THESIS ON NATURAL AND EXACT SCIENCES B36

SYNTHESIS OF 9,11-SECOSTEROLS INTERMEDIATES

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Declaration: *Hereby I declare that this doctoral thesis, original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any degree or examination.*

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I R. Aav , T. Kanger, T. Pehk, M. Lopp. Synthesis of the AB-Ring of 9,11-Secosterols. *Synlett*, **2000**, *4*, 529-531.

II R. Aav, T. Kanger, T. Pehk, M. Lopp. Oxidation of Substituted Bicyclo[4.4.0]decen-3-ones. *Proc. Estonian Acad. Sci. Chem*. **2001**, *50*, 138-146.

III R. Aav, T. Kanger, T. Pehk, M. Lopp, Unexpected Reactivity of Ethyl 2-(diethylphosphono)-propionate toward 2,2-Disubstituted-1,3-cyclopentanediones. *Phosphorus, Sulfur, and Silicon and the Related Elements*, in press, accepted 26.08.**2004**

Abbreviations

$(DHQ)_2AQN$ – 1,4-bis(dihydroquininyl)anthraquinone
$(DHQ)_2PHAL$ – 1,4-bis(dihydroquininyl)phthalazine
9-BBN – 9-borabicyclo[3.3.1]nonane
BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BiTISP – (*N*-2,4,6-*tri*-isopropylbenzenesulfonyl)prolinate
BsCl – benzenesulfonyl chloride
CSA – camphorsulfonic acid
CBS catalyst – oxazaborolidine of diphenyl-pyrrolidin-2-yl-methanol (named after Corey, Bakshi, Shibata)
DBU – 1,8-diazabicyclo[5.4.0]undec-7-ene
de – diastereomeric excess
DIPEA – *N,N*-diisopropylethylamine
DIBALH – diisobutylaluminium hydride
DMAP –*N,N*-dimethyl-4-aminopyridine
DME – 1,2-dimethoxyethane
DMF – dimethylformamide
DMSO – dimethylsulfoxide
ee – enantiomeric excess
GC – gas chromatography
HPLC – high pressure liquid chromatography
HWE – Horner-Wadsworth-Emmons
LDA – lithiumdiisopropylamide
LG – good leaving group
LTEPA – lithium *tris*[(3-ethyl-3-pentyl)oxy]aluminium hydride
MCPBA – metachloroperbensoic acid
MOM – methoxymethyl
MS – molecular sieves
MsN_3 – mesyl azide
NMO – *N*-methylmorpholine-*N*-oxide
NMR – nuclear magnetic resonance
PDC – pyridinium dichlorochromate
Ph – phenyl
PhMent – 8-phenylmenthol
PTAD – 4-phenyl-1,2,4-triazolin-3,5-dione
PTPA – phtaloylphenylalanine
Pyr – pyridine
RT – room temperature
TEA – triethylamine
TBS – tertbutyldimethylsilyl
THF – tetrahydrofurane
WM – Wieland-Miescher

1 Introduction

Target oriented total synthesis has a lasting value as a discipline within chemistry. The original goal of total synthesis to confirm the structure of a natural product has been replaced with objectives toward the exploration and discovery of new chemistry along the pathway to the target molecule. Today, the total synthesis of a natural product is associated with selection of challenging and preferably biologically important target molecules.[1] Often the bioactivity of natural compounds is determined using traces of isolated matter and for a more detailed study of properties, larger quantities are needed. The isolation of secosterols from marine species is not very efficient, for example, from 980 g freeze-dried coral *Gersemia fruticosa* was isolated 1.5 mg of 9,11-secosterol **1**[2] (Figure 1), thus the yield was 0.00015%. In the case of pharmaceutical interest (bioactivity), the need for chemical methods for the preparation of these compounds, in at least gram scale, is obvious.

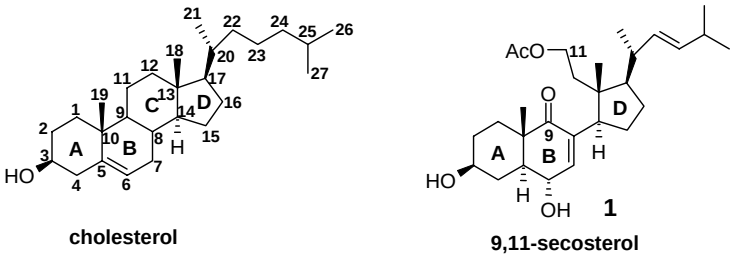


Figure 1. Structure and numeration of cholesterol and 9,11-secosterol

As the nomenclature of sterols is based on cholesterol, the structure of the target molecule and the numeration of carbon atoms and ring labels are depicted in Figure 1 together with cholesterol. The prefix *seco*- in the compound name indicates the cleavage of one sterol ring, which in the case of 9,11-secosterol is C-ring, cleaved between carbons C-9 and C-11.

The sterols are polycyclic compounds that contain several asymmetric centers. It is well known that if the molecule contains n asymmetric centers, the total possible number of isomers is 2^n. The target 9,11-secosterol contains 8 asymmetric centers and the number of all possible isomers is 256. In the case of sterol skeleton, only some of these are of biological importance. As every individual isomer has unique biological properties, the synthesis of the target molecule should be realized in a chemo- and stereocontrolled way.

In the present work an attempt was made to find a general acceptable method for the synthesis of 9,11-secosterol as well as for similar structures. The basic feature of the used synthesis strategy is to use coupling of two main structural units, the A,B- and D-ring moieties. The study of the synthesis of A,B-ring

synthon is realized and described in Articles I and II. The results of the studies of the D-ring synthon that led to a disclosure of a new nucleophilic reaction of ethyl 2-(diethylphosphono)propionate is presented in Article III.

1.1 Bioactive 9,11-secosterols

Marine organisms provide one of the world's richest sources of polyoxygenated sterols.[3] Among others, the 9,11-secosterols are a class of biologically active terpenoids, first isolated from gorgonian Pseudopterogorgia americana by E. L. Enwall *et al.* in 1972.[4] Capon and Faulkner[5] reported first the isolation of bioactive 9,11-secosterol - ichthyotoxic herbasterol from marine sponge Dysidea herbacea in 1985. Since then a number of bioactive 9,11-secosterols have been isolated and they are reported to bear very different biological activity: antihistaminic[6], antiproliferative, anti-inflammatory[7] and cytotoxic[8,9,10]. (See Figure 2)

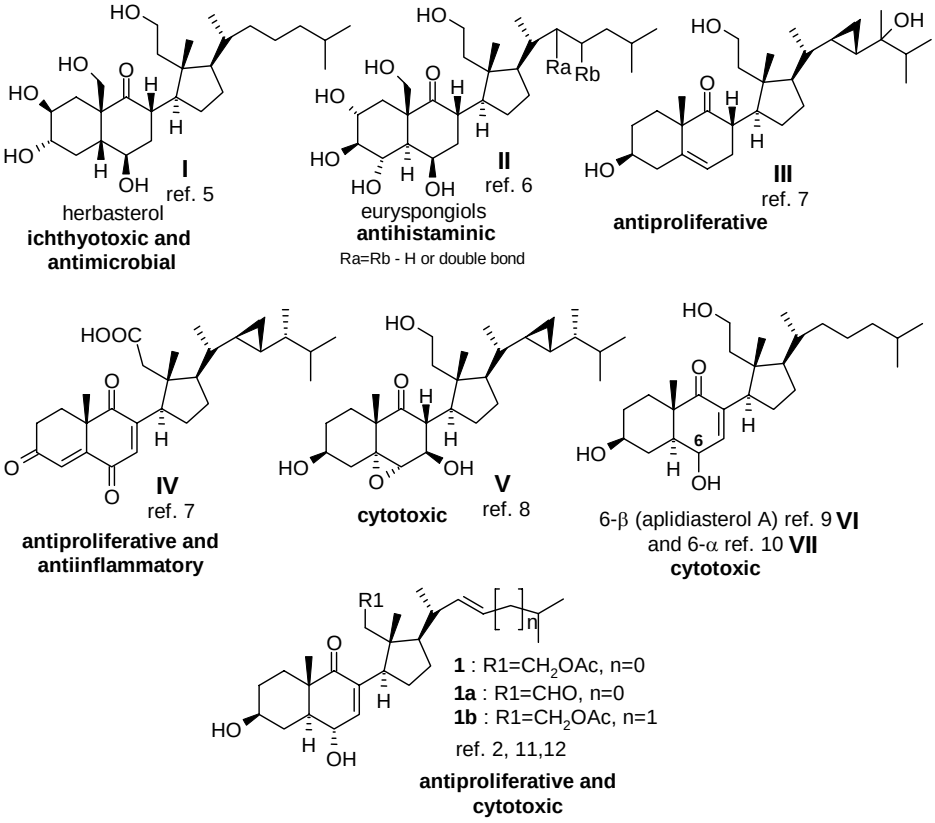


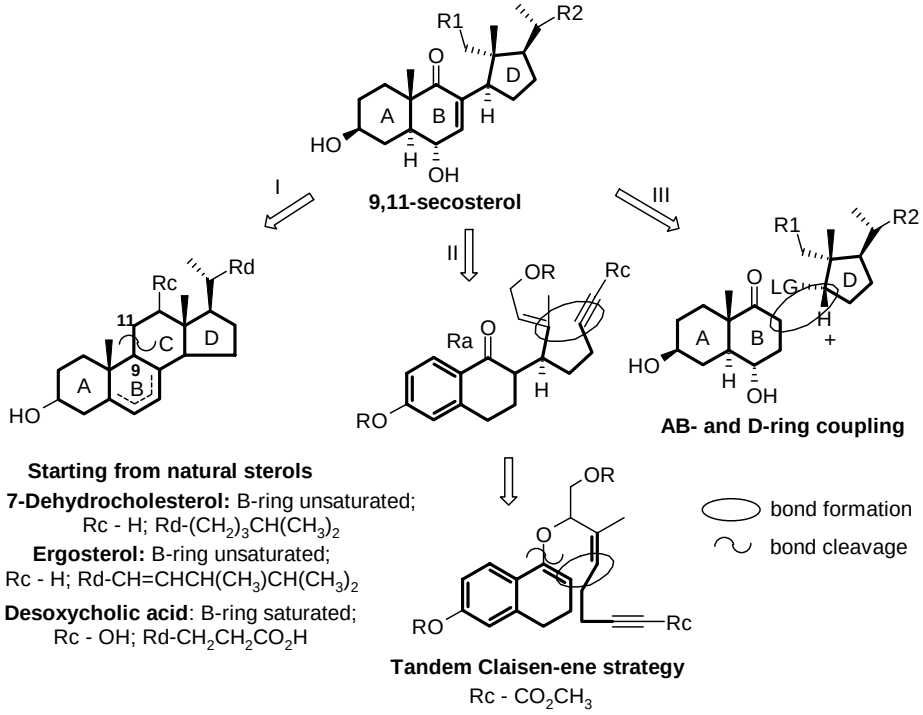
Figure 2. Bioactive 9,11-secosterols

In our faculty, 9,11-secosterols **1** (shown above) were isolated from the White Sea soft coral *Gersemia fruticosa*, their preliminary biological study revealed the antiproliferative and cytotoxic activity.[2,11,12,] Unfortunately, the broader

screening of biological properties was retarded due to unavailability of the sterol of interest. Therefore the study of preparative synthetic methods toward this bioactive natural compound was attempted.

