$ 328.2033; found 328.2033.

Purity (HPLC): > 95% (λ = 210 nm), 90% (λ = 254 nm) (method c).

(3a*R*,3b*S*,5a*R*,6*R*,8a*R*,10a*S*)-6-((*S*)-1-Hydroxypropan-2-yl)-5a-methyl-3b,4,5,5a,6,7,8,8a,10,10a-decahydro-1*H*-cyclopenta[5,6]naphtho[1,2-c]furan-1,3(3a*H*)-dione (45)



45

$C_{19}H_{26}NO_4$

M = 318.41 g/mol

Alcohol **45** was synthesised according to **GP5** (microwave conditions: 125 °C, 8 min, 6 bar, 300 W), using diene **47** (60.0 mg, 0.272 mmol, 1.00 eq) and maleic anhydride (26.7 mg, 0.272 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as white solid (6.60 mg, 0.0207 mmol, 8%).

R_f = 0.31 (hexanes/EtOAc 50:50).

mp: 178 °C.

$[\alpha]_D^{23}$: + 47.2 (c = 0.13, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.52 (dt, *J* = 7.3, 2.8 Hz, 1H, 9-H), 3.65 (dd, *J* = 10.5, 2.9 Hz, 1H, 1'-H), 3.42 – 3.37 (m, 2H, 10a, 1'-H), 3.32 (dd, *J* = 9.6, 6.4 Hz, 1H, 3a-H), 2.80 – 2.72 (m, 1H, 10-H), 2.44 – 2.32 (m, 1H, 3b-H), 2.31 – 2.15 (m, 1H, 4, 7 or 8-H), 2.02 (ddd, *J* = 14.3, 7.9, 1.4 Hz, 1H, 5-H), 1.99 – 1.91 (m, 1H, 4, 7 or 8-H), 1.78 (dt, *J* = 13.3, 5.9 Hz, 1H 4, 7 or 8-H), 1.67 – 1.47 (m, 5H, 5, 6, 10, 2'-H, 4, 7 or 8-H), 1.44 – 1.32 (m, 2H, 4, 7 or 8-H), 1.04 (d, *J* = 6.2 Hz, 3H, 2'-CH_3), 0.55 (s, 3H, 5a-CH_3).

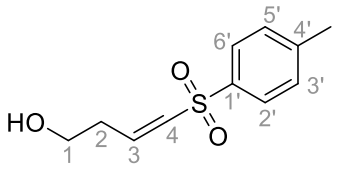
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 174.7 (C-1), 171.9 (C-3), 145.4 (C-8b), 117.2 (C-9), 67.8 (C-1'), 52.6 (C-6), 48.8 (C-8a), 44.4 (C-3a), 42.9 (C-5a), 41.0 (C-10a), 39.3 (C-2'), 36.1 (C-5), 34.3 (C-3b), 28.5 (C-4, 7 or 8), 24.1 (C-10), 23.1 (C-4, 7 or 8), 21.8 (C-4, 7 or 8), 18.5 (5a-CH_3), 16.7 (2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2956, 2163, 1776, 1592, 1468, 1442, 1250, 1025, 959, 821, 686.

HRMS (EI): calculated for $C_{19}H_{26}O_4$ $[M]^{\cdot+}$ 318.1826; found 318.1843.

Purity (HPLC): 77% (λ = 191 nm), > 95% (λ = 210 nm) (method f).

4-Tosylbut-3-en-1-ol (50)[84]



50

$C_{11}H_{14}O_3S$

M = 226.29 g/mol

A suspension of 3-buten-1-ol (**48**, 0.477 mL, 5.55 mmol, 1.00 eq), sodium *p*-toluenesulfinate (1.98 g, 11.1 mmol, 2.00 eq) and iodine (1.69 g, 6.66 mmol, 1.20 eq) in methanol (50.0 mL) was stirred for 2 d at rt. The solvent was removed *in vacuo* and the resulting residue was dissolved in EtOAc (50.0 mL) and washed with aq. 0.2M $Na_2S_2O_3$ (30.0 mL). The organic layer was decanted and aq. 3M NaOH (20.0 mL) was added and stirred for 1 d. The organic layer was separated, washed with brine (3 x 30 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 2:8) and isolated as yellowish oil (664 mg, 2.93 mmol, 53%).

R_f = 0.52 (hexanes/EtOAc 2:8).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.80 – 7.74 (m, 1H, 3', 5'-H), 7.36 – 7.31 (m, 1H, 2', 6'-H), 6.97 (dt, *J* = 15.2, 6.9 Hz, 1H, 3-H), 6.43 (dt, *J* = 15.2, 1.5 Hz, 1H, 4-H), 3.78 (t, *J* = 6.2 Hz, 2H, 1-H), 2.53 – 2.45 (m, 2H, 2-H), 2.43 (s, 3H, 4'-CH_3).

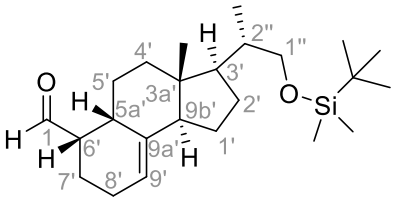
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 144.5 (C-4'), 142.8 (C-3), 137.6 (C-1'), 132.9 (C-4), 130.1 (C-2', 6'), 127.9 (C-3', 5'), 60.6 (C-1), 34.6 (C-2), 21.8 (4'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3498, 2924, 2884, 1632, 1596, 1402, 1314, 1301, 1282, 1138, 1085, 1044, 963, 913, 809, 776, 729, 704, 657.

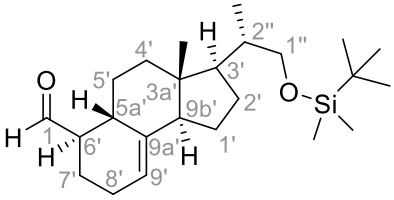
HRMS (EI): *m*/*z* calculated for $C_{11}H_{13}O_3S$ $[M]^{\bullet+}$ 225.0583; found 225.0579.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

(3*R*,3a*R*,5a*S*,6*S*,9b*R*)-3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalene-6-carbaldehyde (54a) and (3*R*,3a*R*,5a*S*,6*R*,9b*R*)-3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalene-6-carbaldehyde (54b)



54a



54b

$C_{24}H_{42}O_2Si$

M = 390.68 g/mol

The inseparable mixture of aldehydes **54a** and **54b** were synthesised according to **GP5**, using diene **25** (217 mg, 0.622 mmol, 1.00 eq) and acrolein (**53**, 41.6 µL, 0.622 mmol, 1.00 eq). The title compounds were purified *via* FCC (hexanes/EtOAc 98:2) and isolated as a white oily solid (224 mg, 0.553 mmol, 89%) in an isomeric ratio of 87:13 (determined *via* ^{1}H NMR).

R_f = 0.16 (hexanes/EtOAc 98:2).

$[\alpha]_D^{23}$: + 30.0 (c = 0.04, $CHCl_3$).

^{1}H NMR (800 MHz, chloroform-*d*) *δ*/ppm = 9.82 (d, *J* = 2.8 Hz, 1H, **a**-1-H), 9.65 (d, *J* = 3.7 Hz, 0.14H, **b**-1-H), 5.26 – 5.24 (m, 1H, **a**-9'-H), 5.24 – 5.22 (m, 0.15H, **b**-9'-H), 3.60 – 3.57 (m, 1.23H, **a**/**b**-1''-H), 3.30 – 3.26 (m, 1.16H, **a**/**b**-1''-H), 2.64 – 2.59 (m, 1H, **a**-5a'-H), 2.57 – 2.52 (m, 0.10H, **b**-5a'-H), 2.48 – 2.43 (m, 2H, **a**-6', **a**-9b'-H), 2.37 – 2.34 (m, 0.10H, **b**-9b'-H), 2.28 – 2.23 (m, 0.12H, **b**-8'-H), 2.19 – 2.10 (m, 3.52H, **b**-6', **a**-8'-H, **a**/**b**-CH_2), 1.93 – 1.87 (m, 2.50H, **a**-4', **b**-3', **b**-7'-H, **a**/**b**-CH_2), 1.86 – 1.74 (m, 3.60H, **a**-5', **a**-7', **b**-4', **b**-7'-H, **a**/**b**-CH_2), 1.69 – 1.64 (m, 0.12H, **b**-7'-H), 1.63 – 1.58 (m, 1.76H, **a**-4'-H, **a**/**b**-CH_2), 1.57 – 1.53 (m, 1H, **a**-5'-H), 1.51 – 1.45 (m, 1.3H, **a**-2''-H), 1.39 – 1.29 (m, 4.1H, **a**-3'**,** **b**-2''-H, **a**/**b**-CH_2), 0.97 (dd, *J* = 10.9, 6.6 Hz, 3.92H, **a**/**b**-2''-CH_3), 0.90 – 0.88 (m, 12H, **a**/**b**-$SiC(CH_3)_3$), 0.77 (s, 0.48H, **b**-3a'-CH_3), 0.74 (s, 3H, **a**-3a'-CH_3), 0.03 – 0.02 (m, 8H, **a**/**b**-$Si(CH_3)_2$).

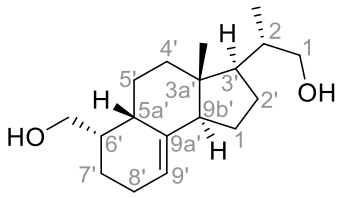
^{13}C NMR (201 MHz, chloroform-*d*) *δ*/ppm = 206.3 (**a**-C-1), 205.8 (**b**-C-1), 140.4 (**b**-C-9a'), 140.1 (**a**-C-9a'), 119.4 (**a**-C-9'), 118.9 (**b**-C-9'), 67.8 (**b**-C-1''), 67.8 (**a**-C-1''), 54.1 (**b**-C-3'), 53.8 (**a**-C-3'), 52.7 (**b**-C-6'), 49.5 (**a**-C-9b'), 49.2 (**a**-C-6'), 48.8 (**b**-C-9b'), 42.0 (**a**-C-3a'), 41.7 (**b**-C-3a'), 39.5 (**a**-C-2''), 39.4 (**b**-C-2''), 37.5 (**a**-C-4'), 37.4 (**b**-C-4'), 36.3 (**a**-C-5a'), 35.1 (**b**-C-5a'), 28.4 (**a**-CH_2), 28.3 (**b**-CH_2), 26.1 (**a**/**b**-$SiC(\underline{C}H_3)_3$), 25.9 (**b**-CH_2), 25.4 (**a**-7'-H), 25.2 (**a**-5'-H), 24.6 (**b**-8'-H), 23.9 (**b**-CH_2), 23.7 (**b**-7'-H), 23.4 (**a**-CH_2), 22.6 (**a**-8'-H), 18.9 (**a**-3a'-CH_3), 18.8 (**b**-3a'-CH_3), 18.5 (**a**/**b**-$Si\underline{C}(CH_3)_3$), 16.9 (**a**-2''-CH_3), 16.8 (**b**-2''-CH_3), -5.2 (**a**/**b**-$Si(CH_3)_2$), -5.2 (**a**/**b**-$Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3393, 2928, 2856, 2359, 1716, 1471, 1462, 1386, 1361, 1250, 1188, 1083, 1029, 1004, 940, 832, 814, 773, 667.

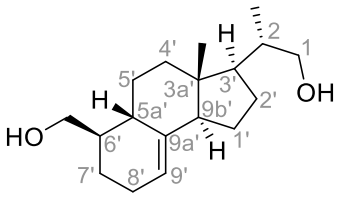
HRMS (EI): *m*/*z* calculated for $C_{24}H_{42}O_2Si$ $[M]^{\bullet+}$ 390.2948; found 390.2944.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-2-((3*R*,3a*R*,5a*S*,6*S*,9b*R*)-6-(Hydroxymethyl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalen-3-yl)propan-1-ol (55a) and (*S*)-2-((3*R*,3a*R*,5a*S*,6*R*,9b*R*)-6-(hydroxymethyl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalen-3-yl)propan-1-ol (55b)



55a



55b

$C_{18}H_{30}O_2$

M = 278.44 g/mol

A solution of the inseparable mixture of aldehydes **54a** and **54b** (100 mg, 0.256 mmol, 1.00 eq) in dry THF (3.00 mL) was added to a mixture of $LiAlH_4$ (10.7 mg, 0.282 mmol, 1.10 eq) in dry THF (5.00 mL) at 0 °C. After 1.5 h the reaction mixture was diluted with water (5.00 mL), conc. H_2SO_4 was added dropwise until the precipitate was dissolved and stirred for additional 30 min. The layers were separated, and the aq. phase was extracted with EtOAc (3 x 10.0 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ solution (5.00 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title products were separated and purified *via* FCC (hexanes/EtOAc 5:5), whereby **55a** was obtained as white solid (57.7 mg, 0.207 mmol, 81%) and diol **55b** was isolated as colourless oil (5.10 mg, 0.0183 mmol, 7%).

Analytical data of diol **55a**:

R_f = 0.33 (hexanes/EtOAc 5:5).

mp: 136 °C.

$[\alpha]_D^{23}$: + 76.0 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.18 (q, *J* = 3.1 Hz, 1H, 9'-H), 3.72 – 3.61 (m, 2H, 1, 6'-CH_2), 3.56 (dd, *J* = 10.6, 8.8 Hz, 1H, 6'-CH_2), 3.38 (dd, *J* = 10.6, 6.7 Hz, 1H, 1-H), 2.60 – 2.50 (m, 1H, 5a'-H), 2.37 – 2.26 (m, 1H, 9b'-H), 2.11 – 2.04 (m, 2H, 8'-H, 1', 2' or 5'-H), 2.03 – 1.82 (m, 4H, 2, 4', 6'-H, 1', 2' or 5'-H), 1.78 – 1.66 (m, 2H, 7'-H), 1.61 – 1.45 (m, 3H, 4'-H, 1', 2' or 5'-H), 1.45 – 1.28 (m, 4H, 3', 8'-H, 1', 2' or 5'-H), 1.02 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 0.74 (s, 3H, 3a'-CH_3).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 139.9 (C-9a'), 118.7 (C-9'), 67.9 (C-1), 61.3 (7'-CH_2), 53.6 (C-3'), 49.2 (C-9b'), 41.8 (C-3a'), 39.3 (C-2), 38.6 (C-6'), 37.7 (C-4'), 37.2 (C-5a'),

28.4 (C-1', 2' or 5'), 25.4 (C-1', 2' or 5'), 25.1 (C-1', 2' or 5'), 23.4 (C-7'), 21.9 (C-8'), 18.9 (3a'-CH_3), 16.6 (2-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3269, 2947, 2873, 2363, 1464, 1379, 1261, 1122, 1076, 1036, 985, 951, 902, 826, 667.

HRMS (EI): *m*/*z* calculated for $C_{18}H_{30}O_2$ $[M]^{\cdot+}$ 278.2240; found 278.2239.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

Analytical data of diol **55b**:

R_f = 0.46 (hexanes/EtOAc 5:5).

$[\alpha]_D^{23}$: + 33.9 (c = 0.16, MeOH).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.22 (t, *J* = 3.3 Hz, 1H, 9'-H), 3.76 (dd, *J* = 10.7, 3.5 Hz, 1H, 6'-CH_2), 3.65 (dd, *J* = 10.5, 3.3 Hz, 1H, 1-H), 3.55 (dd, *J* = 10.7, 6.3 Hz, 1H, 6'-CH_2), 3.39 (dd, *J* = 10.5, 6.7 Hz, 1H, 1-H), 2.38 (d, *J* = 11.1 Hz, 1H, 9b'-H), 2.25 – 2.06 (m, 3H, 5a', 8'-H), 1.96 – 1.73 (m, 5H, 4', 7'-H, 1', 2' or 5'-H), 1.65 – 1.42 (m, 3H, 2, 4', 7'-H), 1.40 – 1.17 (m, 5H, 3', 6'-H, 1', 2' or 5'-H), 1.03 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 0.75 (s, 3H, 3a'-CH_3).

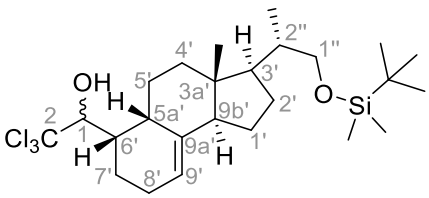
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 141.7 (C-9a'), 119.2 (C-9'), 67.9 (C-1), 66.2 (6'-CH_2), 53.8 (C-3'), 49.1 (C-9b'), 41.6 (C-6'), 41.5 (C-3a'), 39.2 (C-2), 37.7 (C-4'), 36.9 (C-5a'), 28.4 (C-1', 2' or 5'), 26.7 (C-7'), 25.5 (C-8'), 24.8 (C-1', 2' or 5'), 24.0 (C-1', 2' or 5'), 18.7 (3a'-CH_3), 16.6 (2-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3325, 2936, 2871, 2361, 1611, 1564, 1550, 1511, 1483, 1344, 1245, 1125, 986, 813, 751.

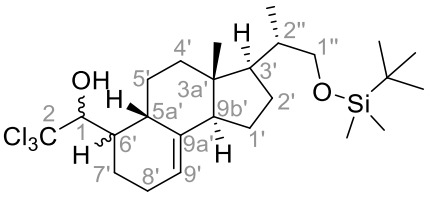
HRMS (EI): *m*/*z* calculated for $C_{18}H_{30}O_2$ $[M]^{\cdot+}$ 278.2240; found 278.2242.

Purity (GC): 94% (scan mode *m*/*z* 50-650 (EI 70 eV)).

1-((3*R*,3a*R*,5a*S*,6*S*,9b*R*)-3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalen-6-yl)-2,2,2-trichloroethan-1-ol (56a) and 1-((3*R*,3a*R*,5a*S*,9b*R*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-3a-methyl-2,3,3a,4,5,5a,6,7,8,9b-decahydro-1*H*-cyclopenta[a]naphthalen-6-yl)-2,2,2-trichloroethan-1-ol (56b)



56a



56b

$C_{25}H_{43}Cl_3O_2Si$

M = 510.05 g/mol

To the inseparable mixture of aldehydes **54a**/**54b** (146 mg, 0.361 mmol, 1.00 eq) chloroform (57.7 µL, 0.722 mmol, 2.00 eq) and DBU (53.9 µL, 0.361 mmol, 1.00 eq) were added. The reaction mixture was stirred at rt for 17 h. The reaction mixture was diluted with DCM (5.00 mL) and sat. aq. NH_4Cl (5.00 mL) was added. The layers were separated, and the aq. layer was extracted with DCM (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compounds were purified and separated *via* FCC (hexanes/$CHCl_3$ 4:6) and **56a** was isolated as white solid (71.0 mg, 0.135 mmol, 15%) and **56b** as light yellow solid (64.0 mg, 0.122 mmol, 13%).

Analytical data of trichloromethylcarbinol derivate **56a**:

R_f: 0.41 (hexanes/$CHCl_3$ 40:60).

mp: 54 °C.

$[\alpha]_D^{23}$: + 12.4 (c = 0.06, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.21 (dt, *J* = 31.5, 3.1 Hz, 1H, 9'-H), 4.09 (dd, *J* = 5.1, 3.7 Hz, 1H, 1-H), 3.59 (dd, *J* = 9.6, 3.4 Hz, 1H, 1''-H), 3.26 (ddd, *J* = 9.6, 7.3, 4.1 Hz, 1H, 1''-H), 2.84 (d, *J* = 5.1 Hz, 1H, OH), 2.52 (tq, *J* = 10.1, 2.9 Hz, 1H, 5a'-H), 2.33 (m, 2H, 9b'-H, 1', 2', 5', 7' or 8'-H), 2.20 – 2.01 (m, 3H, 7'-H, 1', 2', 5' or 8'-H), 1.93 – 1.71 (m, 4H, 4', 6', 7'-H, 1', 2', 5' or 8'-H), 1.64 – 1.57 (m, 1H, 4'-H), 1.52 – 1.45 (m, 1H, 2''-H), 1.41 – 1.18 (m, 5H, 3'-H, 1', 2', 5' or 8'-H), 0.97 (dd, *J* = 6.7, 1.5 Hz, 3H, 2''-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.78 (s, 3H, 3a'-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 142.3 (C-9a'), 118.9 (C-9'), 104.6 (C-2), 87.3 (C-1), 67.9 (C-1''), 54.1 (C-3'), 49.2 (C-9b'), 41.8 (C-6'), 41.2 (C-3a'), 39.5 (C-2''), 37.9 (C-4'), 37.8 (C-5a'), 31.7 (C-7'), 28.4 (C-1', 2', 5' or 8'), 27.9 (C-1', 2', 5' or 8'), 26.1 ($SiC(\underline{C}H_3)_3$), 25.9 (C-

1', 2', 5' or 8'), 24.2 (C-1', 2', 5' or 8'), 18.9 (3a'-CH_3), 18.5 (Si<u>C</u>$(CH_3)_3$), 16.8 (2''-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952, 2928, 2856, 2361, 1715, 1470, 1462, 1386, 1361, 1253, 1085, 1038, 1005, 939, 908, 833, 809, 772, 733, 667.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{43}Cl_3O_2Si$ $[M]^{\bullet+}$ 508.2092; found 508.2077.

Purity (GC): 94% (scan mode *m*/*z* 50-650 (EI 70 eV)).

<u>Analytical data of trichloromethylcarbinol derivate **56b**</u>:

R_f: 0.33 (hexanes/$CHCl_3$ 40:60).

mp: 65 °C.

$[\alpha]_D^{23}$: + 12.5 (c = 0.06, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.27 (t, *J* = 3.3 Hz, 1H, 9'-H), 4.29 (dd, *J* = 6.7, 1.2 Hz, 1H, 1-H), 3.59 (dd, *J* = 9.6, 3.3 Hz, 1H, 1''-H), 3.27 (dd, *J* = 9.7, 7.3 Hz, 1H, 1''-H), 2.69 (dd, *J* = 6.7, 0.6 Hz, 1H, OH), 2.44 – 2.32 (m, 2H, 5a', 9b'-H), 2.25 – 2.17 (m, 2H, 7'-H, 1', 2', 5' or 8'-H), 2.16 – 2.07 (m, 1H, 1', 2', 5' or 8'-H), 2.04 – 1.97 (m, 1H, 6'-H), 1.93 – 1.84 (m, 2H, 4'-H, 2''-H), 1.83 – 1.76 (m, 2H, 1', 2', 5' or 8'-H), 1.70 – 1.57 (m, 2H, 4', 7'-H), 1.49 (m, 1H, 1', 2', 5' or 8'-H), 1.40 – 1.24 (m, 4H, 3'-H, 1', 2', 5' or 8'-H), 0.97 (d, *J* = 6.5 Hz, 3H, 2''-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.77 (s, 3H, 3a'-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

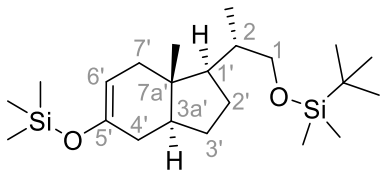
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 141.7 (C-9a'), 119.7 (C-9'), 104.8 (C-2), 82.2 (C-1), 67.8 (C-1''), 54.1 (C-3'), 49.4 (C-9b'), 41.5 (C-3a'), 40.7 (C-6'), 39.5 (C-2''), 38.6 (C-5a'), 37.8 (C-4'), 28.4 (C-1', 2', 5' or 8'), 26.1 (SiC(<u>C</u>$H_3)_3$), 25.8 (C-1', 2', 5' or 8'), 25.5 (C-1', 2', 5' or 8'), 24.1 (C-1', 2', 5' or 8'), 23.2 (C-7'), 18.8 (3a'-CH_3), 18.5 (Si<u>C</u>$(CH_3)_3$), 16.8 (2''-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR) $\tilde{\nu}$/cm^{-1} = 2928, 2856, 2359, 1707, 1462, 1385, 1361, 1251, 1083, 1005, 938, 910, 833, 807, 773, 732, 669.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{43}Cl_3O_2Si$ $[M]^{\bullet+}$ 508.2092; found 508.2077.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

tert-Butyldimethyl((*S*)-2-((1*R*,3a*S*,7a*S*)-7a-methyl-5-((trimethylsilyl)oxy)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)propoxy)silane (64^{e})



64^{e}

$C_{22}H_{44}O_2Si_2$

M = 396.76 g/mol

In an oven dried flask ketone **28^{c}** (150 mg, 0.462 mmol, 1.00 eq) was dissolved in dry THF (3.00 mL) and TEA (0.155 mL, 1.10 mmol, 1.50 eq) and TMSCl (90.0 mg, 0.830 mmol, 3.8 eq) were added dropwise at 0°C. The reaction mixture was stirred for 4.5 d at 70 °C. The reaction mixture was cooled to rt and the reaction was diluted with hexanes (10.0 mL). The organic layer was washed with sat. aq. $NaHCO_3$ solution (3 x 10.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and silyl enol ether **64^{e}** was obtained as a colourless oil (78.8 mg, 0.199 mmol, 43%).

R_f = 0.95 (hexanes/EtOAc 95:5).

$[\alpha]_D^{23}$: + 64.6 (c = 0.11, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.77 (d, *J* = 6.0 Hz, 1H, 6'-H), 3.59 (d, *J* = 13.0 Hz, 1H, 1-H), 3.26 (dd, *J* = 9.6, 7.4 Hz, 1H, 1-H), 2.12 (dd, *J* = 16.2, 5.7 Hz, 1H, 7'-H), 2.03 – 1.98 (m, 1H, 4'-H), 1.98 – 1.93 (m, 1H, 7'-H), 1.88 – 1.82 (m, 1H, 2'-H), 1.82 – 1.76 (m, 1H, 4'-H), 1.75 – 1.67 (m, 1H, 3a'-H), 1.67 – 1.62 (m, 1H, 3'-H), 1.56 – 1.49 (m, 1H, 2-H), 1.40 – 1.31 (m, 1H, 2'-H), 1.28 – 1.21 (m, 1H, 1'-H), 1.21 – 1.15 (m, 1H, 3'-H), 0.99 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.68 (s, 3H, 7a'-CH_3), 0.17 (s, 9H, $Si(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$).

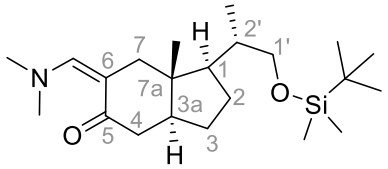
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 149.8 (C-5'), 104.2 (C-6'), 68.0 (C-1), 52.2 (C-1'), 46.3 (C-3a'), 41.3 (C-7a'), 39.1 (C-7'), 33.1 (C-4'), 28.5 (C-2'), 26.6 (C-3'), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 16.7 (2-CH_3), 11.2 (7a'-CH_3), 0.5 ($Si(\underline{C}H_3)_3$), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3747, 2956, 2930, 2857, 1661, 1471, 1250, 1188, 1089, 1031, 1003, 968, 898, 835, 773, 665.

HRMS (EI): *m*/*z* calculated for $C_{22}H_{44}O_2Si_2$ $[M]^{\cdot+}$ 396.2874; found 396.2891.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

(1*R*,3a*S*,7a*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-6-((dimethylamino)methylene)-7a-methyloctahydro-5*H*-inden-5-one (71^{e})



71^{e}

$C_{22}H_{41}NO_2Si$

M = 379.66 g/mol

In an oven dried flask ketone **28^{c}** (100 mg, 0.308 mmol, 1.00 eq) was dissolved in dry DMF (3.00 mL). BREDERECK'S reagent (0.318 mL, 1.54 mmol, 5.00 eq) was added dropwise and the reaction was heated to 100 °C for 2 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in DCM (10.0 mL), washed with water (3 x 5.00 mL) and the aq. layer was extracted with DCM (3 x 10.0 mL). All combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (EtOAc/ MeOH/TEA 94:5:1) gave enaminone **71^{e}** as a colourless oil (107 mg, 0.283 mmol, 46%).

R_f = 0.37 (EtOAc/ MeOH/TEA 94:5:1).

$[\alpha]_D^{23}$: - 119.4 (c = 0.12, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.51 (s, 1H, 6-CH), 3.61 (dd, *J* = 9.6, 3.4 Hz, 1H, 1'-H), 3.30 (dd, *J* = 9.7, 7.3 Hz, 1H, 1'-H), 3.07 (s, 6H, $N(CH_3)_2$), 2.96 (d, *J* = 13.9 Hz, 1H, 7-H), 2.42 – 2.39 (m, 1H, 7-H), 2.38 (d, *J* = 5.5 Hz, 1H, 4-H), 2.09 (dd, *J* = 18.2, 13.3 Hz, 1H, 4-H), 1.87 (dddd, *J* = 9.7, 6.8, 3.2, 1.7 Hz, 1H, 2-H), 1.81 (tdd, *J* = 13.2, 7.0, 3.9 Hz, 1H, 3a-H), 1.73 – 1.67 (m, 1H, 3-H), 1.58 (ddp, *J* = 9.7, 6.4, 3.3 Hz, 1H, 2'-H), 1.44 – 1.36 (m, 1H, 1-H), 1.36 – 1.31 (m, 1H, 2-H), 1.22 – 1.14 (m, 1H, 3-H), 1.03 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.71 (d, *J* = 0.7 Hz, 3H, 7a-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 198.1 (C-5), 152.8 (6-CH), 102.9 (C-6), 67.9 (C-1'), 52.9 (C-1), 45.1 (C-3a), 43.66 ($N(CH_3)_2$), 41.6 (C-7a), 40.8 (C-7), 40.3 (C-4), 38.9 (C-2'), 28.3 (C-2), 27.2 (C-3), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 16.8 (2'-CH_3), 11.5 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.3 ($Si(CH_3)_2$).

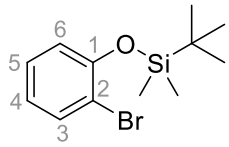
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953, 2928, 2856, 1644, 1544, 1470, 1424, 1372, 1322, 1270, 1249, 1212, 1125, 1084, 1030, 970, 939, 917, 834, 773, 730, 664, 614, 598.

HRMS (EI): *m*/*z* calculated for $C_{22}H_{41}NO_2Si$ $[M]^{\bullet+}$ 379.2901; found 379.2900.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

6.2.4. Procedures and data for seco-steroids with bridging at C-4 (chapter 3.3.1.)

(2-Bromophenoxy)(*tert*-butyl)dimethylsilane (75^{d})



75^{d}

$C_{12}H_{19}BrOSI$

M = 286.04 g/mol

Aryl bromide **75^{d}** was synthesized according to **GP2**, using 2-bromophenol (508 mg, 2.92 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (601 mg, 2.09 mmol, 72%).

R_f = 0.80 (hexanes/EtOAc 95:5).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.51 (dd, *J* = 7.9, 1.7 Hz, 1H, 3-H), 7.16 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H, 5-H), 6.91 – 6.78 (m, 2H, 4-H, 6-H), 1.05 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.25 (s, 6H, Si(C$\underline{H}_3$)$_2$).

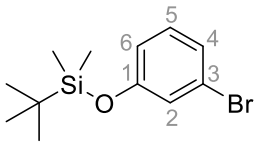
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 152.6 (C-1), 133.4 (C-3), 128.2 (C-5), 122.4 (C-4), 120.3 (C-6), 115.4 (C-2), 25.8 (SiC($\underline{C}$H$_3$)$_3$), 18.4 (Si$\underline{C}$(CH$_3$)$_3$), -4.2 (Si($\underline{C}$H$_3$)$_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2930, 2886, 2859, 1583, 1475, 1440, 1391, 1362, 1282, 1252, 1156, 1121, 1047, 1030, 912, 837, 823, 780, 749, 708, 670.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{19}BrOSi$ $[M]^{\cdot+}$ 286.0383; found 286.0379.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(3-Bromophenoxy)(*tert*-butyl)dimethylsilane (76)



76

$C_{12}H_{19}BrOSi$

M = 286.04 g/mol

Aryl bromide **76** was synthesized according to **GP2** using 3-bromophenol (307 µL, 2.89 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (711 mg, 2.48 mmol, 85%).

R_f = 0.70 (hexanes/toluene 95:5).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.13 – 7.04 (m, 2H, 2-H, 5-H)), 7.01 (ddd, *J* = 2.3, 1.4, 0.8 Hz, 1H, 6-H), 6.81 – 6.73 (m, 1H, 4-H), 0.98 (s, 9H, SiC(C$\underline{H}_3)_3$), 0.20 (s, 6H, Si(C$\underline{H}_3)_2$).

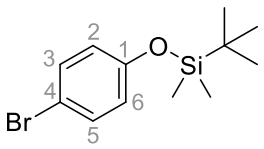
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 156.7 (C-1), 130.6 (C-5), 124.6 (C-2), 123.7 (C-6), 122.6 (C-3), 118.9 (C-4), 25.8 (SiC($\underline{C}H_3)_3$), 18.3 (Si$\underline{C}(CH_3)_3$), -4.3 (Si($\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2956, 2930, 2886, 2859, 1588, 1567, 1472, 1422, 1391, 1362, 1294, 1268, 1253, 1238, 1158, 108, 1062, 1007, 99, 925, 882, 862, 837, 825, 810, 773, 738, 681.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{19}BrOSi$ $[M]^{\bullet+}$ 286.0383; found 286.0379.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(4-Bromophenoxy)(*tert*-butyl)dimethylsilane (78^{d})



78^{d}

$C_{12}H_{19}BrOSi$

M = 286.04 g/mol

Aryl bromide **78^{d}** was synthesized according to **GP2**, using 4-bromophenol (499 mg, 2.88 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (647 mg, 2.25 mmol, 78%).

R_f = 0.83 (hexanes/EtOAc 95:5).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.36 – 7.28 (m, 2H, 3-H, 5-H), 6.76 – 6.67 (m, 2H, 2-H, 6-H), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 6H, $Si(CH_3)_2$).

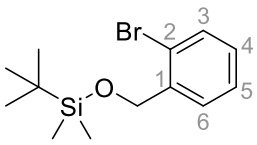
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 154.9 (C-1), 132.3 (C-3, C-5), 121.9 (C-2, C-6), 113.6 (C-4), 25.6 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -4.5 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2956, 2930, 2887, 2360, 2341, 1876, 1586, 1485, 1472, 1464, 1391, 1362, 1252, 1164, 1094, 1070, 1007, 906, 838, 825, 803, 779, 725, 700, 670.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{19}BrOSi$ $[M]^{\bullet+}$ 286.0383; found 286.0382.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

((2-Bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (79^{d})



79^{d}

$C_{13}H_{21}BrOSi$

M = 300.05 g/mol

Aryl bromide **79^{d}** was synthesized according to **GP2**, using 2-bromobenzyl alcohol (495 mg, 2.65 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (620 mg, 2.06 mmol, 78%).

R_f = 0.55 (hexanes/toluene 95:5).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.56 (ddt, J = 7.8, 1.9, 1.0 Hz, 1H, 3-H or 6-H), 7.51 (dd, J = 7.9, 1.2 Hz, 1H, 3-H or 6-H), 7.34 (td, J = 7.5, 1.2 Hz, 1H, 5-H), 7.13 (dddt, J = 8.0, 7.5, 1.6, 0.7 Hz, 1H, 4-H), 4.75 (d, J = 1.0 Hz, 2H, 1-CH_2), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$).

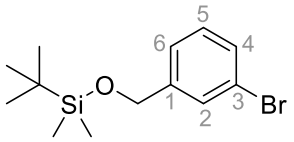
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 141.0 (C-1), 132.6 (C-3 or C-6), 128.8 (C-4), 128.3 (C-3 or C-6), 127.9 (C-5), 121.6 (C-2), 65.2 (1-CH_2), 26.3 ($SiC(\underline{C}H_3)_3$), 18.9 ($Si\underline{C}(CH_3)_3$), -5.1 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3070, 2955, 2929, 2885, 2857, 2360, 2341, 1594, 1570, 1471, 1464, 1443, 1406, 1390, 1254, 1203, 1119, 1095, 1043, 1025, 1006, 939, 834, 815, 775, 745, 673.

HRMS (EI): m/z calculated for $C_{12}H_{18}BrOSi$ $[M]^{\bullet+}$ 285.0305; found 285.0319.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method f).

((3-Bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (80^{d})



80^{d}

$C_{13}H_{21}BrOSi$

M = 300.05 g/mol

Aryl bromide **80^{d}** was synthesized according to **GP2**, using 3-bromobenzyl alcohol (504 mg, 2.69 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (628 mg, 2.09 mmol, 78%).

R_f = 0.44 (hexanes/toluene 95:5).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.49 (ddt, J = 2.2, 1.4, 0.7 Hz, 1H, 2-H), 7.38 (dddd, J = 7.7, 2.7, 1.3, 0.6 Hz, 1H, 4-H), 7.26 (dtt, J = 7.7, 1.5, 0.8 Hz, 1H, 6-H), 7.21 (t, J = 7.7 Hz, 1H, 5-H), 4.71 (q, J = 0.8 Hz, 2H, 1-CH_2), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 6H, $Si(CH_3)_2$).

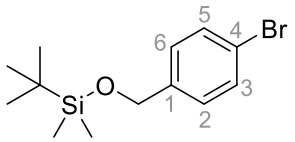
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 144.7 (C-1), 130.5 (C-4 or C-5), 130.4 (C-4 or C-5), 129.6 (C-2), 125.2 (C-6), 122.8 (C-3), 64.7 (1-CH_2), 26.2 ($SiC(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$, -5.1 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954, 2929, 2885, 2857, 2361, 2342, 1599, 1572, 1472, 1462, 1428, 1404, 1390, 1367, 1254, 1198, 1194, 1078, 1067, 1006, 939, 833, 814, 773, 630, 666.

HRMS (EI): m/z calculated for $C_{13}H_{21}BrOSi$ $[M]^{\bullet+}$ 300.0540; found 300.0383.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm) (method f).

((4-Bromobenzyl)oxy)(*tert*-butyl)dimethylsilane (81^{d})



81^{d}

$C_{13}H_{21}BrOSi$

M = 300.05 g/mol

Aryl bromide **81^{d}** was synthesized according to **GP2**, using 4-bromobenzyl alcohol (514 mg, 2.75 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as colourless oil (578 mg, 1.92 mmol, 70%).

R_f = 0.38 (hexanes/toluene 95:5).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.55 – 7.38 (m, 2H, 3-H, 5-H), 7.29 – 7.15 (m, 2H, 2-H, 6-H), 4.68 (d, J = 0.9 Hz, 2H, 1-CH_2), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$).

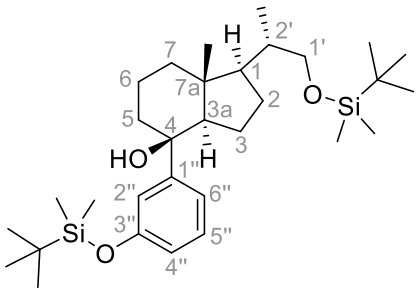
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 141.3 (C-1), 131.7 (C-3, C-5), 128.4 (C-2, C-6), 120.9 (C-4), 64.8 (1-CH_2), 26.2 ($SiC(\underline{C}H_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$), -5.1 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954, 2929, 2885, 2857, 2360, 2342, 1895, 1594, 1486, 1472, 1462, 1406, 1390, 1370, 1296, 1255 1203, 1114, 1084, 1070, 1011, 938, 835, 814, 796, 774, 668.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{20}BrOSi$ $[M]^{\cdot+}$ 299.0461; found 299.0461.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(1*R*,3a*R*,4*S*,7a*R*)-4-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (82)



82

$C_{31}H_{56}O_3Si_2$

M = 532.96 g/mol

Alcohol **82** was synthesised according to **GP6** using silyl ether **76** (180 mg, 0.627 mmol, 1.10 eq) and ketone **26** (184 mg, 0.568 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (195 mg, 0.366 mmol, 64%).

R_f = 0.48 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 48.8 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.17 (t, *J* = 7.9 Hz, 1H, 5''-H), 7.00 (ddd, *J* = 7.8, 1.9, 1.0 Hz, 1H, 6''-H), 6.94 (t, *J* = 2.1 Hz, 1H, 2''-H), 6.68 (ddd, *J* = 8.0, 2.4, 1.0 Hz, 1H, 4''-H), 3.56 (dd, *J* = 9.6, 3.4 Hz, 1H, 1'-H), 3.27 (dd, *J* = 9.6, 7.2 Hz, 1H, 1'-H), 2.11 – 2.04 (m, 1H, 2, 3, 5, 6 or 7-H), 2.02 – 1.92 (m, 1H, 2, 3, 5, 6-H), 1.76 – 1.65 (m, 4H, 3a-H, 2, 3, 5, 6 or 7-H), 1.63 – 1.51 (m, 2H, 2'-H, 2, 3, 5, 6-H), 1.47 (s, 1H, OH), 1.35 – 1.18 (m, 4H, 2, 3, 5, 6 or 7-H), 1.04 (s, 3H, 7a-CH_3), 1.01 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$).

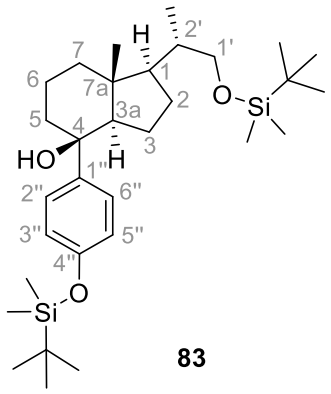
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.7 (C-3''), 150.8 (C-1''), 129.0 (C-5''), 117.9 (C-4'') 117.7 (C-6''), 116.8 (C-2''), 76.3 (C-4), 67.8 (C-1'), 56.3 (C-3a), 53.5 (C-1), 43.1 (C-7a), 40.9 (C-2, 3, 5, 6 or 7), 40.3 (C-2, 3, 5, 6 or 7), 38.7 (C-2'), 26.3 (C-2, 3, 5, 6 or 7), 26.1 ($SiC(\underline{C}H_3)_3$), 25.9 ($SiC(\underline{C}H_3)_3$), 20.4 (C-2, 3, 5, 6 or 7), 19.6 (C-2, 3, 5, 6 or 7), 18.5 ($Si\underline{C}(CH_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), 13.5 (7a-CH_3), -4.2 ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2951, 2928, 2857, 2357, 1600, 1583, 1482, 1471, 1462, 1427, 1388, 1361, 1272, 1251, 1184, 1125, 1089, 1036, 1004, 986, 941, 918, 830, 814, 774, 731, 698, 667.

HRMS (EI): *m*/*z* calculated for $C_{31}H_{56}O_3Si_2$ $[M]^{\bullet+}$ 532.3768; found 532.3771.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

(1*R*,3a*R*,4*S*,7a*R*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (83)



83

$C_{31}H_{56}O_3Si_2$

M = 532.96 g/mol

Alcohol **83** was synthesised according to **GP6** using silylether **78[d]** (159 mg, 0.553 mmol, 1.10 eq) and ketone **26** (164 mg, 0.505 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white solid (239 mg, 0.448 mmol, 89%).

R_f = 0.40 (hexanes/EtOAc 9:1).

mp: 72 °C.

$[\alpha]_D^{23}$: + 35.4 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.30 – 7.25 (m, 2H, 2'', 6''-H), 6.80 – 6.74 (m, 2H, 3'', 5''-H), 3.57 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.28 (dd, *J* = 9.6, 7.1 Hz, 1H, 1'-H), 2.05 (dt, *J* = 12.6, 3.3 Hz, 1H, 6-H), 1.94 (tt, *J* = 13.3, 4.3 Hz, 1H, 2 or 3-H), 1.78 – 1.63 (m, 4H, 3a, 5, 7-H), 1.61 – 1.53 (m, 2H, 2'-H, 2 or 3-H), 1.50 (s, 1H, OH), 1.34 – 1.17 (m, 5H, 1, 6, 7-H, 2 or 3-H), 1.03 (s, 3H, 7a-CH_3), 1.01 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.98 (s, 9H, $Si(CH_3)_3$), 0.89 (s, 9H, $Si(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$), 0.02 (s, 6H, $Si(CH_3)_2$).