2 Synthetic approaches

There are several approaches for synthesis of 9,11-secosterols as shown in Scheme 1.



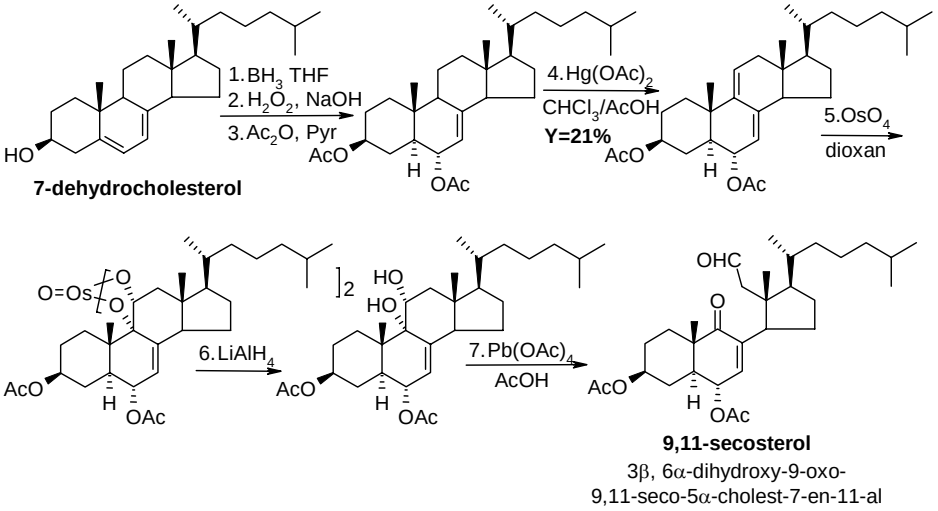
Scheme 1. Synthetic strategies for constructing of the 9,11-secosterol carbon skeleton

The first strategy for constructing the secosterol carbon skeleton is to start from natural sterols (I, Scheme 1). It is possible to choose different natural precursors. Migliuolo *et al.*[13] were the first who attempted to use this approach, starting from 7-dehydrocholesterol. They were followed by Jäälaid *et al.*[14,15,16] who started from ergosterol and Kuhl *et al.*[17,18] who started from desoxycholic acid. This strategy mimics the biological pathway by cleaving the 9,11-bond in sterol and seems to be the most straightforward approach for secosterol skeleton construction. The main advantage of starting from a natural sterol is the circumstance that the appropriate stereochemistry of the carbon skeleton already exists for A, B (6-membered) and D (5-membered) rings. The main disadvantage of the approach is that the molecular weight of the starting material and the product are close, so as all functional group manipulations are accompanied with the loss of material, the quantities of starting sterol should be

quite considerable. This issue will be discussed closer in Section 2.1 "Starting from Natural Sterols (Approach I)". The second very interesting strategy is the tandem Claisen-ene reaction (II, Scheme 1), explored by Mikami *et al.*[19]. The key transformation of the approach is the convergent construction of the A,B- and D-ring synthons by the asymmetric Claisen-ene sequence with high stereochemical control. The tandem reactions shorten synthetic sequence and induce chirality transfer via sigmatropic rearrangement. It is notable that this strategy has been realized only with aromatic A-ring moiety, therefore, it would be only a speculation that Claisen-ene sequence could be successfully exploited for the synthesis of cytotoxic 9,11-secosterol **1**. More details on this approach are given in Section 2.2 "Asymmetric Tandem Claisen-Ene Strategy (Approach II)". Our strategy (III, Scheme 1) is based on the coupling of A,B-ring and D-ring synthons through nucleophilic addition of enolate, generated from A,B-ring, to D-ring synthon containing good leaving group. This approach gives a possibility to synthesize a number of analogs with 9,11-secosterols skeleton by varying A,B-ring or D-ring synthons. Additionally, as most of the functional groups could be manipulated separately and independently in both synthons, the procedure is simplified, making the proposed approach more economical as compared to two previous ones. The retro-synthetic analysis of our strategy is outlined in Section 2.3 "A,B- and D-ring coupling (Approach III)".

2.1 Starting from Natural Sterols (Approach I)

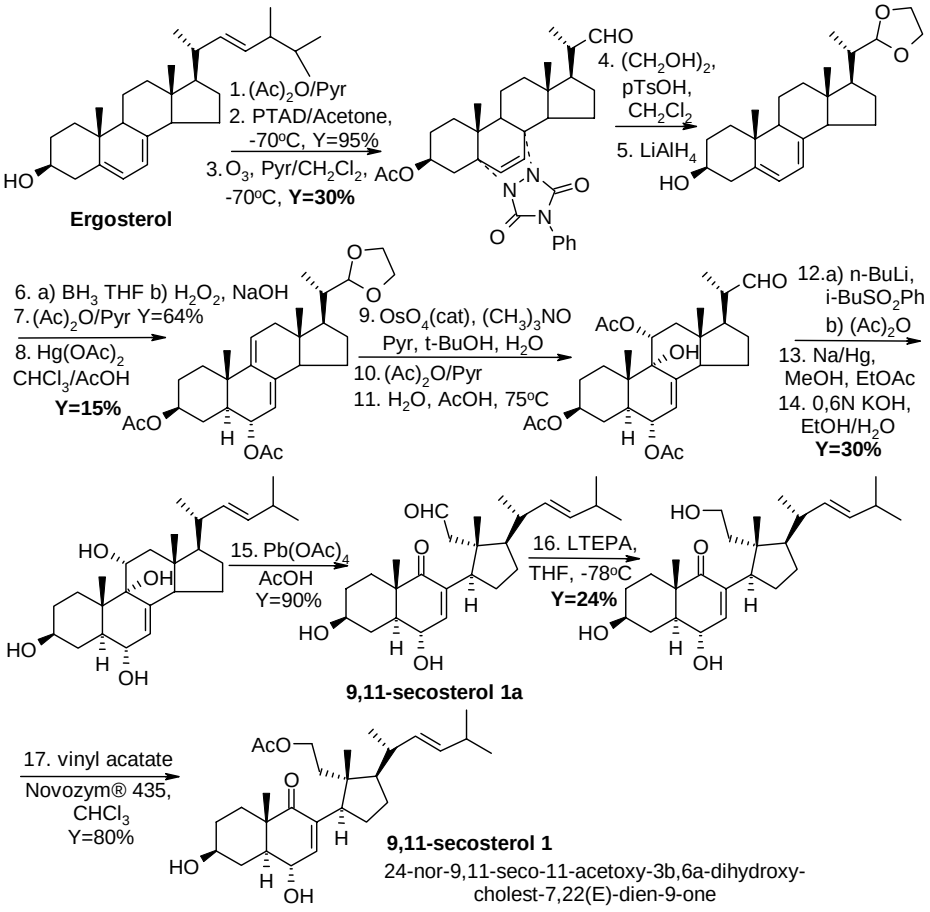
Migliuolo *et al.*[13] isolated the 9,11-secosterol, 3β, 6α-dihydroxy-9-oxo-9,11-seco-5α-cholest-7-en-11-al and to confirm its structure, they synthesized the same secosterol starting from 7-dehydrocholesterol (Scheme 2).



Scheme 2. First synthesis of 9,11-secosterol by Migliuolo, A. *et al.*[13] starting from 7-dehydrocholesterol

First, they functionalized the B-ring by regioselective hydroboration followed by the protection of hydroxyl groups. Then double bond was selectively introduced to the C-ring by dehydrogenation with mercuric acetate, unfortunately, only in 21% yield, oxidized with osmium tetraoxide and performed scission of the 9,11-carbon bond with lead tetraacetate. The main drawback in this synthetic route is the dehydrogenation step because of low yield (where they lost nearly 80% of the material).

In the late 1990s, two research groups attempted almost simultaneously the synthesis of bioactive 9,11-secosterol **1**, starting from the natural sterols. Jäälaid *et al.*[14,15,16] completed this synthesis first. They started with stereochemically appropriately substituted ergosterol (Scheme 3), where functionalization of B-ring, modification of D-ring side-chain and cleavage of 9,11-carbon bond was needed.

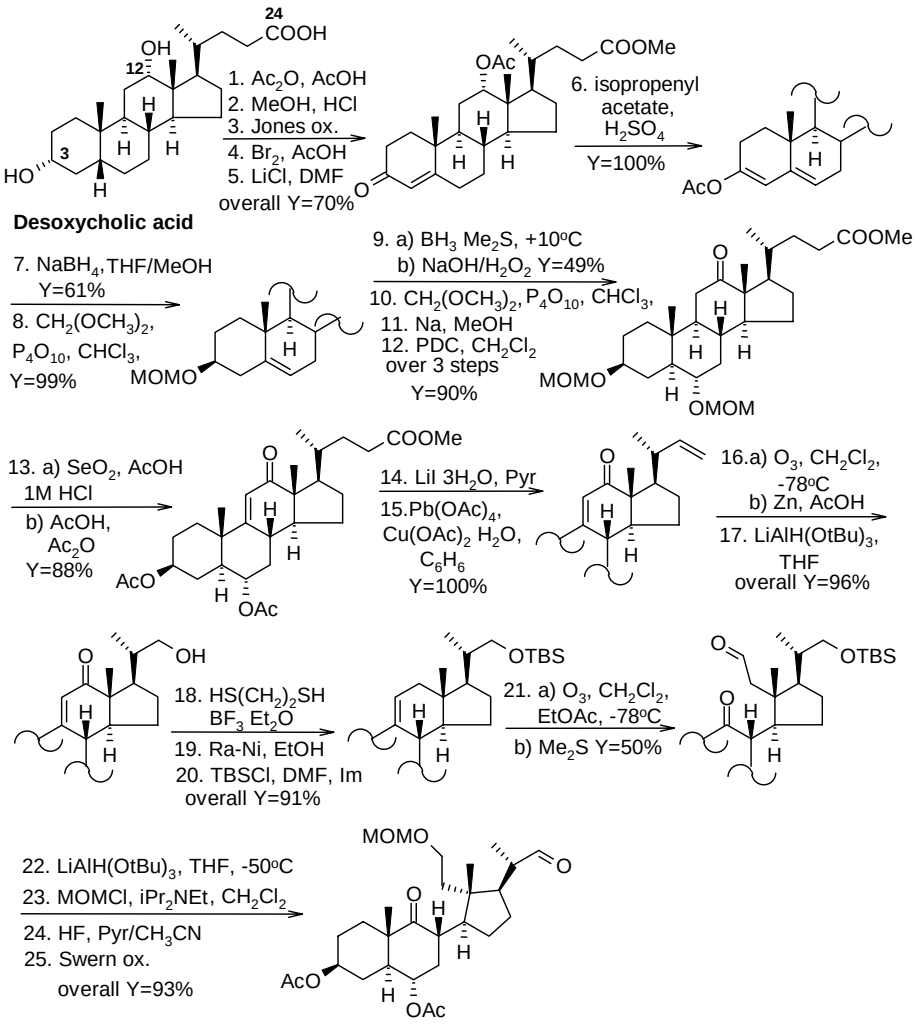


Scheme 3. Synthesis of cytotoxic 9,11-secosterols **1** and **1a** by Jäälaid, R. *et al.*[14] starting from ergosterol

To modify the D-ring side-chain, they first protected conjugated double bonds in B-ring by 4-phenyl-1,2,4-triazolin-3,5-dione (PTAD) and then used

ozonation for cleavage of the double bond in the side-chain of the D-ring. The yield of ozonation was only 30%. In the following steps they used Migliuolo *et al.*[13] method to introduce the hydroxyl group into the B-ring and double bond into the C-ring. Unfortunately, the dehydrogenation proceeded even in lower yield (only 15%) than in Migliuolo synthesis. Thus, this attempt does not work efficiently. The double bond in the C-ring was dihydroxylated with OsO_4 catalysis and by the Julia olefination procedure the appropriate side-chain of the D-ring was built up in a 30% of yield. Cleavage of the 9,11-carbon bond was made with $Pb(OAc)_4$, analogously to that of Migliuolo *et al.*[13]. This procedure led to cytotoxic 9,11-secosterol **1a**. Further, the aldehyde function was reduced with lithium *tris*[(3-ethyl-3-pentyl)oxy]aluminium hydride (LTEPA) in only 24% yield. The derived primary hydroxyl group was acylated regioselectively by lipase Novozym® 435 (*Candida antarctica* lipase B) catalysis, resulting in another cytotoxic 9,11-secosterol **1**. Thus, they succeeded in the synthesis of bioactive 9,11-secosteroids **1** and **1a** in 17 steps, but from a practical point of view, this synthesis is not very efficient because of low overall yield.

Kuhl, A. and Kreiser, W.[17,18] started the synthesis of 9,11-secosterol **1** from desoxycholic acid (Scheme 4), which carried suitable functionalities for modifications at carbons C-3, C-12 and C-24.



Scheme 4. Kuhl, A. *et al.* [17,18] synthesis toward cytotoxic 9,11-secosterol **1** starting from desoxycholic acid

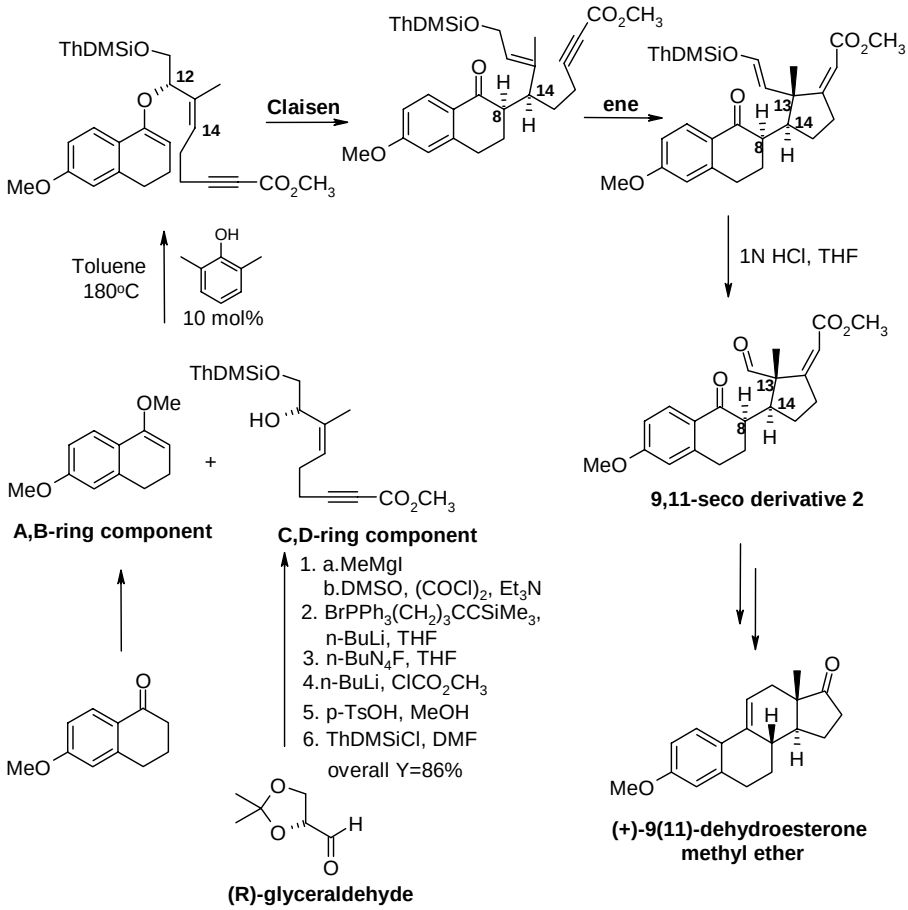
First, they followed the five-step sequence of Burchhardt *et al.*[20] and distinguished between two secondary hydroxyl groups at C-3 and C-12. Thus, they ended up with the enone function in A-ring and acyl-protected hydroxyl group at C-12 position in the C-ring. Further enolization of enone led to dienolacetate of the A,B-ring. Diastereoselective reduction of the acetate gave appropriate stereochemistry at the hydroxyl group of C-3 and a double bond in the B-ring. Using the hydroboration reaction, hydroxyl group into C-6 position was diastereoselectively introduced. As a result, a steroid skeleton with appropriately functionalized A,B-moiety was obtained. By deprotection of hydroxyl group at C-12, and oxidizing it into ketone, they were able to dehydrogenate at the C-9, C-11 carbons in good yield by using selenium

chemistry and prepared thereby the steroid intermediate for 9,11-carbon bond cleavage. After deoxygenation at C-12 the 9,11-double bond was cleaved by ozonolysis in only 50% yield of the reaction. However, it is an alternative for the toxic OsO_4, which was employed in previous examples[13,14]. Finally, they reduced the aldehyde group, protected the formed alcohol, deprotected the side-chain hydroxyl group and after Swern oxidation reached the sterol precursor of 9,11-secosterol **1**. To complete this synthesis, in addition to the described 25-step procedure, several other steps are needed: prolongation of side-chain by some Wittig-type reagent; dehydrogenation at C-7 and C-8; and some protective group manipulations.

Thus, it can be concluded that the functionalization of commercially available sterols proceed through a large number on synthetic steps, involving the use of a high number of protection-deprotection procedures, which are essential for differentiation between similar functionalities in these complex molecules and, as already mentioned, the quantities of starting materials for processing are high, because of the low overall yield of presented approaches.

2.2 Asymmetric Tandem Claisen-Ene Strategy (Approach II)

In the course of asymmetric synthesis of (+)-9(11)-dehydroesterone methyl ether, the Mikami *et al.*[19] developed a strategy of consecutive carbocyclization for the D and C rings of the steroid skeleton based on the asymmetric tandem Claisen-ene sequence. (Scheme 5)



Scheme 5. Synthesis of (+)-9(11)-dehydroesterone methyl ether, through 9,11-seco intermediate **2** developed by Mikami *et al.*[19]

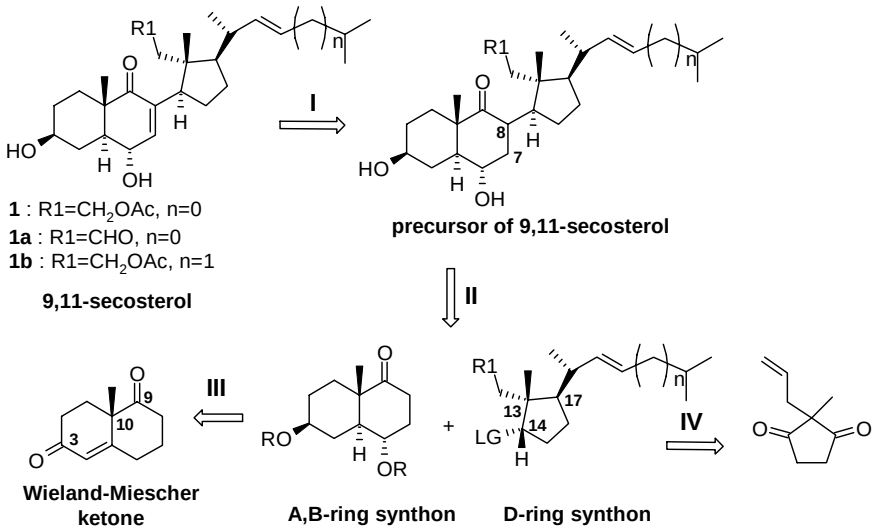
To introduce chirality into the sterol skeleton, they started from a readily available enantiomeric (*R*)-glyceraldehyde from which they synthesized through *Z* selective Still-Wittig olefination and some additional manipulations, stereochemically pure (*S*),(*Z*)-allylic alcohol (the **C,D-ring component**) in an overall yield 86%. The next step, one-pot Claisen-ene sequence with A,B-ring component and C,D-ring component in a sealed tube at 180°C for 60 h afforded after hydrolysis 9,11-seco derivative **2** in 76% yield. The NMR analysis showed that the configuration of 13,14-double bond was predominately *trans* and the configuration at carbons 8,14 was 90% *syn*. Thus, the Claisen rearrangement[21] proceeded in a high level of 1,3-chirality transfer from C-12 to C-14 and in the intramolecular ene-reaction[22], the quaternary carbon center at C-13 was generated at a high level of *trans*-diastereofacial selectivity.