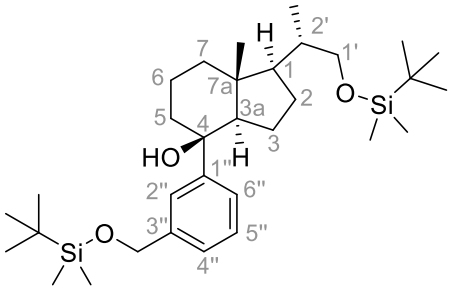
^{13}C NMR (126 MHz, methylene chloride-d_2) δ/ppm = 154.5 (C-4''), 142.6 (C-1''), 126.2 (C-2'', C-6''), 119.8 (C-3'', C-5''), 76.4 (C-4), 68.2 (C-1'), 56.8 (C-3a), 53.9 (C-7a), 43.6 (C-5), 41.5 (C-6), 40.7 (C-2'), 39.2 (C-7), 26.7 ($SiC(\underline{C}H_3)_3$), 26.3 ($SiC(\underline{C}H_3)_3$), 26.0 (C-2 or C-3), 20.9 (C-2 or C-3), 20.1 ($Si\underline{C}(CH_3)_3$), 18.6 ($Si\underline{C}(CH_3)_3$), 17.1 (2'-CH_3), 13.7 (7a-CH_3), -4.2 ($Si(CH_3)_2$), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3579, 2928, 2886, 2856, 2359, 1607, 1505, 1471, 1445, 1387, 1361, 1252, 1215, 1175, 1144, 1080, 1025, 1004, 986, 970, 916, 833, 811, 772, 713, 666.

HRMS (EI): *m*/*z* calculated for $C_{31}H_{56}O_3Si_2$ $[M]^{\cdot+}$ 532.3763; found 532.3763.

Purity (HPLC): > 95% (λ = 210 nm) (method f).

(1*R*,3a*R*,4*S*,7a*R*)-4-(3-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (84)



84

$C_{32}H_{58}O_3Si_2$

M = 546.98 g/mol

Alcohol **84** was synthesised according to **GP6** using silylether **80[d]** (190 mg, 0.631 mmol, 1.10 eq) and ketone **26** (186 mg, 0.573 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white, oily solid (253 mg, 0.463 mmol, 81%).

R_f = 0.50 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 17.9 (c = 0.05, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.39 (t, *J* = 1.7 Hz, 1H, 2''-H), 7.33 (dt, *J* = 7.9, 1.6 Hz, 1H, 6''-H), 7.28 (t, *J* = 7.6 Hz, 1H, 5''-H), 7.17 (dt, *J* = 7.5, 1.5 Hz, 1H, 4''-H), 4.75 (s, 2H, 3''-CH_2), 3.56 (dd, *J* = 9.6, 3.4 Hz, 1H, 1'-H), 3.28 (dd, *J* = 9.6, 7.0 Hz, 1H, 1'-H), 2.08 (dt, *J* = 12.8, 3.4 Hz, 1H, 2, 3, 5 or 6-H), 2.04 – 1.93 (m, 1H, OH), 1.74 (dq, *J* = 9.1, 4.8, 3.8 Hz, 3H, 3a, 7-H), 1.71 – 1.67 (m, 1H, 2, 3, 5 or 6-H), 1.63 – 1.50 (m, 3H, 2'-H, 2, 3, 5 or 6-H), 1.34 – 1.17 (m, 5H, 1-H, 2, 3, 5 or 6-H), 1.05 (s, 3H, 7a-CH_3), 1.02 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 6H, $Si(CH_3)_2$).

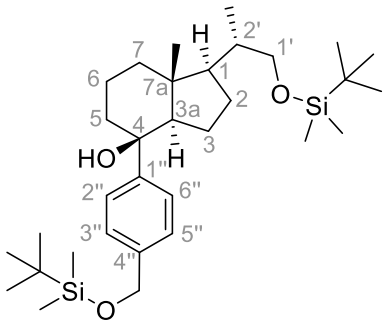
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 149.0 (C-1''), 141.3 (C-3''), 128.1 (C-6''), 124.2 (C-4''), 123.3 (C-5''), 122.5 (C-2''), 76.5 (C-4), 67.8 (C-1'), 65.4 (3''-CH_2), 56.2 (C-3a), 53.5 (C-1), 43.1 (C-7a), 41.1 (C-7), 40.3 (C-2, 3, 5 or 6), 38.7 (C-2'), 26.3 (C-2, 3, 5 or 6), 26.1 ($SiC(\underline{C}H_3)_3$), 26.1 ($SiC(\underline{C}H_3)_3$), 20.4 (C-2, 3, 5 or 6), 19.6 (C-2, 3, 5 or 6), 18.6 ($Si\underline{C}(CH_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 16.9 (2'-CH_3), 13.5 (7a-CH_3), -5.0 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2950, 2928, 2856, 2359, 2342, 1606, 1471, 1385, 1375, 1360, 1333, 1281, 1251, 1180, 1144, 1069, 1033, 1003, 985, 938, 891, 833, 814, 769, 701, 667.

HRMS (EI): *m*/*z* calculated for $C_{32}H_{59}O_3Si_2$ $[M]^{\cdot+}$ 547.3997; found 547.3988.

Purity (HPLC): > 95% (λ = 210 nm) (method e).

(1*R*,3a*R*,4*S*,7a*R*)-4-(4-(((*tert*-Butyldimethylsilyl)oxy)methyl)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (85)



85

$C_{32}H_{58}O_3Si_2$

M = 546.98 g/mol

Alcohol **85** was synthesised according to **GP6** using silylether **81[d]** (180 mg, 0.597 mmol, 1.10 eq) and ketone **26** (177 mg, 0.545 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white solid (206 mg, 0.377 mmol, 69%).

R_f = 0.45 (hexanes/EtOAc 9:1).

mp: 88 °C.

$[\alpha]_D^{23}$: + 17.5 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.43 – 7.37 (m, 2H, 2'', 6''-H), 7.29 – 7.24 (m, 2H, 3'', 5''-H), 4.70 (d, *J* = 0.8 Hz, 2H, 4''-CH_2), 3.60 – 3.54 (m, 1H, 1'-H), 3.32 – 3.25 (m, 1H, 1'-H), 2.07 (dt, *J* = 12.7, 3.3 Hz, 1H, 7-H), 1.97 (ddt, *J* = 17.5, 9.1, 4.4 Hz, 1H, 6-H), 1.80 – 1.66 (m, 4H, 3a, 5, 2-H), 1.62 – 1.48 (m, 3H, 6, 2'-H, OH), 1.37 – 1.19 (m, 5H, 1, 2, 3, 7-H), 1.06 – 1.04 (m, 3H, 7a-CH_3), 1.02 (d, *J* = 6.6 Hz, 3H, 2'-CH_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$), 0.03 (s, 6H, $Si(CH_3)_2$).

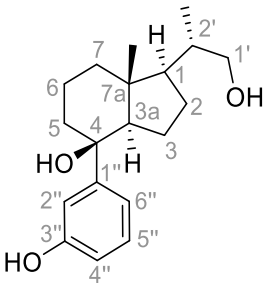
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 148.5 (C-1''), 139.9 (C-4''), 126.5 (C-3'', C-5''), 124.9 (C-2'', C-6''), 76.6 (C-4), 68.2 (C-1'), 65.3 (4''-CH_2), 56.6 (C-3a), 53.9 (C-1), 43.5 (C-7a), 41.6 (C-5), 40.7 (C-7), 39.2 (C-2'), 26.8 (C-2), 26.3 ($SiC(\underline{C}H_3)_3$), 20.8 (C-3), 20.0 (C-6), 18.8 ($Si\underline{C}(CH_3)_3$), 17.2 ($Si\underline{C}(CH_3)_3$), 13.7 (2'-CH_3), -5.0 (7a-CH_3), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3573, 2948, 2928, 2893, 2855, 2360, 1508, 1470, 1377, 1315, 1252, 1219, 1145, 1116, 1076, 1020, 1004, 985, 971, 938, 859, 832, 815, 802, 772, 751, 721, 666.

HRMS (EI): *m*/*z* calculated for $C_{32}H_{57}O_3Si_2$ $[M]^{\cdot+}$ 545.3840; found 545.3840.

Purity (HPLC): > 95% (λ = 210 nm) (method a).

(1*R*,3a*R*,4*S*,7a*R*)-4-(3-Hydroxyphenyl)-1-((*S*)-1-hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (86)



86

$C_{19}H_{28}O_3$

M = 304.43 g/mol

Triol **86** was synthesised according to **GP9**, using alcohol **82** (46.0 mg, 0.0863 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 6:4) and isolated as white solid (25.5 mg, 0.0838 mmol, 97%).

R_f = 0.21 (hexanes/EtOAc 6:4).

mp: 203 °C.

$[\alpha]_D^{23}$: + 22.6 (c = 0.06, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 9.09 (s, 1H, 3''-OH), 7.03 (t, *J* = 7.8 Hz, 1H, 5''-H), 6.88 – 6.84 (m, 1H, 2''-H), 6.81 (dt, *J* = 7.8, 1.3 Hz, 1H, 6''-H), 6.53 (ddd, *J* = 7.9, 2.4, 0.9 Hz, 1H 4''-H), 4.35 (s, 1H, 4-OH), 4.20 (dd, *J* = 5.7, 4.8 Hz, 1H, 1'-OH), 3.37 (dq, *J* = 10.3, 4.0, 3.6 Hz, 1H, 1'-H), 3.10 – 2.99 (m, 1H, 1'-H), 1.94 (d, *J* = 13.0 Hz, 2H, 2, 3, 5, 6 or 7-H), 1.67 – 1.19 (m, 9H, 3a, 2'-H, 2, 3, 5, 6 or 7-H), 1.18 – 1.05 (m, 2H, 1-H, 2, 3, 5, 6 or 7-H), 0.98 (s, 3H, 7a-CH_3), 0.95 (d, *J* = 6.5 Hz, 3H, 2'-CH_3).

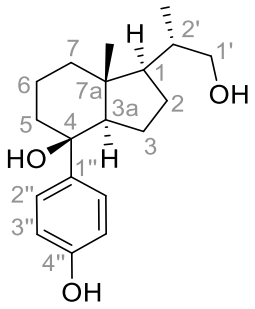
^{13}C NMR (101 MHz, DMSO-d_6) δ/ppm = 156.8 (C-3''), 151.8 (C-1''), 128.4 (C-5''), 115.5 (C-6''), 112.4 (C-4''), 112.2 (C-2''), 74.4 (C-4), 65.6 (C-1'), 56.1 (C-3a), 53.0 (C-1), 42.4 (C-7a), 40.0 (C-2, 3, 5, 6 or 7), 39.9 (C-2, 3, 5, 6 or 7), 38.2 (C-2'), 25.9 (C-2, 3, 5, 6 or 7), 20.1 (C-2, 3, 5, 6 or 7), 19.2 (C-2, 3, 5, 6 or 7), 16.8 (2'-CH_3), 13.4 (7a-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3539, 3473, 3140, 2943, 2928, 2885, 2859, 2359, 1591, 1445, 1395, 1374, 1337, 1285, 1264, 1226, 1190, 1153, 1108, 1087, 1071, 1032, 1022, 1002, 981, 941, 886, 859, 846, 786, 763, 715, 699, 661.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{28}O_3$ $[M]^{\cdot+}$ 304.2033; found 304.2033.

Purity (HPLC): > 95% (λ = 210 nm) (method a).

(1*R*,3a*R*,4*S*,7a*R*)-4-(4-Hydroxyphenyl)-1-((*S*)-1-hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (87)



87

$C_{19}H_{28}O_3$

M = 304.43 g/mol

Triol **87** was synthesised according to **GP9**, using alcohol **83** (42.0 mg, 0.0788 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 6:4) and isolated as white solid (24.0 mg, 0.0788 mmol, quantitative).

R_f = 0.22 (hexanes/EtOAc 6:4).

mp: 212 °C.

$[\alpha]_D^{23}$: + 103.5 (c = 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 9.06 (s, 1H, 4''-OH), 7.21 – 7.16 (m, 2H, 2''-H), 6.67 – 6.61 (m, 2H, 3''-H), 4.25 (s, 1H, 4-OH), 4.20 (t, *J* = 5.2 Hz, 1H, 1'-OH), 3.37 (dq, *J* = 10.3, 4.1, 3.6 Hz, 1H, 1'-H), 3.04 (dt, *J* = 10.3, 6.5 Hz, 1H, 1'-H), 1.96 – 1.83 (m, 2H, 2, 3, 5, 6 or 7-H), 1.67 – 1.19 (m, 9H, 3a, 2'-H, 2, 3, 5, 6 or 7-H), 1.16 – 1.06 (m, 2H, 1-H, 2, 3, 5, 6 or 7-H), 0.97 (s, 3H, 7a-CH_3), 0.94 (d, *J* = 6.5 Hz, 3H, 2'-CH_3).

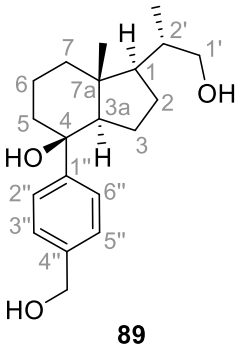
^{13}C NMR (101 MHz, DMSO-d_6) δ/ppm = 155.1 (C-4''), 140.5 (C-1''), 125.8 (C-2''), 114.2 (C-3''), 74.1 (C-4), 65.6 (C-1'), 56.4 (C-3a), 53.1 (C-1), 42.5 (C-7a), 40.3 (C-2, 3, 5, 6 or 7), 40.1 (C-2, 3, 5, 6 or 7), 38.2 (C-2'), 25.9 (C-2, 3, 5, 6 or 7), 20.2 (C-2, 3, 5, 6 or 7), 19.3 (C-2, 3, 5, 6 or 7), 16.8 (2'-CH_3), 13.4 (7a-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3399, 3124, 3021, 2956, 2934, 2891, 2360, 1616, 1596, 1517, 1454, 1377, 1336, 1300, 1249, 1211, 1178, 1161, 1081, 1038, 1020, 1001, 962, 933, 856, 826, 789, 771.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{28}O_3$ $[M]^{\cdot+}$ 304.2033; found 304.2026.

Purity (HPLC): > 95% (λ = 210 nm) (method a).

(1*R*,3a*R*,4*S*,7a*R*)-4-(4-(Hydroxymethyl)phenyl)-1-((*S*)-1-hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (89)



89

$C_{20}H_{30}O_3$

M = 318.46 g/mol

Triol **89** was synthesised according to **GP9**, using alcohol **85** (50 mg, 0.0914 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 4:6) and isolated as white solid (13.6 mg, 0.0427 mmol, 47%).

R_f = 0.24 (hexanes/EtOAc 4:6).

mp: 167 °C.

$[\alpha]_D^{23}$: + 22.7 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm = 7.38 – 7.34 (m, 2H, 2'', 6''-H), 7.22 – 7.18 (m, 2H, 3'', 5''-H), 5.05 (t, *J* = 5.7 Hz, 1H, 4''-CH_2-O<u>H</u>), 4.46 – 4.40 (m, 3H, 4''-CH_2, 4-OH), 4.21 (t, *J* = 5.3 Hz, 1H, 1'-OH), 3.37 (dt, *J* = 8.7, 3.9 Hz, 1H, 1'-H), 3.04 (dt, *J* = 10.3, 6.5 Hz, 1H, 1'-H), 1.93 (t, *J* = 13.6 Hz, 2H, 7-H, 2, 3, 5 or 6-H), 1.71 – 1.54 (m, 4H, 2, 3, 5 or 6-H), 1.50 – 1.22 (m, 5H, 7-H, 2'-H, 2, 3, 5 or 6-H), 1.18 – 1.07 (m, 2H, 1-H, 2, 3, 5 or 6-H), 0.99 (s, 3H, 7a-CH_3), 0.95 (d, *J* = 6.5 Hz, 3H, 2'-CH_3).

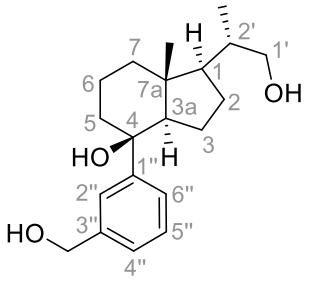
^{13}C NMR (101 MHz, DMSO-d_6) δ/ppm = 148.5 (C-1''), 139.6 (C-4''), 125.8 (C-3'', 5''), 124.5 (C-2'', 6''), 74.5 (C-4), 65.5 (C-1'), 62.8 (4''-CH_2), 56.1 (C-3a), 52.9 (C-1), 42.5 (C-7a), 40.2 (C-2, 3, 5 or 6), 39.9 (C-7), 38.2 (C-2'), 25.9 (C-2, 3, 5 or 6), 20.1 (C-2, 3, 5 or 6), 19.2 (C-2, 3, 5 or 6), 16.8 (2'-CH_3), 13.4 (7a-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3607, 3453, 3253, 2868, 2933, 2359, 1511, 1455, 1403, 1375, 1300, 1261, 1235, 1215, 1187, 1159, 1115, 1083, 1049, 1017, 999, 986, 959, 930, 902, 856, 829, 793, 772.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_3$ $[M]^{\cdot+}$ 318.2189; found 318.2185.

Purity (HPLC): > 95% (λ = 210 nm) (method a).

(1*R*,3a*R*,4*S*,7a*R*)-4-(3-(Hydroxymethyl)phenyl)-1-((*S*)-1-hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (88)



88

$C_{20}H_{30}O_3$

M = 318.46 g/mol

Triol **88** was synthesised according to **GP9**, using alcohol **84** (168 mg, 0.307 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as white solid (40.0 mg, 0.126 mmol, 41%).

R_f = 0.23 (hexanes/EtOAc 50:50).

mp: 58 °C.

$[\alpha]_D^{23}$: + 3.0 (c = 0.17, $CHCl_3$).

^{1}H NMR (400 MHz, methanol-d_4) δ/ppm = 7.43 (d, *J* = 2.0 Hz, 1H, 6''-H), 7.35 (dt, *J* = 7.8, 1.5 Hz, 1H, 2''-H), 7.27 (t, *J* = 7.6 Hz, 1H, 5''-H), 7.17 (dt, *J* = 7.6, 1.4 Hz, 1H, 4''-H), 4.60 (s, 2H, 3''-CH_2), 3.56 (dd, *J* = 10.6, 3.2 Hz, 1H, 1'-H), 3.25 (dd, *J* = 10.6, 7.1 Hz, 1H, 1'-H), 2.13 – 1.98 (m, 2H, 5, 6-H), 1.84 – 1.66 (m, 4H, 7-H, 2 or 3-H, OH), 1.61 – 1.48 (m, 2H, 5 or 6-H, 2'-H), 1.43 – 1.21 (m, 6H, 1, 2, 3-H, 5 or 6-H, 2 x OH), 1.09 (s, 3H, 7a-CH_3), 1.06 (d, *J* = 6.6 Hz, 3H, 2'-CH_3).

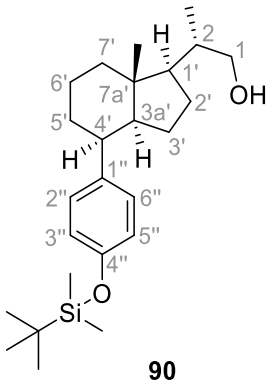
^{13}C NMR (101 MHz, methanol-d_4) δ/ppm = 150.9 (C-1''), 142.2 (C-3''), 128.9 (C-5''), 125.8 (C-4''), 124.9 (C-2''), 124.5 (C-6''), 77.2 (C-4), 67.8 (C-1'), 65.6 (3''-CH_2), 57.5 (C-3a), 54.7 (C-1), 44.2 (C-7a), 42.0 (C-7), 41.7 (C-5 or 6), 39.8 (C-2'), 27.4 (C-2 or 3), 21.3 (C-2 or 3), 20.6 (C-5 or 6), 17.2 (2'-CH_3), 13.9 (7a-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2928, 1603, 1507, 1471, 1255, 1083, 913, 833, 812, 773.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_3$ $[M]^{\cdot+}$ 318.2189; found 318.2184.

Purity (HPLC): > 95% (λ = 210 nm) (method a).

(*S*)-2-((1*R*,3a*S*,4*S*,7a*S*)-4-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (90)



90

$C_{25}H_{42}O_2Si$

M = 402.69 g/mol

Alcohol **90** was synthesised according to **GP8** using alcohol **83** (102 mg, 0.191 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white, oily solid (22.0 mg, 0.0546 mmol, 29%).

R_f = 0.20 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 16.7 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.17 – 7.11 (m, 2H, 2'', 6''-H), 6.78 – 6.64 (m, 2H, 3'', 5''-H), 3.60 (dd, *J* = 10.5, 3.2 Hz, 1H, 1-H), 3.34 (dd, *J* = 10.5, 6.8 Hz, 1H, 1-H), 3.11 (t, *J* = 5.5 Hz, 1H, 4'-H), 2.32 – 2.21 (m, 1H, 5'-H), 2.01 (tt, *J* = 14.2, 13.0, 5.6 Hz, 2H, 6', 7'-H), 1.84 – 1.61 (m, 4H, 3a', 5', 6'-H, 2' or 3'-H), 1.56 – 1.39 (m, 1H, 2-H), 1.31 – 1.13 (m, 5H, 1', 7'-H, 2' or 3'-H), 1.00 (d, *J* = 6.5 Hz, 3H, 2-CH_3), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.38 (s, 3H, 7a'-CH_3), 0.18 (s, 3H, $Si(CH_3)_2$), 0.18 (s, 3H, $Si(CH_3)_2$).

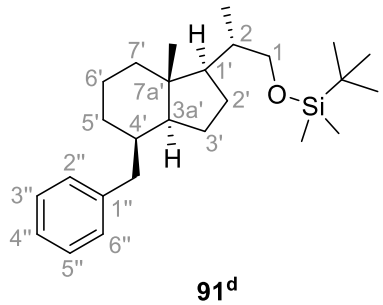
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 153.2 (C-4''), 136.8 (C-1''), 130.1 (C-2'', 6''), 119.1 (C-3'', 5''), 68.1 (C-1), 53.3 (C-1'), 51.9 (C-3a'), 42.6 (C-7a'), 41.0 (C-7'), 39.4 (C-4'), 38.6 (C-2), 29.9 (C-5'), 26.8 (C-2' or 3'), 25.9 ($SiC(\underline{C}H_3)_3$), 25.8 (C-2' or 3'), 20.6 (C-6'), 18.4 ($Si\underline{C}(CH_3)_3$), 16.9 (2-CH_3), 12.3 (7a'-CH_3), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2958, 2925, 2852, 1731, 1704, 1512, 1457, 1368, 1109, 1037, 1024, 1012, 939, 813, 785, 723.

HRMS (EI): *m*/*z* calculated for $C_{25}H_{42}O_2Si$ $[M]^{\cdot+}$ 402.2949; found 402.2951.

Purity (HPLC): n.d.

((*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-Benzyl-7a-methyloctahydro-1*H*-inden-1-yl)propoxy)(tert-butyl)dimethylsilane (91^{d})



91^{d}

$C_{26}H_{44}OSi$

M = 400.72 g/mol

Silyl ether **91^{d}** was synthesised according to **GP7**, using alkene **72** (33.0 mg, 0.102 mmol, 1.10 eq) and bromobenzene (14.6 mg, 0.0930 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/toluene 9:1) and isolated as a colourless oil (14.6 mg, 0.0364 mmol, 39%).

R_f = 0.55 (hexanes/toluene 9:1).

$[\alpha]_D^{23}$: + 37.0 (c = 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.32 – 7.05 (m, 5H, 2'', 3'', 4'', 5'', 6''-H), 3.61 (dd, *J* = 9.6, 3.3 Hz, 1H, 1-H), 3.29 (ddd, *J* = 9.6, 7.3, 0.9 Hz, 1H, 1-H), 2.83 – 2.73 (m, 1H, 4'-CH_2), 2.48 (dd, *J* = 13.4, 11.4 Hz, 1H, 4'-CH_2), 2.03 – 1.92 (m, 2H, 4', 7'-H), 1.89 – 1.79 (m, 1H, 2', 3', 5' or 6'-H), 1.76 – 1.42 (m, 7H, 2, 3a', 7'-H, 2', 3', 5' or 6'-H), 1.35 – 1.14 (m, 4H, 1'-H, 2', 3', 5' or 6'-H), 0.99 (dd, *J* = 6.6, 0.9 Hz, 3H, 2-CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.86 (s, 3H, 7a'-CH_3), 0.04 (s, 6H, $Si(CH_3)_2$).

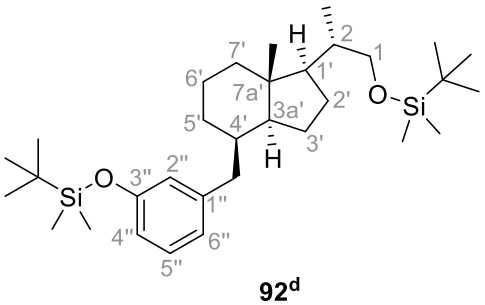
^{13}C NMR (101 MHz, methylene chloride-d_2) *δ*/ppm = 144.5 (C-1''), 129.6 (C-2'', C-6''), 128.7 (C-3'', C-5''), 125.9 (C-4''), 68.3 (C-1), 54.4 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.2 (C-4'), 39.5 (C-2), 35.1 (4'-CH_2), 29.3 (C-5'), 27.4 (C-3'), 26.3 ($SiC(\underline{C}H_3)_3$), 24.4 (C-6'), 18.8 ($Si\underline{C}(CH_3)_3$), 18.6 (C-2'), 17.2 (2-CH_3), 14.1 (7a'-CH_3), -5.1 ($Si(\underline{C}H_3)_2$), -5.2 ($Si(\underline{C}H_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2978, 2856, 1602, 1495, 1470, 1385, 1251, 1120, 1095, 1056, 1032, 1007, 961, 834, 811, 767, 738, 699, 665.

HRMS (EI): *m*/*z* calculated for $C_{28}H_{44}OSi$ $[M]^{\cdot+}$ 400.3156; found 400.3163.

Purity (GC): 84% (scan mode *m*/*z* 50-650 (EI 70 eV)).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-(3-((_tert_-butyldimethylsilyl)oxy)benzyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (92[d])



92[d]

$C_{32}H_{58}O_2Si_2$

M = 530.40 g/mol

Silylether **92[d]** was synthesised according to **GP7**, using alkene **72** (245 mg, 0.759 mmol, 1.00 eq) and aryl bromide **76** (218 mg, 0.759 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/toluene 95:5) and isolated as a colourless oil (102 mg, 0.192 mmol, 25%).

R_f = 0.22 (hexanes/toluene 95:5).

$[\alpha]_D^{23}$: + 27.1 (c = 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm 7.15 – 7.06 (m, 1H, 5''-H), 6.74 (dt, *J* = 7.7, 1.4 Hz, 1H, 6''-H), 6.66 – 6.60 (m, 2H, 2''-H, 4''-H), 3.60 (dd, *J* = 9.6, 3.3 Hz, 1H, 1-H), 3.28 (dd, *J* = 9.6, 7.3 Hz, 1H, 1-H), 2.74 (dd, *J* = 13.8, 2.7 Hz, 1H, 4'-CH_2), 2.43 (dd, *J* = 13.4, 11.3 Hz, 1H, 4'-CH_2), 2.00 – 1.89 (m, 2H, 4', 7'-H), 1.89 – 1.78 (m, 1H, 2', 3', 5' or 6'-H), 1.74 – 1.39 (m, 7H, 2, 7'-H, 2', 3', 5' or 6'-H), 1.34 – 1.10 (m, 4H, 1', 3a'-H, 2', 3', 5' or 6'-H), 1.00 – 0.97 (m, 12H, 2-CH_3, $SiC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.85 (s, 3H, 7a'-CH_3), 0.18 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$).

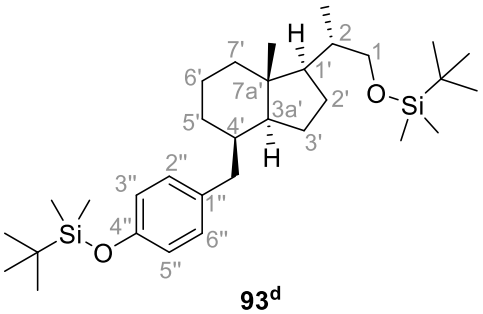
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 156.1 (C-3''), 146.1 (C-1''), 129.5 (C-5''), 122.6 (C-6''), 121.4 (C-2''), 117.6 (C-4''), 68.3 (C-1), 54.4 (C-1'), 53.0 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.1 (C-4'), 39.5 (4'-CH_2), 35.1 (C-2), 29.4 (2', 3', 5' or 6'-H), 27.4 (2', 3', 5' or 6'-H), 26.3 ($SiC(\underline{C}H_3)_3$), 26.0 ($SiC(\underline{C}H_3)_3$), 24.4 (2', 3', 5' or 6'-H), 18.8 ($Si\underline{C}(CH_3)_3$), 18.7 ($Si\underline{C}(CH_3)_3$), 18.6 (2', 3', 5' or 6'-H), 17.2 (2-CH_3), 14.1 (7a'-CH_3), -4.1 ($Si(CH_3)_2$), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2927, 2856, 1602, 1585, 1471, 1362, 1273, 1252, 1157, 1089, 1004, 982, 958, 835, 775, 696, 665.

HRMS (EI): *m*/*z* calculated for $C_{32}H_{58}O_2Si_2$ $[M]^{\cdot+}$ 530.3970; found 530.3966.

Purity (HPLC): 87% (λ = 191 nm) (method f).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-(4-((_tert_-butyldimethylsilyl)oxy)benzyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (93[d])



93[d]

$C_{32}H_{58}O_2Si_2$

M = 530.40 g/mol

Silylether **93[d]** was synthesised according to **GP7**, using alkene **72** (260 mg, 0.806 mmol, 1.00 eq) and bromide **78[d]** (218 mg, 0.759 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/toluene 95:5) and isolated as a colourless oil (139 mg, 0.262 mmol, 33%).

R_f = 0.30 (hexanes/toluene 95:5).

$[\alpha]_D^{23}$: + 18.3 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.02 – 6.94 (m, 2H, 2'', 6''-H), 6.75 – 6.69 (m, 2H, 3'', 5''-H), 3.60 (dd, *J* = 9.6, 3.3 Hz, 1H, 1-H), 3.28 (dd, *J* = 9.6, 7.3 Hz, 1H, 1-H), 2.74 – 2.67 (m, 1H, 4'-CH_2), 2.41 (dd, *J* = 13.6, 11.4 Hz, 1H, 4'-CH_2), 2.00 – 1.90 (m, 2H, 4', 7'-H), 1.87 – 1.78 (m, 1H, 2', 3', 5' or 6'-H), 1.72 – 1.40 (m, 7H, 2, 3a', 7'-H, 2', 3', 5' or 6'-H), 1.31 – 1.10 (m, 4H, 1'-H, 2', 3', 5' or 6'-H), 1.01 – 0.96 (m, 12H, 2-CH_3, $SiC(CH_3)_3$), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.84 (s, 3H, 7a'-CH_3), 0.17 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$).

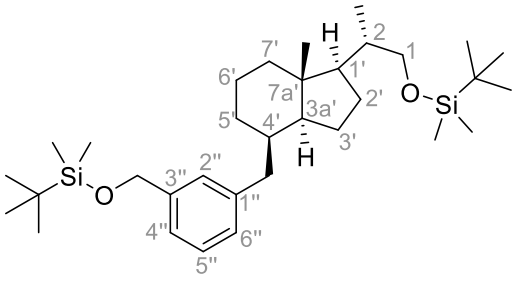
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 153.9 (C-4''), 137.1 (C-1''), 130.3 (C-2'', 6''), 120.2 (C-3'', 5''), 68.3 (C-1), 54.4 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.3 (C-4'), 39.5 (C-1'), 34.3 (4'-CH_2), 29.3 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 26.3 ($SiC(\underline{C}H_3)_3$), 26.0 ($SiC(\underline{C}H_3)_3$), 24.4 (C-2', 3', 5' or 6'), 18.8 ($Si\underline{C}(CH_3)_3$), 18.6 ($Si\underline{C}(CH_3)_3$), 18.6 (C-2', 3', 5' or 6'), 17.2 (2-CH_3), 14.1 (7a'-CH_3), -4.2 ($Si(CH_3)_2$), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2926, 2856, 2361, 1608, 1509, 1471, 1387, 1253, 1167, 1094, 1007, 912, 834, 800, 772, 677.

HRMS (EI): *m*/*z* calculated for $C_{32}H_{58}O_2Si_2$ $[M]^{\cdot+}$ 530.3970; found 530.3976.

Purity (HPLC): > 95% (λ = 210 nm) (method d).

***tert*-Butyl((*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)benzyl)-7a-methyloctahydro-1*H*-inden-1-yl)propoxy)dimethylsilane (94^{d})**



94^{d}

$C_{33}H_{60}O_2Si_2$

M = 544,41 g/mol

Silylether **94^{d}** was synthesised according to **GP7**, using alkene **72** (156 mg, 0.484 mmol, 1.00 eq) and benzyl bromide **80^{d}** (146 mg, 0.484 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/toluene 95:5) and isolated as a colourless oil (35.1 mg, 0.0644 mmol, 13%).

R_f = 0.20 (hexanes/toluene 95:5).

$[\alpha]_D^{23}$: + 55.6 (c = 0.006, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.24 – 7.18 (m, 1H, 5''-H), 7.13 – 7.09 (m, 2H, 2'', 4''-H), 7.02 (d, *J* = 7.5 Hz, 1H, 6''-H), 4.70 (s, 2H, 3''-CH_2), 3.61 (dd, *J* = 9.6, 3.4 Hz, 1H, 1-H), 3.29 (dd, *J* = 9.6, 7.3 Hz, 1H, 1-H), 2.79 (d, *J* = 13.3 Hz, 1H, 4'-CH_2), 2.48 (dd, *J* = 13.4, 11.4 Hz, 1H, 4'-CH_2), 2.01 – 1.93 (m, 2H, 4', 7'-H), 1.90 – 1.78 (m, 1H, 2', 3', 5' or 6'-H), 1.74 – 1.40 (m, 7H, 2, 3a'-H, 2', 3', 5' or 6'-H), 1.35 – 1.09 (m, 4H, 1', 7'-H, 2', 3', 5' or 6'-H), 0.98 (d, *J* = 6.5 Hz, 3H, 2-CH_3), 0.94 (s, 9H, $SiC(CH_3)_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.86 (s, 3H, 7a'-CH_3), 0.10 (s, 6H, $Si(CH_3)_2$), 0.05 – 0.03 (m, 6H, $Si(CH_3)_2$).

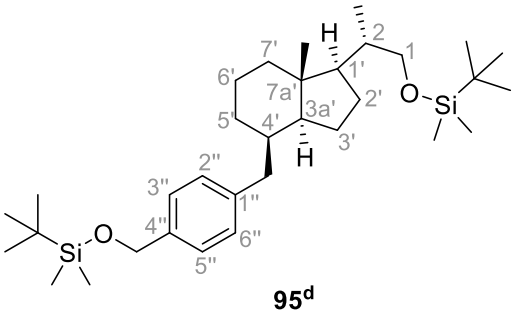
^{13}C NMR (101 MHz, methylene chloride-d_2) *δ*/ppm = 144.4 (C-1''), 141.9 (C-3''), 128.5 (C-5''), 128.1 (C-6''), 127.5 (C-2''), 123.9 (C-4''), 68.3 (C-1), 65.5 (3''-CH_2), 54.4 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.3 (C-4'), 39.5 (C-2), 35.1 (4'-CH_2), 29.3 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 26.3 ($SiC(\underline{C}H_3)_3$), 26.3 ($SiC(\underline{C}H_3)_3$), 24.4 (C-2', 3', 5' or 6'), 18.8 ($Si\underline{C}(CH_3)_3$), 18.8 ($Si\underline{C}(CH_3)_3$), 18.6 (C-2', 3', 5' or 6'), 17.2 (2-CH_3), 14.1 (7a'-CH_3), -5.0 ($Si(CH_3)_2$), -5.1 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2951, 2928, 2856, 2361, 2341, 1609, 1472, 1462, 1446, 1388, 1361, 1252, 1157, 1080, 1033, 1006, 965, 138, 919, 833, 814, 773, 702, 666.

HRMS (EI): *m*/*z* calculated for $C_{32}H_{57}O_2Si_2$ $[M]^{\cdot+}$ 529.3892; found 529.3872.

Purity (HPLC): 85% (λ = 210 nm) (method f).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-(4-(((_tert_-butyldimethylsilyl)oxy)methyl)benzyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (95[d])



95[d]

$C_{33}H_{60}O_2Si_2$

M = 544.41 g/mol

Silylether **95[d]** was synthesised according to **GP7**, using alkene **72** (249 mg, 0.772 mmol, 1.0 eq) and benzyl bromide **81[d]** (233 mg, 0.772 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/toluene 7:3) and isolated as a colourless oil (243 mg, 0.261 mmol, 57%).

R_f = 0.09 (hexanes/toluene 7:3).

$[\alpha]_D^{23}$: + 100.0 (c = 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.23 – 7.17 (m, 2H, 3'', 5''-H), 7.12 – 7.07 (m, 2H, 2'', 6''-H), 4.68 (s, 2H, 4''-CH_2), 3.61 (dd, J = 9.6, 3.3 Hz, 1H, 1-H), 3.32 – 3.26 (m, 1H, 1-H), 2.78 (d, J = 13.5 Hz, 1H, 4'-CH_2), 2.48 (dd, J = 13.4, 11.4 Hz, 1H, 4'-CH_2), 2.01 – 1.93 (m, 2H, 4', 7'-H), 1.89 – 1.78 (m, 1H, 2', 3', 5' or 6'-H), 1.75 – 1.36 (m, 7H, 2, 3a'-H, 2', 3', 5' or 6'-H), 1.37 – 1.12 (m, 4H, 1', 7'-H, 2', 3', 5' or 6'-H), 0.98 (d, J = 6.6 Hz, 3H, 2-CH_3), 0.93 (s, 9H, SiC(CH_3)$_3$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.86 (s, 3H, 7a'-CH_3), 0.10 (s, 6H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$), 0.04 (s, 3H, Si(CH_3)$_2$).

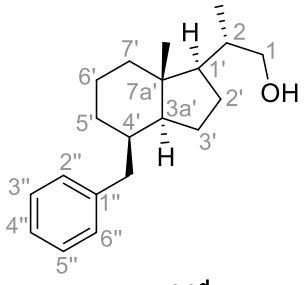
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 143.1 (C-1''), 139.2 (C-4''), 129.4 (C-2'', 6''), 126.7 (C-3'', 5''), 68.3 (C-1), 65.4 (4''-CH_2), 54.4 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.3 (C-4'), 39.5 (C-2), 34.8 (4'-CH_2), 29.3 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 26.3 (SiC($\underline{C}H_3$)$_3$), 24.4 (C-2', 3', 5' or 6'), 18.9 (Si$\underline{C}$(CH_3)$_3$), 18.8 (Si$\underline{C}$(CH_3)$_3$), 18.6 (C-2', 3', 5' or 6'), 17.2 (2-CH_3), 14.1 (7a'-CH_3), -5.0 (Si(CH_3)$_2$), -5.1 (Si(CH_3)$_2$), -5.2 (Si(CH_3)$_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2951, 2927, 2856, 2361, 2341, 1514, 1472, 1462, 1388, 1376, 1361, 1251, 1215, 1177, 1086, 1033, 1020, 1006, 944, 939, 833, 814, 773, 699, 667.

HRMS (EI): m/z calculated for $C_{32}H_{57}O_2Si_2$ $[M]^{\bullet+}$ 529.3892; found 529.3885.

Purity (HPLC): 85% (λ = 210 nm) (method f).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-Benzyl-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (96^{d})



96^{d}

$C_{20}H_{30}O$

M =286.23 g/mol

Alcohol **96^{d}** was synthesised according to **GP9** using silylether **91^{d}** (35.1 mg, 0.0876 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 85:15) and isolated as a colourless oil (16.3 mg, 0.0569 mmol, 65%).

R_f = 0.25 (hexanes/EtOAc 85:15).

$[\alpha]_D^{23}$: + 41.0 (c = 0.18, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.28 – 7.12 (m, 5H, 2'', 3'', 4'', 5'', 6''-H), 3.65 – 3.57 (m, 1H, 1-H), 3.38 – 3.28 (m, 1H, 1-H), 2.79 (d, *J* = 13.6 Hz, 1H, 4'-CH_2), 2.48 (dd, *J* = 13.4, 11.4 Hz, 2H, 4'-CH_2), 2.01 – 1.95 (m, 2H, 4', 7'-H), 1.90 – 1.81 (m, 1H, 2', 3', 5' or 6'-H), 1.75 – 1.41 (m, 7H, 2, 3a'-H, 2', 3', 5' or 6'-H), 1.36 – 1.13 (m, 4H, 1', 7'-H, 2', 3', 5' or 6'-H), 1.02 (d, *J* = 6.7 Hz, 3H, 2-CH_3), 0.87 (s, 3H, 7a'-CH_3).

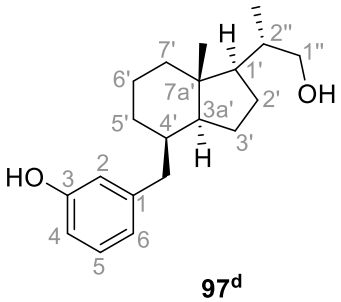
^{13}C NMR (101 MHz, methylene chloride-d_2) *δ*/ppm = 144.5 (C-1''), 129.5 (C-2'', 6''), 128.7 (C-3'', 5''), 125.9 (C-4''), 68.2 (C-1), 54.2 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.2 (C-4'), 39.3 (C-2), 35.1 (4'-CH_2), 29.3 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.4 (C-2', 3', 5' or 6'), 18.6 (C-2', 3', 5' or 6'), 16.9 (2-CH_3), 14.0 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3329, 3062, 3025, 2922, 2870, 2360, 2341, 1603, 1494, 1542, 1378, 1274, 1233, 1181, 1117, 1088, 1032, 1002, 982, 956, 931, 909, 867, 779, 740, 699.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O$ $[M]^{\bullet+}$ 286.2291; found 286.2293.

Purity (HPLC): 92% (λ = 210 nm) (method c).

3-(((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)methyl)phenol (97^{d})



97^{d}

$C_{20}H_{30}O_2$

M = 302.22 g/mol

Diol **97^{d}** was synthesised according to **GP9** using silylether **92^{d}** (163 mg, 0.256 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as a white crystalline solid (25.4 mg, 0.0840 mmol, 33%).

R$_f$ = 0.36 (hexanes/EtOAc 70:30).

mp: 147 °C.

$[\alpha]_D^{23}$: + 54.6 (c = 0.07, $CHCl_3$).

^{1}H NMR (400 MHz, methanol-d_4) δ/ppm = 7.08 – 7.02 (m, 1H, 5-H), 6.63 – 6.55 (m, 3H, 2, 4, 6-H), 3.60 (dd, *J* = 10.6, 3.2 Hz, 1H, 1''-H), 3.28 (dd, *J* = 10.6, 7.1 Hz, 1H, 1''-H), 2.74 (dd, *J* = 13.4, 2.6 Hz, 1H, 4'-CH_2), 2.44 (dd, *J* = 13.3, 11.4 Hz, 1H, 4'-CH_2), 2.05 – 1.96 (m, 2H, 4', 7'-H), 1.95 – 1.86 (m, 1H, 2', 3', 5' or 6'-H), 1.82 – 1.29 (m, 8H, 3a', 2''-H, 2', 3', 5' or 6'-H), 1.27 – 1.15 (m, 3H, 1', 7'-H, 2', 3', 5' or 6'-H), 1.04 (d, *J* = 6.6 Hz, 3H, 2''-CH_3), 0.90 (s, 3H, 7a'-CH_3).

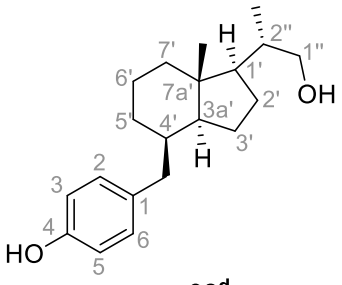
^{13}C NMR (101 MHz, methanol-d_4) δ/ppm = 158.3 (C-3), 146.4 (C-1), 130.1 (C-5), 121.3 (C-2), 116.8 (C-6), 113.4 (C-4), 67.9 (C-1''), 55.0 (C-1'), 53.9 (C-3a'), 43.5 (C-7a'), 42.2 (C-7'), 40.9 (C-4'), 40.0 (C-2''), 35.7 (4'-CH_2), 29.9 (C-2', 3', 5' or 6'), 27.9 (C-2', 3', 5' or 6'), 24.9 (C-2', 3', 5' or 6'), 19.0 (C-2', 3', 5' or 6'), 17.2 (2''-CH_3), 14.2 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3436, 3169, 2928, 2874, 2355, 1728, 1616, 1588, 1499, 1444, 1367, 1268, 1251, 1180, 1157, 1116, 1083, 1027, 999, 970, 948, 938, 928, 875, 804, 786, 773, 763, 694, 678.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_2$ $[M]^{\cdot+}$ 302.2240; found 302.2239.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm) (method c).