This elegant approach has been realized on only one steroid example. For the synthesis of 9,11-secosterol **1**, the A,B-ring component consists of much more sensitive functionalities (non-aromatic A-ring, hydroxyl moieties at C-3 and C-

6), thus there could be difficulties when such harsh conditions have to be applied in such a case. Additionally, according to that sequence, the D-ring side chain is constructed in the presence of A,B-functionalized sterol, which involves the same problems as when starting from natural sterol (see above).

2.3 A,B- and D-ring coupling (Approach III)

Our vision of the synthesis of 9,11-secosterol **1** is concentrated on the applying of the total synthesis concept. The retrosynthetic analysis of the 9,11-secosterol **1** is outlined in Scheme 6 and reveals one possible approach consisting of four main steps: first, coming down to the precursor; second, dividing the sterol into two independent synthons, which could be easily coupled; third, the synthesis of A,B-ring synthon and fourth, the synthesis of D-ring synthon.



Scheme 6. Retrosynthetic analysis of the 9,11-secosterol **1**

We envisage the first task to be solved by the dehydrogenation of precursor of 9,11-secosterol at C-7, C-8, which could be achieved, for example, through selenium chemistry[23], and this precursor to be divided into two constituents: the AB-ring synthon and D-ring synthon. The coupling of those synthons could be realized by S_N2 reaction between nucleophilic enolate of ketone in A,B-ring synthon and good leaving group containing D-ring synthon. Synthesis of A,B-ring synthon could be realized starting from commercially available Wieland-Miecher ketone, which contains the appropriate quaternary carbon center at C-10 and oxy-functionalities at C-3 and C-9. A solution of that task is proposed in Section 4.2 "Synthesis of A,B-ring synthon (Articles I, II)". The original synthesis of D-ring synthon applies a use of the prochiral 1,3-cyclopentanedione

as a promising starting material. The attempts toward D-ring synthon are presented and discussed in Section 5.2 “Our strategies toward D-ring synthon”.

As shown in Figure 2, Section 1.1, many of those bioactive 9,11-secosterols consisted in the similarly substituted D-ring and differ in the A,B-ring functionalities, or the similarly substituted A,B-ring and differ in the D-ring functionalities. The synthesis of these varieties could by easily realized if there is a method for coupling of these synthons. Additionally, many 9,11-secosterols are derivatives of each other, differing by some functionalities presented in A,B- or D-rings (*e.g.*, the saturated or unsaturated D-ring side chain, *etc.*). Thus, by slight modification in the A,B- and/or D-ring synthons, the number of useful derivatives could be generated. The available strategy, discussed in Section 2.1 “Starting from Natural Sterols (Approach I)” presents the consecutive synthetic approach, which is straightened by existent functionalities of starting sterol. Additionally, it has a high risk for failures, related to the need to carry the modified functionalities of sterol along through all synthetic steps. Also, the second presented strategy available, the “Asymmetric Tandem Claisen-Ene Strategy (Approach II)” Section 2.2, is confined to the sterols with aromatic A-ring. Therefore, the strategy proposed by us seems to provide a very flexible and economic method for synthesis of the number of 9,11-secosterol analogues and many other bioactive terpenoic compounds.

3 Aims of the present work

In order to get an access to many secosterols and other terpenoic compounds, an efficient and practical method for their synthesis is needed. It is necessary that the new approach fulfils the requirements for the scaling-up into a preparative method. On the bases of our strategy presented above in Section 2.3, this work studies the synthetic possibilities for stereocontrolled approaches toward 9,11-secosterol **1** intermediates.
The following problems have to be solved in the present work:

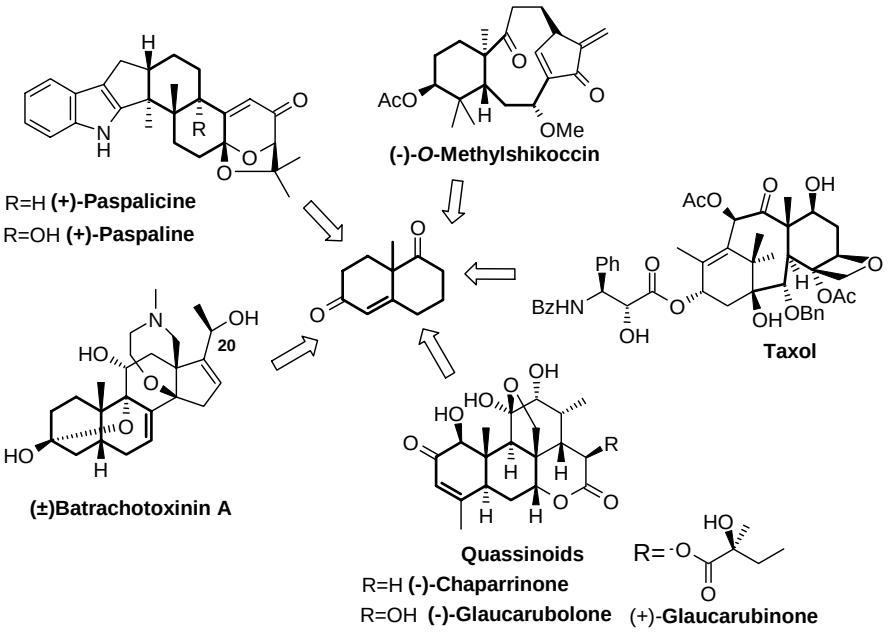
- synthesis of bicyclic A,B-ring synthon starting from Wieland-Miecher ketone
- synthesis of 1,2,3-substituted cyclopentane (considered for the D-ring synthon), starting from prochiral cyclopentanedione.

4 A,B-ring synthon

4.1 Wieland-Miescher ketone

4.1.1 Application of Wieland-Miescher ketone in natural product synthesis

The Wieland-Miescher ketone (WM) is a particularly useful synthon for the construction of a variety of biologically active compounds. Some examples of the use of that compound are given in Scheme 7.



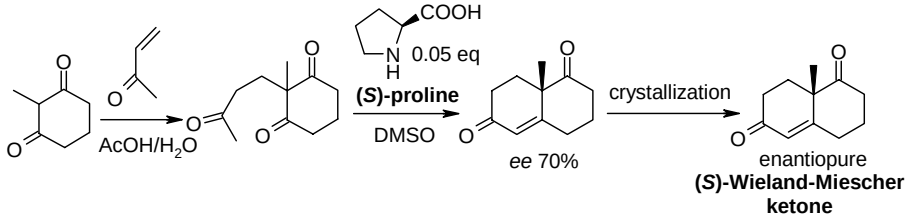
Scheme 7. Some bioactive natural compounds synthesized, starting from Wieland-Miescher ketone

The bold bond lines in Scheme 7 reflect the contribution of Wieland-Miescher ketone in the construction of the target molecule. The most famous example is the cancer and AIDS-related medicine ingredient taxol[24]. Danishefsky *et al.*[25] used the B-ring of (*S*)-WM ketone for the synthesis of taxol C-ring and extended the WM ketone A-ring into 8-membered. Paquette *et al.*[26] synthesized the cytotoxic (-)-*O*-methylshikoccin[27], where they enlarged the 6-membered B-ring of (*R*)-WM ketone into a 10-membered ring. In the synthesis of voltage sensitive sodium channel ligand (±)-Batrachotoxinine A[28] published by Kurosu *et al.*[29] the racemic WM ketone was used for the construction of *cis*-oriented A,B-frame of this steroidal alkaloid. Grieco *et al.*[30] synthesized the cancer therapeutic agents[31] quasinoids from (*R*)-WM ketone. The paspalicine and paspalinine were initially known as tremorgens and insecticides and now also their neuroprotective effect to the eye of a mammalian species, particularly

humans (*e.g.,* for the treatment of glaucoma) are reported[32]. The (*R*)-WM ketone was used in the synthesis of (+)-paspalicine and (+)-paspalinine[33] for constructing their D,E-ring fragment. As is seen from Scheme 7, the WM ketone methyl-substituted quaternary carbon stereogenic center attached to the 6-membered ring has been utilized in all target molecules. The rigid bicyclic structure with functionalities in both cycles and the availability of the starting WM ketone in the enantiopure form makes the latter compound an outstanding synthon for total synthesis of secosterol.

4.1.2 Synthesis of the enantiopure Wieland-Miescher ketone and its derivative

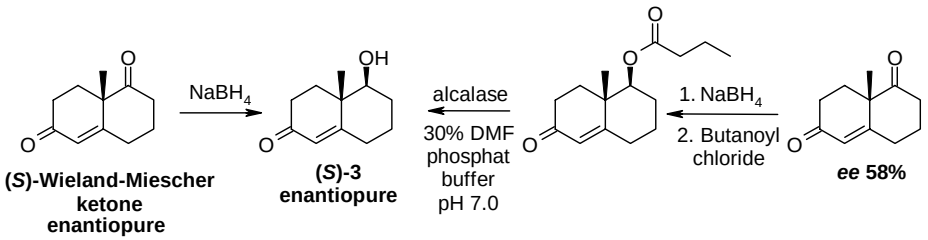
Wieland and Miescher published the first synthesis of racemic Wieland-Miescher ketone in 1950.[34] During recent years, a number of publications appeared concerning synthesis and the mechanism[35,36] of formation of this chiron. Several different approaches, including asymmetric synthesis[37,38,39,40,41,42,43,44], the antibody-catalyzed aldol condenzation[45], enantioselective kinetic resolution by microbial reduction[46,47,48] and classical resolution through a hemiphthalate derivative[49], have been reported for synthesis of enantiopure WM ketone. The most exploited route is the well-described synthetic procedure [37,38,39] optimized by Buchscacher *et al.*[40], which is based on a two-step procedure: Michael addition and the asymmetric intramolecular aldol condensation using (*S*)-(-)-proline catalysis affords a product in *ee* 70%, and after crystallization, enatiopure WM ketone is obtained. (Scheme 8)



Scheme 8. Asymmetric synthesis of WM ketone by Buchscacher *et al.*[40]

Recently, asymmetric one-pot Robinson annulation has also been published.[43,44] However, these synthetic processes are time consuming (3-7 days) and the enantiopurity of the product is *ee* 63-76%, thus, additional crystallization in order to reach an enantiopure WM ketone is needed.

The first step in many synthetic applications of WM ketone is the chemo- and diastereoselective reduction of the enone with $NaBH_4$, leading to a parent hydroxy derivative **3**. (Scheme 9)



Scheme 9. Asymmetric synthesis of (6*S*,7*S*)-6-methyl-7-hydroxyl-bicyclo[4.4.0]dec-1-en-3-one **(*S*)-3**

An alternative approach for enantiomeric **3** was proposed by Lo *et al.*[50] and performed in one gram-scale. They avoided crystallization by applying the kinetic resolution, starting from enantiomerically enriched WM ketone (*ee* 58%). After reduction, esterification and subsequent alcalase-catalyzed diastereoselective hydrolysis of formed esters, the enantiopure **(*S*)-3** (*ee* 98%) was isolated by extraction. (Scheme 9)

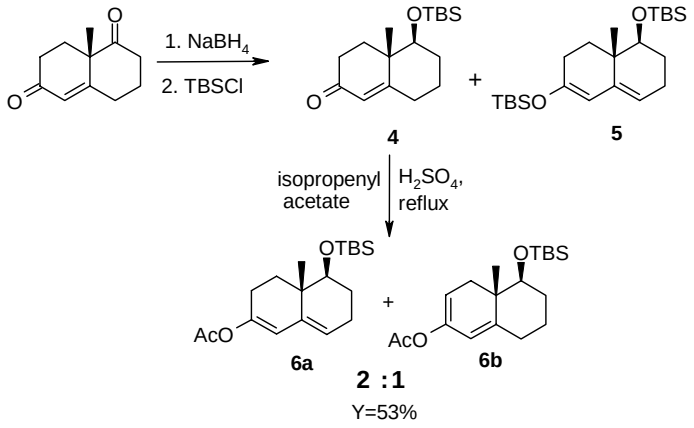
4.2 Synthesis of A,B-ring synthon (Articles I, II)

We started the synthesis of 9,11-secosterol **1** A,B-ring synthon from enantiopure (*S*)-Wieland-Miescher ketone.[40] The numeration of carbon skeleton of all compounds synthesized toward A,B-ring synthon is based on steroid nomenclature.

Scheme 10. Synthesis of 9,11-secosterol **1** A,B-ring synthon (Article I)

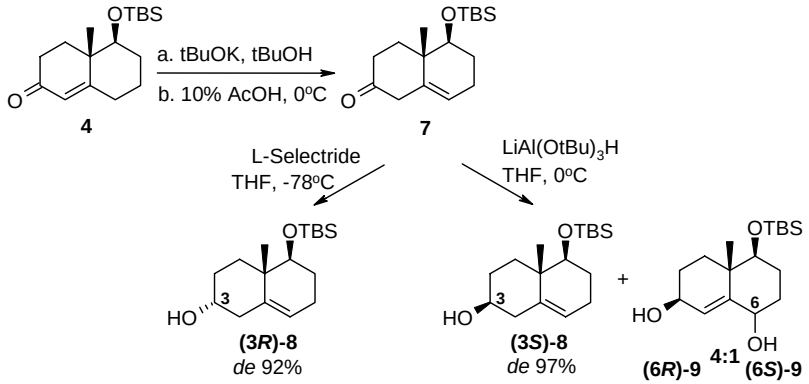
The WM ketone has already an appropriate carbon skeleton and the oxo-functionalities at C-3 and C-9. It means that the modification concerning introduction of additional oxo-functionality into the B-ring and insertion of three new stereogenic centers has to be done. (Scheme 10)

First, the two keto-functionalities of the WM ketone were differentiated by chemo- and diastereoselective reduction with sodium borohydride.[51] (Scheme 11)



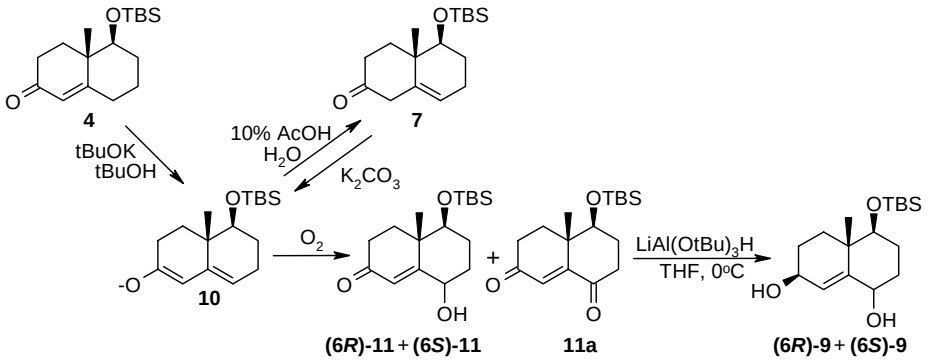
Scheme 11. Reduction of WM ketone, protection of hydroxyl group and formation of dienole derivatives

Protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride afforded enone **4** as a main product with additional dienol silyl ether **5** in *ca* 10% yield. As a next issue in the synthesis of A,B-synthon, the functionalization of the B-ring should be performed. Kuhl *et al.*[17] (Scheme 4, Section 2.1) applied the hydroboration of dienol acetate derivative for inserting the hydroxyl-group into B-ring of the sterol. Encouraged by the formation of byproduct **5** in this reaction, we attempted to synthesize dienol silyl ether **5** directly in the protection step but, unfortunately, neither increase of the amount of the TBSCl nor rise of the reaction temperature improved the yield of **5**. However, from literature it is known that, when *tert*-butyl protecting group is used instead of *tert*-butyldimethylsilyl group for the protection of the hydroxy group at C-9 of the enone **4**, 9-*tert*-butoxy-3-trimethylsilyl dienol ether is produced in good yield.[52] Thus, the synthesis of TMS dienol ether was also attempted, using LDA and TMSCl. However, the isolation of the formed product was unsuccessful. Because of the synthesis of silyl dienol ethers failed, we tried the acylation of enone **4** with isopropenyl acetate in acidic conditions.[53] Unfortunately, inseparable mixture (on silica gel) of dienolates **6a** and **6b** in the ratio of 2:1, respectively, was formed. In addition to difficulties in the formation of dienol derivatives of enone **4**, all the obtained compounds were quite unstable. Finally, the double bond was inserted into the B-ring through potassium dienolate formation and trapping it with 10% acetic acid solution.[54,55] (Scheme 12) In spite of instability of the obtained deconjugated keto-ene **7** (acidic $MgSO_4$ and silica gel caused the migration of double bond back into conjugated position, affording starting enone **4**), and formation of more polar byproducts additionally at prolonged drying on basic K_2CO_3, enough material was obtained to carry out reduction of keto-ene **7** without purification.



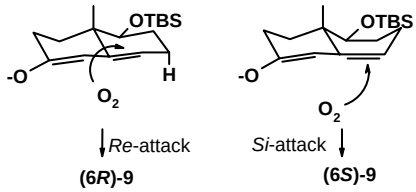
Scheme 12. Functionalization of B-ring, the double bond migration

Reduction of keto-ene **7** with L-Selectride at -78°C gave undesired alcohol **(3*R*)-8** as the main product in diastereomeric excess 92%. (Scheme 12) The reduction of ketone **7** with a lithium tri-*tert*-butoxy aluminium hydride[56] afforded the desired alcohol **(3*S*)-8** in diastereomeric excess 97%, in 54% overall yield, starting from enone **4**. The reduction of **7** with $NaBH_4$ in EtOH at 0°C gave also **(3*S*)-8** as the main diastereomer, but together with byproducts. The result of selective formation of either **(3*R*)-8** or **(3*S*)-8** in high diastereoselectivity is a new and valuable contribution for the synthesis of functionalized decalines. As the L-Selectride and $LiAl(OtBu)_3H$ both are bulky hydrides, and as the reaction was performed in both cases in the same solvent, we assume that the turn in diastereopreference of the reduction is caused by the formation of thermodynamically more favored **(3*S*)-8** with equatorial hydroxy group at C-3 at higher reaction temperature (the difference in the reaction temperature from –78 to 0 °C). Additionally, after reduction of keto-ene **7** the C-6 hydroxylated byproducts **(6*R*)-9** and **(6*S*)-9** (in diastereomeric ratio 4:1, respectively) were isolated together with alcohol **(3*S*)-8**. (Scheme 12) As for the synthesis of A,B-ring synthon the insertion of the hydroxy-moiety at C-6 with *S*-configuration was still needed, we studied the formation of the oxidation products in detail. Description of the oxidation of keto-ene **7** is published in Article II. Here only conclusions concerning the formation of byproducts are given. (Scheme 13)



Scheme 13. The formation of hydroxylated byproducts **(6*R*)-9** and **(6*S*)-9** (Article II)

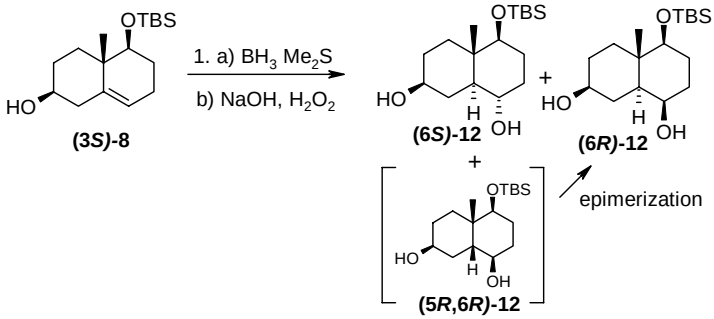
*t*BuOK binds the acidic proton from enone **4** and, as a result, thermodynamically favored potassium dienolate **10** is formed. This dienolate is air sensitive and oxidizes into hydroxy enones **11**, which may further oxidize into ketoenone **12** (*e.g.*, during the quenching of reaction). Additionally, the keto-ene **7,** in the presence of K_2CO_3, results also in dienolate **10**, which in turn, oxidizes further in contact with air oxygen (*e.g.*, during the prolonged drying). Thus, when keto-ene **7** was reduced as a crude mixture in the presence of hydroxy enones **11** and keto enone **11a,** the formation of **(6*R*)-9** and **(6*S*)-9** is clearly observed. The studies on dienolate oxidation showed that the difference in diastereoselectivity of oxidation with a relatively bulky *t*-BuOOH *versus* O_2 and H_2O_2 is not remarkable (4:1 *vs* ~3:1). Therefore, it is very likely that the oxidation diastereoselectivity is controlled by the substrate in a relatively planar conformation. (Scheme 14)