4-(((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)methyl)phenol (98^{d})



98^{d}

$C_{20}H_{30}O_2$

M = 302.22 g/mol

Diol **98^{d}** was synthesised according to **GP9** using silylether **93^{d}** (250 mg, 0.471 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as a white crystalline solid (18.0 mg, 0.0595 mmol, 13%).

R_f = 0.33 (hexanes/EtOAc 7:3).

mp: 130°C.

$[\alpha]_D^{23}$: + 100.0 (c = 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) δ/ppm = 7.03 – 6.95 (m, 2H, 2, 6-H), 6.75 – 6.68 (m, 2H, 3, 5-H), 4.89 (s, 1H, 4-OH), 3.62 (dd, *J* = 10.3, 3.2 Hz, 1H, 1''-H), 3.33 (dd, *J* = 10.5, 7.0 Hz, 1H, 1''-H), 2.74 – 2.68 (m, 1H, 4'-CH_2), 2.41 (dd, *J* = 13.6, 11.4 Hz, 1H, 4'-CH_2), 2.00 – 1.88 (m, 2H, 4', 7'-H), 1.87 – 1.78 (m, 1H, 2', 3', 5' or 6'-H), 1.74 – 1.26 (m, 8H, 3a', 2''-H, 2', 3', 5' or 6'-H), 1.23 – 1.10 (m, 3H, 1', 7'-H, 2', 3', 5' or 6'-H), 1.01 (d, *J* = 6.6 Hz, 3H, 2''-CH_3), 0.85 (s, 3H, 7a'-CH_3).

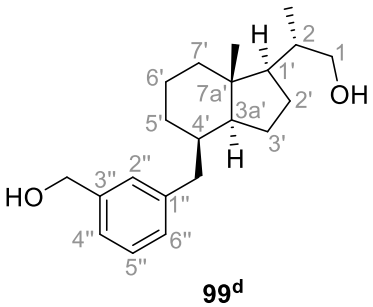
^{13}C NMR (101 MHz, methylene chloride-d_2) δ/ppm = 154.2 (C-4), 136.4 (C-1), 130.5 (C-2, 6), 115.4 (C-3, 5) , 68.3 (C-1''), 54.2 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.4 (C-7'), 40.3 (C-4'), 39.2 (C-2''), 34.1 (4-CH_2), 29.2 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.3 (C-2', 3', 5' or 6'), 18.6 (C-2', 3', 5' or 6'), 16.9 (2''-CH_3), 14.0 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3839, 3854, 3802, 3736, 3690, 3676, 3650, 3630, 3386, 2926, 1734, 1717, 1700, 1684, 1654, 1636, 1616, 1596, 1559, 1540, 1514, 1457, 1375, 1238, 1174, 1099, 1020, 994, 931, 872, 840, 833, 792.

HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_2$ $[M]^{\cdot+}$ 302.2240; found 302.2239.

Purity (HPLC): > 95% (λ = 210 nm) (method c).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(3-(Hydroxymethyl)benzyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (99^{d})



99^{d}

$C_{21}H_{32}O_2$

M = 316.24 g/mol

Diol **99^{d}** was synthesised according to **GP9** using silylether **94^{d}** (250 mg, 0.459 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as a white crystalline solid (43.0 mg, 0.136 mmol, 30%).

R_f = 0.20 (hexanes/EtOAc 7:3).

mp: 141 °C.

$[\alpha]_D^{23}$: + 44.7 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.28 – 7.22 (m, 1H, 5''-H), 7.16 – 7.12 (m, 2H, 2'', 4''-H), 7.09 – 7.05 (m, 1H, 6''-H), 4.63 (s, 2H, 3''-CH_2), 3.61 (dd, *J* = 10.5, 3.3 Hz, 1H, 1-H), 3.37 – 3.31 (m, 1H, 1-H), 2.83 – 2.75 (m, 1H, 4'-CH_2), 2.50 (dd, *J* = 13.4, 11.4 Hz, 1H, 4'-CH_2), 2.02 – 1.94 (m, 2H, 4', 7'-H), 1.91 – 1.80 (m, 1H, 2', 3', 5' or 6'-H), 1.78 – 1.40 (m, 8H, 2, 3a'-H, 2', 3', 5' or 6'-H), 1.38 – 1.13 (m, 3H, 1', 7'-H, 2', 3', 5' or 6'-H), 1.02 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.86 (s, 3H, 7a'-CH_3).

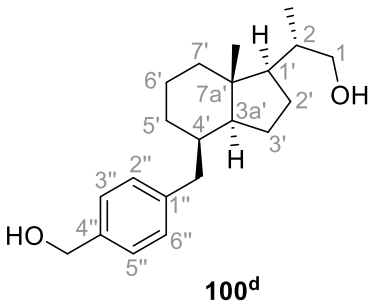
^{13}C NMR (101 MHz, methylene chloride-d_2) *δ*/ppm = 144.7 (C-1''), 141.7 (C-3''), 128.8 (C-6''), 128.8 (C-5''), 128.1 (C-2''), 124.6 (C-4''), 68.2 (C-1), 65.7 (3''-CH_2), 54.2 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.3 (C-7'), 40.2 (C-4'), 39.2 (C-2), 35.1 (4'-CH_2), 29.2 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.4 (C-2', 3', 5' or 6'), 18.6 (C-2', 3', 5' or 6'), 16.9 (2-CH_3), 14.0 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3903, 3854, 3839, 3822, 3802, 3751, 3736, 3712, 3690, 3676, 3650, 3630, 3576, 3337, 2922, 2869, 2360, 1868, 1792, 1772, 1734, 1706, 1684, 1654, 1636, 1608, 1559, 1540, 1522 , 1508, 1489, 1473, 1458, 1363, 1220, 1155, 1089, 1034, 1003, 982, 891, 788, 754, 746, 703.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{32}O_2$ $[M]^{\cdot+}$ 316.2397; found 316.2396.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(4-(Hydroxymethyl)benzyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (100[d])



100[d]

$C_{21}H_{32}O_2$

M = 316.24 g/mol

Diol **100[d]** was synthesised according to **GP9** using silylether **95[d]** (243 mg, 0.446 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as a white crystalline solid (27.9 mg, 0.0882 mmol, 20%).

R_f = 0.20 (hexanes/EtOAc 7:3).

mp: 146 °C.

$[\alpha]_D^{23}$: + 61.3 (c = 0.05, $CHCl_3$).

^{1}H NMR (400 MHz, methylene chloride-d_2) *δ*/ppm = 7.29 – 7.23 (m, 2H, 3'', 5''-H), 7.16 – 7.10 (m, 2H, 2'', 6''-H), 4.61 (d, *J* = 4.5 Hz, 2H, 4''-CH_2), 3.65 – 3.57 (m, 1H, 1-H), 3.37 – 3.29 (m, 1H, 1-H), 2.79 (dd, *J* = 14.2, 2.3 Hz, 1H, 4'-CH_2), 2.49 (dd, *J* = 13.4, 11.4 Hz, 1H, 4'-CH_2), 2.01 – 1.93 (m, 2H, 4', 7'-H), 1.90 – 1.80 (m, 1H, 2', 3', 5' or 6'-H), 1.77 – 1.28 (m, 8H, 2, 3a'-H, 2', 3', 5' or 6'-H), 1.26 – 1.13 (m, 3H, 1', 7'-H, 2', 3', 5' or 6'-H), 1.02 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.86 (s, 3H, 7a'-CH_3).

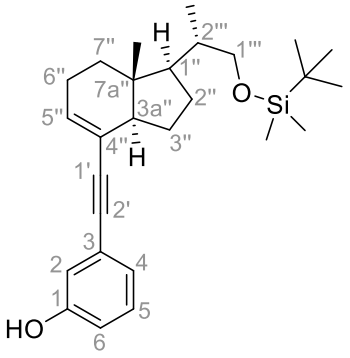
^{13}C NMR (101 MHz, methylene chloride-d_2) *δ*/ppm = 143.8 (C-1''), 138.9 (C-4''), 129.7 (C-2'', 6''), 127.5 (C-3'', 5''), 68.2 (C-1), 65.5 (4''-CH_2), 54.2 (C-1'), 53.1 (C-3a'), 42.9 (C-7a'), 41.3 (C-7'), 40.2 (C-4'), 39.2 (C-2), 34.8 (4'-CH_2), 29.2 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.4 (C-2', 3', 5' or 6'), 18.6 (C-2', 3', 5' or 6'), 16.9 (2-CH_3), 14.0 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3903, 3854, 3839, 3822, 3802, 3751, 3736, 3712, 3690, 3676, 3650, 3630, 3568, 3220, 2928, 2360, 1868, 1830, 1792, 1772, 1734, 1717, 1700, 1684, 1670, 1654, 1636, 1616, 1576, 1559, 1540, 1508, 1490, 1458, 1418, 1375, 1174, 103, 1002, 846, 794.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{32}O_2$ $[M]^{\cdot+}$ 316.2397; found 316.2395.

Purity (HPLC): > 95% (λ = 210 nm) (method c).

3-(((1*R*,3a*R*,7a*R*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)-7a-methyl-2,3,3a,6,7,7a-hexahydro-1*H*-inden-4-yl)ethynyl)phenol (103)



103

$C_{27}H_{40}O_2Si$

M = 424.70 g/mol

Diol **103** was synthesised *via* three steps. For SONOGASHIRA cross-coupling enol triflate **34** (411 mg, 0.900 mmol, 1.00 eq) was dissolved in dry THF (8.00 mL) and 3-hydroxyphenylacetylen (**104**, 118 µL, 1.08 mmol, 1.20 eq), TEA (0.314 mL, 2.25 mmol, 2.50 eq) and CuI (34.3 mg, 0.180 mmol, 20 mol%) were added under N_2 counterflow. After purging the solution with N_2, $PdCl_2(PPh_3)_2$ (63.3 mg, 0.0900 mmol, 10 mol%) was added and the reaction mixture was stirred for 1.5 h. The reaction was stopped with sat. aq. NH_4Cl (10.0 mL) and the aq. phase was extracted with DCM (3 x 15.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as light yellow oil (367 mg, 0.864 mmol, 96%).

R_f = 0.27 (hexanes/EtOAc 9:1).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 23.7 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.15 (t, *J* = 7.9 Hz, 1H, 5-H), 6.98 (dt, *J* = 7.7, 1.2 Hz, 1H, 4-H), 6.87 (dd, *J* = 2.6, 1.4 Hz, 1H, 2-H), 6.78 – 6.71 (m, 1H, 6-H), 6.07 (q, *J* = 3.3 Hz, 1H, 5''-H), 4.89 (s, 1H, OH), 3.61 (dd, *J* = 9.7, 3.4 Hz, 1H, 1'''-H), 3.29 (dd, *J* = 9.7, 7.4 Hz, 1H, 1'''-H), 2.30 – 2.18 (m, 3H, 3a''-H, 2'', 3'' or 6''-H), 2.06 – 1.97 (m, 1H, 7''-H), 1.95 – 1.82 (m, 2H, 2'', 3'' or 6''-H), 1.67 – 1.56 (m, 1H, 2'''-H), 1.54 – 1.38 (m, 3H, 7''-H, 2'', 3'' or 6''-H), 1.35 – 1.22 (m, 1H, 1''-H), 1.03 (d, *J* = 6.5 Hz, 3H, 2'''-CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.74 (s, 3H, 7a''-CH_3), 0.05 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.4 (C-1), 134.5 (C-5''), 129.6 (C-5), 125.3 (C-3), 124.3 (C-4), 122.3 (C-4''), 118.2 (C-2), 115.3 (C-6), 89.9 (C-1'), 87.8 (C-2'), 67.9 (C-1'''), 51.4 (C-1''), 49.9 (C-3a''), 42.1 (C-7a''), 39.5 (C-2'''), 35.9 (C-7''), 27.6 (C-2'', 3'' or 6''), 26.1

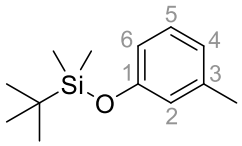
(SiC($\underline{CH_3}$)$_3$), 25.4 (C-2'', 3'' or 6''), 24.3 (C-2'', 3'' or 6''), 18.5 (Si$\underline{C}$(CH$_3$)$_3$), 17.1 (2'''-CH$_3$), 11.4 (7a''-CH$_3$), -5.2 (Si(CH$_3$)$_2$), -5.2 (Si(CH$_3$)$_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2953, 2928, 1708, 1590, 1577, 1471, 1442, 1375, 1250, 1083, 1041, 1003, 934, 909, 832, 774, 731, 685.

HRMS (EI): *m*/*z* calculated for $C_{27}H_{40}O_2Si$ $[M]^{\cdot+}$ 424.2792; found 424.2790.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

3-(*tert*-Butyldimethylsilyloxy)toluene (110^{b})



110^{b}

$C_{13}H_{22}OSi$

M = 222.40 g/mol

Silylether **110^{b}** was synthesised according to **GP2** using *m*-cresol (**108**, 1.00 g, 9.25 mmol, 1.00 eq) The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as a colourless oil (1.95 g, 8.77 mmol, 95%).

R_f = 0.92 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.90 (t, *J* = 7.7 Hz, 1H, 5-H), 6.57 (d, *J* = 8.7 Hz, 1H, 4-H), 6.45 (m, 2H, 2, 6-H), 2.11 (s, 3H, 3-CH_3), 0.79 (s, 9H, $SiC(CH_3)_3$), 0.00 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.6 (C-1), 139.4 (C-3), 129.0 (C-5), 122.1 (C-4), 120.9 (C-2 or C-6), 117.0 (C-2 or C-6), 25.7 ($SiC(\underline{C}H_3)_3$), 21.4 (3-CH_3), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3854, 3750, 3650, 3032, 2957, 2930, 2896, 2859, 2360, 2342, 1748, 1604, 1586, 1488, 1472, 1463, 1407, 1390, 1362, 1277, 1252, 1158, 1084, 1005, 954, 886, 835, 778, 690, 664.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{22}OSi$ $[M]^{\cdot+}$ 222.1440; found 222.1431.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm) (method d).

4-(*tert*-Butyldimethylsilyloxy)toluene (111[b])

111[b]

$C_{13}H_{22}OSi$

M = 222.40 g/mol

Silylether **111[b]** was synthesised according to **GP2** using *p*-cresol (**109**, 1.00 g, 9.25 mmol, 1.00 eq) The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as a colourless oil (1.92 g, 8.63 mmol, 93%).

R_f = 0.88 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.04 – 7.01 (m, 2H, 3, 5-H), 6.74 (d, *J* = 8.4 Hz, 2H, 2, 6-H), 2.28 (s, 3H, 4-CH_3), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$).

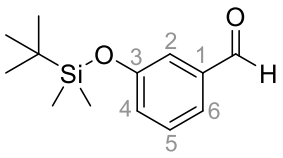
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 153.3 (C-1), 130.4 (C-4), 129.8 (C-3,5), 119.8 (C-2,6), 25.7 ($SiC(\underline{C}H_3)_3$), 20.6 (4-CH_3), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3751, 3650, 3029, 2957, 2930, 2887, 2859, 2361, 2342, 1870, 1613, 1582, 1508, 1472, 1463, 1390, 1362, 1260, 1168, 1103, 1042, 1007, 911, 836, 822, 811, 778, 689.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{22}OSi$ $[M]^{\cdot+}$ 222.1440; found 222.1432.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm) (method d).

3-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde (116^{b})



116^{b}

$C_{13}H_{20}O_2Si$

M = 236.39 g/mol

Benzaldehyde **116^{b}** was synthesised according to **GP2** using 3-hydroxybenzaldehyde (**114**, 1.00 g, 8.19 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as a colourless oil (1.49 g, 6.30 mmol, 77%).

R_f = 0.89 (hexanes/EtOAc 5:5).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 9.95 (s, 1H, CHO), 7.47 (dt, *J* = 7.6, 1.2 Hz, 1H, 6-H), 7.40 (t, *J* = 7.8 Hz, 1H, 5-H), 7.33 (dd, *J* = 2.6, 1.5 Hz, 1H, 2-H), 7.11 (ddt, *J* = 7.7, 2.1, 0.6 Hz, 1H, 4-H), 1.00 (d, *J* = 0.6 Hz, 9H, $SiC(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$).

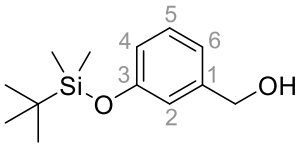
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 192.1 (CHO), 156.4 (C-3), 137.9 (C-1), 130.1 (C-5), 126.6 (C-4), 123.6 (C-6), 119.9 (C-2), 25.6 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2956, 2931, 2887, 2859, 2725, 2360, 2342, 1702, 1597, 1583, 1482, 1472, 1464, 1445, 1387, 1363, 1311, 1277, 1254, 1166, 1144, 1078, 1002, 981, 966, 939, 798, 780, 729, 705, 684, 667.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{20}O_2Si$ $[M]^{\cdot+}$ 236.1233; found 236.1240.

Purity (HPLC): > 95% (λ = 210 nm) (method d).

(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)methanol (118^{b})



118^{b}

$C_{13}H_{22}O_2Si$

M = 238.40 g/mol

A solution of aldehyde **116^{b}** (1.48 g, 6.26 mmol, 1.00 eq) in MeOH (50.0 mL) was cooled to 0 °C and $NaBH_4$ (355 mg, 9.39 mmol, 1.50 eq) was added. The reaction mixture was warmed up to rt and stirred for 1 h. The solvent was removed *in vacuo* and the residue was redissolved in EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The title compound was purified *via* FCC (hexanes/EtOAc 8:2) to give alcohol **118^{b}** as a colourless oil (1.06 g, 4.45 mmol, 71%).

R_f = 0.47 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.21 (t, *J* = 7.8 Hz, 1H, 5-H), 6.94 (ddq, *J* = 7.6, 1.6, 0.8 Hz, 1H, 6-H), 6.88 – 6.84 (m, 1H, 2-H), 6.80 – 6.74 (m, 1H, 4-H), 4.64 (d, *J* = 5.8 Hz, 2H, C$\underline{H}_2$-OH), 1.64 (t, *J* = 6.0 Hz, 1H, OH), 0.99 (s, 9H, SiC$(CH_3)_3$), 0.20 (s, 6H, Si$(CH_3)_2$).

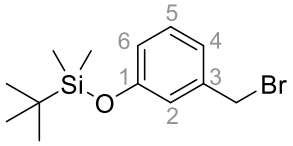
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.9 (C-3), 142.5 (C-1), 129.5 (C-5), 119.8 (C-6), 119.3 (C-2), 118.6 (C-4), 65.2 (CH_2OH), 25.7 (SiC($\underline{C}H_3)_3$), 18.2 (Si$\underline{C}(CH_3)_3$), -4.4 (Si$(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3612, 2956, 2930, 2887, 2858, 2362, 1604, 1587, 1486, 1472, 1463, 1442, 1390, 1362, 1275, 1252, 1153, 1003, 954, 835, 778, 692, 665.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{22}O_2Si$ $[M]^{\cdot+}$ 238.1389; found 238.1381.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 254 nm) (method d).

(3-(Bromomethyl)phenoxy)(*tert*-butyl)dimethylsilane (112^{b})[102]



112^{b}

$C_{13}H_{21}BrOSi$

M = 301.30 g/mol

To a suspension of alcohol **118^{b}** (876 mg, 3.67 mmol, 1.00 eq) and PPh_3 (2.44 g, 7.35 mmol, 2.00 eq) in DCM (80.0 mL), CBr_4 (1.95 g, 7.35 mmol, 2.00 eq) was added portionwise at 0 °C and the reaction mixture was allowed to warm up to rt and stirred for 3 h. The solvent was removed *in vacuo* and the crude product was purified *via* FCC (hexanes/EtOAc 95:5 → 8:2). Benzyl bromide **112^{b}** was obtained as a colourless oil (201 mg, 0.667 mmol, 18%).

R_f = 0.83 (hexanes/EtOAc 9:1).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.19 (t, *J* = 7.9 Hz, 1H, 5-H), 6.98 (ddd, *J* = 7.6, 2.0, 1.1 Hz, 1H, 4-H), 6.88 (t, *J* = 2.0 Hz, 1H, 2-H), 6.77 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H, 6-H), 4.44 (s, 2H, 3-CH_2), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.21 (s, 6H, $Si(CH_3)_2$).

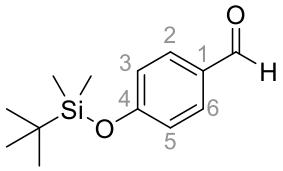
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.9 (C-1), 139.2 (C-3), 129.7 (C-5), 121.9 (C-4), 120.8 (C-2), 120.2 (C-6), 33.4 (3-CH_2), 25.7 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2958, 2930, 2886, 2858, 2362, 1715, 1602, 1586, 1486, 1472, 1463, 1442, 1390, 1362, 1278, 1253, 1214, 1158, 1079, 1003, 978, 939, 835, 778, 723, 692, 665.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{21}OBrSi$ $[M]^{\bullet+}$ 300.0545; found 300.0535.

Purity (HPLC): 82% (λ = 191 nm), 87% (λ = 210 nm), 85% (λ = 254 nm) (method d).

4-((*tert*-Butyldimethylsilyl)oxy)benzaldehyde (117^{b})



117^{b}

$C_{13}H_{20}O_2Si$

M = 236.39 g/mol

Benzaldehyde **117^{b}** was synthesised according to **GP2** using 4-hydroxybenzaldehyde (**115**, 1.00 g, 8.19 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as a white oily solid (1.66 g, 7.02 mmol, 86%).

R_f = 0.70 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 9.89 (s, 1H, CHO), 7.82 – 7.75 (m, 2H, 2, 6-H), 6.98 – 6.90 (m, 2H, 3, 5-H), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.25 (s, 6H, $Si(CH_3)_2$).

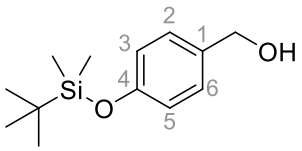
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 190.9 (CHO), 161.5 (C-4), 131.9 (C-2, 6), 130.4 (C-1), 120.5 (C-3, 5) , 25.6 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2955, 2931, 2858, 2833, 1697, 1596, 1575, 1507, 1471, 1463, 1445, 1421, 1391, 1362, 1256, 1210, 1154, 1101, 1006, 938, 903, 836, 797, 780, 702, 666.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{20}O_2Si$ $[M]^{\cdot+}$ 236.1233; found 236.1223.

Purity (HPLC): 76% (λ = 191 nm), 90% (λ = 210 nm), 84% (λ = 254 nm) (method d).

(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)methanol (119^{b})



119^{b}

$C_{13}H_{22}O_2Si$

M = 238.40 g/mol

A solution of aldehyde **117^{b}** (1.00 g, 4.23 mmol, 1.00 eq) in MeOH (50.0 mL) was cooled to 0 °C and $NaBH_4$ (240 mg, 6.35 mmol, 1.50 eq) was added. After stirring the mixture at rt for 1 h, the solvent was removed under reduced pressure. The residue was redissolved in EtOAc (100 mL) and washed with water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (hexanes/EtOAc 8:2) to give alcohol **119^{b}** as a colourless oil (640 mg, 2.68 mmol, 64%).

R_f = 0.36 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.25 – 7.19 (m, 2H, 2, 6-H), 6.85 – 6.78 (m, 2H, 3, 5-H), 4.61 (d, *J* = 5.8 Hz, 2H, 1-CH_2), 1.56 (s, 1H, OH), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$).

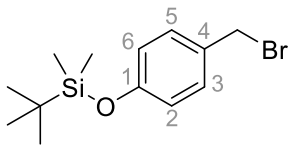
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.3 (C-4), 133.7 (C-1), 128.6 (C-2, 6), 120.2 (C-3, 5), 65.2 (1-CH_2), 25.7 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3032, 2956, 2929, 2885, 2858, 1609, 1582, 1509, 1471, 1463, 1409, 1390, 1362, 1250, 1166, 1102, 1006, 909, 834, 812, 777, 731, 689, 654.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{22}O_2Si$ $[M]^{\cdot+}$ 238.1389; found 238.1380.

Purity (HPLC): > 95% (λ = 191 nm), > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method d).

(4-(Bromomethyl)phenoxy)(*tert*-butyl)dimethylsilane (113[b])



113[b]

$C_{13}H_{21}BrOSi$

M = 301.30 g/mol

To a suspension of alcohol **119[b]** (640 mg, 2.68 mmol, 1.00 eq) and PPh_3 (1.42 g, 5.37 mmol, 2.00 eq) in DCM (60.0 mL) at 0 °C, CBr_4 (1.78 g, 5.37 mmol, 2.00 eq) was added. The reaction was warmed up to rt over 90 minutes, concentrated under reduced pressure and purified *via* FCC (hexanes/EtOAc 95:5) to give benzyl bromide **113[b]** as a colourless oil (198 mg, 0.656 mmol, 25%).

R_f = 0.82 (hexanes/EtOAc 95:5).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.30 – 7.21 (m, 2H, 2, 6-H), 6.79 (d, *J* = 8.5 Hz, 2H, 3, 5-H), 4.49 (s, 2H, 4-CH_2), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.20 (s, 6H, $Si(CH_3)_2$).

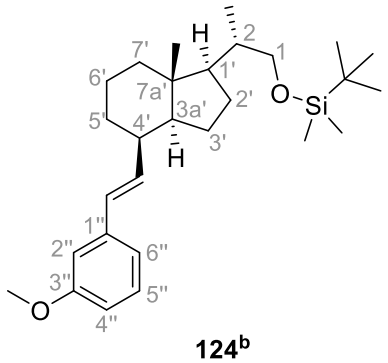
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.9 (C-1), 130.5 (C-4), 130.4 (C-3, 5), 120.3 (C-2, 6), 34.0 (4-CH_2), 25.6 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -4.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3790, 3683, 3662, 2926, 2854, 1960, 1729, 1691, 1658, 1641, 1598, 1579, 1548, 1529, 1513, 1462, 1387, 1360, 1288, 1254, 1191, 1155, 1084, 1051, 1002, 965, 833, 771, 714, 688, 666.

HRMS (EI): *m*/*z* calculated for $C_{13}H_{21}OBrSi$ $[M]^{\bullet+}$ 300.0539; found 300.0532

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-((_E_)-3-methoxystyryl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (124[b])



124[b]

$C_{28}H_{46}O_2Si$

M = 442.76 g/mol

PPh_3 (1.58 g, 5.97 mmol, 1.20 eq) was added to a stirred solution of 3-methoxybenzylbromide (**120**, 1.00 g, 4.97 mmol, 1.00 eq) in toluene (40.0 mL) and the reaction mixture was refluxed for 12 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and the resulting phosphonium salt **121[b]** precipitate was collected by filtration, dried and used without further purification.

A flame-dried round bottom flask was charged with the crude (3-methoxybenzyl)triphenyl-phosphonium bromide (**121[b]**, 714 mg, 1.54 mmol, 1.20 eq) in dry THF (60.0 mL) and the solution was cooled to 0 °C. LDA (2M in THF, 0.96 mL, 1.90 mmol, 1.50 eq) was added and the mixture was stirred for 30 min at 0 °C. A solution of aldehyde **73[b]** (435 g, 1.28 mmol, 1.00 eq) in dry THF (15.0 mL) was added and the reaction mixture was slowly warmed to rt and stirred for 17 h. The reaction was diluted with water (50.0 mL) and the mixture was extracted with EtOAc (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (hexanes/toluene 8:2) and led to olefin **124[b]** as a colourless oil (248 mg, 0.560 mmol, 44%).

R_f = 0.37 (hexanes/toluene 8:2).

$[\alpha]_D^{23}$: + 9.6 (c = 0.06, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.20 (t, *J* = 7.9 Hz, 1H, 5''-H), 6.93 (dt, *J* = 7.7, 1.4 Hz, 1H, 6''-H), 6.87 (dd, *J* = 2.6, 1.6 Hz, 1H, 2''-H), 6.75 – 6.72 (m, 1H, 4''-H), 6.31 (d, *J* = 15.8 Hz, 1H, 1''-CH), 6.03 (dd, *J* = 15.8, 8.2 Hz, 1H, 4'-CH), 3.81 (s, 3H, OCH_3), 3.58 (ddd, *J* = 9.6, 4.4, 3.3 Hz, 1H, 1-H), 3.26 (ddd, *J* = 9.6, 7.5, 4.4 Hz, 1H, 1-H), 2.20 – 2.10 (m, 1H, 4'-H), 1.96 (td, *J* = 9.0, 4.4 Hz, 1H, 7'-H), 1.75 (qq, *J* = 7.0, 3.5 Hz, 3H, 2', 5'-H), 1.56 (tddt, *J* = 13.1, 9.8, 7.0, 3.6 Hz, 4H, 3', 6'-H), 1.22 – 1.08 (m, 5H, 2, 1', 2', 3a', 7'-H), 1.01 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.89 (d, *J* = 1.2 Hz, 9H, $SiC(CH_3)_3$), 0.75 (s, 3H, 7a'-CH_3), 0.03 (s, 6H, $Si(CH_3)_2$).

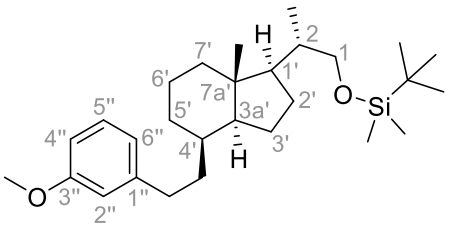
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 159.8 (C-3''), 139.6 (C-1''), 136.1 (4'-CH), 129.4 (C-5''), 127.9 (C-1''), 118.6 (C-6''), 112.3 (C-2''), 111.3 (C-4''), 67.9 (C-1), 55.2 (OCH_3), 54.5 (C-3a'), 52.9 (C-2), 42.8 (C-7a'), 41.3 (C-4'), 39.8 (C-7'), 39.0 (C-1'), 33.1 (C-5'), 27.0 (C-2'), 26.0 ($SiC(\underline{C}H_3)_3$), 25.3 (C-3' or 6'), 21.8 (C-3' or 6'), 18.4 ($Si\underline{C}(CH_3)_3$), 17.0 (2-CH_3), 11.9 (7a'-CH_3), -5.3 ($Si(CH_3)_2$), -5.4 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3790, 3697, 3662, 2956, 2928, 2857, 1970, 1729, 1711, 1691, 1665, 1641, 1608, 1549, 1509, 1470, 1390, 1362, 1254, 1231, 1202, 1168, 1092, 1006, 909, 836, 779, 691.

HRMS (EI): *m*/*z* calculated for $C_{28}H_{46}O_2Si$ $[M]^{\cdot+}$ 442.3267; found 442.3258.

Purity (GC): 71% (scan mode *m*/*z* 50-650 (EI 70 eV)).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-(3-methoxyphenethyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (127[b])



127[b]

$C_{28}H_{48}O_2Si$

M = 444.78 g/mol

To a solution of olefin **124[b]** (248 mg, 0.560 mmol, 1.00 eq) palladium on carbon (10% Pd/C, 24.8 mg, 0.0230 mmol, 10 wt%) was added. The flask was filled with H_2 and stirred at rt for 18 h. The Pd/C catalyst was removed by filtration with a celite pad and the resulting filtrate was concentrated under reduced pressure. The crude product was purified *via* FCC (hexanes 100% → hexanes/EtOAc 75:25) to give silylether **127[b]** as a colourless oil (202 mg, 0.454 mmol, 81%).

R_f = 0.46 (hexanes 100%).

$[\alpha]_D^{23}$ = + 2.5 (c = 0.08, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.19 (ddd, *J* = 7.6, 6.7, 2.1 Hz, 1H, 5''-H), 6.77 (dt, *J* = 7.5, 1.2 Hz, 1H, 6''-H), 6.72 (dd, *J* = 6.7, 1.1 Hz, 2H, 2'', 4''-H), 3.80 (s, 3H, OCH_3), 3.59 (dd, *J* = 9.6, 3.4 Hz, 1H, 1-H), 3.24 (dd, *J* = 9.6, 7.6 Hz, 1H, 1-H), 2.67 (ddd, *J* = 13.4, 11.3, 5.1 Hz, 1H, 1''-CH_2), 2.45 (ddd, *J* = 13.5, 11.0, 5.7 Hz, 1H, 1''-CH_2), 1.97 – 1.91 (m, 1H, 4'-CH_2), 1.87 (dd, *J* = 12.9, 3.3 Hz, 1H, 5'-H), 1.81 – 1.62 (m, 3H, 2', 3' or 6', 7'-H), 1.60 – 1.41 (m, 4H, 1', 3' or '6-H), 1.41 – 1.17 (m, 4H, 4', 5', 7'-H), 1.17 – 1.05 (m, 3H, 2', 3a'-H, 4'-CH_2), 1.00 (d, *J* = 6.5 Hz, 3H, 2-CH_3), 0.89 (s, 9H, $SiC(CH_3)_2$), 0.68 (s, 3H, 7a'-CH_3), 0.03 (s, 3H, $Si(CH_3)_2$), 0.03 (s, 3H, $Si(CH_3)_2$).

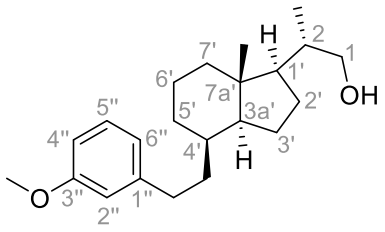
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 159.73 (C-3''), 145.3 (C-1''), 129.3 (C-5''), 120.9 (C-6''), 114.3 (C-2''), 110.9 (C-4''), 68.1 (C-1), 55.5 (C-3a'), 55.3 (OCH_3), 53.2 (C-2), 43.3 (C-7a'), 40.2 (4'-CH_2), 39.2 (C-1'), 37.1 (C-7'), 36.4 (C-4'), 33.3 (1''-CH_2), 32.4 (C-5'), 27.4 (C-2'), 26.1 ($SiC(\underline{C}H_3)_3$), 25.0 (C-3' or 6'), 22.4 (C-3' or 6'), 18.5 ($Si\underline{C}(CH_3)_3$), 17.1 (2-CH_3), 12.1 (7a'-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2926, 2855, 2215, 1601, 1584, 1488, 1462, 1387, 1360, 1255, 1152, 1083, 1041, 1004, 972, 938, 833, 812, 772, 713, 694, 666.

HRMS (EI): *m*/*z* calculated for $C_{28}H_{48}O_2Si$ $[M]^{\cdot+}$ 444.3424; found 444.3419.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(3-Methoxyphenethyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (128)



128

$C_{22}H_{34}O_2$

M = 330.51 g/mol

Alcohol **128** was synthesised according to **GP9** using silylether **127[b]** (47.0 mg, 0.106 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (26.0 mg, 0.0787 mmol, 74%).

R_f = 0.17 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 15.7 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.23 – 7.14 (m, 1H, 5''-H), 6.81 – 6.75 (m, 1H, 6''-H), 6.74 – 6.70 (m, 2H, 2'', 4''-H), 3.80 (m, 3H, OCH_3), 3.68 – 3.60 (m, 1H, 1-H), 3.41 – 3.29 (m, 1H, 1-H), 2.72 – 2.60 (m, 1H, 1''-CH_2), 2.50 – 2.39 (m, 1H, 1''-CH_2), 1.97 – 1.84 (m, 2H, 7'-H, 2', 3', 5' or 6'-H), 1.83 – 1.65 (m, 4H, 4'-CH_2, 2', 3', 5' or 6'-H), 1.61 – 1.43 (m, 3H, 2, 1'-H, 2', 3', 5' or 6'-H), 1.37 – 1.19 (m, 5H, 4'-CH_2, 2', 3', 5' or 6'-H), 1.17 – 1.09 (m, 3H, 3a', 7'-H, 2', 3', 5' or 6'-H), 1.05 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.69 (s, 3H, 7a'-CH_3).

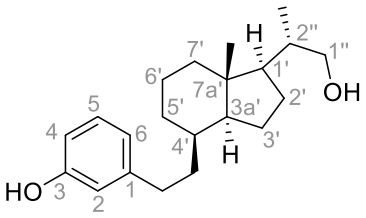
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 159.7 (C-3''), 145.2 (C-1''), 129.3 (C-5''), 120.9 (C-6''), 114.3 (C-2''), 110.9 (C-4''), 68.2 (C-1), 55.5 (C-3a'), 55.3 (OCH_3), 52.9 (C-1'), 43.3 (C-7a'), 40.2 (C-7'), 38.9 (C-2), 37.0 (4'-CH_2), 36.4 (C-4'), 33.3 (1''-CH_2), 32.4 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.9 (C-2', 3', 5' or 6'), 22.4 (C-2', 3', 5' or 6'), 16.9 (2-CH_3), 12.1 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2922, 2854, 1727, 1601, 1584, 1488, 1454, 1438, 1378, 1259, 1164, 1152, 1044, 983, 909, 871, 775, 733, 694.

HRMS (EI): *m*/*z* calculated for $C_{22}H_{34}O_2$ $[M]^{\cdot+}$ 330.2559; found 330.2551.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

3-(2-((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)ethyl)phenol (101)



101

$C_{21}H_{32}O_2$

M = 316.49 g/mol

Alcohol **128** (13.0 mg, 0.0393 mmol, 1.00 eq) was dissolved in dry DCM (1.00 mL) and cooled to - 78 °C. BBr_3 (1M in DCM, 0.118 mL, 0.118 mmol, 3.00 eq) was added dropwise. The reaction mixture was stirred at - 78 °C for 16 h. The reaction was stopped with brine (3.00 mL), allowed to warm up to rt and stirred for 1 h. The solution was neutralised with $NaHCO_3$ and the aq. layer was extracted with EtOAc (3 x 5.00 mL). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as colourless oil (7.60 mg, 0.0240 mmol, 61%).

R_f = 0.30 (hexanes/EtOAc 7:3).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 17.1 (c = 0.02, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.16 – 7.10 (m, 1H, 5-H), 6.75 (tt, *J* = 7.5, 1.2 Hz, 1H, 6-H), 6.68 – 6.60 (m, 2H, 2, 4-H), 4.80 (s, 1H, OH), 3.67 – 3.60 (m, 1H, 1''-H), 3.40 – 3.33 (m, 1H, 1''-H), 2.68 – 2.59 (m, 1H, 1-CH_2), 2.46 – 2.34 (m, 1H, 1-CH_2), 1.95 – 1.84 (m, 2H, 7'-H, 2', 3', 5' or 6'-H), 1.82 – 1.63 (m, 4H, 4''-CH_2, 2', 3', 5' or 6'-H), 1.61 – 1.46 (m, 5H, 1', 2''-H, 2', 3', 5' or 6'-H), 1.41 – 1.15 (m, 6H, 3a', 4'-H, 2', 3', 5' or 6'-H), 1.05 (d, *J* = 6.7 Hz, 3H, 2''-CH_3), 0.69 (s, 3H, 7a'-CH_3).

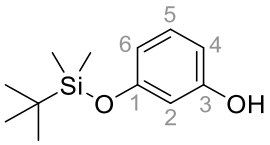
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 155.7 (C-3), 145.5 (C-1), 129.6 (C-5), 120.9 (C-6), 115.3 (C-2), 112.6 (C-4), 68.3 (C-2''), 55.5 (C-3a'), 52.9 (C-1'), 43.3 (C-7a'), 40.2 (C-7'), 38.9 (C-2''), 36.9 (C-2', 3', 5' or 6'), 36.4 (C-4'), 33.1 (1''-CH_2), 32.4 (C-2', 3', 5' or 6'), 27.4 (C-2', 3', 5' or 6'), 24.9 (4'-CH_2), 22.4 (C-2', 3', 5' or 6'), 16.9 (2''-CH_3), 12.1 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3312, 3183, 2936, 1588, 1549, 1512, 1484, 1334, 1251, 1119, 998, 884, 812.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{32}O_2$ $[M]^{\cdot+}$ 316.2397; found 316.2394.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

3-((*tert*-Butyldimethylsilyl)oxy)phenol (130^{e})[105]



130^{e}

$C_{12}H_{20}O_2Si$

M = 224.38 g/mol

To a solution of resorcinol (**129**, 100 mg, 0.908 mmol, 1.00 eq) in dry THF (10.0 mL) at 0 °C, imidazole (92.7 mg, 1.36 mmol, 1.50 eq) and TBDMSCl (151 mg, 0.999 mmol, 1.10 eq) was added. The reaction mixture was warmed to rt and stirred for 48 h. The solution was filtered, and the filtrate was concentrated *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 95:5) and isolated as a light brown oil (76 mg, 0.34 mmol, 38%).

R_f = 0.19 (hexanes/EtOAc 95:5).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.07 (t, *J* = 8.1 Hz, 1H, 5-H), 6.43 (dd, *J* = 8.2, 2.3 Hz, 2H, 4-H and 6-H), 6.35 (t, *J* = 2.3 Hz, 1H, 2-H), 4.82 (s, 1H, OH), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.20 (s, 6H, $Si(CH_3)_2$).

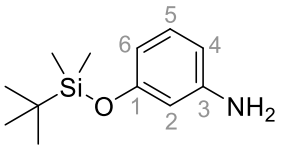
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 157.1 (C-3), 156.7 (C-1), 130.1 (C-5), 112.9 (C-6), 108.6 (C-4), 107.7 (C-2), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2957, 2930, 2885, 2858, 1591, 1490, 1472, 1293, 1254, 1166, 1144, 1074, 979, 835, 780, 686, 663.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{20}O_2Si$ $[M]^{\cdot+}$ 224.1227; found 224.1231.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

3-((*tert*-Butyldimethylsilyl)oxy)aniline (142^{e})[112]



142^{e}

$C_{12}H_{21}NOSi$

M = 223.39 g/mol

Aniline **142^{e}** was synthesised according to **GP1**, using 3-aminophenol (**141**, 101 mg, 0.926 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as brown oil (117 mg, 0.524 mmol, 57%).

R_f = 0.47 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.99 (t, *J* = 8.0 Hz, 1H, 5-H), 6.30 (ddd, *J* = 7.9, 2.2, 0.9 Hz, 1H, 4-H), 6.26 (ddd, *J* = 8.0, 2.3, 0.9 Hz, 1H, 6-H), 6.20 (t, *J* = 2.2 Hz, 1H, 2-H), 3.59 (s, 2H, NH_2), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.19 (s, 6H, $Si(CH_3)_2$).

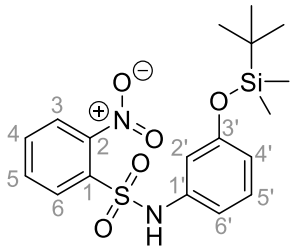
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 156.8 (C-1), 147.8 (C-3), 130.0 (C-5), 110.6 (C-6), 108.6 (C-4), 107.3 (C-2), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2955, 2929, 2857, 1620, 1597, 1491, 1461, 1311, 1284, 1253, 1191, 1154, 978, 836, 779, 686, 664.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{21}NOSi$ $[M]^{\cdot+}$ 223.1387; found 223.1368.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

N-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)-2-nitrobenzenesulfonamide (143^{e})



143^{e}

$C_{18}H_{24}N_2O_5SSi$

M = 408.54 g/mol

Aniline **142^{e}** (280 mg, 1.25 mmol, 1.00 eq) was dissolved in dry DCM (5.00 mL) and the solution was cooled to 0°C. TEA (0.524 mL, 3.76 mmol, 3.00 eq) and a solution of 2-nitrobenzenesulfonyl chloride (278 mg, 1.25 mmol, 1.50 eq) in dry DCM (5.00 mL) was added dropwise. The reaction mixture was warmed up to rt and stirred for 16 h. The organic layer was washed with water (5.00 mL) and the aqueous layer was extracted with DCM (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product was purified *via* FCC (hexanes/EtOAc 7:3) and the title compound **143^{e}** was obtained as a light brown solid (232 mg, 0.568 mmol, 45%).

R_f = 0.57 (hexanes/EtOAc 7:3).

mp: 100°C.

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.84 (dd, *J* = 7.9, 1.4 Hz, 2H, 3-H and 6-H), 7.63 (dtd, *J* = 55.7, 7.7, 1.3 Hz, 2H, 4-H and 5-H), 7.18 (s, 1H, NH), 7.10 (t, *J* = 8.1 Hz, 1H, 5'-H), 6.77 (ddd, *J* = 8.0, 2.1, 1.0 Hz, 1H, 6'-H), 6.73 (t, *J* = 2.2 Hz, 1H, 2'-H), 6.65 (ddd, *J* = 8.2, 2.4, 1.0 Hz, 1H, 4'-H), 0.93 (s, 9H, $SiC(CH_3)_3$), 0.13 (s, 6H, $Si(CH_3)_2$).

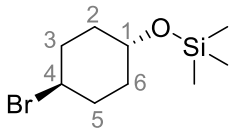
^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 156.6 (C-3'), 148.4 (C-2), 136.6 (C-1'), 134.08 (C-4), 132.6 (C-5), 132.3 (C-1), 132.1 (C-6), 130.2 (C-5'), 125.4 (C-3), 118.6 (C-4'), 116.1 (C-6'), 115.1 (C-2'), 25.7($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$, -4.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3289, 2951, 2931, 2857, 1599, 1541, 1499, 1467, 1395, 1370, 1339, 1260, 1153, 1125, 1058, 994, 902, 835, 777, 719, 688, 653, 583, 556.

HRMS (EI): *m*/*z* calculated for $C_{18}H_{24}N_2O_5SSi$ $[M]^{\cdot+}$ 408.11807; found 408.11371.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

(((1*R*,4*R*)-4-Bromocyclohexyl)oxy)trimethylsilane (146)



146
rac

$C_9H_{19}BrOSi$

M = 251.24 g/mol

TMSBr (1.54 mL, 11.7 mmol, 1.20 eq) was added dropwise to a solution of 7-oxabicyclo[2.2.1]heptane (**145**, 975 mg, 9.93 mmol, 1.00 eq) in dry DCM (18 mL) and the resulting mixture was stirred at rt for 18 h. The solvent was removed *in vacuo* and the crude product was purified *via* FCC (hexanes/EtOAc 7:3). Silylether **146** was isolated as colourless oil (1.06 g, 4.22 mmol, 43%).

R_f = 0.90 (hexanes/EtOAc 7:3).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 4.18 – 4.07 (m, 1H, 4-H), 3.70 (tt, *J* = 8.6, 3.8 Hz, 1H, 1-H), 2.32 – 2.22 (m, 2H, 3, 5-H), 1.93 – 1.84 (m, 2H, 2, 6-H), 1.84 – 1.76 (m, 2H, 3, 5-H), 1.42 (m, 2H, 2, 6-H), 0.10 (s, 9H, $Si(CH_3)_3$).

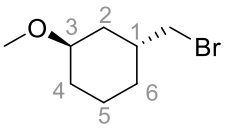
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 68.6 (C-1), 51.9 (C-2), 34.6 (C-2, 3, 5, 6), 0.3 ($Si(CH_3)_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2948, 2863, 2360, 1454, 1439, 1376, 1335, 1249, 1086, 1042, 1011, 875, 835, 788, 746, 697, 673.

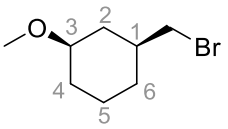
HRMS (EI): *m*/*z* calculated for $C_9H_{18}BrOSi$ $[M]^{\bullet+}$ 249.0310; found 249.0303.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3*R*)-1-(Bromomethyl)-3-methoxycyclohexane / (1*S*,3*S*)-1-(bromomethyl)-3-methoxycyclohexane (152a) and (1*S*,3*R*)-1-(bromomethyl)-3-methoxycyclohexane / (1*R*,3*S*)-1-(bromomethyl)-3-methoxycyclohexane (152b)



152a
rac



152b
rac

$C_8H_{15}BrO$

M = 207.11 g/mol

Racemic bromides **152a** and **152b** were synthesised over two steps. To a solution of *cis*/*trans* mixture of 3-methoxycyclohexanecarboxylic acid (**153**, 844 mg, 5.17 mmol, 1.00 eq) in dry THF (30.0 mL), dimethyl sulfide borane (2M in THF, 3.36 mL, 6.73 mmol, 1.30 eq) was added dropwise at - 78 °C and the mixture was stirred for 5 h at 0°C. The reaction was stopped with aq. sat. $NaHCO_3$ solution (20.0 mL) and the mixture was extracted with EtOAc (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give (3-methoxycyclohexyl)methanol (**154**) as a colourless oil (746 mg, 5.17 mmol, quantitative). Alcohol **154** was used without further purification.

R_f = 0.20 (DCM/MeOH 99:1).

HRMS (EI): *m*/*z* calculated for $C_8H_{16}O_2$ $[M]^{\bullet+}$ 144.1144; found 144.1143.

To a suspension of crude alcohol **154** (746 mg, 5.17 mmol, 1.00 eq) and PPh_3 (2.74 g, 10.3 mmol, 2.00 eq) in DCM (50.0 mL) at 0 °C, CBr_4 (3.43 g, 10.3 mmol, 2.00 eq) was added. The reaction was warmed up to rt and after 2 h the solvent was removed *in vacuo* and the title compounds were separated and purified *via* FCC (hexanes/EtOAc 97:3) and **152a** (436 mg, 2.11 mmol, 41%) and **152b** (421 mg, 2.03 mmol, 39%) were both obtained as light yellow oil.

Analytical data of **152a***:

R_f = 0.29 (hexanes/EtOAc 97:3).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 3.54 (p, *J* = 3.2 Hz, 1H, 3-H), 3.32 – 3.28 (m, 5H, OCH_3, 1-CH_2), 2.07 – 1.95 (m, 2H, 1, 2-H), 1.90 – 1.77 (m, 2H, 4, 6-H), 1.68 – 1.47 (m, 2H, 5-H), 1.35 – 1.25 (m, 1H, 4-H), 1.20 (tt, *J* = 12.3, 2.5 Hz, 1H, 2-H), 1.08 (tdd, *J* = 12.5, 11.0, 4.0 Hz, 1H, 6-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 75.1 (C-3), 55.8 (OCH_3), 41.0 (1-CH_2), 34.9 (C-2), 34.2 (C-1), 31.1 (C-6), 29.3 (C-4), 19.9 (C-8).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2929, 2858, 2821, 1738, 1445, 1363, 1250, 1233, 1083, 965, 944, 886, 807, 685.

HRMS (EI): *m*/*z* calculated for $C_8H_{14}BrO$ $[M\text{-}H]^{\cdot+}$ 205.0234; found 205.0220.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

Analytical data of **152b***:

R_f = 0.20 (hexanes/EtOAc 97:3).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 3.36 (s, 3H, OCH_3), 3.31 (dd, *J* = 6.3, 1.5 Hz, 2H, 1-CH_2), 3.14 (tt, *J* = 10.8, 4.2 Hz, 1H, H-3), 2.23 (dtt, *J* = 11.9, 4.1, 2.0 Hz, 1H, 2-H), 2.08 – 2.00 (m, 1H, 4-H), 1.87 – 1.78 (m, 2H, 5, 6-H), 1.74 – 1.63 (m, 1H, 1-H), 1.33 – 1.20 (m, 1H, 5-H), 1.16 – 1.03 (m, 1H, 4-H), 1.01 – 0.88 (m, 2H, 2, 6-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 78.9 (C-3), 55.9 (OCH_3), 39.8 (1-CH_2), 38.9 (C-1), 37.2 (C-2), 31.8 (C-4), 31.1 (C-6), 23.6 (C-5).

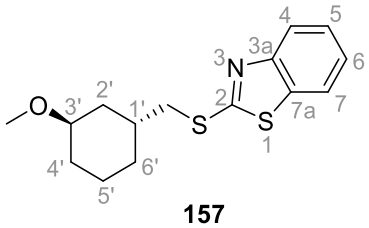
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2929, 2857, 2821, 1463, 1450, 1373, 1276, 1232, 1166, 1110, 1088, 976, 923.

HRMS (EI): *m*/*z* calculated for $C_8H_{14}BrO$ $[M\text{-}H]^{\cdot+}$ 205.0234; found 205.0220.

Purity (GC): 92% (scan mode *m*/*z* 50-650 (EI 70 eV)).

*The *cis*/*trans* identification was performed retrospectively from **158** and **160**, respectively.

2-((((1*R*,3*R*)-3-Methoxycyclohexyl)methyl)thio)benzo[*d*]thiazole and 2-((((1*S*,3*S*)-3-methoxycyclohexyl)methyl)thio)benzo[*d*]thiazole (157)



157
rac

$C_{15}H_{19}NOS_2$

M = 293.44 g/mol

To a solution of bromide **152a** (400 mg, 1.93 mmol, 1.00 eq) and 2-mercaptobenzthiazole (388 mg, 2.32 mmol, 1.20 eq) in DCM (32.0 mL) at 0 °C TEA (0.538 mL, 3.86 mmol, 2.00 eq) was added and the reaction mixture was stirred at rt for 17 h. The reaction was stopped with water (20.0 mL) and the extracted with DCM (3 x 35.0 mL). The combined organic layers were washed with water (50.0 mL), brine (50.0 mL) and then dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (172 mg, 0.586 mmol, 30%).

R_f = 0.40 (hexanes/EtOAc 90:10).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.85 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H, 4-H), 7.74 (ddd, *J* = 7.9, 1.3, 0.6 Hz, 1H, 7-H), 7.40 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H, 5-H), 7.31 – 7.25 (m, 1H, 6-H), 3.57 – 3.52 (m, 1H, 3'-H), 3.32 – 3.26 (m, 5H, OCH_3, 1'-CH_2), 2.18 – 2.06 (m, 2H, 1', 2'-H), 1.94 – 1.80 (m, 2H, 4', 6'-H), 1.69 – 1.49 (m, 3H, 4', 5'-H), 1.41 – 1.31 (m, 1H, 2'-H), 1.19 – 1.08 (m, 1H, 6'-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 167.9 (C-2), 153.3 (C-3a), 135.3 (C-7a), 126.2 (C-5), 124.3 (C-6), 121.5 (C-4), 121.0 (C-7), 75.2 (C-3'), 55.8 (OCH_3), 40.3 (1'-CH_2), 35.6 (C-2'), 32.3 (C-1'), 31.9 (C-6'), 29.5 (C-4'), 20.2 (C-5').

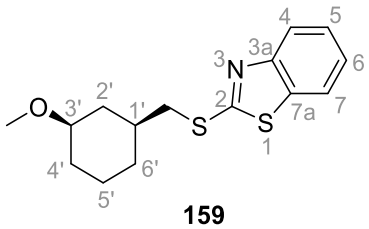
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2925, 2858, 1455, 1425, 1238, 1105, 1083, 991, 943, 753, 725.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{19}ONS_2$ $[M]^{\cdot+}$ 293.0902; found 293.0899.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

*The *trans* identification was performed retrospectively from **158**.

2-((((1*S*,3*R*)-3-Methoxycyclohexyl)methyl)thio)benzo[*d*]thiazole and 2-((((1*R*,3*S*)-3-methoxycyclohexyl)methyl)thio)benzo[*d*]thiazole (159)



159
rac

$C_{15}H_{19}NOS_2$

M = 293.44 g/mol

To a solution of bromide **152b** (206 mg, 0.995 mmol, 1.00 eq) and 2-mercaptobenzthiazole (200 mg, 1.19 mmol, 1.20 eq) in DCM (16.0 mL) at 0 °C TEA (0.277 mL, 1.99 mmol, 2.00 eq) was added and the reaction mixture was stirred at rt for 17 h. The reaction was stopped with water (10.0 mL) and the extracted with DCM (3 x 17.0 mL). The combined organic layers were washed with water (25.0 mL), brine (25.0 mL) and then dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as light yellow oil (122 mg, 0.416 mmol, 42%).

R_f = 0.27 (hexanes/EtOAc 9:1).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.86 (ddd, *J* = 8.1, 1.2, 0.6 Hz, 1H, 4-H), 7.75 (ddd, *J* = 8.0, 1.3, 0.6 Hz, 1H, 7-H), 7.41 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H, 5-H), 7.29 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H, 6-H), 3.36 (s, 3H, OCH_3), 3.31 (dd, *J* = 6.8, 5.2 Hz, 2H, 1‘-CH_2), 3.14 (tt, *J* = 10.8, 4.1 Hz, 1H, 3‘-H), 2.35 – 2.28 (m, 1H, 2‘-H), 2.12 – 2.04 (m, 1H, 6‘-H), 1.93 – 1.88 (m, 1H, 6‘-H), 1.87 – 1.74 (m, 2H, 1‘, 5‘-H), 1.59 – 1.52 (m, 2H, 4‘-H), 1.40 – 1.32 (m, 1H, 5‘-H), 1.04 – 0.96 (m, 1H, 2‘-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 167.6 (C-2), 153.4 (C-3a), 135.3 (C-7a), 126.2 (C-5), 124.3 (C-6), 121.6 (C-4), 121.1 (C-7), 79.1 (C-3‘), 55.9 (OCH_3), 41.0 (C-4‘), 40.1 (1‘-CH_2), 38.1 (C-2‘), 36.8 (C-1‘), 31.9 (C-6‘), 23.8 (C-5‘).

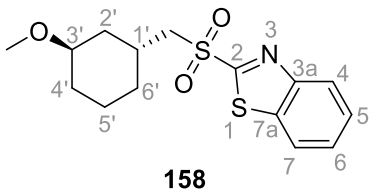
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2927, 2856, 1456, 1426, 1087, 993, 921, 755, 726, 704.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{19}ONS_2$ $[M]^{\cdot+}$ 293.0908; found 293.0901.

Purity (HPLC): 62% (λ = 210 nm), 69% (λ = 254 nm) (method c).

*The *cis* identification was performed retrospectively from **160**.

2-((((1*S*,3*S*)-3-Methoxycyclohexyl)methyl)sulfonyl)benzo[*d*]thiazole and 2-((((1*R*,3*R*)-3-methoxycyclohexyl)methyl)sulfonyl)benzo[*d*]thiazole (158)



158
rac

$C_{15}H_{19}NO_3S_2$

M = 325.44 g/mol

To a solution of **157** (154 mg, 0.525 mmol, 1.00 eq) in DCM (20.0 mL), *m*-CPBA (647 mg, 2.89 mmol, 5.50 eq) was added and the reaction mixture was stirred for 24 h at rt. The reaction was stopped with sat. aq. $Na_2S_2O_3$ (10.0 mL) and sat. aq. $NaHCO_3$ (10.0 mL) and the aq. phase was extracted with DCM (3 x 30.0 mL). The combined organic layers were washed with brine (30.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as white oily solid (156 mg, 0.479 mmol, 91%).

R_f = 0.22 (hexanes/EtOAc 8:2).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.21 (ddd, *J* = 8.1, 1.4, 0.7 Hz, 1H, 4-H), 8.02 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H, 7-H), 7.67 – 7.55 (m, 2H, 5, 6-H), 3.51 – 3.47 (m, 1H, 3'-H), 3.44 (t, *J* = 6.3 Hz, 2H, 1'-CH_2), 3.26 (s, 3H, OCH_3), 2.57 – 2.46 (m, 1H, 1'-H), 2.21 – 2.12 (m, 1H, 2'-H), 1.93 – 1.84 (m, 1H, 6'-H), 1.83 – 1.74 (m, 1H, 4'-H), 1.70 – 1.57 (m, 1H, 5'-H), 1.54 – 1.43 (m, 1H, 5'-H), 1.42 – 1.27 (m, 3H, 2', 4', 6'-H).

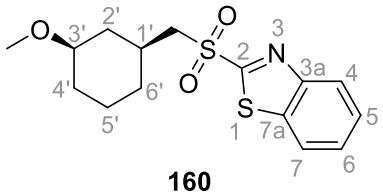
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 166.9 (C-2), 152.8 (C-3a), 136.9 (C-7a), 128.1 (C-6), 127.8 (C-5), 125.6 (C-4), 122.5 (C-7), 74.7 (C-3'), 60.6 (1'-CH_2), 55.8 (OCH_3), 35.5 (C-2'), 32.3 (C-6'), 29.6 (C-4'), 27.7 (C-1'), 20.1 (C-5').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2929, 1471, 1323, 1315, 1146, 1105, 1082, 1023, 944, 852, 759, 729, 689.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{18}O_3NS_2$ $[M]^{\cdot+}$ 324.0723; found 324.0718.

Purity (HPLC): 93% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

2-((((1*S*,3*R*)-3-Methoxycyclohexyl)methyl)sulfonyl)benzo[*d*]thiazole and 2-((((1*R*,3*S*)-3-methoxycyclohexyl)methyl)sulfonyl)benzo[*d*]thiazole (160)



160
rac

$C_{15}H_{19}NO_3S_2$

M = 325.44 g/mol

To a solution of **159** (108 mg, 0.368 mmol, 1.00 eq) in DCM (14.0 mL), *m*-CPBA (349 mg, 2.02 mmol, 5.50 eq) was added and the reaction mixture was stirred for 24 h at rt. The reaction was stopped with sat. aq. $Na_2S_2O_3$ (8.00 mL) and sat. aq. $NaHCO_3$ (8.00 mL) and the aq. phase was extracted with DCM (3 x 25.0 mL). The combined organic layers were washed with brine (15.0 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as white solid (120 mg, 0.368 mmol, quantitative).

R_f = 0.20 (hexanes/EtOAc 8:2).

mp: 55 °C.

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.21 (ddd, *J* = 8.1, 1.4, 0.7 Hz, 1H, 4-H), 8.02 (ddd, *J* = 7.8, 1.5, 0.7 Hz, 1H, 7-H), 7.68 – 7.54 (m, 2H, 5, 6-H), 3.50 (d, *J* = 6.3 Hz, 2H, 1'-CH_2), 3.31 (s, 3H, OCH_3), 3.14 (tt, *J* = 10.7, 4.0 Hz, 1H, 3'-H), 2.32 – 2.16 (m, 2H, 1', 2'-H), 2.06 – 1.89 (m, 2H, 4', 6'-H), 1.84 – 1.75 (m, 1H, 5'-H), 1.37 – 1.22 (m, 2H, 4', 5'-H), 1.15 – 1.01 (m, 2H, 2', 6'-H).

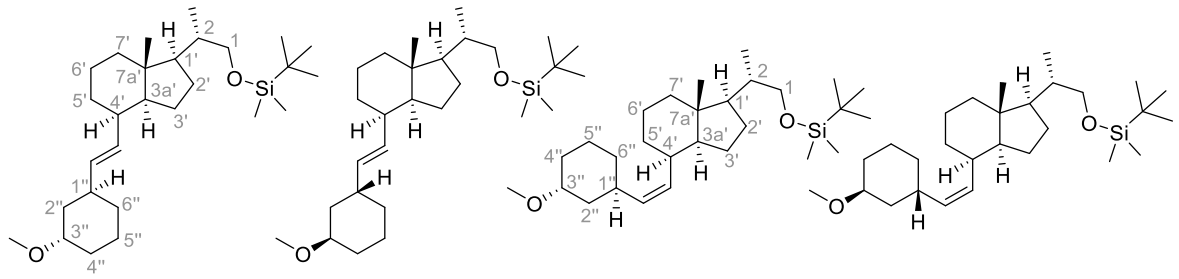
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 166.8 (C-2), 152.8 (C-3a), 136.9 (C-7a), 128.2 (C-6), 127.8 (C-5), 125.6 (C-4), 122.5 (C-7), 78.4 (C-3'), 60.7 (1'-CH_2), 55.9 (OCH_3), 38.3 (C-2'), 32.3 (C-6'), 31.4 (C-4'), 31.4 (C-1'), 23.3 (C-5').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2935, 2859, 1474, 1309, 1198, 1143, 1111, 1072, 1024, 978, 929, 840, 756, 747, 731, 687.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{20}O_3NS_2$ $[M]^{\cdot+}$ 326.0879; found 326.0877.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

tert-Butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-((_E_)-2-((1_S_/_R_,3_S_/_R_)-3-methoxycyclohexyl)vinyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane and _tert_-butyl((_S_)-2-((1_R_,3a_S_,4_R_,7a_S_)-4-((_Z_)-2-((1_R_/_S_,3_R_/_S_)-3-methoxycyclohexyl)vinyl)-7a-methyloctahydro-1_H_-inden-1-yl)propoxy)dimethylsilane (150)



150
_E_/_Z_ ratio 55:45

$C_{28}H_{52}O_2Si$

M = 448.81 g/mol

In an oven-dried two-necked Schlenk-flask, sulfone **158** (207 mg, 0.636 mmol, 1.00 eq) was dissolved in dry THF (6.00 mL) and the solution was cooled to - 78 °C. LDA (2M in THF, 0.382 mL, 0.763 mmol, 1.20 eq) was added and the reaction mixture was stirred for 30 min at - 78 °C. A solution of aldehyde **73[b]** (258 mg, 0.763 mmol, 1.20 eq) in dry THF (7.00 mL) was added dropwise. The reaction mixture was slowly warmed to - 50 °C and stirred for 18 h. The reaction was stopped with sat. aq. NH_4Cl (7.00 mL), the layers were separated, and the aq. phase was extracted with EtOAc (3 x 20.0 mL). The combined organic layers were washed with brine (30.0 mL), dried over Na_2SO_4, filtered and the solvent was removed _in vacuo_. The title compounds were purified twice _via_ FCC (hexanes/EtOAc 98:2) to give _seco_-steroids **150** as an inseparable _E_/_Z_ mixture (_E_/_Z_ ratio 55:45 determined _via_ ^{1}H, 4:5:43:48 determined _via_ GC/MS) of four isomers as a light yellow oil (196 mg, 0.437 mmol, 69%).

<u>The analytical data refers to the mixture of the four isomers:</u>

R_f = 0.27 (hexanes/EtOAc 98:2).

$[\alpha]_D^{23}$: + 26.9 (c = 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-_d_) _δ_/ppm = 5.57 (m, 2H, 4'-CH(_E_)), 5.48 (m, 2H, 4'-CH(_Z_)), 5.25 (m, 2H, 1''-CH(_E_)), 5.17 (m, 2H, 1''-CH(_Z_)), 3.58 (m, 4H, 1-H), 3.51 – 3.44 (m, 4H, 3''-H), 3.32 – 3.28 (m, 12H, OCH_3), 3.23 (m, 4H, 1-H), 2.87 – 2.78 (m, 2H, 4'-H(_Z_)), 2.67 – 2.54 (m, 2H, 1''-H(_Z_)), 2.44 – 2.39 (m, 2H, 4'-H(_E_)), 2.38 – 2.29 (m, 2H, 1''-H(_E_)), 1.99 – 1.88 (m, 4H, 7'-H), 1.87 – 1.71 (m, 13H, CH_2), 1.69 – 1.28 (m, 51H, 2, 3a'-H, CH_2), 1.27 – 1.04 (m, 20H, 1'-H, CH_2), 0.98 – 0.93 (m, 12H, 2-CH_3), 0.89 (s, 37H, $SiC(CH_3)_3$), 0.74 (m, 6H, 7a'-CH_3), 0.70 (s, 6H, 7a'-CH_3), 0.06 – 0.02 (m, 24H, $Si(CH_3)_2$).

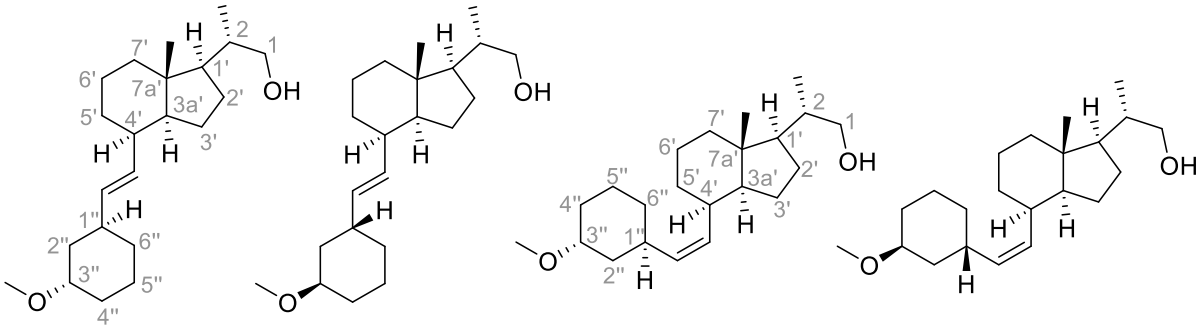
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 135.3 (CH), 135.2 (CH), 134.6 (CH), 129.6 (CH), 129.4 (CH), 129.4 (CH), 75.6 (C-3''), 75.5 (C-3''), 75.5 (C-3''), 68.1 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 53.8 (OCH_3), 55.8 (OCH_3), 53.8 (C-1‘), 53.5 (C-1‘), 52.7 (C-3a‘), 52.5 (C-3a‘), 52.5 (C-3a‘), 42.7 (C-7a’), 42.6 (C-7a’), 40.8 (C-7‘), 40.7 (C-7‘), 40.7 (C-7‘), 39.0 (C-4’(*E*)), 38.9 (C-2), 36.7 (CH_2), 36.6 (CH_2), 36.5 (CH_2), 35.8 (CH_2), 35.3 (C-1''(*E*)), 35.2 (C-1''(*E*)), 34.9 (C-4’(*Z*)), 34.8 (C-4’(*Z*)), 32.9 (CH_2) , 32.7 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 30.9 (CH_2), 30.3 (C-1''(*Z*)), 30.2 (C-1''(*Z*)), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 27.0 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.1 ($SiC(\underline{C}H_3)_3$), 24.9 (CH_2), 24.8 (CH_2), 24.1 (CH_2), 20.3 (CH_2), 20.2 (CH_2), 20.1 (CH_2), 18.7 (CH_2), 18.5 ($Si\underline{C}(CH_3)_3$), 16.9 (2-CH_3), 16.9 (2-CH_3), 16.9 (2-CH_3), 14.3 (7a’-CH_3), 13.8 (7a’-CH_3), 13.8 (7a’-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR) $\tilde{\nu}$/cm^{-1} = 3725, 3705, 2927, 2856, 1473, 1460, 1440, 1361, 1250, 1089, 1032, 1006, 835, 773, 670, 662.

HRMS (EI): *m*/*z* calculated for $C_{28}H_{52}O_2Si$ $[M]^{\cdot+}$ 448.3731; found 448.3738.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-((*E*)-2-((1*S*/*R*,3*S*/*R*)-3-Methoxycyclohexyl)vinyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol and (*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-((*Z*)-2-((1*R*/*S*,3*R*/*S*)-3-methoxycyclohexyl)vinyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (161)



E-**161a** *E*-**161b** *Z*-**161c** *Z*-**161d**

161

$C_{22}H_{38}O_2$

M = 334.54 g/mol

The (inseparable) mixture of *E*/*Z* isomers **161** was synthesised according to **GP9**, using *E*/*Z* mixture of four isomers **150** (51.0 mg, 0.110 mmol, 1.00 eq). *Z*-Isomer *Z*-**161c** or *Z*-**161d** could be separated from the mixture of *E*-isomers *E*-**161a**/*E*-**161b** and from the appropriate *Z*-isomer *via* FCC (hexanes/EtOAc 8:2). The *E*/*Z* ratio of the three isomers is 71:29 (determined *via* ^{1}H NMR).

Analytical data of inseparable mixture of *E*-**161a** / *E*-**161b** / *Z*-**161c** or *Z*-**161d** (three isomers):

Yield: 20.0 mg, 0.0598 mmol, 53%.

Appearance: colourless oil.

$\mathbf{R_f}$ = 0.30 (hexanes/EtOAc 8:2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$: + 32.0 (c = 0.03, $CHCl_3$).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.59 – 5.53 (m, 2H, 4'-CH(*E*)), 5.51 – 5.45 (m, 0.8H, 4'-CH(*Z*)), 5.29 – 5.23 (m, 2H, 1''-CH(*E*)), 5.20 – 5.14 (m, 0.8H, 1''-CH(*Z*)), 3.64 – 3.59 (m, 3H, 1-H), 3.53 – 3.44 (m, 3H, 3''-H), 3.39 – 3.34 (m, 3H, 1-H), 3.33 – 3.28 (m, 9H, OCH_3), 2.85 – 2.77 (m, 0.8H, 4'-H(*Z*)), 2.66 – 2.53 (m, 0.8H, 1''-H(*Z*)), 2.45 – 2.39 (m, 2H, 4'-H(*E*)), 2.38 – 2.28 (m, 2H, 1''-H(*E*)), 1.96 – 1.89 (m, 4H, 7'-H), 1.88 – 1.72 (m, 12H, CH_2), 1.70 – 1.35 (m, 42H, 2, 3a'-H, CH_2), 1.31 – 1.10 (m, 10H, 1'-H, CH_2), 1.02 – 0.98 (m, 9H, 7a'-CH_3), 0.78 – 0.68 (m, 9H, 2-CH_3).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 135.4 (CH), 134.7 (CH), 129.5 (CH), 129.3 (CH), 129.3 (CH), 75.6 (C-3''), 75.5 (C-3''), 68.1 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 53.5

(C-1'), 53.2 (C-1'), 52.7 (C-3a'), 52.5 (C-3a'), 42.7 (C-7a'), 42.6 (C-7a'), 40.8 (C-7'), 40.6 (C-7'), 38.9 (C-2), 38.7 (CH), 38.7 (C-4'(*E*)), 36.7 (CH_2), 36.6 (CH_2), 36.5 (CH_2), 35.3 (C-1''(*E*)), 35.2 (C-1''(*E*)), 34.8 (C-4'(*Z*)), 32.7 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 32.3 (CH_2), 30.9 (CH_2), 30.3 (C-1''(*Z*)), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.0 (CH_2), 27.0 (CH_2), 24.7 (CH_2), 24.0 (CH_2), 24.0 (CH_2), 23.9 (CH_2), 20.3 (CH_2), 20.1 (CH_2), 18.7 (CH_2), 16.8 (2-CH_3), 16.7 (2-CH_3), 14.3 (7a'-CH_3), 13.8 (7a'-CH_3), 13.8 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3725, 3709, 3622, 3598, 2929, 2360, 1218, 771, 676, 652, 566.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{34}O$ $[M\text{-}OCH_3]^{\cdot+}$ 302.2604; found 302.2612.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

Analytical data of *Z*-**161c** or *Z*-**161d** (one isomer):

Yield: 6.00 mg, 0.0179 mmol, 16%.

Appearance: colourless oil.

$\mathbf{R_f}$ = 0.23 (hexanes/EtOAc 8:2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 13.5 (c = 0.04, $CHCl_3$).

^{1}H NMR (800 MHz, chloroform-*d*) *δ*/ppm = 5.48 (td, *J* = 10.8, 1.0 Hz, 1H, 4'-CH), 5.18 (ddd, *J* = 11.0, 9.9, 1.2 Hz, 1H, 1''-CH), 3.63 (dd, *J* = 10.5, 3.2 Hz, 1H, 1-H), 3.49 – 3.46 (m, 1H, 3''-H), 3.36 (dd, *J* = 10.5, 6.9 Hz, 1H, 1-H), 3.30 (s, 3H, OCH_3), 2.85 – 2.79 (m, 1H, 4'-H), 2.62 – 2.55 (m, 1H, 1''-H), 1.96 – 1.91 (m, 1H, 7'-H), 1.83 – 1.75 (m, 3H, 2'', 4''-H, 2', 3', 5' or 6'-H), 1.69 – 1.62 (m, 2H, 2', 3', 5' or 6'-H), 1.60 – 1.54 (m, 3H, 5'', 6''-H, 2', 3', 5' or 6'-H), 1.54 – 1.41 (m, 5H, 2, 3a', 5''-H, 2', 3', 5' or 6'-H), 1.40 – 1.29 (m, 2H, 4''-H, 2', 3', 5' or 6'-H), 1.27 – 1.22 (m, 1H, 2', 3', 5' or 6'-H), 1.21 – 1.13 (m, 3H, 1', 7', 2''-H), 1.07 – 1.02 (m, 1H, 6''-H), 1.01 (d, *J* = 6.6 Hz, 3H, 2-CH_3), 0.76 (s, 3H, 7a'-CH_3).

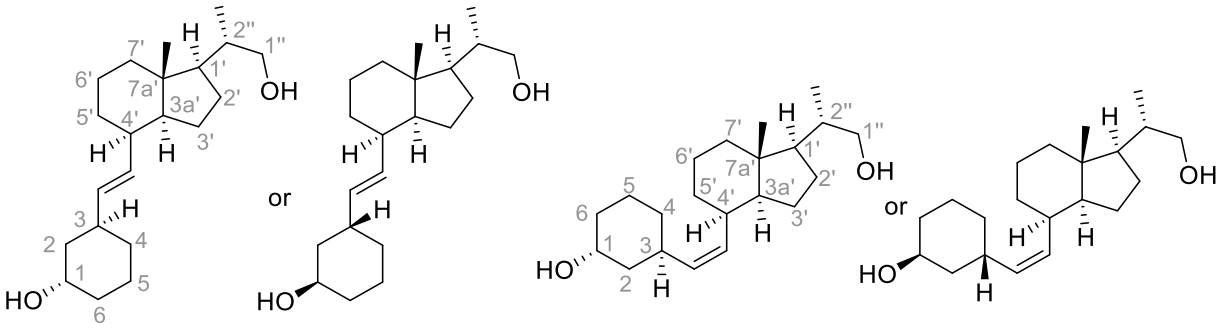
^{13}C NMR (201 MHz, chloroform-*d*) *δ*/ppm = 135.4 (1''-CH), 129.5 (4'-CH), 75.5 (C-3''), 68.1 (C-1), 55.9 (OCH_3), 53.2 (C-1'), 52.5 (C-3a'), 42.6 (C-7a'), 40.6 (C-7'), 38.7 (C-2), 35.8 (C-2''), 34.8 (C-4'), 32.9 (C-6''), 32.3 (C-2', 3', 5' or 6'), 30.2 (C-1''), 29.9 (C-4''), 27.1 (C-2', 3', 5' or 6'), 24.8 (C-2', 3', 5' or 6'), 20.2 (C-5''), 18.7 (C-2', 3', 5' or 6'), 16.7 (2-CH_3), 14.3 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3727, 3624, 2934, 2875, 1445, 1112, 1089, 1039, 763, 671, 656.

HRMS (EI): *m*/*z* calculated for $C_{22}H_{38}O_2$ $[M]^{\cdot+}$ 334.2866; found 334.2861.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*S*/*R*,3*S*/*R*)-3-((*E*)-2-((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)vinyl)cyclohexan-1-ol and (1*R*/*S*,3*R*/*S*)-3-((*Z*)-2-((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)vinyl)cyclohexan-1-ol (149, two isomers, *E*/*Z*)



149

$C_{21}H_{36}O_2$

M = 320.52 g/mol

The inseparable mixture of *E*/*Z* isomers **161** (two *E*-isomers, one *Z*-isomer, 14.0 mg, 0.0418 mmol, 1.00 eq) and NaI (6.90 mg, 0.0460 mmol, 1.10 eq) were dissolved in 1:1 DCM/MeCN (500 µL). $SiCl_4$ (5.27 µL, 0.0460 mmol, 1.10 eq) was added and the mixture was heated to 60 °C for 8 h. The reaction was stopped with water (1.00 mL) and extracted with EtOAc (3 x 2.00 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and the inseparable mixture of *E*/*Z* diols **149** (ratio 59:41, determined *via* ^{1}H NMR) was isolated as colourless oil (4.40 mg, 0.0137 mmol, 33%).

R_f = 0.16 (hexanes/EtOAc 7:3).

$[\alpha]_D^{23}$: + 30.7 (c = 0.03, $CHCl_3$).

^{1}H NMR (800 MHz, chloroform-*d*) *δ*/ppm = 5.60 – 5.55 (m, 1H, 4'-CH(*E*)), 5.50 – 5.47 (m, 0.7H, 4'-CH(*Z*)), 5.29 – 5.25 (m, 1H, 3-CH(*E*)), 5.22 – 5.18 (m, 0.7H, 3-CH(*Z*)), 4.09 – 4.01 (m, 3H, 1-H(*E*/*Z*), OH), 3.65 – 3.62 (m, 2H, 1''-H(*E*/*Z*)), 3.38 – 3.34 (m, 2H, 1''-H(*E*/*Z*)), 2.84 – 2.79 (m, 0.7H, 4'-H(*Z*)), 2.69 – 2.63 (m, 0.7H, 3-H(*Z*)), 2.45 – 2.39 (m, 2H, 4'-H(*E*), 3-H(*E*)), 1.96 – 1.89 (m, 2H, 7'-H(*E*/*Z*)), 1.82 – 1.76 (m, 3H, CH_2), 1.70 – 1.58 (m, 10H, CH_2), 1.57 – 1.37 (m, 11H, 3a'-H(*E*/*Z*), 2''-H(*E*/*Z*), CH_2), 1.28 – 1.10 (m, 6H, 1'-H(*E*/*Z*), 7'-H(*E*/*Z*), CH_2), 1.02 – 1.00 (m, 5.1H, 2''-CH_3(*E*/*Z*)), 0.75 (s, 2.1H, 7a'-CH_3(*Z*)), 0.72 (s, 3H, 7a'-CH_3(*E*))

^{13}C NMR (201 MHz, chloroform-*d*) *δ*/ppm = 134.9 (3-CH_2(*Z*)), 134.3 (3-CH_2(*E*)), 129.6 (4'-CH_2(*Z*)), 129.6 (4'-CH_2(*E*)), 68.1 (C-1''(*E*/*Z*)), 66.9 (C-1(*E*)), 66.7 (C-1(*Z*)), 53.5 (C-1'(*E*)), 53.2 (C-1'(*Z*)), 52.7 (C-3a'(*E*)), 52.5 (C-3a'(*E*)), 42.7 (C-7a'(*E*)), 42.6 (C-7a'(*Z*)), 40.8 (C-7'(*E*)), 40.6 (C-7'(*Z*)), 39.9 (CH_2), 39.9 (CH_2), 38.9 (CH_2), 38.9 (C-4'(*E*)), 38.7 (C-2''(*Z*)), 38.7 (C-2''(*E*)),

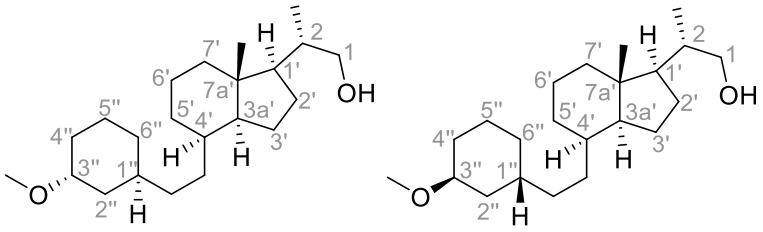
35.1 (C-3(*E*)), 34.8 (C-4'(*Z*)), 32.4 (CH_2), 32.3 (CH_2), 32.3 (CH_2), 30.8 (CH_2), 30.1 (C-3(*Z*)), 29.9 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 24.7 (CH_2), 24.0 (CH_2), 20.1 (CH_2), 19.8 (CH_2), 18.7 (CH_2), 18.7 (CH_2), 16.8 (2''-CH_3(*E*)), 16.7 (2''-CH_3(*Z*)), 14.2 (7a'-CH_3(*E*)), 13.8 (7a'-CH_3(*Z*)).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3725, 3711, 3696, 3621, 3592, 2918, 2860, 1458, 1220, 1025, 971, 769, 673, 647.

HRMS (EI) calculated for $C_{18}H_{40}O4$ $[M]^{\cdot+}$ 320.2709; found 320.2704.

Purity (GC): 84% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(2-((1*S*,3*R*)-3-Methoxycyclohexyl)ethyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol and (*S*)-2-((1*R*,3a*S*,4*R*,7a*S*)-4-(2-((1*R*,3*S*)-3-methoxycyclohexyl)ethyl)-7a-methyloctahydro-1*H*-inden-1-yl)propan-1-ol (162)



162

$C_{22}H_{40}O_2$

M = 336.56 g/mol

The inseparable mixture of racemic *E*/*Z* isomers **150** (125 mg, 0.279 mmol, 1.00 eq) was dissolved in EtOAc (10.0 mL) and Pd/C (12.5 mg, 0.0117 mmol, 10 wt%) was added. The flask was filled with H_2 and the reaction mixture was stirred at rt for 18 h. The Pd/C catalyst was removed *via* filtration through a celite pad and the resulting filtrate was concentrated under reduced pressure. The crude product was used without further purification.

HRMS (EI): *m*/*z* calculated for $C_{28}H_{53}O_2Si$ $[M]^{\cdot+}$ 449.3809; found 449.3801.

The hydrogenated crude product (0.279 mmol) was TBDMS deprotected using **GP9** and the title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as colourless oil (48.6 mg, 0.144 mmol, 52% over two steps).

R_f = 0.53 (hexanes/EtOAc 8:2).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 37.0 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 3.74 – 3.60 (m, 2H, 1-H), 3.51 – 3.44 (m, 2H, 3''-H), 3.41 – 3.33 (m, 2H), 3.30 (d, *J* = 1.1 Hz, 6H, OCH_3), 1.92 – 1.64 (m, 14H, CH, CH_2), 1.59 – 1.31 (m, 24H, CH, CH_2), 1.28 – 1.11 (m, 12H, CH, CH_2), 1.07 – 0.97 (m, 12H, 2-CH_3, CH, CH_2), 0.85 (s, 6H, 7a'-CH_3).

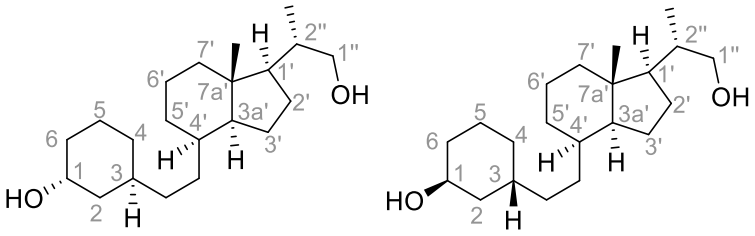
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 75.9 (C-3''), 75.8 (C-3''), 68.6 (C-2), 68.3 (CH_2), 68.1 (CH_2), 66.8 (CH_2), 55.8 (OCH_3), 55.5 (CH), 54.6 (C-3a'), 54.6 (OCH_3), 54.2 (CH), 52.9 (CH), 44.2 (C-7a'), 42.6 (C-7a'), 42.4 (C-1'), 41.1 (CH_2), 40.2 (CH_2), 38.9 (CH), 38.6 (CH), 38.2 (C-2), 37.9 (CH_2), 37.2 (CH_2), 36.8 (CH_2), 36.4 (CH_2), 35.8 (C-7'), 34.3 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 29.8 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 27.1 (CH_2), 25.7 (CH_2), 24.6 (7a'-CH_3), 23.9 (CH_2), 22.4 (CH_2), 22.1 (CH_2), 21.1 (CH_2), 21.1 (CH_3), 20.5 (CH_2), 18.0 (CH_3), 17.4 (2-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3726, 3708, 3693, 3623, 3599, 2364, 1218, 772, 678, 651, 617.

HRMS (EI): *m*/*z* calculated for $C_{22}H_{40}O_2$ $[M]^{\cdot+}$ 336.3023; found 336.3013.

Purity (GC): n.d.

(1*R*,3*S*)-3-(2-((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)ethyl)cyclohexan-1-ol and (1*S*,3*R*)-3-(2-((1*R*,3a*S*,4*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-4-yl)ethyl)cyclohexan-1-ol (151)



151

$C_{21}H_{38}O_2$

M = 322.53 g/mol

Mixture of ethers **162** (34.0 mg, 0.100 mmol, 1.00 eq) and NaI (16.7 mg, 0.111 mmol, 1.10 eq) were dissolved in 1:1 DCM/MeCN (1.00 mL). $SiCl_4$ (12.7 µL, 0.111 mmol, 1.10 eq) was added and the mixture was stirred at 60 °C for 8 h. The reaction was stopped with water (2.00 mL) and extracted with EtOAc (3 x 3.00 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and diol **151** was isolated as colourless oil (10.0 mg, 0.0310 mmol, 31%).

R_f = 0.17 (hexanes/EtOAc 7:3).

$[\alpha]_D^{23}$: + 16.7 (c = 0.04, $CHCl_3$).