Scheme 14. Probable conformations for either **(6*R*)-9** or **(6*S*)-9**-alcohol formation[57]

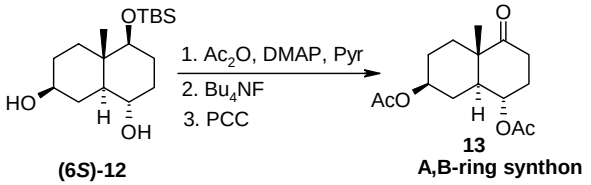
The diastereoselectivity of the oxidation at C-6 was in favor to undesired (6*R*)-alcohol proceeding through the more stable double-chair conformation of dienolate. As our target, the 9,11-secosterol **1**, bears the hydroxyl group at C-6 with an opposite configuration, we used this knowledge only for avoiding the oxidation of dienolate during the synthesis toward A,B-ring synthon. As a result, the isolated yield of the alcohol **(3*S*)-8**, starting from enone **4**, was increased from 54% to 86%. As a comment to this effort is noteworthy to paraphrase Tomas Hudlicky: "it is far more important to pursue yield improvements for the individual steps in the range 50-57% than in the higher range 75-90%, because the overall improvement factor does not increase sufficiently at the higher individual yield to warrant the extra effort."[58]

Thus, we reached the enantiopure **(3*S*)-8**, which bears a hydroxyl group with appropriate stereochemistry and a double bond in the B-ring.
Through double bond hydroboration, the hydroxy-moiety and two new stereogenic centers were introduced. (Scheme 15)



Scheme 15. Hydroboration of **(3*S*)-8**

As described in Article I, the hydroboration of alkene **(3*S*)-8** afforded together with desired diol **(6*S*)-12** its epimer **(6*R*)-12**. The formation of the latter is probably possible through *Re*-attack of hydroborane to **(3*S*)-8**, followed by epimerization at C-5 of produced unstable diol **(5*R*,6*R*)-12**. The diastereoselectivity of hydroboration was highly dependent on reaction temperature (see Article I). Performing the hydroboration of alkene **(3*S*)-8** in reflux conditions gave the diol **(6*S*)-12** in 76% of isolated yield.



Scheme 16. Converting the diol **(6*S*)-12** into A,B-ring synthon **13** of 9,11-secosterol **1**

Further hydroxyl-groups of diol **(6*S*)-12** (Scheme 16) were protected as acetates (benzylation and methoxymethylation was also tried for diol protection, but mainly mono-O-alkylated decalines were isolated). Next, after removal of silyl protecting group and oxidation of the resulted hydroxyl group at C-9, the enantiomerically pure A,B-ring synthon **13** for 9,11-secosterol **1** was obtained.

4.3 Conclusions

On the basis of highly diastereoselective functionalization of rigid bicyclic Wieland-Miesher ketone, the following results could be drawn:

- Synthesis of A,B-ring synthon **13** for cytotoxic and antiproliferative 9,11-secosterol **1** and its derivatives **1a** and **1b** was successfully completed in 8 steps.

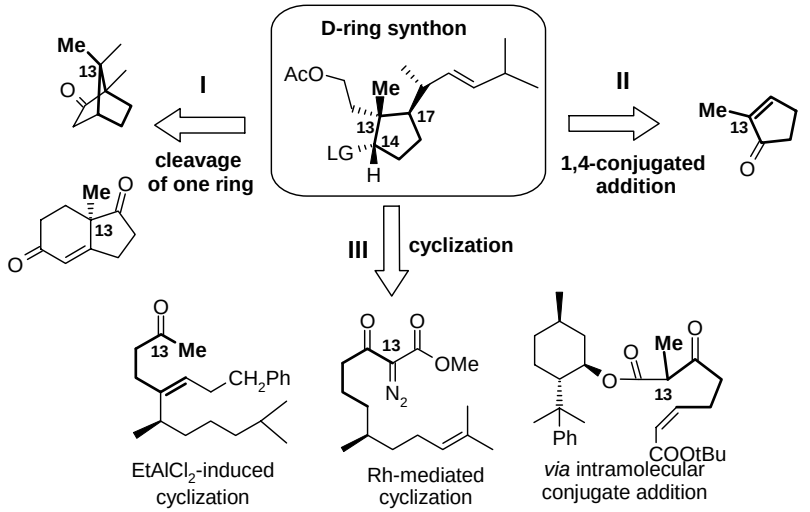
- On the bases of studies concerning the auto-oxidation of intermediate dienolate **10**, the improvements in the chemical yield of the double bond migration step, raised the overall yield of A,B-ring synthon **13** from 15% to 25% . According to the developed scheme, a preparative amount of **13** (7 g) was synthesized.

- The same method can be applied for the synthesis of the intermediates of the other sterols (*e.g.*, synthon **13** for sterol **VII** (Figure 2, Section 1.1), alcohol **(3*S*)-8** for **III** (Figure 2) and keto enone **11a**, for **IV** (Figure 2).

5 D-ring synthon

5.1 Strategies toward D-ring synthon, the literature overview

A number of bioactive natural compounds bear similarly substituted cyclopentane fragments. There are several methods for the synthesis of similar compounds. We have picked up from literature three general approaches that are suitable also for synthesis of D-ring of 9,11-secosterol **1**. (Scheme 17)



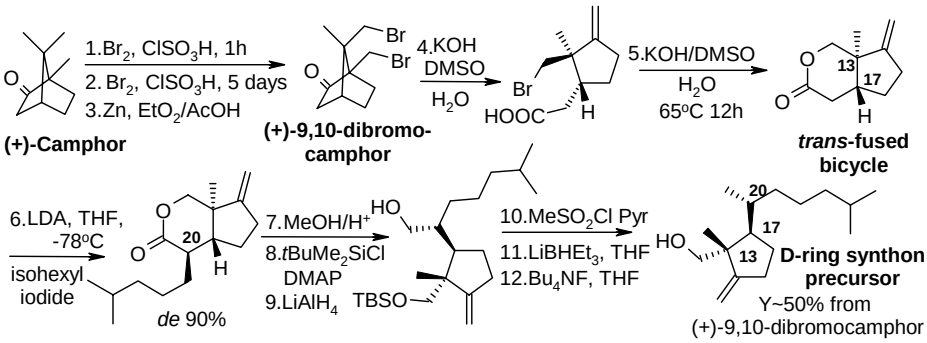
Scheme 17. Approaches toward the synthesis of enantiomeric D-ring synthon

As shown in Scheme 17 these three selected approaches of the synthesis of enantiomeric D-ring synthon are:

- **I** cleavage of one ring in a bicyclic enantiomerically pure substrate;
- **II** asymmetric 1,4-conjugated addition to 2-methylcyclopentenone;
- **III** asymmetric cyclization of chiral aliphatic substrate.

5.1.1 Starting from enantiomerically pure bicyclic substrate

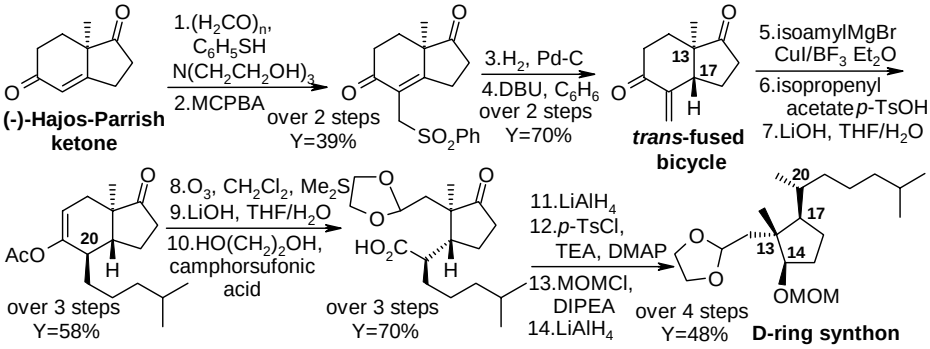
Hutchinson and Money[59] started from (+)-camphor and synthesized the intermediates of D-ring system of steroids with functionalized side-chain. (Scheme 18) First, they converted enatiomerically pure (+)-camphor into (+)-9,10-dibromocamphor[60], which had a stereogenic methyl-substituted quaternary carbon atom and two 5-membered rings.



Scheme 18. The Hutchinson J. H. and Money T. approach starting from (+)-camphor

Via base-promoted ring cleavage and intramolecular lactonization, they reached a *trans*-fused bicyclic compound. The latter has appropriate stereocenters at C-13 and C-17 of the steroid D-ring (steroid numeration for intermediates on Scheme 18) and a new stereocenter at C-20 that was generated through diastereoselective alkylation (*de* 90%) with a suitable side-chain precursor. After ring opening of the lactone and protection of the primary hydroxyl group, the carboxyl-moiety in side-chain was converted into methyl group in several steps conversion sequence. This chemistry leads to D-ring synthon precursor in very good yield (50% for 9 last steps). However, in spite of a suitable substitution pattern and right stereocenters at C-13, C-17 and C-20, additionally several manipulations are needed in order to get the D-ring synthon (Scheme 17).