^{1}H NMR (800 MHz, chloroform-*d*) *δ*/ppm = 4.06 – 4.02 (m, 2H, 1-H), 3.72 – 3.60 (m, 2H, 1''-H), 3.41 – 3.30 (m, 2H, 1''-H), 1.92 – 1.83 (m, 3H, CH_2), 1.81 – 1.70 (m, 6H, CH, CH_2), 1.67 – 1.57 (m, 9H, CH, CH_2), 1.54 – 1.36 (m, 16H, CH, CH_2), 1.25 – 1.12 (m, 24H, CH, CH_2), 1.06 (d, *J* = 6.7 Hz, 3H, 2''-CH_3), 1.01 (dd, *J* = 6.6, 1.5 Hz, 3H, 2''-CH_3), 0.86 – 0.79 (m, 6H, 7a'-CH_3).

^{13}C NMR (201 MHz, chloroform-*d*) *δ*/ppm = 68.6 (C-1''), 67.1 (C-1), 67.1 (C-1''), 66.8 (C-1), 54.6 (C-3a'), 54.6 (C-3a'), 44.2 (C-7a'), 42.6 (C-7a'), 42.4 (C-1'), 42.4 (C-1'), 40.3 (CH_2), 39.6 (CH_2), 38.6 (CH_2), 38.5 (C-2''), 38.2 (C-2''), 37.8 (CH_2), 37.0 (C-7'), 35.8 (C-7'), 33.7 (CH_2), 33.6 (CH_2), 32.7 (CH_2), 32.1 (C-4'), 32.1 (CH_2), 31.9 (CH_2), 31.8 (C-4'), 29.5 (CH_2), 27.8 (CH_2), 26.1 (C-3), 25.7 (C-3), 24.9 (CH_2), 24.6 (7a'-CH_3), 23.9 (7a'-CH_3), 22.9 (CH_2), 21.1 (CH_2), 21.0 (CH_2), 20.2 (CH_2), 20.2 (CH_2), 20.2 (CH_2), 17.4 (2''-CH_3), 16.9 (2''-CH_3).

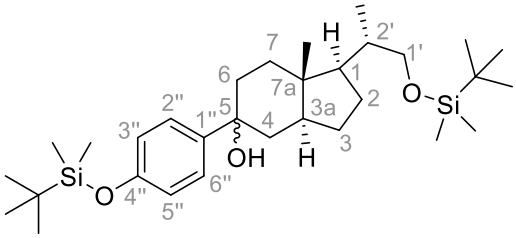
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3726, 3708, 3693, 3623, 3599, 2360, 1218, 772, 720, 671, 654.

HRMS (EI): *m*/*z* calculated for $C_{21}H_{38}O_2$ $[M]^{\cdot+}$ 322.2866; found 322.2867.

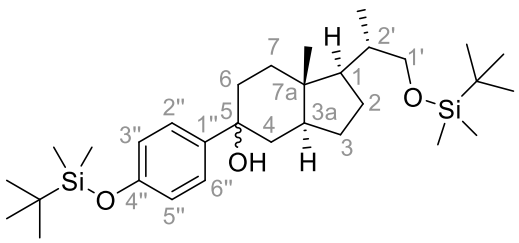
Purity (GC): n.d.

6.2.5. Procedures and data for seco-steroids with bridging at C-5 (chapter 3.3.2.)

((1*R*,3a*S*,7a*S*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-5-ol (164a) and (1*R*,3a*S*,7a*S*)-5-(4-((*tert*-Butyldimethylsilyl)oxy)phenyl)-1-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)-7a-methyloctahydro-1*H*-inden-5-ol (164b)



164a



164b

$C_{31}H_{56}O_3Si_2$

M = 532.96 g/mol

Alcohols **164a** and **164b** were synthesised according to **GP6** using ketone **28[c]** (264 mg, 0.814 mmol, 1.00 eq) and aryl bromide **78[d]** (258 mg, 0.898 mmol, 1.10 eq). The title compounds were separated and purified *via* FCC (hexanes/EtOAc 9:1) and **164a** was isolated as white oily solid (6.00 mg, 0.011 mmol, 1%) and **164b** as white solid (192 mg, 0.360 mmol, 44%).

Analytical data of **164a***:

R_f = 0.55 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 45.9 (c = 0.08, C HCl_3).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.38 – 7.32 (m, 2H, 2'', 6''-H), 6.83 – 6.77 (m, 2H, 3'', 5''-H), 3.61 (dd, *J* = 9.6, 3.3 Hz, 1H, 1'-H), 3.29 (dd, *J* = 9.7, 7.4 Hz, 1H, 1'-H), 2.06 – 1.83 (m, 4H, 3a, 7-H, 2, 3, 4 or 6-H), 1.83 – 1.73 (m, 1H, OH), 1.70 – 1.48 (m, 5H, 7, 2'-H, 2, 3, 4 or 6-H), 1.39 – 1.11 (m, 3H, 1-H, 2, 3, 4 or 6-H), 1.03 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.76 (s, 3H, 7a-CH_3), 0.19 (s, 6H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$), 0.05 (s, 3H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 154.5 (C-4''), 142.5 (C-1''), 125.7 (C-2'', 6''), 119.7 (C-3'', 5''), 73.7 (C-5), 68.0 (C-1'), 52.4 (C-1), 44.6 (C-3a), 42.0 (C-7a), 39.5 (C-2, 3, 4 or 6), 39.3 (C-2'), 35.9 (C-7), 35.9 (C-2, 3, 4 or 6), 27.8 (C-2, 3, 4 or 6), 26.4 (C-2, 3, 4 or 6), 26.2 ($SiC(\underline{C}H_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), 17.1 (2'-CH_3), 10.5 (7a-CH_3), -4.3 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2928, 1603, 1508, 1471, 1251, 1084, 912, 832, 807, 773, 674.

HRMS (EI): *m*/*z* calculated for $C_{31}H_{56}O_3Si_2$ $[M]^{\cdot+}$ 532.3768; found 532.3760.

Purity (HPLC): 91% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

Analytical data of **164b***:

R_f = 0.26 (hexanes/EtOAc 9:1).

$[\alpha]_D^{23}$: + 46.9 (c = 0.03, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.43 – 7.37 (m, 2H, 2'', 6''-H), 6.84 – 6.77 (m, 2H, 3'', 5''-H), 3.55 (dd, *J* = 9.6, 3.5 Hz, 1H, 1'-H), 3.17 (dd, *J* = 9.7, 7.7 Hz, 1H, 1'-H), 2.32 – 2.15 (m, 2H, 7-H, 2, 3, 4 or 6-H), 2.05 – 1.90 (m, 2H, OH, 2, 3, 4 or 6-H), 1.81 – 1.39 (m, 5H, 3a, 7, 2'-H, 2, 3, 4 or 6-H), 1.36 – 1.12 (m, 5H, 1-H, 2, 3, 4 or 6-H), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.95 (d, *J* = 6.5 Hz, 3H, 2'-CH_3), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.83 (s, 3H, 7a-CH_3), 0.21 (s, 6H, $Si(CH_3)_2$), 0.00 (s, 6H, $Si(CH_3)_2$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 154.6 (C-4''), 135.4 (C-1''), 125.9 (C-2'', 6''), 119.9 (C-3'', 5''), 68.1 (C-5), 52.7 (C-1'), 46.1 (C-1), 44.6 (C-2, 3, 4 or 6), 42.3 (C-3a), 40.9 (C-7), 39.2 (C-7a), 30.4 (C-2'), 28.0 (C-2, 3, 4 or 6), 27.0 (C-2, 3, 4 or 6), 26.1 (C-2, 3, 4 or 6), 25.9 ($SiC(\underline{C}H_3)_3$), 18.6 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), 16.8 ($Si\underline{C}(CH_3)_3$), 11.5 (2'-CH_3), -4.3 (7a-CH_3), -5.2 ($Si(CH_3)_2$), -5.2 ($Si(CH_3)_2$).

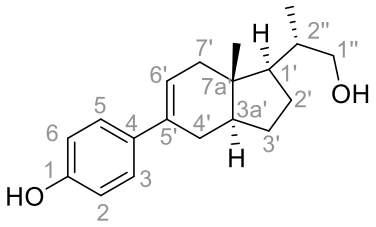
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2928, 1603, 1507, 1471, 1254, 1081, 912, 832, 807, 773.

HRMS (EI): *m*/*z* calculated for $C_{31}H_{56}O_3Si_2$ $[M]^{\cdot+}$ 532.3768; found 532.3755.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method e).

*Due to very fast dehydratision the stereoconfiguration at C-5 could not be determined.

4-((1*R*,3a*S*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl)phenol (166)



166

$C_{19}H_{26}O_2$

M = 286.42 g/mol

Diol **166** was synthesised according to **GP9** using silyl ether **164b** (50.0 mg, 93.8 µmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as off-white solid (18.0 mg, 62.8 µmol, 67%).

R_f = 0.26 (hexanes/EtOAc 7:3).

mp: 169 °C.

$[\alpha]_D^{23}$: + 67.9 (c = 0.03, MeOH).

^{1}H NMR (400 MHz, methanol-d_4) δ/ppm = 7.26 – 7.20 (m, 2H, 2, 6-H), 6.75 – 6.69 (m, 2H, 3, 5-H), 6.63 (s, 1H, 1-OH), 5.92 – 5.85 (m, 1H, 6'-H), 3.62 (dd, *J* = 10.6, 3.2 Hz, 1H, 1''-H), 3.34 – 3.28 (m, 2H, 1''-H, collapses with methanol-d_4), 2.48 – 2.35 (m, 2H, 4', 7'-H), 2.20 – 2.06 (m, 2H, 4', 7'-H), 2.01 – 1.91 (m, 1H, 2' or 3'-H), 1.84 – 1.71 (m, 2H, 3a'-H, 2' or 3'-H), 1.59 (m, 1H, 2''-H), 1.49 – 1.26 (m, 4H, 1', 2', 3'-H, 1''-OH), 1.10 (d, *J* = 6.5 Hz, 3H, 2''-CH_3), 0.74 (d, *J* = 0.6 Hz, 3H, 7a'-CH_3).

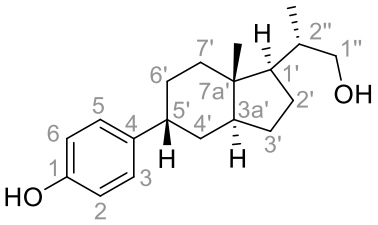
^{13}C NMR (101 MHz, methanol-d_4) δ/ppm = 157.3 (C-1), 136.7 (C-4), 135.1 (C-5'), 127.1 (C-2, 6), 122.7 (C-6'), 115.9 (C-3, 5), 67.9 (C-1''), 53.7 (C-1'), 47.4 (C-3a'), 43.3 (C-7a'), 41.9 (C-7'), 40.2 (C-2''), 31.5 (C-4'), 28.9 (C-2' or 3'), 27.9 (C-2' or 3'), 17.0 (2''-CH_3), 11.6 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3419, 2880, 1608, 1513, 1468, 1373, 1260, 1233, 1181, 1111, 1020, 991, 974, 835, 806, 788.

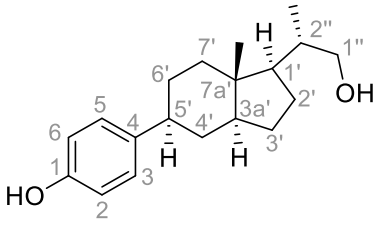
HRMS (EI): *m*/*z* calculated for $C_{19}H_{26}O_2$ $[M]^{\cdot+}$ 286.1927; found 286.1927.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

4-((1*R*,3a*S*,5*R*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-5-yl)phenol (163a) and 4-((1*R*,3a*S*,5*S*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-5-yl)phenol (163b)



163a



163b

$C_{19}H_{28}O_2$

M = 288.43 g/mol

Diols **163a** and **163b** were prepared over two steps. According to **GP8**, **164b** (94.9 mg, 0.178 mmol, 1.00 eq) was dehydrated and hydrogenated. The solvent was removed *in vacuo* and the crude mixture of silylethers (0.178 mmol) was then used for the preparation of diols **163a** and **163b** *via* **GP9**. The title compounds were purified and separated *via* FCC (hexanes/EtOAc 7:3) and diol **163a** was obtained as light yellow oily solid (21.0 mg, 0.0728 mmol, 41%) and diol **163b** was obtained as beige, crystalline solid (9.00 mg, 0.0312 mmol, 18%).

Analytical data of diol **163a**:

R_f = 0.63 (hexanes/EtOAc 70:30).

$[\alpha]_D^{23}$: + 4.9 (c = 0.48, $CHCl_3$).

^{1}H NMR (400 MHz, methanol-d_4) δ/ppm = 7.08 – 7.03 (m, 2H, 3, 5-H), 6.73 – 6.68 (m, 2H, 2, 6-H), 4.43 (dd, *J* = 10.7, 3.4 Hz, 1H, 1''-H), 4.17 (dd, *J* = 10.7, 7.1 Hz, 1H, 1''-H), 2.52 – 2.41 (m, 1H, 5'-H), 2.06 (dt, *J* = 12.7, 3.4 Hz, 1H, 7'-H), 1.91 (dqd, *J* = 13.0, 6.4, 3.1 Hz, 2H, 2''-H, 2', 3', 4' or 6'-H), 1.66 (qd, *J* = 10.3, 8.6, 5.2 Hz, 3H, 2', 3', 4' or 6'-H), 1.59 – 1.22 (m, 6H, 1', 3a', 7'-H, 2', 3', 4' or 6'-H), 1.11 (d, *J* = 6.7 Hz, 3H, 2''-CH_3), 0.85 (s, 3H, 7a'-CH_3).

^{13}C NMR (101 MHz, methanol-d_4) δ/ppm = 156.4 (C-1), 139.7 (C-4), 128.7 (C-3, 5), 116.0 (C-2, 6), 74.3 (C-1''), 53.6 (C-1'), 51.7 (C-3a'), 45.5 (C-5'), 43.3 (C-7a'), 41.3 (C-7'), 37.1 (C-2''), 34.8 (C-2', 3', 4' or 6'), 31.7 (C-2', 3', 4' or 6'), 28.5 (C-2', 3', 4' or 6'), 27.5 (C-2', 3', 4' or 6'), 17.3 (2''-CH_3), 11.6 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3726, 3705, 3623, 3598, 2938, 2860, 1783, 1514, 1221, 1171, 1032, 831, 777, 671, 649.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{28}O_2$ $[M]^{\cdot+}$ 288.2084; found 288.2088.

Purity (HPLC): > 95% (λ = 210 nm), 95% (λ = 254 nm) (method c).

Analytical data of diol **163b**:

R_f = 0.30 (hexanes/EtOAc 70:30).

mp: 154 °C.

$[\alpha]_D^{23}$**:** + 28.9 (c = 0.03, MeOH).

^{1}H NMR (400 MHz, methanol-d_4) δ/ppm = 7.07 – 7.01 (m, 2H, 3, 5-H), 6.72 – 6.66 (m, 2H, 2, 6-H), 3.59 (dd, *J* = 10.6, 3.2 Hz, 1H, 1''-H), 3.27 (dd, *J* = 10.6, 7.1 Hz, 1H, 1''-H, collapses with methanol-d_4), 2.44 (tt, *J* = 10.7, 4.9 Hz, 1H, 5'-H), 2.06 (dt, *J* = 12.6, 3.3 Hz, 1H, 7'-H), 1.91 (dtd, *J* = 12.5, 9.1, 6.0 Hz, 1H, 2', 3', 4' or 6'-H), 1.67 – 1.60 (m, 2H, 2', 3', 4' or 6'-H), 1.60 – 1.42 (m, 5H, 3a', 2''-H, 1''-OH, 2', 3', 4' or 6'-H), 1.41 – 1.19 (m, 5H, 1, 7'-H, 2', 3', 4' or 6'-H), 1.06 (d, *J* = 6.6 Hz, 3H, 2''-CH_3), 0.82 (s, 3H, 7a'-CH_3).

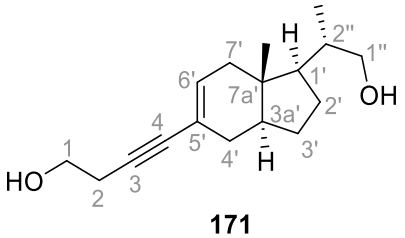
^{13}C NMR (101 MHz, methanol-d_4) δ/ppm = 156.3 (C-1), 139.9 (C-4), 128.7 (C-3, 5), 116.0 (C-2, 6), 68.0 (C-1''), 53.8 (C-1'), 51.8 (C-3a'), 45.6 (C-5'), 43.2 (C-7a'), 41.5 (C-7'), 40.4 (C-2''), 34.9 (C-2', 3', 4' or 6'), 31.8 (C-2', 3', 4' or 6'), 28.8 (C-2', 3', 4' or 6'), 27.6 (C-2', 3', 4' or 6'), 17.4 (2''-CH_3), 11.7 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3185, 2361, 1612, 1550, 1514, 1346, 1248, 1121, 1002, 813.

HRMS (EI): *m*/*z* calculated for $C_{19}H_{28}O_2$ $[M]^{\bullet+}$ 288.2084; found 288.2086.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

(4-((1*R*,3a*S*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-5-yl)but-3-yn-1-ol (171)



171

$C_{17}H_{26}O_2$

M = 262.39 g/mol

Diol **171** was synthesised over two steps. In an oven-dried two-necked Schlenk flask enol triflate **172** (260 mg, 0.569 mmol, 1.00 eq) was dissolved in dry THF (5.00 mL) and 3-butyn-1-ol (**173**, 53.3 µL, 0.683 mmol, 1.20 eq), TEA (0.198 mL, 1.42 mmol, 2.50 eq) and CuI (21.7 mg, 0.114 mmol, 20 mol%) were added under N_2 counter-flow. After purging of the solution with N_2, $PdCl_2(PPh_3)_2$ (40.0 mg, 0.0569 mmol, 10 mol%) was added and the reaction mixture was stirred at rt for 1.5 h. Subsequently, the reaction was quenched with sat. aq. NH_4Cl (5.00 mL) and the aq. phase was extracted with DCM (3 x 10.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude product **170** was purified *via* a short silica plug and was used without further purification.

Diol **171** was synthesised according to **GP9**, using alcohol **170** (0.569 mmol) and the title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as white oily solid (129 mg, 0.492 mmol, 86% over two steps).

R_f = 0.33 (hexanes/EtOAc 5:5).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{23}}$: + 83.7 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.95 (dt, *J* = 5.6, 2.6 Hz, 1H, 6'-H), 3.72 (t, *J* = 6.2 Hz, 1H, 1-H), 3.65 (dd, *J* = 10.5, 3.2 Hz, 1H, 1''-H), 3.39 (dd, *J* = 10.5, 6.7 Hz, 1H, 1''-H), 2.57 (t, *J* = 6.2 Hz, 1H, 2-H), 2.26 (ddd, *J* = 18.2, 5.7, 2.3 Hz, 1H, 7'-H), 2.21 – 2.13 (m, 1H, 4'-H), 2.05 (d, *J* = 18.6 Hz, 1H, 7'-H), 1.96 – 1.80 (m, 2H, 4'-H, 2' or 3'-H), 1.76 – 1.53 (m, 3H, 3a', 2''-H, 2' or 3'-H), 1.41 – 1.14 (m, 3H, 1', 2', 3'-H), 1.04 (d, *J* = 6.6 Hz, 3H, 2''-CH_3), 0.65 (s, 3H, 7a'-CH_3).

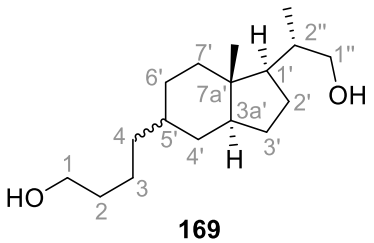
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 133.9 (C-6'), 119.9 (C-5'), 84.3 (C-4), 83.6 (C-3), 68.0 (C-1''), 61.4 (C-1), 52.3 (C-1'), 45.3 (C-3a'), 42.0 (C-7'), 40.6 (C-7a'), 38.7 (C-2''), 32.7 (C-4'), 27.8 (C-2' or 3'), 26.6 (C-2' or 3'), 23.9 (C-2), 16.5 (2''-CH_3), 11.4 (7a'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3347, 2933, 2908, 2876, 1467, 1427, 1370, 1040, 1029, 994, 968, 907, 853, 813, 731.

HRMS (EI): *m*/*z* calculated for $C_{17}H_{26}O_2$ $[M]^{\cdot+}$ 262.1927; found 262.1924.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

4-((1*R*,3a*S*,7a*S*)-1-((*S*)-1-Hydroxypropan-2-yl)-7a-methyloctahydro-1*H*-inden-5-yl)butan-1-ol (169)



169

$C_{17}H_{32}O_2$

M = 268.44 g/mol

Diol **169** was synthesised *via* three steps. For SONOGASHIRA cross-coupling enol triflate **172** (260 mg, 0.569 mmol, 1.00 eq) was dissolved in dry THF (4.00 mL) and but-3-yn-1-ol (**173**, 49.4 mg, 0.683 mmol, 1.20 eq), TEA (0.198 mL, 1.42 mmol, 2.50 eq) and CuI (21.7 mg, 0.114 mmol, 20 mol%) were added under N_2 counterflow. After purging the solution with N_2, $PdCl_2(PPh_3)_2$ (40.0 mg, 0.0569 mmol, 10 mol%) was added and the reaction mixture was stirred for 1.5 h. The reaction was stopped with sat. aq. NH_4Cl (5.00 mL) and the aq. phase was extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to give crude alkyne **170**. For the following hydrogenation, **170** (0.569 mmol) was dissolved in EtOAc (5.00 mL) and AcOH (30.0 µL, 0.569 mmol, 1.00 eq). The solution was degassed and PtO_2 (2.59 mg, 0.0114 mmol, 2.00 mol%) was added under N_2 counterflow. The reaction mixture was stirred at H_2 atmosphere for 21 h and then filtered through a celite pad and concentrated under reduced pressure. The crude intermediate (0.569 mmol) was deprotected according to **GP9** and purified *via* FCC (hexanes/EtOAc 6:4) to give diol **169** as colourless oil (32.0 mg, 0.119 mmol, 21% over three steps).

R_f = 0.17 (hexanes/EtOAc 6:4).

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$: + 13.6 (c = 0.04, $CHCl_3$).

^{1}H NMR (400 MHz, chloroform-*d*) δ/ppm = 3.70 – 3.51 (m, 3H, 1, 1''-H), 3.36 (dd, *J* = 10.5, 6.9 Hz, 1H, 1''-H), 1.94 – 1.87 (m, 1H, 7'-H), 1.85 – 1.75 (m, 1H, 2', 3', 4' or 6'-H), 1.62 – 1.44 (m, 7H, 5', 2''-H, 2, 3, 4, 2', 3', 4' or 6'-H), 1.40 – 1.13 (m, 9H, 1', 3a', 7'-H, 2, 3, 4, 2', 3', 4' or 6'-H), 1.04 (d, *J* = 6.6 Hz, 3H, 2''-CH_3), 0.65 (s, 3H, 7a'-CH_3).

^{13}C NMR (101 MHz, chloroform-*d*) δ/ppm = 68.2 (C-2''), 63.2 (C-1), 52.4 (C-1'), 50.2 (C-3a'), 42.6 (C-7a'), 39.9 (C-7'), 39.0 (C-5'), 38.2 (C-2''), 37.2 (C-2', 3', 4' or 6'), 33.2 (C-2, 3 or 4), 32.5 (C-2, 3 or 4), 29.2 (C-2', 3', 4' or 6'), 27.8 (C-2', 3', 4' or 6'), 26.7 (C-2', 3', 4' or 6'), 23.4 (C-2, 3 or 4), 16.9 (2''-CH_3), 11.3 (7a'-CH_3).

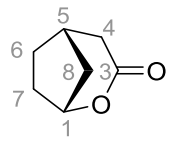
IR (ATR): $\tilde{\nu}$/cm^{-1} = 3726, 3708, 3623, 3599, 2932, 2846, 1218, 1040, 770, 676, 657.

HRMS (EI): *m*/*z* calculated for $C_{17}H_{31}O_2$ $[M]^{\cdot+}$ 267.2319; found 267.2322.

Purity (GC): 80% (scan mode *m*/*z* 50-650 (EI 70 eV), compound undergoes dehydration during the measurement, resulting in 20% dehydrated compound).

6.2.6. Procedures and data for seco-steroids with “broken” ring C (chapter 3.4.)

(1*R*,5*S*)-2-Oxabicyclo[3.2.1]octan-3-one and (1*S*,5*R*)-2-Oxabicyclo[3.2.1]octan-3-one (180[a])



180[a]

rac

$C_7H_{10}O_2$

M = 126.16 g/mol

In an oven-dried 100 mL round bottom flask racemic 2-norboranone (3.00 g, 27.3 mmol, 1.00 eq) was dissolved in DCM (35.0 mL) and *m*-CPBA (12.2 g, 54.5 mmol, 2.00 eq) was added. The reaction mixture was stirred at rt for 24 h. The solution was washed with aq. 2M NaOH (50.0 mL) and H_2O (50.0 mL), the combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and obtained as a colourless oil (2.77 g, 22.9 mmol, 80%).

R_f = 0.15 (hexanes/EtOAc 8:2).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.84 (tt, *J* = 2.9, 1.4 Hz, 1H, 1-H), 2.70 (ddd, *J* = 18.5, 5.1, 2.2 Hz, 1H, 4-H), 2.56 – 2.49 (m, 1H, 5-H), 2.46 (dt, *J* = 18.4, 2.0 Hz, 1H, 4-H), 2.14 (td, *J* = 9.6, 2.6 Hz, 1H, 6-H), 2.00 – 1.93 (m, 1H, 7-H), 1.93 – 1.84 (m, 2H, 6-H, 8-H), 1.75 – 1.59 (m, 2H, 7-H, 8-H).

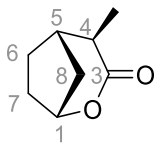
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 170.9 (C-3), 81.1 (C-1), 40.8 (C-4), 35.9 (C-7), 32.6 (C-6), 31.9 (C-5), 29.4 (C-8).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2941, 2879, 1729, 1465, 1439, 1374, 1345, 1222, 1195, 1162, 1128, 1068, 1015, 999, 977, 923, 900, 880, 844, 725, 577, 555.

HRMS (EI): *m*/*z* calculated for $C_7H_{11}O_2$ $[M]^{\bullet+}$ 127.0754; found 127.0754.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,4*R*,5*S*)-4-Methyl-2-oxabicyclo[3.2.1]octan-3-one and (1*S*,4*S*,5*R*)-4-Methyl-2-oxabicyclo[3.2.1]octan-3-one (181[a])



DH-AS-2[a]

rac

$C_8H_{12}O_2$

M = 140.18 g/mol

Lactone **180[a]** (2.00 g, 15.9 mmol, 1.00 eq) was dissolved in dry THF (15.0 mL), cooled down to - 78 °C and LDA (2M in THF/hexane/ethylbenzene, 15.9 mL, 31.7 mmol, 2.00 eq) was slowly added. After 1 h CH_3I (2.96 mL, 47.6 mmol, 3.00 eq) was added and the mixture was allowed to warm up to - 40 °C and stirred for 2 h. The reaction was stopped with aq. sat. NH_4Cl (10.0 mL), the two layers were separated, and the aq. layer was extracted with Et_2O (3 x 40.0 mL). The combined organic layers were washed with brine (2 x 20.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified *via* FCC (hexanes/EtOAc 5:5) and the methylated lactone **181[a]** was obtained as a colourless oil (1.71 g, 12.2 mmol, 77 %).

R_f = 0.6 (hexanes/EtOAc 5:5).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.81 (ddt, *J* = 4.3, 2.9, 1.4 Hz, 1H, 1-H), 2.52 (m, *J* = 7.5, 1.5 Hz, 1H, 4-H), 2.29 – 2.22 (m, 1H, 5-H), 2.17 – 2.05 (m, 2H, 7-H, 8-H), 2.00 – 1.83 (m, 2H, 6-H, 7-H), 1.75 – 1.67 (m, 1H, 6-H) 1.56 – 1.47 (m, 1H, 8-H) 1.32 (d, *J* = 7.5 Hz, 3H, 4-CH_3).

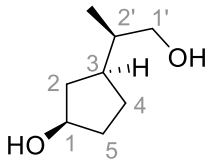
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 174.7 (C-3), 80.9 (C-1), 45.6 (C-4), 38.7 (C-5), 32.4 (C-7), 32.2 (C-8), 29.9 (C-6), 19.3 (4-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2967, 2943, 2877, 1724, 1495, 1377, 1317, 1303, 1282, 1230, 1210, 1195, 116, 1132, 1093, 1056, 1029, 991, 931, 888, 845, 816, 787, 748, 675, 645, 595.

HRMS (EI): *m*/*z* calculated for $C_8H_{13}O_2$ $[M]^{\cdot+}$ 141.0910; found 141.0911.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3*S*)-3-((*R*)-1-Hydroxypropan-2-yl)cyclopentan-1-ol and (1*S*,3*R*)-3-((*S*)-1-Hydroxypropan-2-yl)cyclopentan-1-ol (182[a])



182[a]

rac

$C_8H_{16}O_2$

M = 144.21 g/mol

A solution of lactone **181[a]** (1.20 g, 8.56 mmol, 1.00 eq) in dry THF (5.00 mL) was added to a suspension of $LiAlH_4$ (0.357 g, 9.42 mmol, 1.10 eq) in dry THF (50.0 mL) at 0 °C and stirred for 1 h. The reaction mixture was stopped with aq. 2M NaOH (10.0 mL) and the aq. phase was extracted with Et_2O (3 x 50.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification of the title compound *via* FCC (DCM/MeOH 95:5) yielded diol **182[a]** as a colourless oil (1.06 g, 7.38 mmol, 86%).

R_f = 0.14 (DCM/MeOH 95:5).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.31 – 4.19 (m, 1H, 1-H), 3.58 (dd, *J* = 10.7, 4.9 Hz, 1H, 1'-H), 3.39 (dd, *J* = 10.7, 6.7 Hz, 1H, 1'-H), 2.48 (s, 2H, 1'-OH, 1-OH), 2.14 – 2.01 (m, 1H, 2-H), 1.70 (m, 3H, 3-H, 4-H, 5-H), 1.63 – 1.43 (m, 3H, 2'-H, 4-H, 5-H), 1.27 (m,1H, 2-H), 0.93 (d, *J* = 6.7 Hz, 3H, 2'-CH_3).

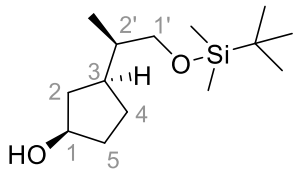
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 73.6 (C-1) 67.2 (C-1'), 41.1 (C-2' or C-3), 41.0 (C-2' or C-3), 39.9 (C-2), 35.3 (C-4 or C-5), 28.0 (C-4 or C-5), 15.7 (2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2952, 2868, 2857, 2375, 1725, 1710, 1455, 1378, 1348, 1073, 1022, 993, 961, 810, 736, 661, 649, 615, 592, 578, 555.

HRMS (EI): *m*/*z* calculated for $C_8H_{15}O_2$ $[M]^{\bullet+}$ 143.1067; found: 143.1067.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(1*R*,3*S*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)cyclopentan-1-ol and (1*S*,3*R*)-3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)cyclopentan-1-ol (183a[a])



183a[a]

rac

$C_{14}H_{30}O_2Si$

M = 258.48 g/mol

Alcohol **183a[a]** was synthesised according to **GP1**, using diol **182[a]** (0.684 g, 4.74 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated the desired alchol **183a[a]** as colourless oil (564 mg, 2.18 mmol, 46%) and the double protected diol **183b[a]** as a side product (R_f = 0.92, hexanes/EtOAc 8:2), 609 mg, 1.63 mmol, 35%).

R_f = 0.41 (hexanes/EtOAc 8:2).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 4.30 – 4.20 (m, 1H, 1-H), 3.55 (dd, *J* = 9.9, 4.7 Hz, 1H, 1'-H), 3.39 (dd, *J* = 9.8, 6.5 Hz, 1H, 1'-H), 2.18 – 2.06 (m, 1H, 5-H), 1.72 (m, 4H, 2-H, 3-H, 4-H), 1.55 – 1.42 (m, 3H, 2-H, 2'-H, 1-OH), 1.29 – 1.21 (m, 1H, 5-H), 0.91 (d, *J* = 6.7 Hz, 3H, 3'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$).

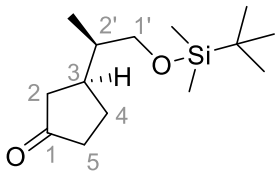
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 73.8 (C-1), 67.5 (C-1'), 41.3(C-2' or C-3), 41.1 (C-2' or C-3), 40.6 (C-5), 35.5 (C-2), 27.9 (C-4), 26.1 ($SiC(\underline{C}H_3)_3$), 18.5 ($Si\underline{C}(CH_3)_3$), 15.6 (3'-CH_3), -5.2 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3506, 3461, 3439, 341, 3379, 3354, 2954, 2929, 2889, 2875, 2857, 2359, 2347, 1471, 1387, 1360, 1252, 1086, 1005, 990, 953, 833, 809, 773, 664.

HRMS (EI): *m*/*z* calculated for $C_{10}H_{19}OSi$ $[M\text{-}t\text{Bu}]^{\bullet+}$ 183.1200; found 183.1200.

Purity (GC): 94% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-3-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)cyclopentan-1-one and (*R*)-3-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)propan-2-yl)cyclopentan-1-one (177[a])



177[a]

rac

$C_{14}H_{28}O_2Si$

M = 256.46 g/mol

Ketone **177[a]** was synthesised according to **GP3**, using alcohol **183a[a]** (0.510 g, 1.97 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as a colourless oil (447 mg, 1.74 mmol, 88 %).

R_f = 0.40 (hexanes/EtOAc 8:2).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 3.56 – 3.43 (m, 2H, 1'-H), 2.44 – 2.26 (m, 2H, 2-H, 5-H), 2.20 – 2.01 (m, 3H, 2-H, 4-H), 1.89 (m, 1H, 5-H), 1.59 – 1.47 (m, 2H, 2'-H, 3-H), 0.97 (d, *J* = 6.7 Hz, 3H, 2'-CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$).

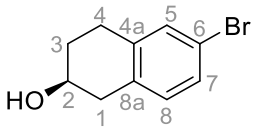
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 220.1 (C-1), 67.2 (C-1'), 44.1 (C-5), 41.2 (C-2'), 40.0 (C-3), 39.0 (C-2), 27.7 (C-4), 26.1 ($SiC(\underline{C}H_3)_3$), 18.4 ($Si\underline{C}(CH_3)_3$), 14.8 (3'-CH_3), -5.3 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3219, 3185, 2958, 2929, 2883, 2857, 235, 1743, 1471, 1405, 1390, 1361, 1253, 1161, 1129, 1094, 1079, 1027, 1006, 983, 939, 835, 811, 774, 670, 613.

HRMS (EI): *m*/*z* calculated for $C_{10}H_{19}O_2Si$ $[M\text{-}t\text{Bu}]^{\cdot+}$ 199.1149; found 199.1149.

Purity (GC): > 95% (scan mode *m*/*z* 50-650 (EI 70 eV)).

(*S*)-6-Bromo-1,2,3,4-tetrahydronaphthalen-2-ol and (*R*)-6-Bromo-1,2,3,4-tetrahydronaphthalen-2-ol (184[a])



184[a]

rac

$C_{10}H_{11}BrO$

M = 227.10 g/mol

A solution of 6-bromo-2-tetralone (**178**, 253 mg, 1.09 mmol, 1.00 eq) in MeOH (10.0 mL) was cooled to 0 °C and $NaBH_4$ (62.0 mg, 1.64 mmol, 1.50 eq) was slowly added. After stirring for 20 min the mixture was allowed to warm up to rt and stirred for further 45 min. The reaction was stopped with ice cold water (5.00 mL) and concentrated *in vacuo*. The residue was treated with water (10.0 mL) and extracted with EtOAc (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 5:5) and isolated as a colourless oil (252 mg, 1.11 mmol, quantitative).

R_f = 0.49 (hexanes/EtOAc 5:5).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.25 – 7.21 (m, 2H, 5-H, 7-H), 6.96 – 6.93 (m, 1H, 8-H), 4.20 – 4.13 (m, 1H, 2-H), 3.02 (dd, *J* = 16.5, 5.0 Hz, 1H, 1-H), 2.94 (dt, *J* = 17.2, 6.0 Hz, 1H, 4-H), 2.87 – 2.74 (m, 1H, 4-H), 2.74 – 2.65 (m, 1H, 1-H), 2.03 (m, 1H, 3-H), 1.86 – 1.75 (m, 1H, 3-H).

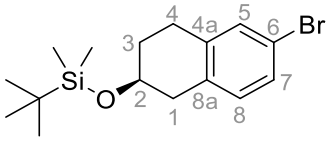
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 138.1 (C-4a), 133.3 (C-8a), 131.5 (C-5), 131.3 (C-8), 129.1 (C-7), 119.7 (C-6), 66.9 (C-2), 37.9 (C-1), 31.2 (C-3), 26.7 (C-4).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3018, 2924, 2857, 2355, 1894, 1737, 1590, 156, 1482, 1435, 1404, 1359, 1328, 1281, 1233, 1179, 1119, 1044, 100, 962, 923, 903, 854, 801, 738, 693.

HRMS (EI): *m*/*z* calculated for $C_{10}H_{11}BrO$ $[M]^{\bullet+}$ 225.9988; found 225.9988.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 250 nm) (method b).

(*S*)-((6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)(*tert*-butyl)dimethylsilane and (*R*)-((6-Bromo-1,2,3,4-tetrahydronaphthalen-2-yl)oxy)(*tert*-butyl)dimethylsilane (176[a])



176[a]

rac

$C_{16}H_{25}BrOSi$

M = 341.36 g/mol

Bromotetraline derivative **176[a]** was synthesised according to **GP1**, using alcohol **184[a]** (252 mg, 1.11 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as a colourless oil (248 gm, 0.728 mmol, 66 %).

R_f = 0.9 (hexanes/EtOAc 8:2).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.23 – 7.19 (m, 2H, 5-H, 7-H), 6.91 (d, *J* = 8.0 Hz, 1H, 8-H), 4.11 – 4.05 (m, 1H, 2-H), 2.95 – 2.87 (m, 2H, 1-H, 4-H), 2.74 (ddd, *J* = 16.4, 9.2, 5.7 Hz, 1H, 4-H), 2.67 (dd, *J* = 16.4, 7.6 Hz, 1H, 1-H), 1.92 (dtdd, *J* = 13.0, 5.7, 3.1, 1.6 Hz, 1H, 3-H), 1.76 (dtd, *J* = 12.8, 9.2, 5.6 Hz, 1H, 3-H), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 3H, $Si(CH_3)_2$), 0.08 (s, 3H, $Si(CH_3)_2$).

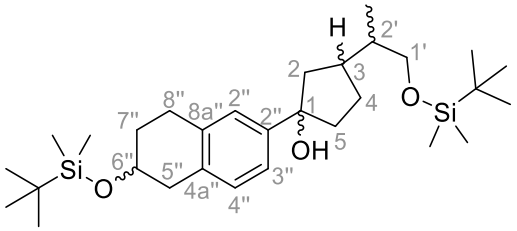
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 138.5 (C-4a), 134.2 (C-8a), 131.3 (C-5), 131.1 (C-8) 128.8 (C-7), 119.4 (C-6), 67.6 (C-2), 38.6 (C-1), 31.8 (C-3), 27.2 (C-4), 26.0 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -4.5 ($Si(CH_3)_2$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 295, 2929, 891, 2857, 2381, 2358, 2298, 1529, 1484, 1472, 1436, 1406, 1360, 1252, 1181, 1092, 1018, 983, 931, 880, 835, 810, 775, 738, 672, 649, 560.

HRMS (EI): *m*/*z* calculated for $C_{12}H_{16}BrOSi$ $[M]^{\bullet+}$ 283.0154; found 283.0150.

Purity (HPLC): > 95% (λ = 210 nm), > 95% (λ = 254 nm) (method c).

1-(6-((*tert*-Butyldimethylsilyl)oxy)-5,6,7,8-tetrahydronaphthalen-2-yl)-3-(1-((*tert*-butyldimethylsilyl)oxy)propan-2-yl)cyclopentan-1-ol (175[a], mixture of stereoisomers)



175[a]

$C_{30}H_{54}O_3Si_2$

M = 518.93 g/mol

Alcohol **175[a]** was synthesised according to **GP6**, using racemic bromotetraline derivative **176[a]** (73.4 mg, 0.215 mmol, 1.10 eq) and racemic mixture of ketone **177[a]** (50.1 mg, 0.195 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 8:2) and isolated as a colourless oil (21.0 mg, 0.0405 mmol, 21 %).

R_f = 0.59 (hexanes/EtOAc 8:2).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.21 (q, *J* = 5.3, 4.6 Hz, 2H, 1''-H, 3''-H), 7.10 – 7.00 (m, 1H, 4''-H), 4.12 – 4.00 (m, 1H, 6''-H), 3.58 (ddd, *J* = 9.9, 8.1, 4.7 Hz, 1H, 1'-H), 3.45 – 3.35 (m, 1H, 1'-H), 2.95 (dd, *J* = 16.6, 5.6 Hz, 2H, 5''-H, 8''-H), 2.81 (td, *J* = 11.1, 10.7, 5.0 Hz, 1H, 8''-H), 2.73 (dd, *J* = 16.3, 8.5 Hz, 1H, 5''-H), 2.33 – 2.18 (m, 1H, 2-H), 2.14 – 2.04 (m, 1H, 2-H), 2.04 – 1.89 (m, 3H, 3-H, 5-H, 7''-H,), 1.84 – 1.69 (m, 3H, 4-H, 5-H, 7''-H), 1.54 (ddt, *J* = 15.2, 12.9, 5.5 Hz, 3H, 3-H, 4-H, 2'-H), 0.96 (d, *J* = 6.7 Hz, 3H, 2'-CH_3), 0.92 – 0.88 (m, 18H, SiC(CH_3)$_3$), 0.10 – 0.03 (m, 12H, Si(CH_3)$_2$).

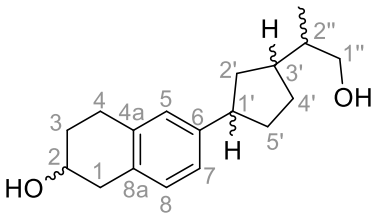
^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 145.2 (C-2''), 135.9 (C-8a''), 133.9 (C-4a''), 129.3 (C-4''), 125.1 (C-1''), 122.6 (C-3''), 83.1 (C-1), 68.4 (C-6''), 67.52(C-1'), 47.1 (C-5), 42.4 (C-3), 41.4 (C-2'), 40.8 (C-2), 38.9 (C-5''), 32.5 (C-7''), 29.6 (C-4), 28.2 (C-8''), 26.2 (SiC($\underline{C}H_3$)$_3$), 26.1 (SiC($\underline{C}H_3$)$_3$), 18.5 (Si$\underline{C}$(CH_3)$_3$), 18.4 (Si$\underline{C}$(CH_3)$_3$), -4.5 (Si($\underline{C}H_3$)$_2$), -5.2 (Si($\underline{C}H_3$)$_2$), 15.6 (2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2954, 2928, 2857, 2360, 2341, 2298, 1498, 1471, 1440, 1360, 1252, 1189, 1087, 1018, 1006, 933, 911, 879, 833, 811, 772, 713, 670.

HRMS (EI): *m*/*z* calculated for $C_{30}H_{53}O_3Si_2$ $[M]^{\bullet+}$ 517.3525; found 517.3525.

Purity (HPLC): n.d.

6-(3-(1-Hydroxypropan-2-yl)cyclopentyl)-1,2,3,4-tetrahydronaphthalen-2-ol (174ª, mixture of stereoisomers)



174ª

$C_{18}H_{26}O_2$

M = 274.40 g/mol

Alcohol **175ª** (62.9 mg, 0.121 mmol, 1.00 eq), TES (48.4 µL, 0.303 mmol, 2.50 eq) and TFA (0.0500 mL, 0.667 mmol, 5.50 eq) were dissolved in dry DCM (1.00 mL) and stirred at rt for 2 h. The reaction was stopped with water (5.00 mL), conc. H_2SO_4 (300 µL) were added and the solution was stirred for 1 h. Aq. sat. $NaHCO_3$ solution (3 mL) was added and the aq. layer was extracted with DCM (3 x 10.0 mL) and washed with water (2 x 10.0 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The title compound was purified *via* FCC (hexanes/EtOAc 7:3) and isolated as colourless oil (13.1 mg, 0.0260 mmol, 22%).

R_f = 0.09 (hexanes/EtOAc 7:3).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.00 (dd, *J* = 4.0, 1.7 Hz, 2H, 7-H, 8-H), 6.96 (d, *J* = 5.1 Hz, 1H, 5-H), 4.15 (dddd, *J* = 9.1, 8.0, 5.0, 3.1 Hz, 1H, 2-H), 3.66 (ddd, *J* = 10.6, 4.6, 2.1 Hz, 1H, 1''-H), 3.44 (ddd, *J* = 13.0, 10.5, 7.1 Hz, 1H, 1''-H), 3.06 (dd, *J* = 16.3, 4.9 Hz, 1H, 1-H), 2.97 – 2.90 (m, 1H, 4-H), 2.87 – 2.79 (m, 1H, 4-H), 2.73 (dd, *J* = 16.1, 7.9 Hz, 1H, 1-H), 2.18 – 2.00 (m, 3H, 3-H, 2', 3', 4' or 5'-H), 1.99 – 1.77 (m, 4H, 3-H, 2''-H, 2', 3', 4' or 5'-H), 1.69 – 1.44 (m, 4H, 1'-H, 2', 3', 4'or 5'-H), 1.00 (dd, *J* = 6.7, 3.6 HzF, 3H, 2''-CH_3).

^{13}C NMR (125 MHz, chloroform-*d*) *δ*/ppm = 144.9 (C-6), 135.5 (C-8a), 131.8 (C-4a), 129.6 (C-8), 127.2 (C-5), 124.8 (C-7), 67.7 (C-1''), 67.5 (C-2), 45.6 (C-3'), 42.8 (C-2''), 41.5 (C-1'), 41.37(C-2', C-4' or C-5'), 38.2 (C-1), 33.19 (C-2', C-4' or C-5') 31.7 (C-3), 29.47 (C-2', C-4' or C-5'), 27.24 (C-4), 15.47 (2''-CH_3).

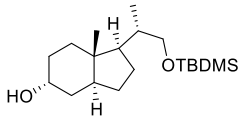
IR (ATR): $\tilde{\nu}$/cm^{-1} = 2930, 291, 2871, 2360, 2348, 2296, 174, 1698, 1610, 1502, 1456, 1365, 1230, 1160, 1128, 1047, 1025, 950, 879, 813, 679, 649, 616.

HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^{\cdot+}$ 274,1927; found 274,1926.

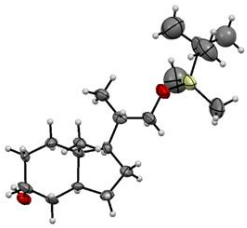
Purity (HPLC): n.d.

6.3. Crystallographic data

Table 10. Crystallographic information of **35a**.

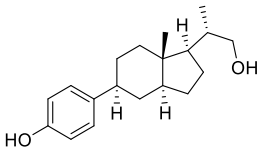


35a

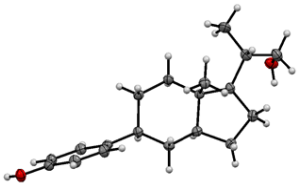


Compound	**35a**
net formula	$C_{19}H_{38}O_2Si$
M_r/g mol^{-1}	326.58
crystal size/mm	0.100 × 0.040 × 0.030
T/K	173.(2)
radiation	MoKα
diffractometer	'Bruker D8Quest'
crystal system	triclinic
space group	'P 1'
a/Å	7.4415(4)
b/Å	15.6254(10)
c/Å	19.5018(12)
α/°	105.466(2)
β/°	100.025(2)
γ/°	101.490(2)
V/Å^3	2078.8(2)
Z	4
calc. density/g cm^{-3}	1.043
μ/mm^{-1}	0.119
absorption correction	Multi-Scan
transmission factor range	0.85–1.00
refls. measured	7525
R_{int}	0.0897
mean σ(*I*)/*I*	0.0778
θ range	3.158–25.342
observed refls.	5721
x, y (weighting scheme)	0.0925, 3.5506
hydrogen refinement	constr
Flack parameter	0.0(2)
refls in refinement	7525
parameters	804
restraints	81
$R(F_{obs})$	0.1036
$R_w(F^2)$	0.2547
S	1.089
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.921
min electron density/e Å^{-3}	−0.644

Table 11. Crystallographic information of **163b**.



163b



Compound	**163b**
net formula	$C_{19}H_{28}O_2$
M_r/g mol^{-1}	288.41
crystal size/mm	0.100 × 0.090 × 0.030
T/K	102.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	orthorhombic
space group	'P 21 21 21'
a/Å	6.2460(2)
b/Å	10.2989(3)
c/Å	26.0457(8)
α/°	90
β/°	90
γ/°	90
V/Å^3	1675.44(9)
Z	4
calc. density/g cm^{-3}	1.143
μ/mm^{-1}	0.072
absorption correction	Multi-Scan
transmission factor range	0.97–1.00
refls. measured	30409
R_{int}	0.0308
mean σ(*I*)/*I*	0.0191
θ range	3.069–28.270
observed refls.	3980
x, y (weighting scheme)	0.0483, 0.2941
hydrogen refinement	H(C) constr, H(O) refall
Flack parameter	−0.1(3)
refls in refinement	4144
parameters	200
restraints	0
$R(F_{obs})$	0.0351
$R_w(F^2)$	0.0917
S	1.095
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.241
min electron density/e Å^{-3}	−0.152

6.4. Procedures for biological testing

The agar diffusion assay as well as the MTT assay were performed by MARTINA STADLER. The cholesterol biosynthesis assay was performed by DR. CHRISTOPH MÜLLER.

6.4.1. Agar diffusion assay

The test compounds were dissolved in DMSO to receive a 1% (*w*/*v*) solution. In each case, 3.00 µL were applied onto filter plates (d = 6.0 mm, dried for 24 h) from Macherey-Nagel (Düren, Germany), which correspond to 30.0 µg substance per filter plates. As reference substances, the antimycotic clotrimazole and antibiotic tetracycline (1% (*w*/*v*) solution in DMSO, 3.00 µL ≙ 30.0 µg onto filter plates). For the blank values, 3.00 µL DMSO was applied onto the filter plates.

The fungi and bacteria were purchased from the German Collection of Microorganisms and Cell Cultures GmbH (DMSZ) in Braunschweig and cultivated according to the supplied procedures. As culture medium for *Escherichia coli*, *Pseudomonas marginalis* and *Yarrowia lipolytica* All Culture Agar (AC agar) from Sigma-Aldrich was used, whereby AC agar (35.2 g) and agar (20.0 g) were suspended in water (1.00 L). For *Saccharomyces cerevisiae* AC agar (35.2 g) was suspended in water (1.00 L). For *Streptococcus entericus* and *Straphylococcus equorum* casein peptone (10.0 g), yeast extract (5.00 g), glucose (5.00 g) and NaCl (5.00 g) were suspended in water (1.00 L). All culture media were autoclaved, and 15 mL of the still warm and fluid agar were filled in petri dishes and for at least 1 h at 8 °C cooled. The petrified agar plates were coated with a cotton swab, soaked with the fluid culture of the respective germ. Four substance filter plates, as well as filter plates with the blank value and the reference were setted on the agar plates. The prepared agar plates were incubated 36 h at 32 °C for bacteria and 28 °C for fungi, respectively. The diametres of the inhibition zones were measured manually.

6.4.2. MTT assay

The MTT assay was performed using human leukemia cell line HL-60, whereby the cell count per mL was adjusted to 9 x 10^5 cells. The cell density of the culture was determined using a Fuchs-Rosenthal hemocytometer. The suspension was diluted with medium to receive the required cell density.

The test compounds were dissolved in DMSO to receive a 10 mM solution, which was diluted at least six times in a ratio of 1:2. As control DMSO was used and for the control cells pure medium. Triton X-100 was used as positive control with a concentration of 1.00 µg/mL.

For the MTT solution, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (**185**, 5.00 mg) was dissolved in PBS (1.00 mL).

In a 96-well plate, the cell suspension (99.0 µL) was filled in each well and incubated for 24 h at 37 °C with 5% CO_2. Subsequently, the test solutions (1.00 µL) were added to the well plate and incubated for additional 24 h at 37 °C with 5% CO_2. MTT solution (10.0 µL) was added to each well, incubated for 2 h and DMSO (190 µL) was added in each well. After 1 h with occasional shaking, the absorption of the 96-well plate was measured photometricly at a wavelength of 570 nm (reference wavelength 630 nm), using an MRX microplate reader (DYNEX Technologies, Chantilly, USA). The analysis, as well as the calculations of the IC_{50} values were perfomed using Prism 4 (GraphPad, La Jolla, USA).

6.4.3. Cholesterol biosynthesis assay

An assay developed in our group by GIERA *et al.* was used.[130] The test compounds were tested in final assay concentrations of 1 µM and 50 µM.

For this assay, human leukemia cell line HL-60 is used, whereby 1 x 10^6 cells are transferred into a 24-well plate and filled up with a lipid and cholesterol free RPMI 1640 medium (PAN Biotech GmbH, Aidenbach, Germany), which contains 10% fetal bovine serum, to a volume of 990 µL. The appropriate test compound solutions (10.0 µL), as well as the negative control ethanol (10.0 µL), were added. The plate was shaked gently for 30 sec and incubated for 24 h at 37 °C with 5% CO_2.

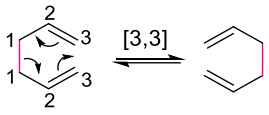
The content of the wells was transferred into 2 mL tubes and every well was rinsed with 750 µL PBS. After centrifugation (540 x g, 5 min) the supernatant was separated, and the residue was washed with PBS (1.00 mL). Under inert atmosphere 1M NaOH (1.00 mL) was added, vortexed and transferred into a 5 mL glass vial and heated for 1 h at 70 °C. After cooling to rt, 50 µL of the internal standard cholestane (10 µg/mL in TBME) and TBME (700 µL) were added. The samples were vortexed for 1 min and centrifugated (9200 x g, 5 min). Phases were separated and the procedure was repeated once. The combined organic layers were transferred into a 2 mL tube, containing Na_2SO_4 and PSA (7:1, 40 mg) and vortexed for 30 sec. After centrifugation (9200 x g, 5 min), 1 mL of the supernatant was transferred into a 1.5 mL brown glass vial and dried. The residue was dissolved in TBME (950 µL), 2,2,2-trifluoro-*N*-methyl-*N*-(trimethylsilyl)acetamide (MSTFA containing 10% TSIM, 50 µL) was added and incubated for 30 min at rt. These samples were analysed *via* GC/MS.

For GC/MS analysis, characteristic sterols were identified with the measured chromatograms and the inhibited enzymes with the evidence of one or several characteristic sterols. The evaluation of the chromatograms is performed by comparison of the AUCs (area under the curve) for the certain sterol.

Chapter 2 - Traceless isoprenylation of aldehydes *via N*-Boc-*N*-allylhydrazones

1. Introduction

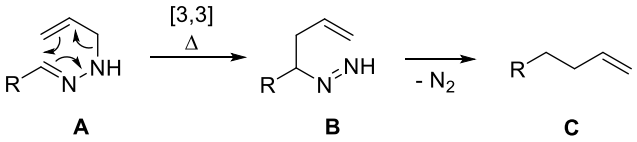
Sigmatropic rearrangements are a popular tool for the formation of new σ-bonds in synthetic chemistry.[134-136] WOODWARD and HOFFMANN explained that the [i,j] sigmatropic rearrangement is thermally allowed, if 1 > i,j and i+j = 4n+2.[137] In this chapter, we focused on the [3,3] sigmatropic rearrangement, whose mechanistic process is depicted in **Scheme 115**.



Scheme 115. General example of a [i,j] sigmatropic rearrangement with i = j = 3. The new and the old bond is marked in pink.

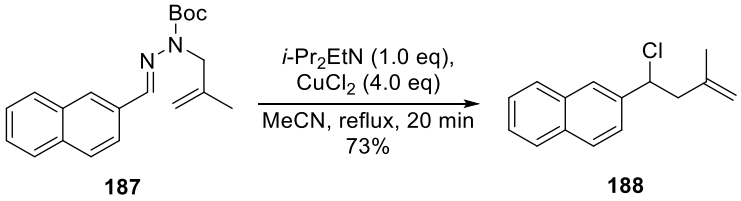
1.1. Sigmatropic rearrangement of *N*-allylhydrazones

Besides famous sigmatropic rearrangements like the CLAISEN-HURD rearrangement[138-139] or COPE rearrangement[140], *N*-allylhydrazones can also undergo a [3,3] sigmatropic rearrangement. Hereby the driving force is the formation of N_2. In 1973, STEVENS *et al.* published the first successful rearrangement of *N*-allylhydrazones (**A**, **Scheme 116**).[141] Under drastic thermal induction mono-alkylated diazene **B** decompose with subsequent [3,3] sigmatropic rearrangement resulting in N_2 release to the appropriate olefin (**C**, **Scheme 116**).



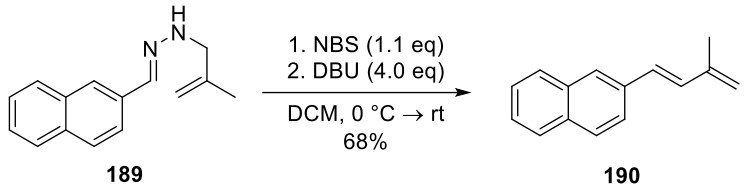
Scheme 116. [3,3] Sigmatropic rearrangement of *N*-allylhydrazone **A** under thermal conditions.

Nevertheless, due to very harsh reaction conditions, e.g. 300 °C reaction temperature, and low yields, this reaction was limited in its applicability. In 2008, MUNDAL *et al.* published the $CuCl_2$-catalysed rearrangement of *N*-Boc-*N*-allylhydrazones, whereby the Boc-protection entails higher stability of the starting material, resulting in ease of handling during purification process and storage of the compound.[142] **Scheme 117** depicts the rearrangement of *N*-Boc-*N*-allylhydrazone **187** mediated by $CuCl_2$ and *i*-Pr_2EtN.



Scheme 117: $CuCl_2$ catalysed rearrangement of *N*-Boc-*N*-allylhydrazone **187**.

Besides a C-C bond formation, a C-Cl bond is formed, which means, that this reaction is a tandem reaction. The desired rearranged product **188** was obtained in 73% yield. With this method, several variations of the allylic tail could be synthesised.[142] Since the stereoselective elimination of the chlorine atom was very slow and the resulting alkenes were formed in low yields, one year later, MUNDAL *et al.* reported a one-pot method using NBS and DBU, which results in the desired diene **190** with a good yield of 68% (**Scheme 118**).[143]

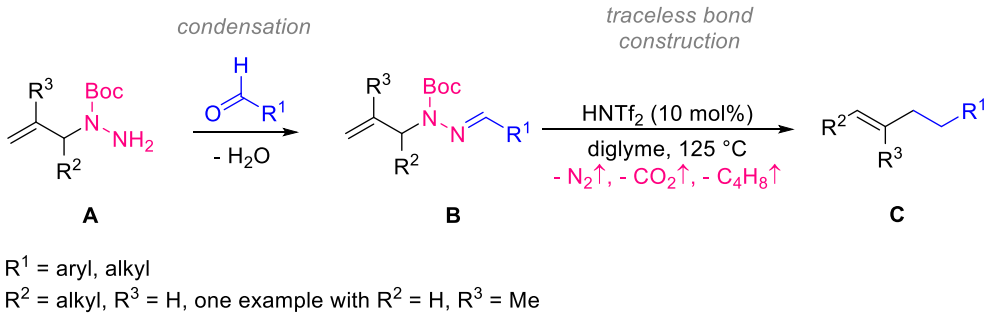


Scheme 118. Rearrangement of *N*-allylhydrazone **189** using NBS and DBU results in the diene **190**.

With both methods, the fundamental work for the development of the traceless bond construction, a method, which does not result in the chlorinated product or diene, were made.

1.2. Traceless bond construction in STEVENS-type rearrangements and its mechanism

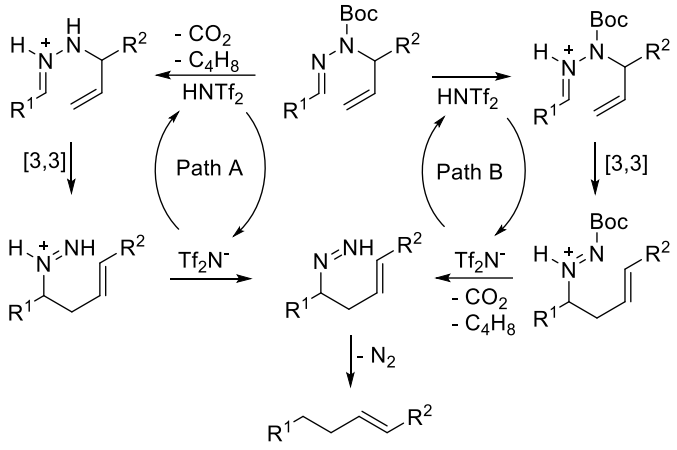
In 2010, THOMSON and co-workers published the traceless bond construction (TBC), a [3,3] sigmatropic rearrangement of *N*-Boc-*N*-allylhydrazones using catalytic amounts of the Brønsted superacid triflimide ($HNTf_2$).[144] With the usage of triflimide, the reaction temperature of the rearrangement could be lowered to 125 °C. During the rearrangement only gaseous side products are formed (N_2 from the hydrazine group and CO_2 and 2-methylprop-1-ene from the Boc deprotection), which makes the reaction *traceless*. In **Scheme 119** the synthesised products are summarised.[144] With *N*-Boc-*N*-allylhydrazine precursor **A**, various 1,2-disubstituted olefins and one 1,1-disubstituted olefin could be synthesised in 49 – 75%.



Scheme 119. TBC published by THOMSON and co-workers, starting with condensation of *N*-Boc-*N*-allylhydrazine **A** and an aldehyde (marked in blue). The formed *N*-Boc-*N*-allylhydrazone **B** undergoes [3,3] sigmatropic rearrangement in the presence of $HNTf_2$ to the appropriate olefin. The elimination products are marked in pink.[144]

MUNDAL *et al.* also proposed a potential mechanism of the TBC, which is illustrated in **Scheme 120**. While path A starts with Boc cleavage, followed by the triflimide catalysed rearrangement

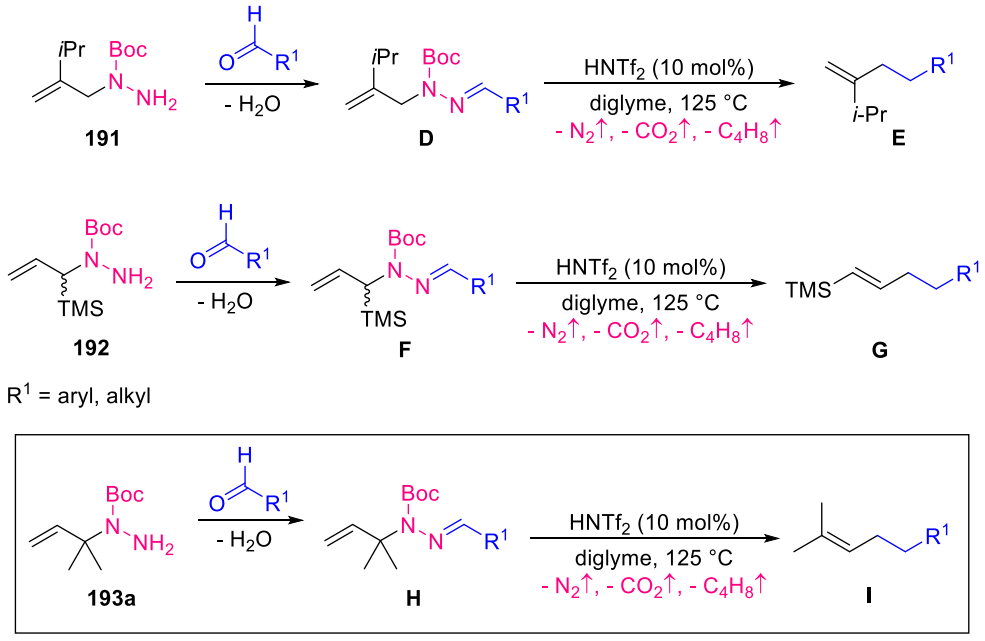
of the *N*-allylhydrazone, the initial step of path B is the rearrangement with subsequent Boc cleavage.



Scheme 120. Proposed mechanism of TBC. Path A shows Boc cleavage with subsequent [3,3] sigmatropic rearrangement. Path B shows [3,3] sigmatropic rearrangement followed by Boc cleavage (*cf.* [144]).

1.3. Development of novel *N*-Boc-*N*-allylhydrazine precursors

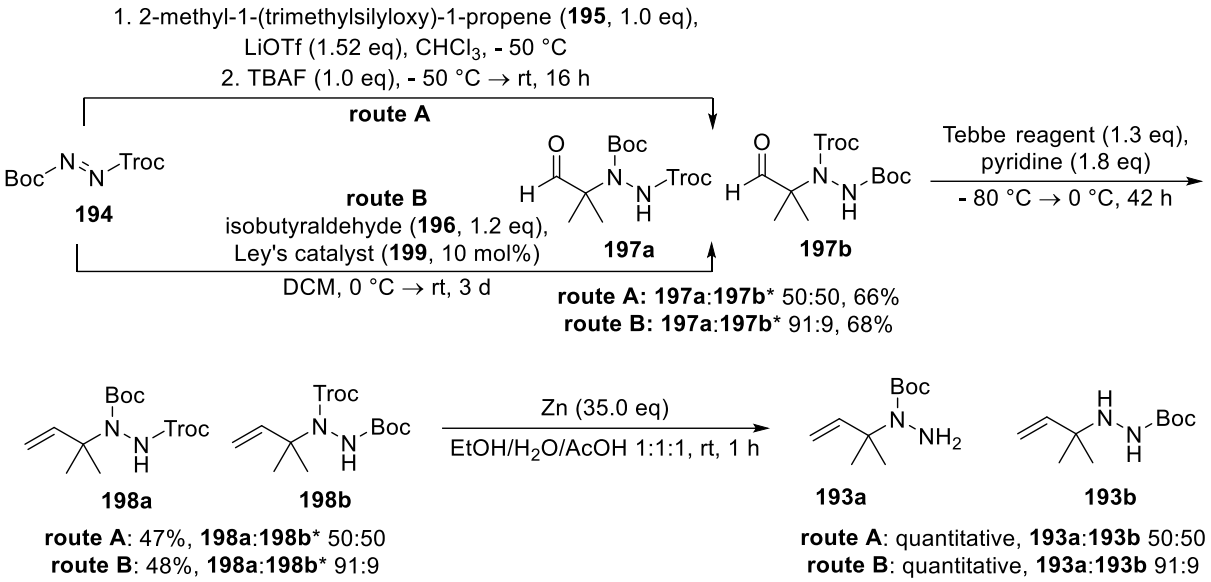
SEBASTIAN DITTRICH from our research group extended the scope of the TBC, developing novel *N*-Boc-*N*-allylhydrazine precursors (**Scheme 121**).[145] With precursor **191** bearing an *i*-Pr group in 1-position, 1,1-disubstituted olefins (**E**) with a terminal methylene could now be obtained.[146] This methylene branched end can be found in sidechains of steroidal natural product, for example episterol. Another precursor is allylhydrazine **192**, which results in terminal vinylsilanes (**G**) *via* TBC.[147]



Scheme 121. *N*-Boc-*N*-allylhydrazine precursors designed and synthesised by DITTRICH.[145-147]

The main focus of this thesis was to explore the scope and limitations of rearrangements with precursor *N*-Boc-*N*-allylhydrazine **193**, which was designed and synthesised by DITTRICH as well. With the two geminal methyl groups in α-position to the hydrazine moiety, an isoprenyl group can be introduced to the appropriate aldehyde using TBC, resulting in olefins of type **I**. This novel precursor comes with several benefits. In previous studies of DITTRICH, undesired subsequent acid-catalysed isomerisation of the formed double bonds could be observed, which can lead to isomeric mixtures of alkenes.[146, 148] In this case, the desired trisubstituted olefin should be already the thermodynamically most stable isomer. Moreover, with the presence of the two geminal methyl groups, no *E*/*Z* isomers can be formed and additionally, the methyl groups may facilitate the TBC, because of the so-called gem-dimethyl effect (THORPE-INGOLD effect).[149-150]

All results regarding to the novel precursor **193a** in DITTRICH'S dissertation and my master thesis as well as the following studies were published in 2020.[2] **Scheme 122** shows the synthesis of *N*-Boc-*N*-allylhydrazine **193**. Route A was previously performed by DITTRICH in his dissertation, starting with commercially available silyl enol ether **195**, which was activated with LiOTf and TBAF to form the appropriate lithium enolate. The addition of **195** to mixed azodicarboxylate **194** did not proceed regioselectively and resulted in an inseparable mixture of aldehydes **197a** and **197b** as an equimolar mixture. NMR spectroscopy showed only one set of signals and only after the final step, the Troc deprotection, the ratio could be determined. Consequently, the ratios for the aldehydes **197a**/**197b** and olefins **198a**/**198b** were only determined retrospectively. Olefins **198a** and **198b** were formed *via* methylenation of the formyl group using TEBBE reagent, and subsequent Troc deprotection gave *N*-Boc-*N*-allylhydrazines **193a** and **193b** in 50:50 ratio. After this step, both isomers could be distinguished *via* ^{1}H NMR spectroscopy, but still could not be separated on a preparative scale.



Scheme 122. Synthesis of *N*-Boc-*N*-allylhydrazine **193a** and its regioisomer **193b**. Route A (performed by DITTRICH) gave an isomeric ratio of 50:50 and route B an isomeric ratio of 91:9.

During my master thesis on "Triflimide-catalysed [3,3]-sigmatropic rearrangement of novel *N*-Boc-*N*-allylhydrazones" a new route to the desired *N*-Boc-*N*-allylhydrazine was found, whereby the regioisomeric mixture could be improved to 91:9 (route B).[151] Starting with an organocatalysed reaction between azodicarboxylate **194** and isobutyraldehyde **196**, different catalysts were tested, whereby L-proline gave an isomeric ratio of 83:17 and (*S*)-5-(pyrrolidine-2-yl)-1*H*-tetrazole (**199**), a catalyst developed by LEY and co-workers,[152] a ratio of 91:9. The following steps were performed as described by DITTRICH.[145]

The structure of the desired *N*-Boc-*N*-allylhydrazine **193a** was confirmed by X-ray crystallography (**Figure 23**).

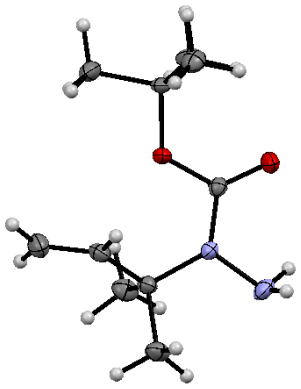
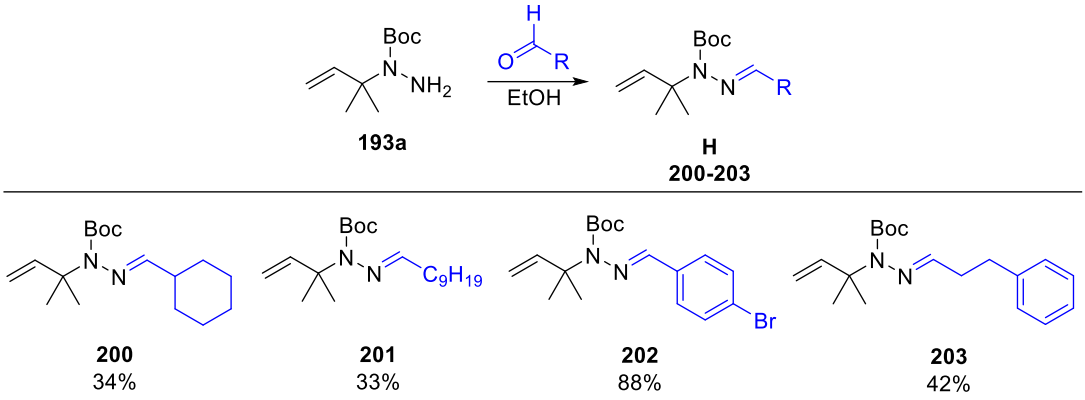


Figure 23. Mercury depiction of the structure of *N*-Boc-*N*-allylhydrazine **193a** in the crystalline state.

The isomeric mixture (91:1) of *N*-Boc-*N*-allylhydrazine **193a** and its regioisomer **193b**, was used without further purification, since only isomer **193a** undergoes the following condensation with the appropriate aldehydes, providing the corresponding *N*-Boc-*N*-allylhydrazones **H** (**Scheme 121**). Regioisomer **193b** remains unreacted and is separated *via* FCC after condensation.

2. Objective

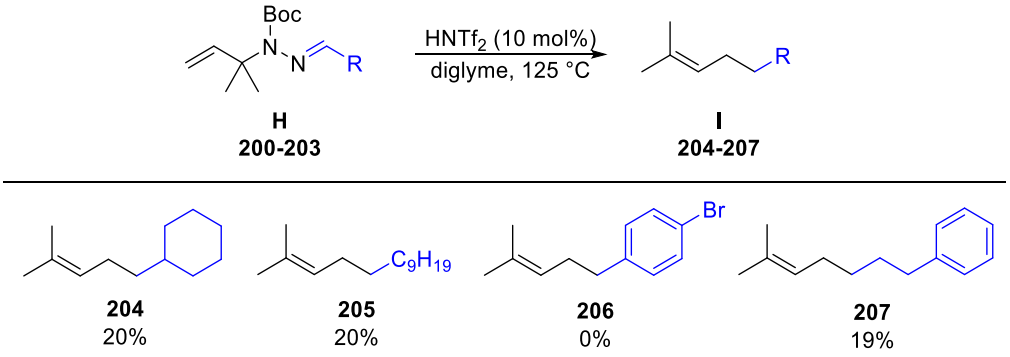
Besides the improvement of the synthesis of precursor **193a** which was developed during my master thesis (see chapter 1.3.), three *N*-Boc-*N*-allylhydrazones were synthesised and their rearrangement was studied.[151] **Scheme 123** depicts the *N*-Boc-*N*-allylhydrazones which were synthesised in DITTRICH'S dissertation[145] and in my master thesis[151].



Scheme 123. *N*-Boc-*N*-allylhydrazones **200**-**203**. Allyhydrazone **200** was synthesised during the dissertation of Dr. SEBASTIAN DITTRICH. Allylhydrazones **201**, **202** and **203** were synthesised (with improved building block mixture **193a**/**193b**) during my master thesis. The yields refer to the content of **193a** in the applied hydrazines **193a/193b** mixture.

The first allylhydrazone was **200** bearing a cyclohexyl methylene residue.[145] The other three allylhydrazones are **201** with an aliphatic chain, **202** with a benzylbromide residue and **203** containing a phenyl propylene residue.

The following rearrangement was performed using the standard conditions of MUNDAL *et al.*, $HNTf_2$ in diglyme at 125 °C. The results are shown in **Scheme 124**.



Scheme 124. Results of the rearrangement of *N*-Boc-*N*-allylhydrazones **200**-**203** using the conditions of THOMSON ($HNTf_2$, diglyme, 125 °C)[144]. Olefin **206** could not be obtained *via* this method.

Allyhydrazone **200** underwent rearrangement and olefin **204** was with a yield of 38%. In my master thesis olefins **205** and **207** could be prepared using TBC and were isolated in 20% and

19%, respectively. Olefin **206**, bearing an aromatic residue directly attached to the allylhydrazine, did not undergo the rearrangement.

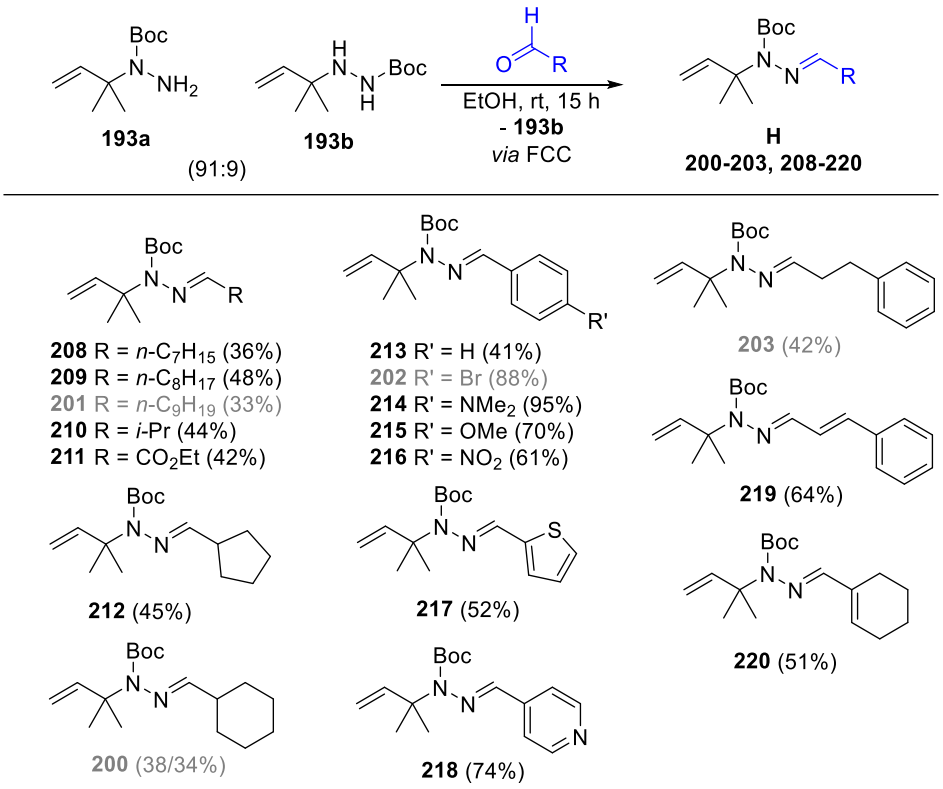
During this dissertation, the aim of this project was to synthesise further *N*-Boc-*N*-allylhydrazones based on *N*-Boc-*N*-allylhydrazine **193a**, to study the scope and the limitations using TBC.

3. Results and Discussion

In this chapter the syntheses of various *N*-Boc-*N*-allylhydrazones based on precursor **193a** are shown, as well as the attempts of their rearrangement.[2]

3.1. Synthesis of further *N*-Boc-*N*-allylhydrazones and their rearrangement

With the isomeric mixture of building blocks **193a**/**193b** (ratio 91:1), further *N*-Boc-*N*-allylhydrazones were synthesised *via* condensation between the desired regioisomer **193a** and the appropriate aldehyde, whereby undesired isomer **193b** remained unreacted. **Scheme 125** depicts all synthesised *N*-Boc-*N*-allylhydrazones. The grey marked allylhydrazones were synthesised in previous theses (see chapter 2.).[145, 151]



Scheme 125. Synthesised *N*-Boc-*N*-allylhydrazones based on isomeric mixture of building block **193a**, contaminated with **193b** (ratio 91:9). The yields refer to starting material **193a**. The grey marked allylhydrazones were synthesised in a previous dissertation[145] or master thesis[151].

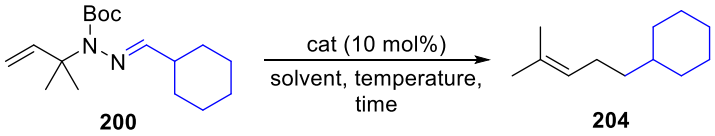
All in all, 17 *N*-allylhydrazones were successfully synthesised using the new hydrazine precursor **193a**. The first column shows, *inter alia*, aliphatic residues like aliphatic chains (**201**, **208**, **209**, **210**) or cycloaliphatic residues like cyclopentyl (**212**) and cyclohexyl (**200**), whereby the latter was already synthesised by DITTRICH with a yield of 38%. The synthesis of **200** was repeated and the allylhydrazone was isolated with 34% yield. The introduction of an ester group to **193a** resulted in ester **211** with 42% yield. Although THOMSON explained the introduction of the Boc group results in a higher stability of the *N*-Boc-*N*-allylhydrazones, a

slow decomposition on the column was observed, which explains the moderate yields of 33 – 48%. The second column of **Scheme 125** shows (hetero)aromatic residues. Allylhydrazones **213**-**216** contain benzylidene residues with distinction of the substituent in *para* position: electron withdrawing groups (nitro, bromine (weak)) as well as electron donating groups (methoxy, dimethylamino) should reveal if the substituents influence the rearrangement. Heteroaromatic residues like thiophene (**217**) and pyridine (**218**) were incorporated as well. Except benzylidene allylhydrazone **213**, the yields were higher than those obtained for aliphatic residues (52 – 95%). This can be explained by the conjugation of the allylhydrazine moiety and the aromatic residues. The third column shows, *inter alia*, the 3-phenyl propylidene residue, which was already synthesised in the master thesis. In addition, the unsaturated form **219** derived from cinnamaldehyde was synthesised in a good yield of 64%. The allylhydrazone bearing a cyclohexene residue (**220**) was synthesised in 51% yield.

3.2. Optimisation reactions for the rearrangement of *N*-Boc-*N*-allylhydrazones based on the novel *N*-Boc-*N*-allylhydrazine precursor **193a**

Before studying the scope of the rearrangement of the further synthesised *N*-Boc-*N*-allylhydrazones, we identified the optimum reaction conditions for the rearrangement. On the model compound **200**, test reactions (0.050 mmol scale) were carried out, with change of the catalyst, solvent, time and reaction temperature using an internal standard (cholestane). With the usage of a measured standard curve, the outcomes of the test reactions could be compared to each other by GC/MS analysis. **Table 12** shows all reaction conditions and the results.

Table 12. Optimisation of reaction conditions for the rearrangement of **200**.



200 **204**

entry[c]	solvent	catalyst (10 mol %)	T [°C]	t [min]	yield (**204**) [%][b]
1	diglyme	$HNTf_2$	23	15	1
2	diglyme	$HNTf_2$	23	45	1
3	diglyme	$HNTf_2$	23	75	1
4	diglyme	$HNTf_2$	50	15	1
5	diglyme	$HNTf_2$	50	45	2
6	diglyme	$HNTf_2$	50	75	1
7	diglyme	$HNTf_2$	75	15	8
8	diglyme	$HNTf_2$	75	45	11
9	diglyme	$HNTf_2$	75	75	11
10	diglyme	$HNTf_2$	100	15	16

11	diglyme	$HNTf_2$	100	45	19
12	diglyme	$HNTf_2$	100	75	20
13	diglyme	$HNTf_2$	125	15	26
14	diglyme	$HNTf_2$	125	45	28
15	diglyme	$HNTf_2$	125	75	31
16	diglyme	$HNTf_2$	125	15	20
17	diglyme	$HNTf_2$	125	45	21
18	diglyme	$HNTf_2$	125	75	23
19	THF	$HNTf_2$	70	15	2
20	THF	$HNTf_2$	70	45	3
21	THF	$HNTf_2$	70	75	5
22	diglyme	TfOH	125	15	17
23	diglyme	TfOH	125	45	17
24	diglyme	TfOH	125	75	20
25	THF	TfOH	70	15	1
26	THF	TfOH	70	45	1
27	THF	TfOH	70	75	2
28	diglyme	TFA	125	15	1
29	diglyme	TFA	125	45	1
30	diglyme	TFA	125	75	1
31	THF	TFA	70	15	1
32	THF	TFA	70	45	1
33	THF	TFA	70	75	1

First, the optimum reaction temperature was analysed (entries 1 – 15). Reactions were performed at 23, 50, 75, 100 and 125 °C, whereby after 15, 45 and 75 min an aliquot was taken out and analysed by GC/MS. A conversion could not be observed at 23 and 50 °C, respectively. When raising the temperature to 75 °C a rearrangement could now be observed, resulting in 11% yield. The yield could be further increased at 100 °C, but the best yield was obtained when using the standard conditions of Mundal *et al.* with 125 °C for 75 min (marked in yellow). Furthermore, besides diglyme as solvent, THF was used as a more common alternative and other acidic catalysts like TFA and TfOH were used (entries 16 – 33). These reactions were measured on another day with another calibration curve. Therefore, the reaction using triflimide in diglyme at 125 °C was again measured (entries 16 – 18). No conversion was observed in THF (entries 19 – 21). The reactions were only heated to 70 °C, since the boiling point of THF is 66 °C. Therefore, another reason for the failure of this reaction could be, that the temperature was too low, since a reaction in diglyme was only observed at a temperature of 75 °C or higher. Looking at the catalysts, no reaction could be observed when using TFA, neither in diglyme (entries 28 – 30) nor in THF (entries 31 – 33). The use of TfOH in THF also showed no rearrangement, but a reaction could be observed using TfOH in diglyme

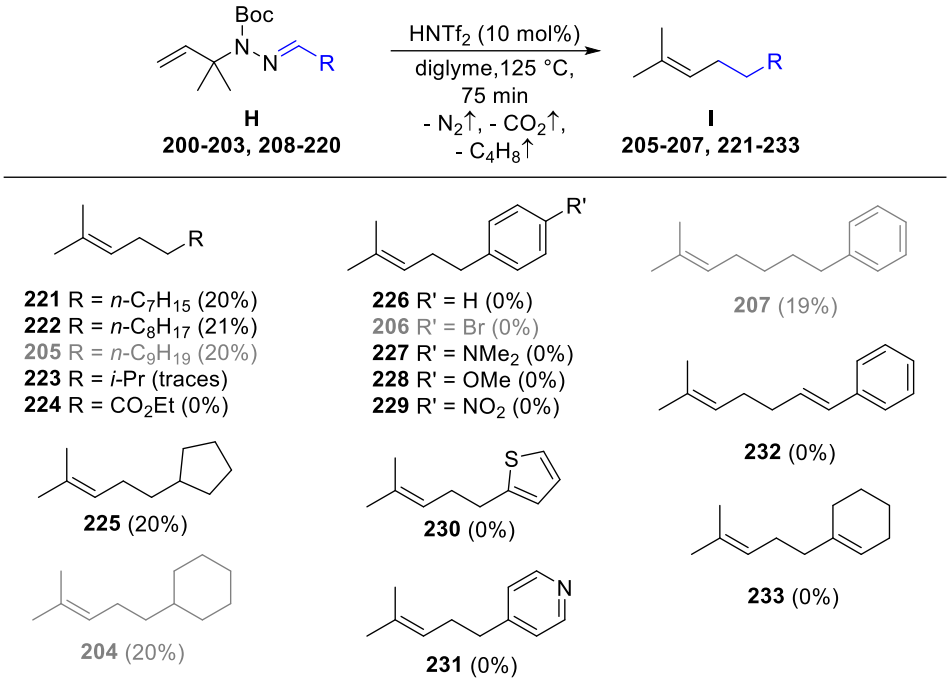
(entries 22 – 24). After 75 min at 125 °C, **204** could be detected with 20% yield (marked in pink). The use of TfOH instead of triflimide could be a good alternative, due to the laborious handling of triflimide, since it decomposes immediately at air. Nevertheless, the best reaction conditions were again the use of triflimide in diglyme at 125 °C (marked in blue). The differences in the yields of entries 15 and 18 can be explained by limited reproducibility on a small scale. As in every chemical reaction the results are not perfectly reproducible and especially in this case as the extremely dry conditions required for triflimide are an error factor. In addition, it is crucial that the reaction mixture is immediately heated in a pre-heated oil bath, whereby this step influence the reproducibility. Therefore, an error of 10% yield must be expected for this reaction.

The rearrangements described above were performed exclusively with BRØNSTED acids. Therefore, another attempt was the use of a LEWIS acid. The reaction was performed in a 0.5 mmol scale using $AlCl_3$ in diglyme at 125 °C. No conversion could be monitored by TLC. Instead, after 2 h, Boc deprotected allylhydrazone was observed by GC/MS analysis, which is in accordance to a publication of BOSE and LAKSHMINARAYANA, in which the *N*-Boc removal using $AlCl_3$ was presented.[153]

In conclusion, it could be shown, that the conditions of MUNDAL *et al.* are best suited for the rearrangement of *N*-Boc-*N*-allylhydrazones based on novel *N*-Boc-*N*-allylhydrazine precursor **193a**.