In the same year, Nemoto *et al.*[61] published an approach of the stereocontrolled synthesis of the sterol D-ring side chains and, as application of the latter, the synthesis of vitamin D_3. (Scheme 19)



Scheme 19. The Nemoto *et al.*[61] approach, starting from Hajos-Parrish ketone

The synthesis started from enantiomerically pure and readily available (*R*)-Hajos-Parrish ketone. Through alkylation, sulfonation, reduction and elimination, the *trans*-fused bicycle with appropriate stereocenters of steroid D-ring at C-13 and C-17 was reached. The side chain was introduced into D-ring using diastereoselective 1,4-conjugate addition, with generation of the new

stereocenter at C-20. The 6-membered ring was cleaved *via* acyl enol ether ozonolysis and converted into acetal carboxylic acid. Analogously to Hutchinson (Scheme 18), the carboxyl-moiety in the side-chain was converted into a methyl group through reduction, thus converting the resulted hydroxyl group into a good leaving group and reduction. Finally, the keto-group at C-14 was diastereoselectively reduced and the derived alcohol protected with methoxymethyl group. So, the enantiomerically pure substituted cyclopentane derivative with appropriate carbon skeleton and stereocenters at C-13, C-17 and C-20 was synthesized. The absolute configuration at C-14 could be inverted in a stereocontrolled way and, therefore, it is a good synthon for the D-ring of the sterols with saturated side-chain (***e.g.***, for synthesis of bioactive 9,11-secosterols **I**, **II**, **VI** and **VII** shown in Figure 2, Section 1.1).

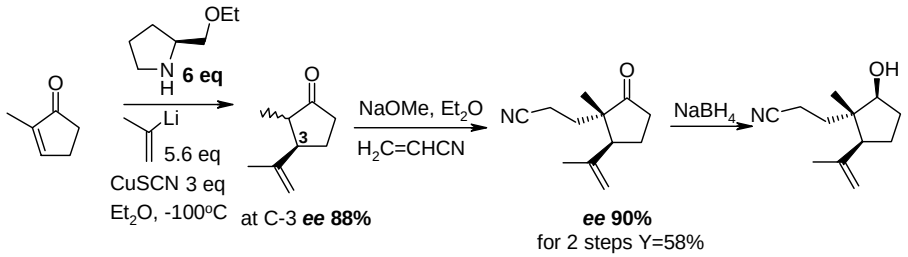
In conclusion, the stereocontrolled synthesis of both 1,2,3-substituted cyclopentane derivative described above, is based on:

1. starting from readily available enantiopure substrate from "chiral pool", equipped with the stereogenic methyl-substituted quaternary carbon center;
2. constructing of a rigid *trans*-fused bicycle;
3. conformationally diastereocontrolled alkylation of that bicycle for building up the appropriate side-chain of the D-ring.

These consecutive methods lead diastereoselectively to the appropriate substitution pattern for 9,11-secosterol D-ring, but the number of synthetic steps is large.

5.1.2 Asymmetric 1,4-conjugated addition to 2-methylcyclopentenone

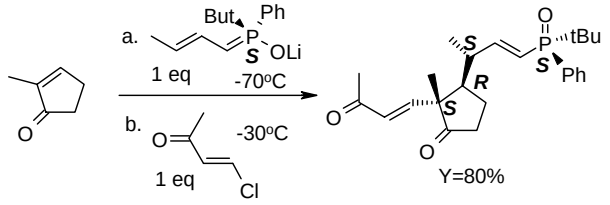
The approach toward enantioselective conjugate addition reaction is currently a developing area.[62] A number of publications concerning diastereoselective tandem conjugate addition to 2-methylcyclopentenone[63,64,65,66,67,68,69,70] as well as two-step alkylation procedures[71,72,73] for the constructing of racemic 1,2,3-substituted cyclopentane derivatives have been published in the literature. Also, an example of enantioselective 1,4-conjugate addition to 2-methylcyclopentenone has been published by Quinkert *et al.*[74] (Scheme 20)



Scheme 20. The Quinkert *et al.*[74] enantioselective conjugate addition to 2-methylcyclopentenone

The enantio-differentiation in the course of conjugate addition was catalyzed by proline-derived amine, which was used in 6-fold excess and led to a mixture of diastereoisomers of 3-alkylated-2-methylcyclopentanone with *ee* 88%. Further diastereoselective *trans*- alkylation of sodium enolate with acrylonitrile afforded cyclopentanone derivative with 2-methyl substituted quaternary carbon center in enantiomeric excess ~90%.

Additionally, there is one synthetic route published by Haynes *et al.*[75] to enantiomerically pure 1,2,3-substituted cyclopentane derivative. (Scheme 21)



Scheme 21. The Haynes[75] approach to enantioselective 1,4-conjugate addition

Enantioselective alkylation of lithiated (*S*)-phosphine oxide with allylic carbanion results in simultaneous generation of two stereogenic centers in the side-chain and the tandem alkylation with 4-chlorobut-3-en-2-one gives enantiomerically pure *trans*-2,3-substituted cyclopentanone.[a] Thus, with one tandem conjugate addition, the appropriate stereochemistry for D-ring synthon is generated. However, from the point of view of the 9,11-secosterol syntheses, the second alkylation should be made by a reagent having two carbons. After reduction of the double bond in side-chain, the phosphine oxide can be removed *via* Horner-Wittig reaction, keeping in mind the chain extension.

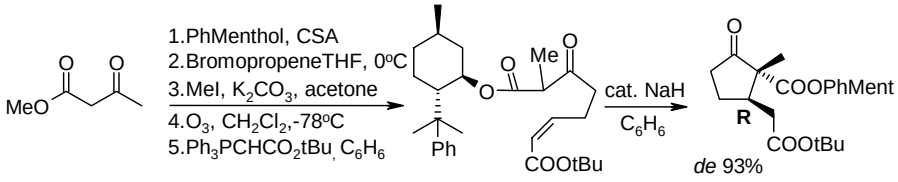
It could be added, as a comment, that the first example is an enantioselective conjugate addition reaction through asymmetric catalysis, although the necessary amount of the catalyst is 6 equivalents. The second example, on the other hand, uses an auxiliary based induction of chirality and needs stoichiometric amount (in this case only 1 equivalent) of previously prepared

[a] The relative configuration of new generated stereocenters was confirmed with X-Ray analysis.

enantiomeric (*S*)-phosphine oxide. The conjugate addition is a very straightforward approach toward D-ring synthon, requiring a low number of the synthetic steps, however, the asymmetric induction is not catalytic.

5.1.3 Cyclization of chiral aliphatic substrates

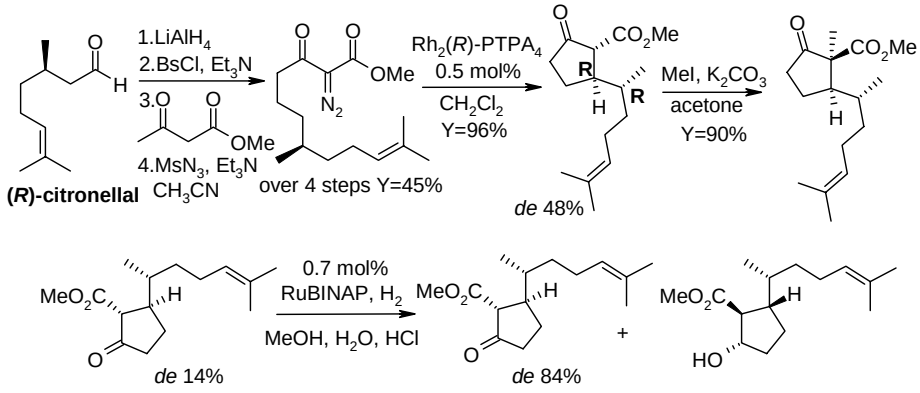
Stork *et al.*[76,77] have demonstrated the possible use of intramolecular Michael reaction of β-ketoester anions in the diastereoostereoselective construction of vicinally substituted carbocycles. (Scheme 22)



Scheme 22. Intramolecular conjugate addition of chiral β-ketoester[77]

As shown in Scheme 22, two new *trans*-oriented stereogenic centers are generated during intramolecular cyclization, inducing diastereopreference with the widely used chiral 8-phenylmethol auxiliary. For the synthesis of the D-ring synthon, additionally, the construction of the side-chain carbon skeleton with a new stereogenic center should be carried out.

Taber *et al.*[78] have recently published the synthesis of (-)-astrogorgiadiol *via* synthesis of 2,3-substituted cyclopentanone. (Scheme 23)

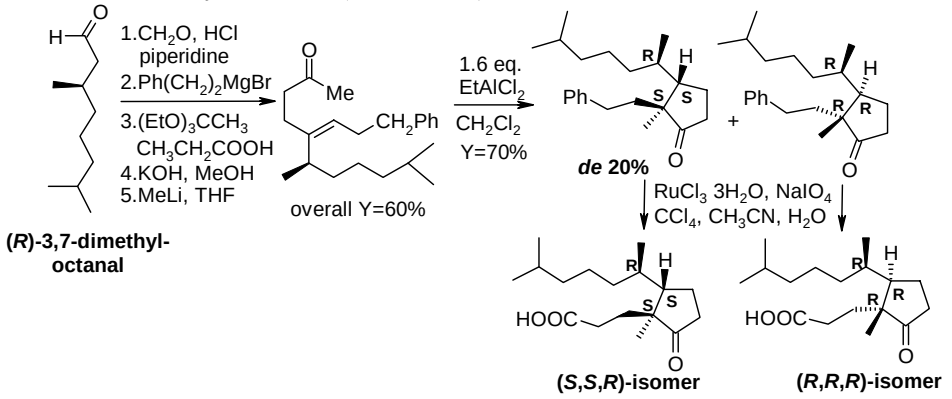


Scheme 23. Synthesis of cyclopentane derivative, the intermediate of (-)-astrogorgiadiol

They started from (*R*)-citronellal, converted it to α-diazo-β-ketoester and then, the key step, the rhodium-mediatiated cyclization was performed. The substituents of the obtained cyclopentane derivatives were *trans*-oriented, however, the diastereoselectivity of cyclization was moderate (*e.g.*, in the presence of $Rh_2(BiTISP)_4$ *de* was 58% (yield 38%), dirhodium *tetrakis*-(*R*)-*N*-

phtaloylphenylalanine (Rh_2(*R*)-PTPA$_4$) *de* 48% (yield 96%) and in the presence of achiral rhodium octanoate *de* was 14%). As the cyclization did not afford directly the products of high enantiomeric purity, kinetic resolution of mixture by hydrogenation with RuBINAP catalysis was performed. (Scheme 23, second line) It is interesting to note that methylation of 2,3-substituted cyclopentanone with MeI gave methyl substituent in *trans*-configuration in respect to already existing side-chain. Thus, unfortunately, the synthesis of cyclopentanone with unsuitable configuration of substituents for synthesis of 9,11-secosterol D-ring was accomplished.