3.3. [3,3] Sigmatropic rearrangement of the *N*-Boc-*N*-allylhydrazones

After determination of the optimum reaction conditions, the rearrangement of the further synthesised *N*-Boc-*N*-allylhydrazones, which were discussed in chapter 3.1., were performed. **Scheme 126** shows the results of the triflimide catalysed rearrangements.

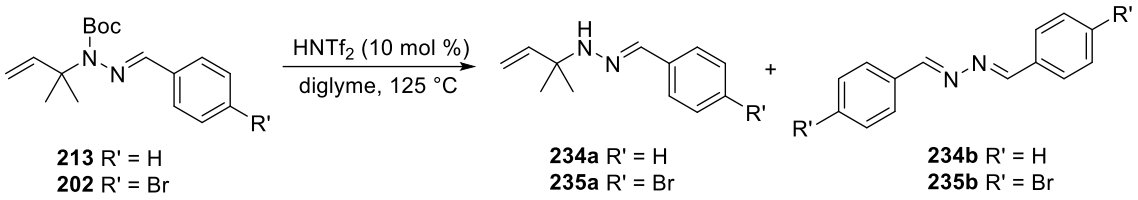


Scheme 126. Triflimide catalysed [3,3] sigmatropic rearrangement of all *N*-Boc-*N*-allylhydrazones based on novel precursor **193a**. The grey marked allylhydrazones were synthesised in a previous dissertation[145] or master thesis[151].

The allylhydrazones bearing an aliphatic residue underwent the rearrangement (first column). Besides **205**, which was synthesised already in the master thesis, olefins **221**, **222** and **223** could be synthesised. Olefins **221** and **222** were isolated in 20% and 21% yield, respectively. Olefin **223** could only be detected by GC/MS but could not be isolated. A possible reason can be the low boiling point of the product. Ester **224** could not be obtained *via* this rearrangement. Only Boc-deprotected allylhydrazone was observed in this experiment. Besides **204**, which was synthesised by DITTRICH, olefin **225**, bearing a cyclopentyl residue was isolated in 20% yield. The second column of **Scheme 126** shows the (hetero)aromatic residues. Unfortunately, none of these olefins could be obtained *via* this rearrangement. With the aid of the observations of the results in column 1, it can be derived which *N*-Boc-*N*-allylhydrazones will undergo this rearrangement and will not. Non-conjugated allylhydrazones like the ones bearing an aliphatic residue, undergo the rearrangement, while attempted rearrangements using conjugated allylhydrazones do not result in the appropriate olefins (column 2). This assumption could be confirmed with the rearrangement of allylhydrazones **203** and **219**. While the saturated form

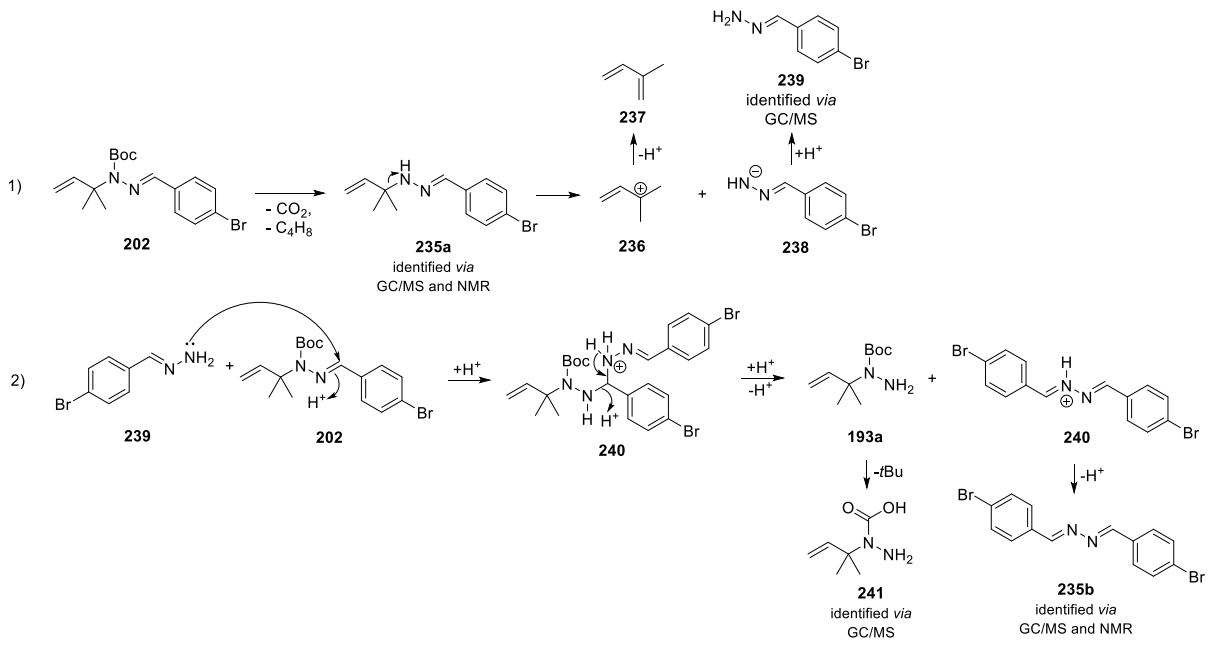
203 did undergo the rearrangement with 19% yield, in case of the unsaturated version **219** the rearrangement did not take place and only Boc-deprotected allylhydrazone was obtained. Also, allylhydrazone **220** bearing a cyclohexenyl residue did not undergo the rearrangement, since the double bond is in conjugated position to the hydrazine moiety and therefore, **233** could not be isolated.

All in all, it could be shown that with the novel precursors only non-conjugated residues undergo the TBC. In case of **213** and **202**, a crystalline solid was obtained besides the Boc-deprotected allylhydrazones **234a** and **235a**, respectively. This crystalline solid was identified as the bishydrazones **234b** and **235b** (**Scheme 127**).



Scheme 127. Rearrangement of *N*-Boc-*N*-allylhydrazone **213** and **202** resulting in Boc-deprotected allylhydrazones **234a** and **235a** and bishydrazones **234b** and **235b**, respectively.

Scheme 128 shows a proposed mechanism for the formation of the bishydrazones **234b** and **235b** by the example of allyhydrazone **202**. In the presence of triflimide, Boc-cleavage of **202** takes place, which is unfortunately inevitable. The Boc deprotected allylhydrazone **235a** was identified by GC/MS and NMR analysis. Hydrazine **239** is formed *via* elimination of isoprene **237** of **235a**. This step could only be confirmed by the GC/MS identification of hydrazine **239**. In the second part, nucleophile hydrazine **239** attacks allylhydrazone **202** and intermediate **240** is formed. By elimination of hydrazine precursor **193a**, **235b** is formed *via* **240**. Bishydrazone **235b** was identified by GC/MS and NMR analysis. Since only **235a** and **235b** could be isolated and identified *via* NMR, the real mechanism is not clear.



Scheme 128. Proposed mechanism of the formation of bishydrazones **234b** and **235b** by the example of allylhydrazone **202**.

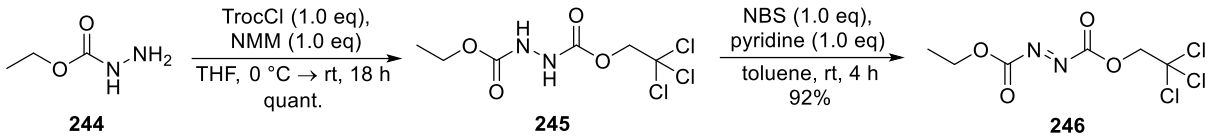
Furthermore, we identified, that the presence of the Boc group in the non-conjugated *N*-Boc-*N*-allylhydrazones is crucial for the rearrangement. During the rearrangements always Boc-deprotected allylhydrazone could be observed. But the Boc-deprotected allylhydrazones do not undergo the desired rearrangement. Thus, it can be shown, that the proposed mechanism of MUNDAL *et al.* follows path B, in the case of our rearrangements with precursor **193a**.

3.4. Traceless isoprenylation of aldehydes *via* *N*-CO_2Et-*N*-allylhydrazones

Due to very low yields as well as the limitation in the residues (only non-conjugated *N*-Boc-*N*-allylhydrazones), another protecting group was explored as an alternative to the *N*-Boc group. Moreover, a premature acidic deprotection should be prevented with the new protecting group. To maintain a traceless rearrangement, only carbamates were worth considering. Ethoxy carbonyl was a promising protecting group. Therefore, the synthesis of the desired *N*-CO_2Et-*N*-allylhydrazine precursor **243** was performed following a synthetic protocol closely related to the one developed for the *N*-Boc analogue described above.

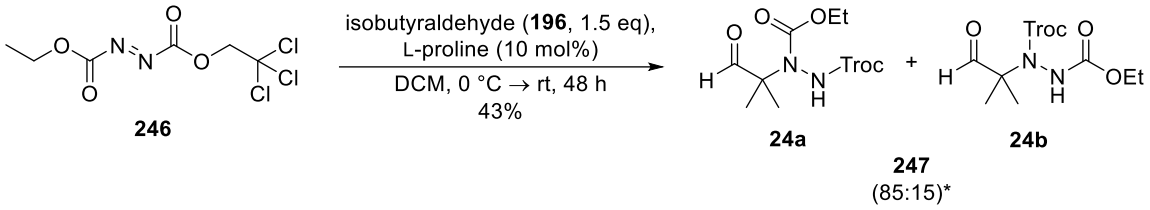
3.4.1. Synthesis of *N*-CO_2Et-*N*-allylhydrazine precursor **243**

The first two steps were the synthesis of azodicarboxylate **246**, which was synthesised according to literature (**Scheme 129**).[154]



Scheme 129. Synthesis of diazene **246** bearing and ethoxycarbamate and Troc residue.

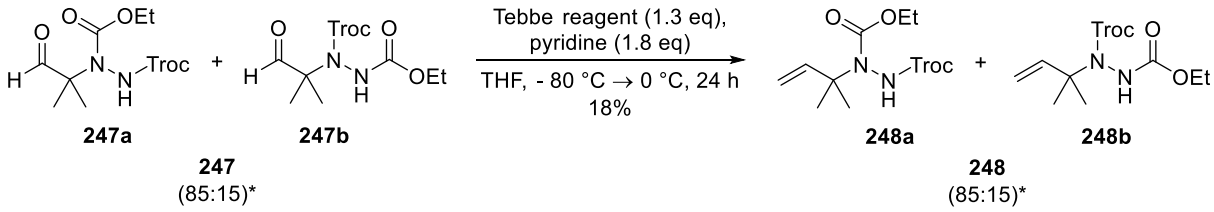
The formation of hydrazine **245** from ethyl carbazate (**244**) in the presence of *N*-methyl morpholine (NMM) proceeded in quantitative yield. The following oxidation using NBS and pyridine gave diazene **246** in 92% yield. The next step was the introduction of an aldehyde function under organocatalysis (**Scheme 130**). The inseparable mixture of aldehydes **247** (85:15) was obtained with a moderate yield of 43%. The ratio was determined retrospectively, since in this and the following step NMR spectroscopy showed only one set of signals.



Scheme 130. Synthesis of aldehyde **247** *via* organocatalysis. *Ratio determined retrospectively from ^{1}H NMR of **249**.

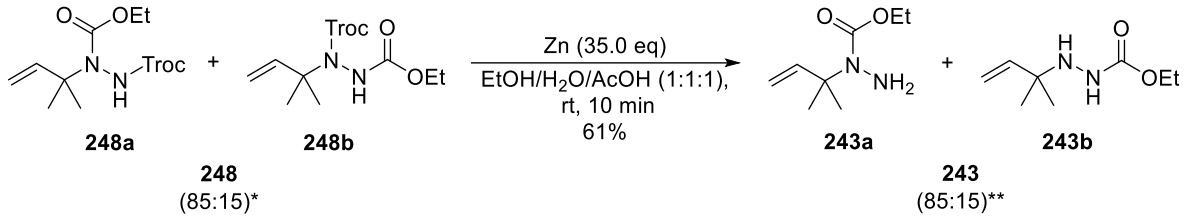
In the synthesis of previous *N*-Boc-*N*-allyhydrazine precursor **193a** a catalyst designed by AUREGGI *et al.* was used ((*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole),[152] which gave a slightly better regioisomeric ratio of 91:9 of **193a** and **193b**. But because this catalyst is really expensive, we decided to use L-proline as the catalyst of choice in this step.

Olefination of the aldehyde function was performed using TEBBE reagent. **Scheme 131** depicts this methylenation. The inseparable mixture of olefins **248** was isolated with a poor yield of 18%. The regioisomeric mixture of 85:15 was again determined retrospectively, since NMR spectra showed only one set of signals at this stage.



Scheme 131. Methylenation of the aldehyde function of **247** using TEBBE reagent. *Ratio determined retrospectively from ^{1}H NMR of **243**.

The last step was Troc deprotection under standard reductive conditions (**Scheme 132**). The desired *N*-CO_2Et-*N*-allylhydrazine precursor **243a** was isolated as inseparable mixture with its regioisomer **243b**. Nevertheless, the ratio could now be determined *via* ^{1}H NMR spectroscopy.

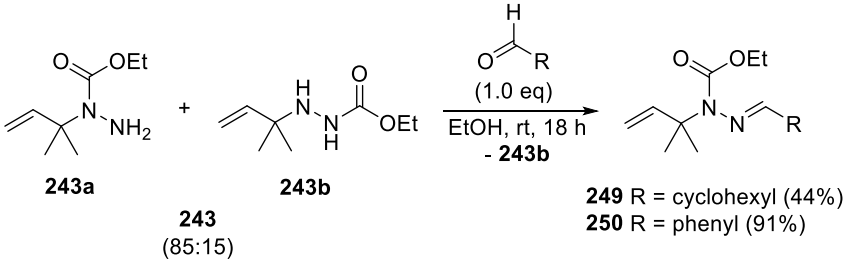


Scheme 132. Reductive Troc deprotection resulting in the desired *N*-CO_2Et-*N*-allylhydrazine precursor **243a** and its regioisomer **243b** in an isomeric ratio of 85:15. **Ratio determined (*retrospectively) *via* ^{1}H NMR.

The mixture was used without further purification since the following condensation with an aldehyde only occurs with hydrazine **243a** and regioisomer **243b** will remain unreacted.

3.4.2. Synthesis of two model *N*-CO_2Et-*N*-allylhydrazones

Two *N*-CO_2Et-*N*-allylhydrazones were synthesised *via* condensation of cyclohexane-carbaldehyde and benzaldehyde with **243a**, resulting in allylhydrazones **249** and **250** (**Scheme 133**). Besides cyclohexyl residue (**249**), a phenyl residue (**250**) was introduced in order to explore whether conjugated hydrazones would undergo the rearrangement with this new carbamate protecting group.

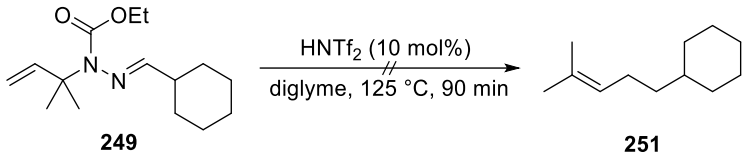


Scheme 133. Synthesis of *N*-CO_2Et-*N*-allylhydrazones **249** and **250**.

The yield of **249** with 44% is much lower than of the aromatic conjugated version **250** with 91%. In the synthesis of *N*-Boc-*N*-allylhydrazones in chapter 3.1., the same observations were made.

3.4.3. Attempted TBC of *N*-CO_2Et-*N*-allylhydrazones **249** and **250**

The rearrangements were performed in a 0.5 mmol scale using THOMSON'S conditions (triflimide, diglyme, 125 °C)[144]. First, the rearrangement of allylhydrazone **249** was tried (**Scheme 134**).

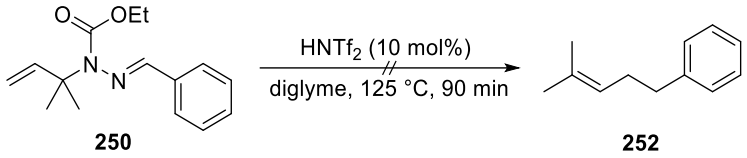


249 **251**

Scheme 134. Attempted TBC of *N*-CO_2Et-*N*-allylhydrazone **249**.

The reaction was monitored by TLC. The nonpolar product **251** should have a very high R_f value (R_f = 0.91, pentane), but no product could be detected. The reaction was stopped after 90 min and after work up only indefinable aliphatic decomposition fragments could be isolated after FCC.

The rearrangement of the conjugated aromatic version **250** showed the same outcome and only unidentifiable fragments were isolated (**Scheme 135**).



250 **252**

Scheme 135. Attempted TBC of *N*-CO_2Et-*N*-allylhydrazone **250**.

In conclusion, the Boc group is crucial for this type of rearrangement. Probably, a protecting group is necessary, which can be cleaved fast in the presence of acids.

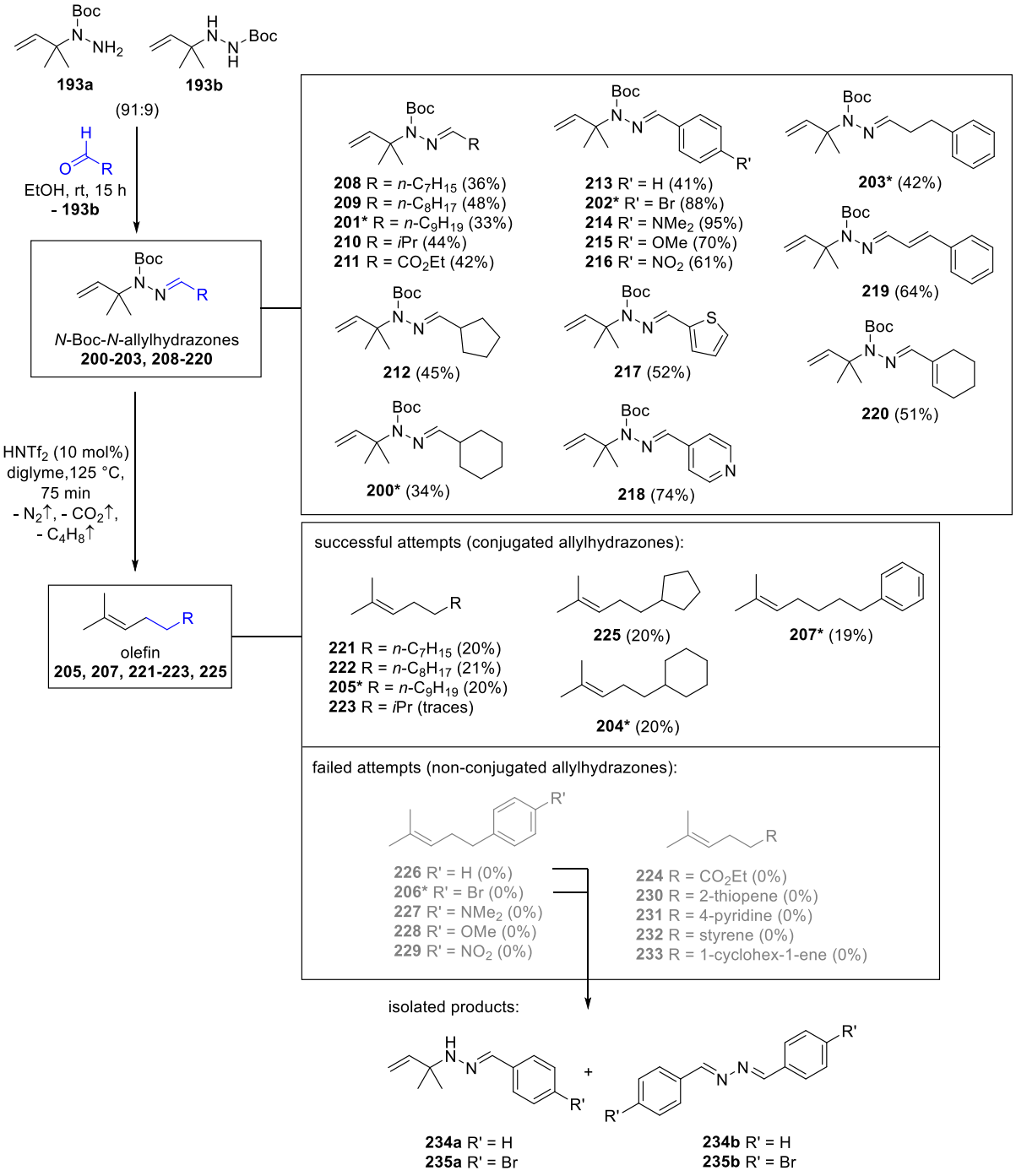
4. Summary and Conclusion

The traceless bond construction published by THOMSON and co-workers, is a unique [3,3] sigmatropic rearrangement of *N*-Boc-*N*-allylhydrazones in the presence of superacid triflimide, liberating only gaseous by-products. In this project, TBC was used for the isoprenylation of aldehydes *via* *N*-Boc-*N*-allyhydrazones.[2] **Scheme 136** shows an overview of the studies towards the novel *N*-Boc-*N*-allylhydrazine precursor **193a**, with the synthesis of various *N*-Boc-*N*-allylhydrazones and their rearrangements.

The novel *N*-Boc-*N*-allylhydrazine precursor **193a** was used as a regioisomeric mixture of the desired allylhydrazine **193a** and **193b** (ratio 91:1). Based on this precursor, which was designed and synthesised in previous theses, 17 *N*-Boc-*N*-allylhydrazones were synthesised. Besides cycloaliphatic residues (**208**, **209**, **201**, **210**, **212** and **200**) and functional groups like an ester (**211**) or an alkene (**220**), (hetero)aromatic residues were attached. In addition to a plain benzylidene residue (**213**), the benzylic residues contain an electron withdrawing or donating substituent in *para* position. Furthermore, a cinnamylidine (**219**) and the corresponding non-conjugated phenylpropylidene (**203**) *N*-Boc-*N*-allylhydrazone were synthesised. The yields of the intermediate *N*-Boc-*N*-allylhydrazones are in a range of 33 – 95%.

Before the following [3,3] sigmatropic rearrangement was performed, various optimisation reactions were made to determine the optimum reaction conditions for the TBC. Variations of the catalyst, the solvent, the reaction temperature, and the time were made. Moreover, the LEWIS acid $AlCl_3$ was used instead of LEWIS acids. Nevertheless, the best reaction conditions were the standard conditions of the TBC (triflimide, diglyme, 125 °C).

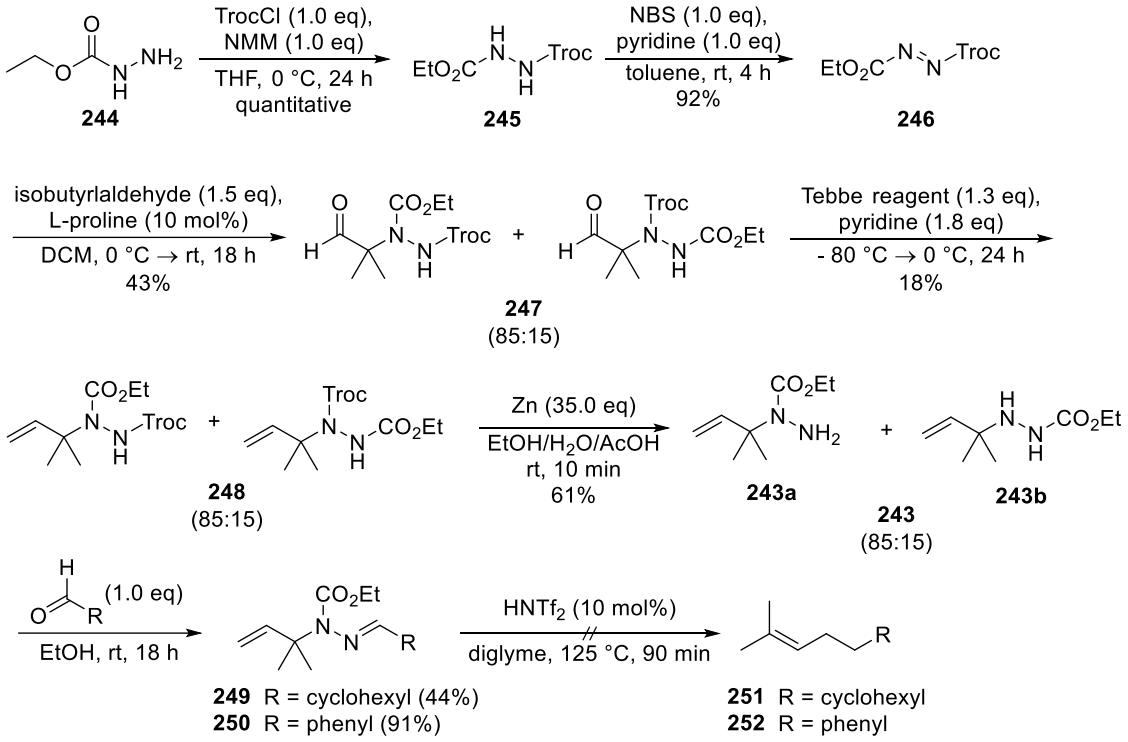
The following rearrangement was only successful with non-conjugated systems, the *N*-Boc-*N*-allyhydrazones derived from aliphatic aldehydes, but with very low yields (19 – 20%). Conjugated systems (marked in grey) did not undergo the desired rearrangement. This could be confirmed by the unsaturated and saturated version of (hydro)cinnamaldeyde-derived allylhydrazones. Only the saturated version (**203**) did undergo the rearrangement, while in the reaction of **219** only Boc-deprotected allylhydrazone was found. In all conjugated allylhydrazones, Boc-deprotected allylhydrazones could be detected by GC/MS analysis and no [3,3] rearrangement was observed. Hence, the mechanism of the TBC, which was proposed by MUNDAL *et al.* as well, could be confirmed as following path B (Boc deprotection after [3,3] sigmatropic rearrangement).



Scheme 136. Overview of the studies towards the novel *N*-Boc-*N*-allylhydrazine precursor **193a** and its *N*-Boc-*N*-allylhydrazones **200-203** and **208-220** with following rearrangements.

Since the TBC with precursor **193a** is limited in its application, another protecting group instead of Boc was explored. Carbamate protecting groups were studied to adhere the *traceless* rearrangement by liberating only gaseous byproducts. Ethoxy carbamate was used as protecting group and the *N*-CO_2Et-*N*-allylhydrazine precursor **243** was synthesised according to the synthesis of *N*-Boc-*N*-allylhydrazine **193a** (**Scheme 137**). *N*-CO_2Et-*N*-allylhydrazine **243a** and its regioisomer **243b** were synthesised in five steps and isolated in a ratio of 85:15.

Instead of ((*S*)-5-(pyrrolidin-2-yl)-1*H*-tetrazol (**199**)), which was used in the synthesis of precursor **193a**, L-proline was used in the organocatalytic step.



Scheme 137. CO_2Et as protecting group, instead of Boc.

With the preservation of hydrazine **243a**, two model compounds were synthesised: *N*-CO_2Et-*N*-allylhydrazone bearing a cyclohexyl residue (**249**) and the conjugated version, bearing a phenyl residue (**250**). Unfortunately, the rearrangement of these model compounds was not successful, and the desired olefins could not be isolated.

All in all, the scope and limitations of the rearrangements of the *N*-Boc-*N*-allylhydrazones resulting from novel precursor **193a** were studied and as a result, the first isoprenylation of aldehydes, bearing non-conjugated residues could be developed using TBC.

5. Experimental Part

5.1. Materials and methods

General conditions

All oxygen- and moisture-sensitive reactions were carried out in oven-dried glassware under nitrogen atmosphere using Schlenk-technique. Anhydrous solvents and reagents were transferred through syringes under nitrogen.

Reagents and solvents

Solvents used for anhydrous reactions were dried by standard methods of distillation over drying agents. DCM was dried over molecular sieve (3Å) after distillation. THF was distilled over sodium and benzophenone. All other solvents and reagents were obtained from commercial sources (abcr, Acros, Fluka, Merck, Sigma-Aldrich or TCI in the qualities puriss., p.a., or purum) and used without further purification.

Chromatography

Thin layer chromatography (TLC) for qualitative reaction and fraction controls was performed using pre-coated polyester sheets polygram SIL G/UV254 with SiO_2 coating (0.2 mm, 40 x 80 mm) by Macherey-Nagel. As visualisation method CAM stain (ceric ammonium molybdate) with subsequent heating was used. Flash column chromatography (FCC) was carried out using SiO_2 60 (particle size 40 – 63 µm) by Merck.

Analytical data

Melting points were measured in single determination on a Büchi Melting Point B-540 device and are stated in °C.

All NMR spectra were recorded at room temperature using JNM-Eclipse 400 (400 MHz), JNM-Eclipse 500 (500 MHz), Avance III HD 400 MHz Bruker Biospin (400 MHz) and Avance III HD 500 MHz Bruker Biospin (500 MHz) mit CryoProbe™ Prodigy through the NMR-division of the Department of Pharmacy of the LMU. Chemical shifts δ are reported as δ-values in ppm (parts per million) and refer to the deuterated solvent peak. Coupling constants (J) of protons are stated in Hz. The signal multiplicities are defined using the following abbreviations: s (singlet), d (doublet), dd (double doublet), dt (double triplet), t (triplet), q (quartet), p (pentet), ddd (doublet of doublet of doublets), tdd (triplet of doublet of doublets), dtd (doublet of triplet of doublets) and m (multiplet). The signal assignment was carried out using HMQC, HMBC, COSY and DEPT spectra. All spectra were evaluated using MestReNova by Mestrelab Research S.L.

Infrared spectra were measured on a JASCO FT/IR-4100 infrared spectrometer, using a Smiths Detection DuraSamp IR II Diamond ATR sensor for detection. The measured wavenumbers $\tilde{\nu}$ are reported in cm^{-1}.

High resolution mass spectra (HRMS) were recorded on a Jeol Mstation 700 or JMS GCmate II Jeol instrument for electron ionisation (EI). Electrospray ionisation (ESI) was measured on a Thermo Finnigan LTQ-FT. All measurements were performed by the mass spectroscopy service of the LMU. The mass is reported in *m*/*z* units with the mass of the molecular ion.

Gas chromatography (GC) was performed on a Varian 3800 gas chromatograph coupled to a Saturn 2200 ion trap from Varian (Darmstadt, Germany). The auto sampler was from CTC Analytics (Zwingen, Switzerland) and the split/splitless injector was a Varian 1177 (Darmstadt, Germany). Instrument control and data analysis were carried out with Varian Workstation 6.9 SP1 software. A VF-5-ms capillary column of 30 m length, 0.25 mm i.d. and 0.25 µm film thickness was used at a constant flow rate of 1.4 mL/min. Carrier gas was helium 99.999% from Air Liquide (Düsseldorf, Germany). The inlet temperature was kept at 300 °C and injection volume was 1 µL with splitless time 1.0 min. The initial column temperature was 50 °C and was held for 1.0 min. Then temperature was ramped up to 250 °C with 50 °C/min. Then the sterols were eluted at a rate of 5 °C/min until 310 °C (hold time 3 min). Total run time was 20 min. Transfer line temperature was 300 °C and the ion trap temperature was 150 °C. The ion trap was operated with electron ionization (EI) at 70 eV in scan mode (m/z 50 - 650) with a solvent delay of 6.3 min.

The X-ray intensity data were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror monochromator and a Mo Kα rotating anode X-ray tube (λ = 0.71073 Å). The frames were integrated with the Bruker SAINT software package. Data were corrected for absorption effects using the Multi-Scan method (SADABS). The structure was solved and refined using the Bruker SHELXTL Software Package.

5.2. Synthetic procedures and analytical data

5.2.1. General procedures for synthesis

General procedure 1 (GP1): Synthesis of *N*-Boc-*N*-allylhydrazones

The mixture of allylhydrazines **193a/193b** (1.00 eq) was dissolved in absolute EtOH to receive a concentration of 0.1 mmol/mL and the appropriate aldehyde (1.00 eq) was added. The reaction mixture was stirred at rt for 18 h. The solvent was removed *in vacuo* and the crude product was purified *via* FCC. Isolated yields are correlated to the amount of **193a** in the isomeric mixture.

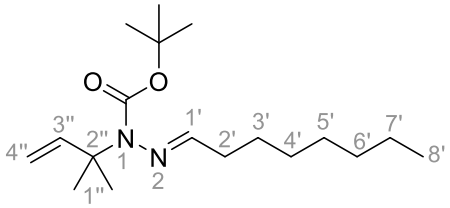
General procedure 2 (GP2): Synthesis of olefins *via* triflimide catalysed rearrangement

In an oven dried two-necked Schlenk flask, triflimide (10 mol%) was dissolved in dry diglyme (1.00 mL). A solution of the appropriate *N*-Boc-*N*-Allylhydrazone (1.00 eq) in dry diglyme (2.00 mL + 1.00 mL rinse) was added at rt. The reaction mixture was fitted with a N_2 flashed reflux condenser and then immediately stirred at 125 °C in a pre-heated oil bath.

After completion of the rearrangement detected by TLC, the reaction was cooled to rt and then quenched with sat. aq. $NaHCO_3$ (5.00 mL). Pentane (10.0 mL) was added and the organic layer was washed with at least 100 mL water. The solvent was removed *in vacuo* (30 °C, max. 700 mbar) and the crude product was purified *via* FCC.

5.2.2. Procedures and data

***tert*-Butyl 1-(2-methylbut-3-en-2-yl)-2-octylidenehydrazine-1-carboxylate (208)**



208

$C_{18}H_{34}N_2O_2$

M = 310.48 g/mol

N-Boc-*N*-allylhydrazone **208** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (250 mg, 1.75 mmol ≙ 1.59 mmol of isomer **193a**, 1.00 eq) and octanal (0.298 mL, 1.75 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (178 mg, 0.576 mmol, 36% referred to isomer **193a**).

R_f = 0.58 (hexanes/EtOAc 9:1).

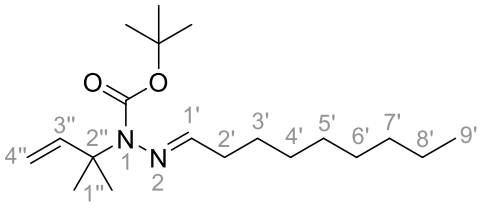
^{1}H-NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.71 (t, *J* = 5.6 Hz, 1H, 1'-H), 6.11 (dd, *J* = 17.5, 10.8 Hz, 1H, 3''-H), 5.07 – 4.86 (m, 2H, 4''-H), 2.35 (td, *J* = 5.6 Hz, 2H, 2'-H), 1.59 – 1.50 (m, 2H, 3'-H), 1.42 (s, 9H, $C(CH_3)_3$), 1.39 (s, 6H, 1''-H), 1.34 – 1.24 (m, 8H, 4', 5', 6', 7'-H), 0.87 (t, 3H, 8'-H).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 169.5 (C-1'), 154.3 (CO_2*t*Bu), 146.3 (C-3''), 109.4 (C-4''), 80.9 ($\underline{C}(CH_3)_3$), 61.7 (C-2''), 33.0 (C-2'), 31.9 (C-3', 4', 5', 6' or 7'), 29.5 (C-3', 4', 5', 6' or 7'), 29.2 (C-3', 4', 5', 6' or 7'), 28.6 ($C(\underline{C}H_3)_3$), 26.7 (C-1''), 26.2 (C-3', 4', 5', 6' or 7'), 22.8 (C-3', 4', 5', 6' or 7'), 14.3 (C-8').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3084, 3004, 2972, 2958, 2927, 2857, 1698, 1641, 1455, 1412, 1391, 1366, 1302, 1244, 1157, 1101, 1003, 991, 901, 855, 757, 724, 686.

HRMS (ESI): *m*/*z* = calculated for $C_{18}H_{35}N_2O_2$ $[M+H]^+$ 311.2693; found: 311.2694.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-nonylidenehydrazine-1-carboxylate (209)



209

$C_{19}H_{36}N_2O_2$

M = 324.51 g/mol

N-Boc-*N*-allylhydrazone **209** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (404 mg, 2.02 mmol ≙ 1.83 mmol of isomer **193a**, 1.00 eq) and nonanal (0.346 mL, 2.02 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (284 mg, 0.877 mmol, 48% referred to isomer **193a**).

R_f = 0.58 (hexanes/EtOAc 9:1).

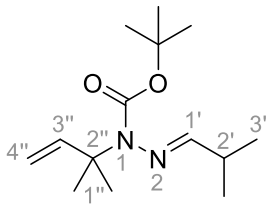
^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 7.71 (t, *J* = 5.6 Hz, 1H, 1'-H), 6.11 (dd, *J* = 17.5, 10.8 Hz, 1H, 3''-H), 5.05 – 4.89 (m, 2H, 4''-H), 2.34 (td, *J* = 5.6 Hz, 2H, 2'-H), 1.55 (m, 2H, 3'-H), 1.42 (s, 9H, $C(CH_3)_3$), 1.39 (s, 6H, 1''-H), 1.36 – 1.21 (m, 10H, 4', 5', 6', 7', 8'-H), 0.89 – 0.85 (m, 3H, 9'-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 169.4 (C-1'), 154.3 (CO_2*t*Bu), 146.3 (C-3''), 109.4 (C-4''), 80.9 (C-2'), 61.7 (C-2''), 33.0 (C-3'), 31.9 (C-4', 5', 6', 7', 8' or 9'), 29.5 (C-4', 5', 6', 7', 8' or 9'), 29.4 (C-4', 5', 6', 7', 8' or 9'), 29.3 (C-4', 5', 6', 7', 8' or 9'), 28.5 ($C(\underline{C}H_3)_3$), 26.7 (C-1''), 26.2 (C-4', 5', 6', 7', 8' or 9'), 22.8 (C-4', 5', 6', 7', 8' or 9'), 14.2 (C-9').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3086, 2972, 2956, 2926, 2856, 1698, 1640, 1455, 1412, 1390, 1366, 1302, 1244, 1157, 1100, 1003, 992, 900, 874, 857, 783, 756, 723, 687, 599.

HRMS (ESI): *m*/*z* = calculated for $C_{19}H_{37}N_2O_2$ $[M+H]^+$ 325.2849; found: 325.2849.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(2-methylpropylidene)hydrazine-1-carboxylate (210)



210

$C_{14}H_{26}N_2O_2$

M = 254.37 g/mol

N-Boc-*N*-allylhydrazone **210** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (519 mg, 2.59 mmol ≙ 2.36 mmol of isomer **193a**, 1.00 eq) and isobutyraldehyde (0.237 mL, 2.59 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (262 mg, 1.03 mmol, 44% referred to isomer **193a**).

R_f = 0.55 (hexanes/EtOAc 9:1).

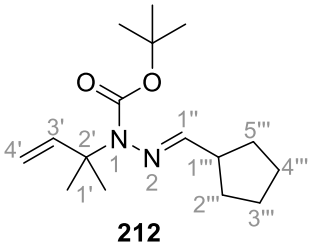
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.61 (d, *J* = 5.9 Hz, 1H, 1'-H), 6.11 (dd, *J* = 17.6, 10.8 Hz, 1H, 3''-H), 5.03 – 4.90 (m, 2H, 4''-H), 2.66 – 2.56 (m, 1H, 2'-H), 1.42 (s, 9H, $C(CH_3)_3$), 1.39 (s, 6H, 1''-H), 1.13 (s, 3H, 3'-H), 1.12 (s, 3H, 2'-CH_3).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 173.2 (C-1'), 154.1 (CO_2*t*Bu), 146.3 (C-3''), 109.4 (C-4''), 80.9 ($\underline{C}(CH_3)_3$), 61.9 (C-2''), 32.2 (C-2'), 28.6 ($C(\underline{C}H_3)_3$), 26.6 (C-1''), 19.6 (C-3', 2'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3086, 3008, 2973, 2930, 2872, 1698, 1641, 1456, 1412, 1390, 1366, 1304, 1289, 1244, 1156, 1092, 1058, 992, 970, 902, 879, 856, 756, 686, 599, 588.

HRMS (ESI): *m*/*z* = calculated for $C_{14}H_{27}N_2O_2$ $[M+H]^+$ 255.2067; found: 255.2066.

tert-Butyl 2-(cyclopentylmethylene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (212)



212

$C_{16}H_{28}N_2O_2$

M = 280.41 g/mol

N-Boc-*N*-allylhydrazone **212** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (430 mg, 2.15 mmol ≙ 1.96 mmol of isomer **193a**, 1.00 eq) and cyclopentane carboxaldehyde (0.229 mL, 2.15 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (245 mg, 0.874 mmol, 45% referred to isomer **193a**).

R_f = 0.57 (9:1 hexanes/EtOAc).

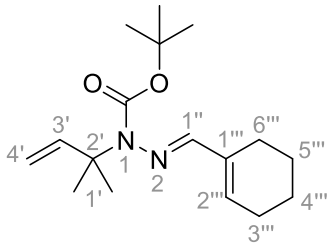
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.62 (d, *J* = 6.8 Hz, 1H, C-1''), 6.11 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.08 – 4.82 (m, 2H, 4'-H), 2.87 – 2.71 (m, 1H, 1'''-H), 1.95 – 1.79 (m, 2H, 2''', 3''', 4''' or 5'''-H), 1.73 – 1.54 (m, 6H, 2''', 3''', 4''' or 5'''-H), 1.42 (s, 9H, $C(CH_3)_3$), 1.38 (s, 6H, 1'-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 172.6 (C-1''), 154.2 (CO_2*t*Bu), 146.2 (C-3'), 109.4 (C-4'), 80.8, 61.8 (C-2'), 42.9 (C-1'''), 30.3 (C-2''', 3''', 4''' or 5'''), 28.6 ($C(\underline{C}H_3)_3$), 28.5 (C-2''', 3''', 4''' or 5'''), 26.6 (C-1'), 25.7 (Cy-CH_2).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3084, 2968, 2956, 2869, 1697, 1639, 1476, 1454, 1412, 1390, 1366, 1304, 1244, 1156, 1101, 1061, 1003, 992, 900, 877, 856, 783, 757, 687.

HRMS (ESI): *m*/*z* = calculated for $C_{16}H_{29}N_2O_2$ $[M+H]^+$ 281.2224; found: 281.2225.

tert-Butyl 2-(cyclohex-1-en-1-ylmethylene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (220)



220

$C_{17}H_{28}N_2O_4$

M = 292.42 g/mol

N-Boc-*N*-allylhydrazone **220** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (200 mg, 0.999 mmol ≙ 0.909 mmol of isomer **193a**, 1.00 eq) and 1-cyclohexene-1-carboxaldehyde (0.114 mL, 0.990 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (135 mg, 0.460 mmol, 51% referred to isomer **193a**).

R_f = 0.52 (9:1 hexanes/EtOAc).

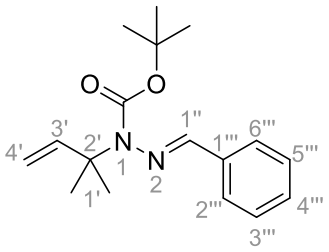
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.99 (s, 1H, 1''-H), 6.18 – 6.05 (m, 2H, 3', 2'''-H), 5.05 – 4.85 (m, 2H, 4'-H), 2.37 – 2.12 (m, 4H, 3''', 6'''-H), 1.70 – 1.61 (m, 4H, 4''', 5'''-H), 1.43 (s, 9H, $C(CH_3)_3$), 1.41 (s, 6H, 1'-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 163.9 (C-1''), 153.9 (CO_2*t*Bu), 146.6 (C-3'), 138.2 (C-2'''), 136.3 (C-1'''), 109.1 (C-4'), 81.2 ($\underline{C}(CH_3)_3$), 62.7 (C-2'), 28.6 ($C(\underline{C}H_3)_3$), 26.9 (C-1'), 26.3 (3''' or 6'''-H), 23.4 (3''' or 6'''-H), 22.5 (4''' or 5'''-H), 22.1 (4''' or 5'''-H).

IR (ATR): *ṽ*/cm^{-1} =2976, 2931, 2859, 1697, 1639, 1596, 1366, 1291, 1243, 1152, 1107, 902, 881, 754, 699.

HRMS (ESI): *m*/*z* = calculated for $C_{17}H_{29}N_2O_2$ $[M+H]^+$ 293.2224; found: 293.2223.

tert-Butyl 2-benzylidene-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (213)



213

$C_{17}H_{24}N_2O_2$

M = 288.39 g/mol

N-Boc-*N*-allylhydrazone **213** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (580 mg, 2.90 mmol ≙ 2.64 mmol of isomer **193a**, 1.00 eq) and benzaldehyde (0.294 mL, 2.90 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (312 mg, 1.08 mmol, 41% referred to isomer **193a**).

R_f = 0.64 (hexanes/EtOAc 9:1).

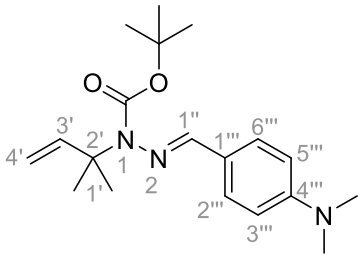
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.65 (s, 1H, 1''-H), 7.74 – 7.68 (m, 2H, 2''', 6'''-H), 7.43 – 7.34 (m, 3H, 3''', 4''', 5'''-H), 6.17 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.11 – 4.90 (m, 2H, 4'-H), 1.52 (s, 6H, 1'-H), 1.47 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 157.1 (C-1''), 153.6 (CO_2tBu), 146.4 (C-3'), 135.4 (C-1'''), 130.2 (C-4'''), 128.7 (C-3''', C-5'''), 127.7 (C-2''', C-6'''), 109.4 (C-4'), 81.8 ($\underline{C}(CH_3)_3$), 63.6 (C-2'), 28.5 ($C(\underline{C}H_3)_3$), 27.2 (C-1').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3083, 3062, 2976, 2932, 1697, 1642, 1574, 1476, 1449, 1412, 1391, 1366, 1289, 1243, 1149, 1109, 1071, 992, 947, 898, 856, 784, 753, 692, 659, 563.

HRMS (ESI): *m*/*z* = calculated for $C_{17}H_{25}N_2O_2$ $[M+H]^+$ 289.1910; found: 289.1909.

tert-Butyl 2-(4-(dimethylamino)benzylidene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (214)



214

$C_{19}H_{29}N_3O_2$

M = 331.46 g/mol

N-Boc-*N*-allylhydrazone **214** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (100 mg, 0.499 mmol ≙ 0.454 mmol of isomer **193a**, 1.00 eq) and 4-dimethylaminobenzaldehyde (74.5 mg, 0.499 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as white crystalline solid (143 mg, 0.431 mmol, 95% referred to isomer **193a**).

R_f = 0.35 (hexanes/EtOAc 9:1).

mp: 74 °C.

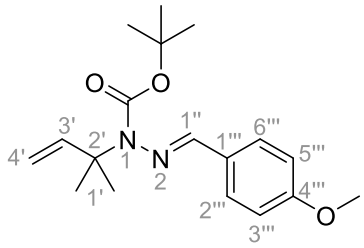
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.30 (s, 1H, 1''-H), 7.61 (d, *J* = 8.9 Hz, 2H, 2''', 6'''-H), 6.69 (d, *J* = 8.9 Hz, 2H, 3''', 5'''-H), 6.19 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.08 – 4.90 (m, 2H, 4'-H), 3.01 (s, 6H, $N(CH_3)_2$), 1.47 (s, 6H, 1'-H), 1.44 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 162.4 (C-1''), 154.2 (CO_2*t*Bu), 152.2 (C-4'''), 146.6 (C-3'), 129.4 (C-2''', C-6'''), 122.4 (C-1'''), 111.8 (C-3''', C-5'''), 109.2 (C-4'), 80.9 ($\underline{C}(CH_3)_3$), 62.6 (C-2'), 40.4 ($N(CH_3)_2$), 28.6 ($C(\underline{C}H_3)_3$), 26.9 (C-1').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2976, 2930, 1693, 1616, 1601, 1528, 1477, 1455, 1363, 1300, 1237, 1155, 1100, 1060, 894, 859, 816, 755, 731.

HRMS (ESI): *m*/*z* = calculated for $C_{19}H_{30}N_3O_2$ $[M+H]^+$ 332.2333; found: 332.2333.

tert-Butyl 2-(4-methoxybenzylidene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (215)



215

$C_{18}H_{26}N_2O_3$

M = 318.42 g/mol

N-Boc-*N*-allylhydrazone **215** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (150 mg, 0.749 mmol ≙ 0.682 mmol of isomer **193a**, 1.00 eq) and 4-anisaldehyde (102 mg, 91.1 µL, 0.749 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as colourless oil (151 mg, 0.475 mmol, 70% referred to isomer **193a**).

R_f = 0.42 (hexanes/EtOAc 9:1).

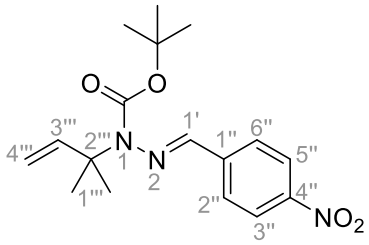
^{1}H NMR (400 MHz, Chloroform-*d*) *δ*/ppm = 8.48 (s, 1H, 1''-H), 7.66 (d, *J* = 8.8 Hz, 2H, 2''', 6'''-H), 6.91 (d, *J* = 8.9 Hz, 2H, 3''', 5'''-H), 6.17 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.08 – 4.92 (m, 2H, 4'-H), 3.84 (s, 3H, OCH_3), 1.49 (s, 6H, 1'-H), 1.45 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) *δ*/ppm = 161.5 (C-4'''), 159.0 (C-1''), 153.9 ($\underline{C}O_2t$Bu), 146.5 (C-3'), 129.3 (C-2''' and C-6'''), 127.8 (C-1'''), 114.1 (C-3''' and C-5'''), 109.3 (C-4'), 81.4 ($\underline{C}(CH_3)_3$), 63.1 (C-2'), 55.5 (OCH_3), 28.6 ($C(\underline{C}H_3)_3$), 27.0 (C-1').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2975, 2932, 1693, 1606, 1512, 1456, 1366, 1293, 1245, 1150, 1104, 1031, 900, 859, 831.

HRMS (ESI): *m*/*z* = calculated for $C_{18}H_{27}N_2O_3$ $[M+H]^+$ 319.2016; found: 319.2015.

***tert*-Butyl 1-(2-methylbut-3-en-2-yl)-2-(4-nitrobenzylidene)hydrazine-1-carboxylate (216)**



216

$C_{17}H_{23}N_3O_4$

M = 333.39 g/mol

N-Boc-*N*-allylhydrazone **216** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (250 mg, 1.25 mmol ≙ 1.14 mmol of isomer **193a**, 1.00 eq) and 4-nitrobenzaldehyde (0.126 mL, 1.25 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as yellow solid (233 mg, 0.698 mmol, 61% referred to isomer **193a**).

R_f = 0.51 (hexanes/EtOAc 9:1).

mp: 67 °C.

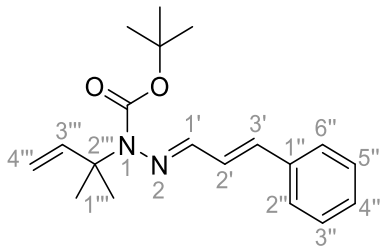
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 9.02 (s, 1H, 1'-H), 8.24 – 8.19 (m, 2H, 3'', 5''-H), 7.82 – 7.75 (m, 2H, 2'', 6''-H), 6.12 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'''-H), 5.10 – 4.93 (m, 2H, 4'''-H), 1.56 (s, 6H, 1'''-H), 1.50 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 152.9 (CO_2*t*Bu), 148.1 (C-4''), 147.7 (C-1'), 145.9 (C-3'''), 142.7 (C-1''), 127.6 (C-2'', 6''), 124.0 (C-3'', 5''), 110.1 (C-4'''), 82.9 ($\underline{C}(CH_3)_3$), 65.0 (C-2'''), 28.5 ($C(\underline{C}H_3)_3$), 27.6 (C-1''').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1699, 1598, 1572, 1518, 1368, 1343, 1286, 1246, 1146, 1107, 907, 849, 832, 729, 692, 647.

HRMS (EI): *m*/*z* = calculated for $C_{17}H_{23}N_3O_4$ $[M]^{\cdot+}$ 333.1683; found: 333.1710.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-((_E_)-3-phenylallylidene)hydrazine-1-carboxylate (219)



219

$C_{19}H_{26}N_2O_2$

M = 314.43 g/mol

N-Boc-*N*-allylhydrazone **219** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (250 mg, 1.25 mmol ≙ 1.13 mmol of isomer **193a**, 1.00 eq) and cinnamaldehyde (0.157 mL, 1.25 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as yellow oil (228 mg, 0.725 mmol, 64% referred to isomer **193a**).

R_f = 0.56 (hexanes/EtOAc 9:1).

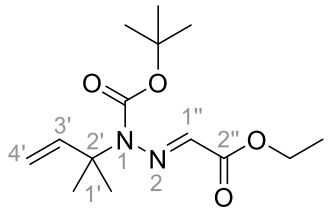
^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 8.33 (dd, *J* = 7.2, 1.5 Hz, 1H, 1'-H), 7.49 – 7.47 (m, 2H, 2', 6'-H), 7.38 – 7.33 (m, 2H, 3', 5'-H), 7.32 – 7.28 (m, 1H, 4''-H), 6.96 – 6.93 (m, 2H, 2', 3'-H), 6.14 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'''-H), 5.07 – 4.92 (m, 2H, 4'''-H), 1.47 (s, 6H, 1'''-H), 1.46 (s, 9 H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 161.7 (C-1'), 153.7 (CO_2*t*Bu), 146.2 (C-3'''), 140.5 (C-3'), 136.2 (C-1''), 128.9 (C-4''), 128.9 (C-3', 5'), 127.2 (C-2', 6'), 126.0 (C-2'), 109.5 (C-4'''), 81.6 ($\underline{C}(CH_3)_3$), 62.9 (C-2'''), 28.5 ($C(\underline{C}H_3)_3$), 26.9 (C-1''').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1694, 1449, 1366, 1289, 1243, 1148, 1109, 1051, 973, 906, 879, 850, 749, 689.

HRMS (ESI): *m*/*z* = calculated for $C_{19}H_{27}N_2O_2$ $[M+H]^+$ 315.2067; found: 315.2066.

tert-Butyl 2-(2-ethoxy-2-oxoethylidene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (211)



211

$C_{14}H_{24}N_2O_4$

M = 284.36 g/mol

N-Boc-*N*-allylhydrazone **211** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (200 mg, 0.990 mmol, ≙ 0.901 mmol of isomer **193a**, 1.00 eq) and ethyl glyoxalate solution (~ 50% in toluene, 0.198 mL, 0.990 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as yellow oil (108 mg, 0.380 mmol, 42% referred to isomer **193a**).

R_f = 0.44 (hexanes/EtOAc 9:1).

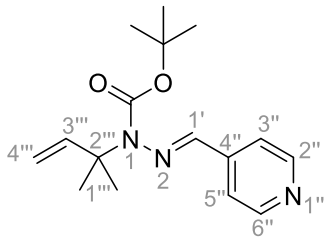
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.41 (s, 1H, 1''-H), 6.05 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.07 – 4.93 (m, 2H, 4'-H), 4.26 (q, *J* = 7.1 Hz, 2H, $OC\underline{H_2}CH_3$), 1.52 (s, 6H, 1'-H), 1.48 (s, 9H, $C(CH_3)_3$), 1.31 (t, *J* = 7.1 Hz, 3H, $OCH_2C\underline{H_3}$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 164.9 (C-2''), 151.9 (CO_2*t*Bu), 145.5 (C-3'), 135.7 (C-1''), 110.6 (C-4'), 83.6 ($\underline{C}(CH_3)_3$), 65.9 (C-2'), 60.9 ($O\underline{C}H_2CH_3$), 28.3 ($C(\underline{C}H_3)_3$), 27.7 (C-1'), 14.4 ($OCH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1742, 1708, 1585, 1477, 1456, 1369, 1339, 1288, 1242, 1206, 1181, 1148, 1113, 1093, 1044, 911, 848, 798, 759, 744, 576.

HRMS (EI): *m*/*z* = calculated for $C_9H_{16}N_2O_2$ $[M\text{-}CO_2tBu]^{\bullet+}$ 184.1206, found: 184.1205.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(pyridin-4-ylmethylene)hydrazine-1-carboxylate (218)



218

$C_{16}H_{23}N_3O_4$

M = 289.38 g/mol

N-Boc-*N*-allylhydrazone **218** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (350 mg, 1.75 mmol ≙ 1.59 mmol of isomer **193a**, 1.00 eq) and 4-pyridinecarboxaldehyde (0.165 mL, 1.75 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as light yellow oil (342 mg, 1.18 mmol, 74% referred to isomer **193a**).

R_f = 0.12 (hexanes/EtOAc 9:1).

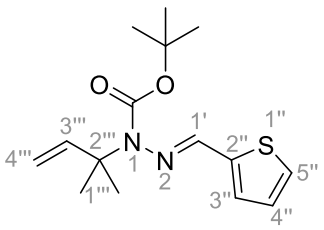
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.90 (s, 1H, 1'-H), 8.65 – 8.55 (m, 2H, 2'', 6''-H), 7.50 (dd, *J* = 6.1, 0.4 Hz, 2H, 3'', 5''-H), 6.11 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'''-H), 5.11 – 4.90 (m, 2H, 4'''-H), 1.54 (s, 6H, 1'''-H), 1.49 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 152.9 (CO_2*t*Bu), 150.3 (C-2', 6'), 147.7 (C-1'), 146.0 (C-3'''), 143.8 (C-4''), 121.1 (C-3'', 5''), 109.9 (C-4'''), 82.8 ($\underline{C}(CH_3)_3$), 64.9 (C-2'''), 28.5 ($C(\underline{C}H_3)_3$), 27.6 (C-1''').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2977, 2933, 1698, 1590, 1367, 1287, 1246, 1147, 989, 903, 859, 814, 755, 732, 656.

HRMS (ESI): *m*/*z* = calculated for $C_{16}H_{24}N_3O_2$ $[M+H]^+$ 290.1863; found: 290.1862.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(thiophen-2-ylmethylene)hydrazine-1-carboxylate (217)



217

$C_{15}H_{22}N_2O_2S$

M = 294.41 g/mol

N-Boc-*N*-allylhydrazone **217** was synthesised according to **GP1**, using mixture of allylhydrazines **193a**/**193b** (150 mg, 0.749 mmol ≙ 0.681 mmol of isomer **193a**, 1.00 eq) and 2-thiophenecarboxaldehyde (70.0 µL, 0.749 mmol, 1.00 eq). The title compound was purified *via* FCC (hexanes/EtOAc 9:1) and isolated as light yellow oil (104 mg, 0.352 mmol, 52% referred to isomer **193a**).

R_f = 0.60 (hexanes/EtOAc 9:1).

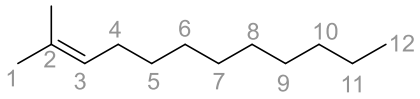
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 8.85 – 8.83 (m, 1H, 1'-H), 7.32 (dt, *J* = 5.0, 1.0 Hz, 1H, 5''-H), 7.24 (dd, *J* = 3.6, 1.2 Hz, 1H, 3''-H), 7.04 (dd, *J* = 5.1, 3.6 Hz, 1H, 4''-H), 6.14 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'''-H), 5.08 – 4.91 (m, 2H, 4'''-H), 1.49 (s, 6H, 1'''-H), 1.47 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 153.6 (CO_2*t*Bu), 150.2 (C-1'), 146.3 (C-3'''), 140.9 (C-2''), 129.7 (C-3''), 127.9 (C-5''), 127.4 (C-4''), 109.5 (C-4'''), 81.9 ($\underline{C}(CH_3)_3$), 63.7 (C-2'''), 28.5 ($C(\underline{C}H_3)_3$), 27.2 (C-1''').

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2985, 2938, 1742, 1708, 1585, 1369, 128, 1242, 1181, 1148, 1113, 1093, 1044, 911, 848, 759, 744, 576.

HRMS (EI): *m*/*z* = calculated for $C_{15}H_{22}N_2O_2S$ $[M]^{\bullet+}$ 294.1396; found: 294.1392.

2-Methyldodec-2-ene (221)



221

$C_{13}H_{26}$

M = 182.35 g/mol

Olefin **221** was synthesised according to **GP2**, using *N*-Boc-*N*-allylhydrazone **208** (155 mg, 0.500 mmol, 1.00 eq). The title compound was purified *via* FCC (pentane 100%) and isolated as colourless oil (18.0 mg, 0.0987 mmol, 20%).

R_f = 0.94 (pentane 100%).

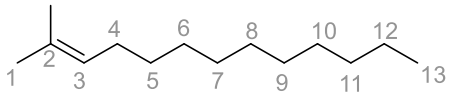
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.15 – 5.08 (m, 1H, 3-H), 1.96 (q, *J* = 7.1 Hz, 2H, 4-H), 1.69 (d, *J* = 1.4 Hz, 3H, 1-H or 2-CH_3), 1.60 (d, *J* = 1.3 Hz, 3H, 1-H or 2-CH_3), 1.26 (s, 14H, 5, 6, 7, 8, 9, 10 and 11-H), 0.88 (t, *J* = 2.9 Hz, 3H, 12-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 131.3 (C-2), 125.1 (C-3), 32.1 (C-5, 6, 7, 8, 9, 10 or 11), 30.1 (C-5, 6, 7, 8, 9, 10 or 11), 29.8 (C-5, 6, 7, 8, 9, 10 or 11), 29.8 (C-5, 6, 7, 8, 9, 10 or 11), 29.5 (C-5, 6, 7, 8, 9, 10 or 11), 29.5 (C-5, 6, 7, 8, 9, 10 or 11), 28.2 (C-4), 25.9 (C-1 or 2-CH_3), 22.9 (C-5, 6, 7, 8, 9, 10 or 11), 17.8 (C-1 or 2-CH_3), 14.3 (C-12).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2956, 2922, 2853, 1462, 1376, 1094, 985, 886, 833, 722.

HRMS (EI): *m*/*z* = calculated for $C_{13}H_{26}$ $[M]^{\cdot+}$ 182.2029, found: 182.2027.

2-Methyltridec-2-ene (222)



222

$C_{14}H_{28}$

M = 196.38 g/mol

Olefin **222** was synthesised according to **GP2**, using *N*-Boc-*N*-allylhydrazone **209** (162 mg, 0.500 mmol, 1.00 eq). The title compound was purified *via* FCC (pentane 100%) and isolated as colourless oil (18.8 mg, 0.103 mmol, 21%).

R_f = 0.88 (pentane/Et_2O 9:1).

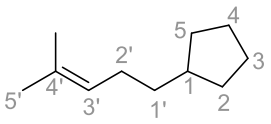
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.12 (tdt, *J* = 7.2, 2.9, 1.5 Hz, 1H, 3-H), 1.96 (q, *J* = 6.8 Hz, 2H, 4-H), 1.69 (d, *J* = 1.4 Hz, 3H, 1-H or 2-CH_3), 1.60 (d, *J* = 1.3 Hz, 3H, 1-H or 2-CH_3), 1.26 (s, 16H, 5, 6, 7, 8, 9, 10, 11 and 12 -H), 0.93 – 0.83 (m, 3H, 13-H).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 131.3 (C-2), 125.1 (C-3), 32.1 (C-5, 6, 7, 8, 9, 10, 11 or 12), 30.1 (C-5, 6, 7, 8, 9, 10, 11 or 12), 29.8 (C-5, 6, 7, 8, 9, 10, 11 or 12), 29.8 (C-5, 6, 7, 8, 9, 10, 11 or 12), 29.8 (C-5, 6, 7, 8, 9, 10, 11 or 12), 29.5 (C-5, 6, 7, 8, 9, 10, 11 or 12), 29.5 (C-5, 6, 7, 8, 9, 10, 11 or 12), 28.2 (C-4), 25.9 (C-1 or 2-CH_3), 22.9 (C-5, 6, 7, 8, 9, 10, 11 or 12), 17.8 (C-1 or 2-CH_3), 14.3 (C-13).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2955, 2922, 2853, 1456, 1376, 1094, 984, 886, 832, 721, 593, 556.

HRMS (EI): *m*/*z* = calculated for $C_{14}H_{28}$ $[M]^{\bullet+}$ 196.2185, found: 196.2183.

(4-Methylpent-3-en-1-yl)cyclopentane (225)



225

$C_{11}H_{20}$

M = 152.28 g/mol

Olefin **225** was synthesised according to **GP2**, using *N*-Boc-*N*-allylhydrazone **212** (140 mg, 0.500 mmol, 1.00 eq). The title compound was purified *via* FCC (pentane 100%) and isolated as colourless oil (15.0 mg, 0.0985 mmol, 20%).

R_f = 0.95 (pentane 100%).

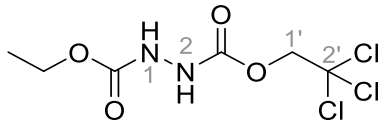
^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 5.15 – 5.10 (m, 1H, 3'-H), 2.01 – 1.95 (m, 2H, 2'-H), 1.77 – 1.73 (m, 2H, 1'-H), 1.69 (d, *J* = 1.4 Hz, 3H, 5'-H or 4'-CH_3), 1.60 (d, *J* = 1.2 Hz, 3H, 5'-H or 4'-CH_3), 1.52 – 1.46 (m, 2H, 2, 3, 4 or 5-H), 1.34 – 1.30 (m, 2H, 2, 3, 4 or 5-H, 1-H), 1.11 – 1.05 (m, 2H, 2, 3, 4 or 5-H), 0.91 – 0.86 (m, 3H, 2, 3, 4 or 5-H).

^{13}C NMR (126 MHz, chloroform-*d*) *δ*/ppm = 131.1 (C-4'), 125.2 (C-3'), 39.9 (C-1'), 36.6 (C-1), 32.8 (C-2, 3, 4 or 5), 27.4 (C-2'), 25.9 (C-5' or 4'-CH_3), 25.4 (C-2, 3, 4 or 5), 17.8 (C-5' or 4'-CH_3).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2983, 2950, 2922, 2857, 1452, 1376, 1105, 985, 907, 830, 735, 650, 574, 560.

HRMS (EI): *m*/*z* = calculated for $C_{11}H_{20}$ $[M]^{\bullet+}$ 152.1559, found: 152.1558.

1-Ethyl 2-(2,2,2-trichloroethyl) hydrazine-1,2-dicarboxylate (245)



245

$C_6H_9Cl_3N_2O_4$

M = 279.49 g/mol

To a solution of ethyl carbazate (5.20 g, 49.9 mmol, 1.00 eq) and NMM (5.55 mL, 49.9 mmol, 1.00 eq) in THF (100 mL), 2,2,2-trichloroethylchloroformat (6.88 mL, 49.9 mmol, 1.00 eq) was added at 0 °C. The reaction mixture was allowed to warm up to rt and stirred for 24 h. The suspension was filtered and concentrated *in vacuo*. Purification *via* FCC (hexanes/EtOAc 7:3) gave hydrazine **245** (14.0 g, 50.1 mmol, quantitative) as a colourless oil.

R_f = 0.28 (hexanes/EtOAc 7:3).

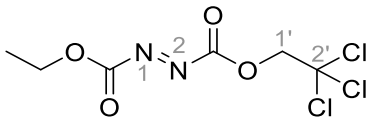
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.91 (d, *J* = 146.8 Hz, 2H, 1, 2-H), 4.78 (s, 2H, 1'-H), 4.21 (q, *J* = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 1.27 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 156.6 ($\underline{C}O_2Et$), 155.3 ($\underline{C}O_2CH_2CCl_3$), 94.9 (C-2'), 75.2 (C-1'), 62.7 ($\underline{CH_2}CH_3$), 14.5 ($CH_2\underline{CH_3}$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3258, 1762, 1735, 1697, 1524, 1441 1367, 1259, 1208, 1095, 1053, 1023, 978, 886, 824, 776, 737, 707.

HRMS (EI): *m*/*z* calculated for $C_6H_9O_4N_2Cl_3$ $[M]^{\bullet+}$ 277.9622; found 277.9617.

1-Ethyl 2-(2,2,2-trichloroethyl) (*E*)-diazene-1,2-dicarboxylate (246)



246

$C_6H_7Cl_3N_2O_4$

M = 277.48 g/mol

Hydrazine **245** (14.6 g, 52.2 mmol, 1.00 eq) was dissolved in toluene (120 mL), before pyridine (4.22 mL, 52.2 mmol, 1.00 eq) and NBS (9.30 g, 52.2 mmol, 1.00 eq) were added. The reaction mixture was stirred for 3 h at rt. The mixture was diluted with toluene (50.0 mL), washed with water (120 mL), sat. aq. $Na_2S_2O_3$ solution (100 mL), aq. 1M HCl (100 mL), sat. aq. $NaHCO_3$ solution (100 mL), water (100 mL) and brine (110 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Azodicarboxylate **246** (13.4 g, 48.3 mmol, 92%) was obtained as an orange oil and was used without further purification.

R_f = 0.75 (hexanes/EtOAc 7:3).

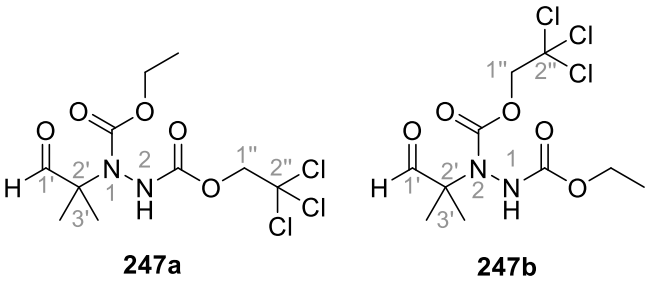
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 5.03 (s, 2H, 1'-H), 4.54 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.47 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 159.9 ($\underline{C}O_2CH_2CCl_3$), 159.0 ($\underline{C}O_2Et$), 93.4 (C-2'), 76.9 (C-1'), 65.9 ($\underline{CH_2}CH_3$), 14.2 ($CH_2\underline{CH_3}$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1770, 1370, 1200, 1097, 1059, 1015, 854, 801, 718.

HRMS (EI): *m*/*z* calculated for $C_6H_7O_4N_2Cl_3$ $[M]^{\bullet+}$ 275.9466; found 275.9458.

1-Ethyl 2-(2,2,2-trichloroethyl) 1-(2-methyl-1-oxopropan-2-yl)hydrazine-1,2-dicarboxylate (247a) and 2-ethyl 1-(2,2,2-trichloroethyl) 1-(2-methyl-1-oxopropan-2-yl)hydrazine-1,2-dicarboxylate (247b)



247a **247b**

247

$C_{10}H_{15}Cl_3N_2O_5$

M = 349.59 g/mol

Azodicarboxylate **246** (6.00 g, 21.6 mmol, 1.00 eq) and L-proline (249 mg, 2.16 mmol, 10 mol%) were disperged in dry DCM (120 mL) and the suspension was cooled to 0 °C. Isobutyraldehyde (2.96 mL, 32.4 mmol, 1.50 eq) was added and the reaction mixture was allowed to warm up to rt and stirred for 18 h. The solvent was removed *in vacuo* and the title compound was purified *via* FCC (hexanes/EtOAc 7:3). An inseparable mixture of aldehydes **247** were obtained as a colourless oil (3.23 g, 9.24 mmol, 43%) in an isomeric mixture of 85:15 (determined retrospectively *via* ^{1}H NMR).

R_f = 0.75 (hexanes/EtOAc 7:3).

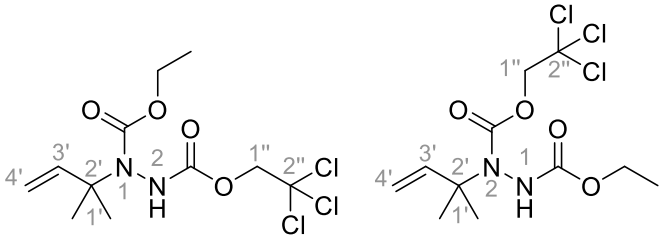
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 9.51 (s, 1H, 1'-H), 7.02 – 6.57 (m, 1H, NH), 4.78 (d, *J* = 31.6 Hz, 2H, C-1''), 4.20 (dd, *J* = 7.1, 2.4 Hz, 2H, $C\underline{H}_2CH_3$), 1.47 – 1.20 (m, 9H, 3'-H, $CH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 198.1 (C-1'), 155.6 ($\underline{C}O_2Et$ or $\underline{C}O_2CH_2CCl_3$), 155.2 ($\underline{C}O_2Et$ or $\underline{C}O_2CH_2CCl_3$), 95.0 (C-2''), 75.1 (C-1''), 67.7 (C-2'), 63.6 ($\underline{C}H_2CH_3$), 20.4 (C-3'), 14.4 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3306, 1733, 1707, 1514, 1469, 1407, 1379, 1342, 1216, 1173, 1096, 1047, 818, 757, 719.

HRMS (ESI): *m*/*z* calculated for $C_{10}H_{16}O_5N_2Cl_3$ $[M+H]^+$ 349.0119; found 349.0123.

1-Ethyl 2-(2,2,2-trichloroethyl) 1-(2-methylbut-3-en-2-yl)hydrazine-1,2-dicarboxylate (248a) and 2-ethyl 1-(2,2,2-trichloroethyl) 1-(2-methylbut-3-en-2-yl)hydrazine-1,2-dicarboxylate (248b)



248a **248b**

248

$C_{11}H_{17}Cl_3N_2O_4$

M = 347.62 g/mol

The isomeric mixture of aldehydes **247** (3.1 g, 8.87 mmol, 1.00 eq) and pyridine (1.29 mL, 16.0 mmol, 1.80 eq) were added to a flame dried flask and cooled to - 80 °C. TEBBE reagent (0.5M in toluene, 23.1 mL, 11.5 mmol, 1.30 eq) was added carefully by adding it along the flask. The reaction mixture was warmed up to 0 °C and stirred for 24 h. The reaction was quenched with a sat. aq. $NaHCO_3$ solution (10.0 mL) at - 80 °C and extracted with DCM (3 x 30.0 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Purification *via* FCC (hexanes/EtOAc 9:1 → 4:1) gave an inseparable mixture of olefines **248** as a colourless oil (556 mg, 1.60 mmol, 18%) in an isomeric mixture of 85:15 (determined retrospectively *via* ^{1}H NMR).

R_f = 0.39 (hexanes/EtOAc 8:2).

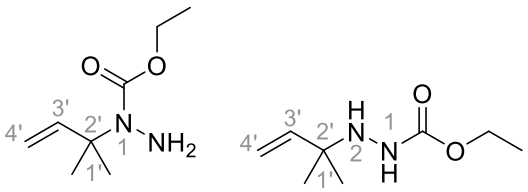
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 6.63 (s, 1H, NH), 6.10 (dd, *J* = 17.5, 10.7 Hz, 1H, 3'-H), 5.10 (dd, *J* = 17.9, 6.7 Hz, 1H, 4'-H), 5.03 (dd, *J* = 10.7, 0.7 Hz, 1H, 4'-H), 4.90 – 4.68 (m, 2H, 1''-H), 4.19 – 4.09 (m, 2H, $C\underline{H}_2CH_3$), 1.52 (s, 3H, 1'-H), 1.45 (s, 3H, 1'-H), 1.25 – 1.20 (m, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 155.4 ($\underline{C}O_2Et$ or $\underline{C}O_2CH_2CCl_3$), 155.2 ($\underline{C}O_2Et$ or $\underline{C}O_2CH_2CCl_3$), 143.8 (C-3'), 111.8 (C-4'), 74.9 (C-1''), 63.2 (C-2'), 62.4 ($\underline{C}H_2CH_3$), 26.3 (C-1'), 26.1 (C-1'), 23.9 (C-2''), 14.5 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 3291, 2985, 1749, 1695, 1517, 1403, 1375, 1338, 1251, 1216, 1181, 1096, 1051, 915, 821, 765, 739, 719.

HRMS (ESI): *m*/*z* calculated for $C_{11}H_{16}O_4N_2Cl_3$ $[M-H]^-$ 345.0181; found 345.0182.

Ethyl 1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (243a) and ethyl 2-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (243b)



243a **243b**

243

$C_8H_{16}N_2O_2$

M = 172.23 g/mol

The mixture of olefins **248** (550 mg, 1.58 mmol, 1.00 eq) was dissolved in a 1:1:1 mixture of ethanol (1.00 mL), water (1.00 mL) and acetic acid (1.00 mL). Zinc powder (3.62 g, 55.4 mmol, 35.0 eq) was added and the reaction mixture was stirred for 10 min at rt. After filtration of the reaction mixture, the filtrate was extracted with DCM (3 x 10.0 mL). The combined organic layers were washed was sat. aq. $NaHCO_3$ solution (15.0 mL) and dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. Allyhydrazines **243a** and **243b** was obtained as a colourless oil (167 mg, 0.970 mmol, 61%) as an isomeric mixture of 85:15 (determined *via* ^{1}H NMR) and was used without further purification.

R_f = 0.47 (hexanes/EtOAc 8:2).

^{1}H NMR (**243a**) (500 MHz, chloroform-*d*) *δ*/ppm = 6.05 (dd, *J* = 17.5, 10.7 Hz, 1H, 3'-H), 5.01 – 4.92 (m, 2H, 4'-H), 4.13 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 3.80 (s, 2H, NH_2), 1.44 (s, 6H, 1'-H), 1.25 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (**243a**) (101 MHz, chloroform-*d*) *δ*/ppm = 157.9 ($\underline{C}O_2Et$), 145.3 (C-3'), 109.9 (C-4'), 61.9 (C-2'), 61.7 ($\underline{C}H_2CH_3$), 26.5 (C-1'), 14.7 ($CH_2\underline{C}H_3$).

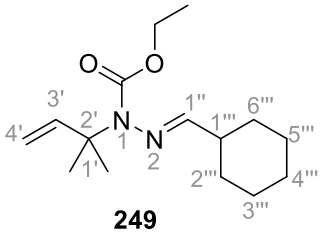
^{1}H NMR (**243b**) (500 MHz, chloroform-*d*) *δ*/ppm = 5.97 (dd, *J* = 17.4, 10.7 Hz, 1H, 3'-H), 5.14 – 5.05 (m, 2H, 4'-H), 4.10 – 4.04 (m, 2H, $C\underline{H}_2CH_3$), 1.39 (s, 6H, 1'-H), 1.23 – 1.20 (m, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (**243b**) (101 MHz, chloroform-*d*) *δ*/ppm = 155.8 ($\underline{C}O_2Et$), 144.2 (C-3'), 111.8 (C-4'), 61.5 ($\underline{C}H_2CH_3$), 53.6 (C-2'), 26.5 (C-1'), 14.5 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 2980, 1686, 1465, 1400, 1374, 1318, 1246, 1181, 1081, 1007, 910, 859, 769, 686.

HRMS (ESI): *m*/*z* calculated for $C_8H_{17}O_2N_2$ $[M+H]^+$ 173.1285; found 173.1283.

Ethyl 2-(cyclohexylmethylene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (249)



249

$C_{15}H_{26}N_2O_2$

M = 266.39 g/mol

N-CO_2Et-*N*-allylhydrazone **249** was synthesised according to **GP1** using mixture of olefins **243a/243b** (200 mg, 1.16 mmol ≙ 0.986 mmol of isomer **243a**, 1.00 eq) and cyclohexane carboxaldehyde (130 mg, 1.16 mmol, 1.00 eq). The title compound was purified *via* FCC (pentane/Et_2O 9:1) and isolated as colourless oil (115 mg, 0.432 mmol, 44% referred to isomer **243a**).

R_f = 0.32 (pentane/Et_2O 9:1).

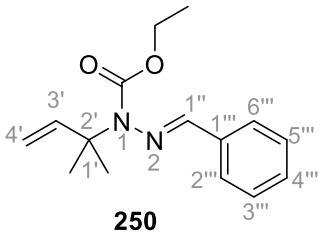
^{1}H NMR (400 MHz, chloroform-*d*) *δ*/ppm = 7.60 (d, *J* = 6.0 Hz, 1H, 1''-H), 6.11 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.10 – 4.90 (m, 2H, 4'-H), 4.07 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 2.42 – 2.32 (m, 1H, 1'''-H), 1.89 – 1.62 (m, 6H, 2''', 3''', 4''', 5''' and/or 6'''-H), 1.41 (s, 6H, 1'-H), 1.37 – 1.28 (m, 4H, 2''', 3''', 4''', 5''' and/or 6'''-H), 1.20 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).

^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 173.9 (C-1''), 154.9 ($\underline{C}O_2Et$), 145.4 (C-3'), 110.1 (C-4'), 61.9 (C-2'), 61.4 ($\underline{C}H_2CH_3$), 41.4 (C-1'''), 29.7 (C-2''', 3''', 4''', 5''' and/or 6'''), 26.5 (C-1'), 26.1 (C-2''', 3''', 4''', 5''' and/or 6'''), 25.4 (C-2''', 3''', 4''', 5''' and/or 6'''), 14.5 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} =2979, 2927, 2853, 1699, 1448, 1369, 1281, 1240, 1177, 1097, 1004, 911, 758, 684.

HRMS (EI): *m*/*z* calculated for $C_{15}H_{26}O_2N_2$ $[M]^{\bullet+}$ 266.1989; found 266.1989.

Ethyl 2-benzylidene-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (250)



250

$C_{15}H_{20}N_2O_2$

M = 260.34 g/mol

N-CO_2Et-*N*-allylhydrazone **250** was synthesised according to **GP1** using mixture of olefins **243a/243b** (200 mg, 1.16 mmol ≙ 0.986 mmol of isomer **243a**, 1.00 eq) and benzaldehyde (123 mg, 1.16 mmol, 1.00 eq). The title compound was purified *via* FCC (pentane/Et_2O 9:1) and isolated as colourless oil (234 mg, 0.899 mmol, 91% referred to isomer **243a**).

R_f = 0.38 (pentane/Et_2O 9:1).

^{1}H NMR (500 MHz, chloroform-*d*) *δ*/ppm = 8.60 (s, 1H, 1''-H), 7.74 – 7.70 (m, 2H, 2''', 6'''-H), 7.44 – 7.38 (m, 3H, 3''', 4''', 5'''-H), 6.18 (dd, *J* = 17.5, 10.8 Hz, 1H, 3'-H), 5.11 – 4.96 (m, 2H, 4'-H), 4.17 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 1.53 (s, 6H, 1'-H), 1.25 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$).

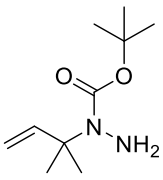
^{13}C NMR (101 MHz, chloroform-*d*) *δ*/ppm = 159.0 (C-1''), 154.6 ($\underline{C}O_2$Et), 145.7 (C-3'), 134.9 (C-1'''), 130.5 (C-4'''), 128.7 (C-3''', 5'''), 127.8 (C-2''', 6'''), 110.0 (C-4'), 63.6 (C-2'), 61.7 ($\underline{C}H_2CH_3$), 26.9 (C-1'), 14.5 ($CH_2\underline{C}H_3$).

IR (ATR): $\tilde{\nu}$/cm^{-1} = 1698, 1597, 1455, 1368, 1282, 1202, 1166, 1098, 1073, 1015, 906, 827, 743, 687.

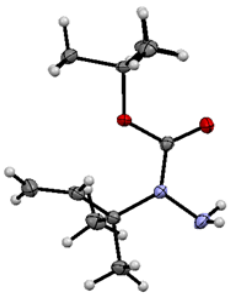
HRMS (ESI): *m*/*z* calculated for $C_{15}H_{21}O_2N_2$ $[M+H]^+$ 261.1597; found 261.1596.

5.3. Crystallographic data

Table 13. Crystallographic information of **193a**.



193a



Compound	**193a** CCDC 1907495
net formula	$C_{10}H_{20}N_2O_2$
M_r/g mol^{-1}	200.28
crystal size/mm	0.100 × 0.060 × 0.050
T/K	103.(2)
radiation	MoKα
diffractometer	'Bruker D8 Venture TXS'
crystal system	triclinic
space group	'P -1'
a/Å	5.9860(5)
b/Å	9.0630(7)
c/Å	11.4665(9)
α/°	105.616(3)
β/°	99.965(3)
γ/°	97.087(3)
V/Å^3	580.52(8)
Z	2
calc. density/g cm^{-3}	1.146
μ/mm^{-1}	0.080
absorption correction	Multi-Scan
transmission factor range	0.95–1.00
refls. measured	5785
R_{int}	0.0312
mean σ(*I*)/*I*	0.0416
θ range	3.444–26.370
observed refls.	1982
x, *y* (weighting scheme)	0.0299, 0.2047
hydrogen refinement	H(C) constr, H(N) refall
refls in refinement	2368
parameters	140
restraints	0
$R(F_{obs})$	0.0411
$R_w(F^2)$	0.0961
S	1.072
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.242
min electron density/e Å^{-3}	−0.205

I. Appendix

Designation and nomenclature

Compounds which were synthesised by undergraduate students in the course of bachelor theses are marked as follows:

[a]: ANNA J. STEINMETZ

[b]: DOREEN REUTER (née KREMER)

[c]: KATHARINA N. KRIEGLER

[d]: MORITZ M. KORNMAYER

[e]: PATRICIA L. SKOWRONEK

The indicated nomenclature in all compounds follows the IUPAC rules.

Abbreviations

17β-HSD	17β-hydroxysteroid-dehydrogenase
4-nitrobenzenesulfonyl	nosyl
9-BBN	9-borabicyclo(3.3.1)nonane
Å	Angstrom
abs.	absolute
ACAT	acetyl-CoA-acetyltransferase (Thiolase II)
AcOH	acetic acid
AIBN	azobisisobutyronitrile
Alzheimer's disease	AD
aq.	aqueous
atm	atmospheric pressure
Bu	butyl
CoA	coenzyme A
CVD	cardiovascular diseases
CYP51A1	lanosterol 14a-demethylase
DCM	dichloromethane
DHCR14	Δ14-sterol reductase
DHCR7	Δ7-dehydrocholesterol reductase
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMSO	dimethyl sulfoxide
EBP	sterol-Δ8/7-Isomerase

e.g.	exempli gratia
eq	equivalent
ESI	electron spray ionization
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron volt
FCC	flash column chromatography
FPPS	farnesyl-PP synthase
g.i.	growth inhibition
GGPPS	geranylgeranyl-PP synthase
h	hour
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HMGCR	hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase)
HMGCS	hydroxymethylglutaryl-CoA synthase (HMG-CoA synthase)
HRMS	high-resolution mass spectroscopy
Hz	hertz
i-PrOH	isopropanol
IDI	isopentenyl diphosphate isomerase
LDA	lithium diisopropylamide
LG	leaving group
LS	lanosterol synthase
LXR	liver X receptor
m	*meta*
M	molar mass
M	molar
m	multiplet (NMR)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
min	minutes
mmol	millimole
mol	mole
mp	melting point

MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromid
MVD	diphosphomevalonate decarboxylase
MVK	mevalonate kinase
mw	microwave
n	unbranched/primary
n.d.	not determinable
n.t.	not tested
NAFLD	non-alcoholic fatty liver disease
NaHMDS	sodium bis(trimethylsilyl)amide
NASH	non-alcoholic steatohepatitis
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
NsCl	2-nitrobenzenesulfonyl chloride
NSDHL	sterol-4a-carboxylate-3-dehydrogenase
o	*ortho*
p	*para*
p.a.	pro analysi
PBS	phosphate buffered saline
Pd(dppf)Cl_2	(1,1′-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II)
PDC	pyridinium dichromate
PMVK	phosphomevalonate kinase
ppm	parts per million
Pr	propyl
q	quartet (NMR)
quant.	quantitative
rac	racemic
RCT	reverse cholesterol transport
R_f	retardation factor
rt	room temperature
RXR	retinoid X receptor
s	secondary
s	singlet (NMR)
sat.	saturated
SC5D	lathosterol oxidase (Δ7-sterol-C5-desaturase)
SM	squalene monooxygenase
SMO	sterol-C4-methyl oxidase

SQS	squalene synthase
t	tertiary
t	triplet (NMR)
t.i.	total inhibition
TBDMSCl	*tert*-butyldimethylsilyl chloride
TEA	triethylamine
TES	triethylsilane
TFA	trifluoroacetic acid
THF	tetrahydrofurane
TLC	thin layer chromatography
TMS	trimethylsilyl
$\tilde{\nu}$	wavenumber [cm^{-1}]

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