Recently, Snider *et al.*[79] published $EtAlCl_2$-induced cyclization of chiral γ,δ-unsaturated methyl ketones. (Scheme 24)



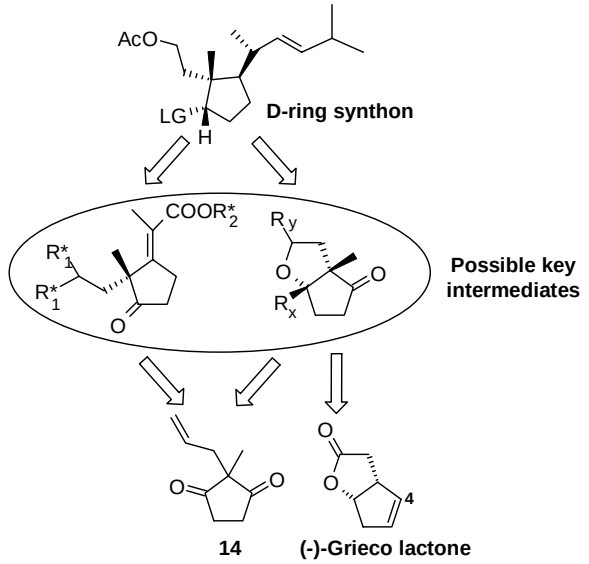
Scheme 24. $EtAlCl_2$-induced cyclization of chiral γ,δ-unsaturated methyl ketones

The synthesis started from enantiopure (*R*)-3,7-dimethyloctanal, which was converted into γ,δ-unsaturated ketone. The cyclization of the latter provided two diastereoisomers of *trans*-2,3-substituted cyclopentanones in a 60:40 ratio, in favor to (*S*,*S*,*R*)-isomer. Subsequently, the phenyl substituent of cyclized products was oxidized by Ru-catalyst to the corresponding carboxylic acids. Unfortunately, the minor (*R*,*R*,*R*)-diastereomer has stereochemically appropriate substituents for the synthesis of 9,11-secosterol D-ring.

On the basis of these cyclization methods, it can be concluded that the first example, the use of bulky chiral auxiliary 8-phenylmenthol, provided the best asymmetric induction. In the two last examples, the methyl substituted stereogenic center, adjacent to the cyclization site, did not provide sufficient diastereo-induction. Neither did the approach, proposed by Taber *et al.*[78] to use additionally the support of chiral catalyst in cyclization reaction led to very good results. Furthermore, methylation of already 2,3-substituted cyclopentanone gave the *cis*-substituted cyclopentanone, which is not suitable for the synthesis of secosterol D-ring synthon.

5.2 Our strategies toward D-ring synthon

The strategies envisioned in the previous Section do not provide a complet solution for the synthesis of 9,11-secosterol **1** D-ring synthon (Scheme 17, Section 5.1). The approaches based on enantiomerically pure bicyclic starting materials consisted of a large number of synthetic steps and were neither very flexible in side-chain functionalization, nor for the synthesis of various analogs and homologs. The asymmetric induction in the examples of 1,4-conjugate addition to 2-methylcyclopentenone and in the described cyclization methods was not efficient enough. Therefore, we made an attempt to screen possible new approaches toward the synthesis of the D-ring synthon.



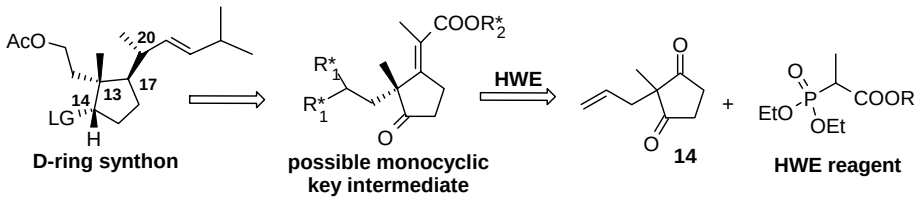
Scheme 25. Proposed retrosynthetic routes through possible key intermediates toward the D-ring synthon

The D-ring synthon is a derivative of asymmetric 1,2,3-substituted cyclopentane. Scheme 25 presents retrosynthetic pathways toward the D-ring synthon through monocyclic and bicyclic possible key intermediates. These key intermediates could be synthesized from a common prochiral 1,3-cyclopentanedione *via* desymmetrization. The most straightforward approach to monocyclic target intermediate is the asymmetric Horner-Wadsworth-Emmons (HWE) olefination of 2-allyl-2-methyl-1,3-cyclopentanedione **14**. However, we found that the reaction does not proceed as expected, discussed in Section 5.2.1. The synthesis of possible bicyclic key intermediate of the D-ring synthon could be realized *via* asymmetric reduction of 1,3-diketone **14**, discussed in Section 5.2.2. As an alternative approach, we propose Grieco lactone as a promising starting material for the same bicyclic key intermediate. As Grieco lactone is readily available in enantiomerically pure form and the functionalization of the latter at position C-4 will provide 1,2,3-substituted cyclopentane moiety,

necessary for constructing the D-ring synthon. Derivatization of Grieco lactone is discussed in Section 5.2.3. Finally, the synthesis of analogous bicyclic key intermediate was attempted *via* the desymmetrization of 1,3-diketone through dihydroxylation **14**, discussed in Section 5.2.4.

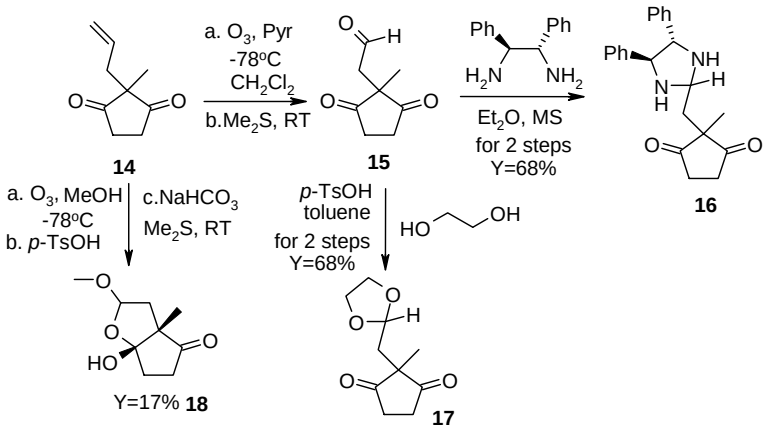
5.2.1 Horner-Wadsworth-Emmons reagent in reaction with prochiral 1,3-cyclopentanedione (Article III)

The core of our strategies toward the D-ring synthon is based on of the idea of the desymmetrization of prochiral 2-allyl-2-methyl-1,3-cyclopentanedione. First, we made an attempt to achieve that goal through the Horner-Wadsworth-Emmons (HWE) olefination. (Scheme 26)



Scheme 26. The approach to the D-ring synthon *via* Horner-Wadsworth-Emmons olefination

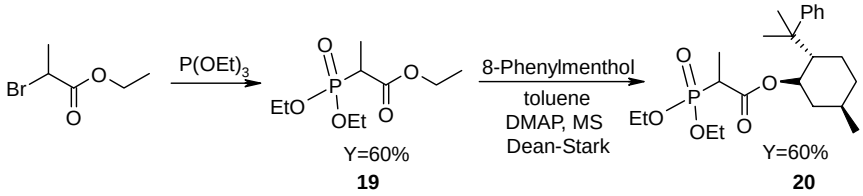
Thus, the general idea is as follows: 2-allyl-2-methyl-1,3-cyclopentanedione **14** has an appropriately 1,2,3-substituted cyclopentane ring equipped with methyl-substituted quaternary carbon center and the allyl group, which could be converted through double bond cleavage into a two-carbon atom chain. Mono-olefination of diketone **14** changes the achiral center at methyl- substituted carbon atom into a stereocenter. Additionally, the HWE reagent, 2-(diethylphosphono)propionic acid ester is suitable for the D-ring carbon skeleton construction. The key intermediate proposed on Scheme 26 could be further converted into the D-ring synthon through stereocontrolled double bond reduction, side-chain extension and carbonyl group reduction. The stereodifferentiation between the two carbonyl groups of compound **14** in the olefination reaction could be induced by either the use of chiral auxiliary in the alkyl chain (R_1*) or by the chiral HWE reagent[80] (R_2*). All the considerations are based on the known approach from the literature where intramolecular asymmetric olefination of 2,2-disubstituted-1,3-diketone with phosphoryl-stabilized carbanion of 8-phenylmenthyl ester has been successfully realized.[81]
In order to realize this approach, first, the ozonation[82] of the terminal alkene in **14**, followed by protection of derived aldehyde, was accomplished. (Scheme 27)



Scheme 27. Ozonation of cyclopentanedione **14** and protection of derived aldehyde **15**

The protection of aldehyde **15** with either a chiral auxilliary (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine affording aminal **16** or with an achiral protection group 1,2-ethanediol providing acetal **17**, succeeded well. When ozonation, according to a known protocol[83], together with *in situ* acetalization with methanol was performed, unexpected bicyclic hemiacetal **18** was isolated as the main product of this reaction, together with a certain amount of unprotected aldehyde **15**. Because of the achiral conditions, the formed desymmetrisized acetal **18** is racemic and thus such a compound does not suit for the next step.

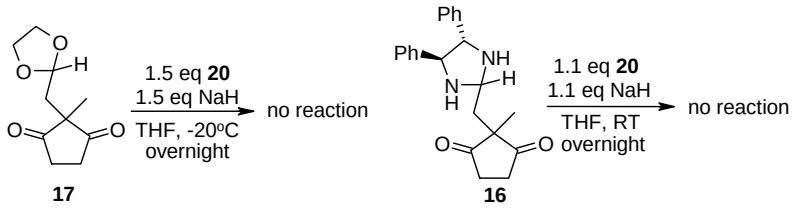
To prepare the HWE reagent, the Arbuzov rearrangement[84] of triethoxyphosphine with ethyl 2-bromopropionate was applied, resulting in ethyl 2-(diethylphosphono)propionate **19**. (Scheme 28)



Scheme 28. Synthesis of (1'*R*,2'*S*,5'*R*)–8'-phenylmenthyl 2-(diethylphosphono)propionate

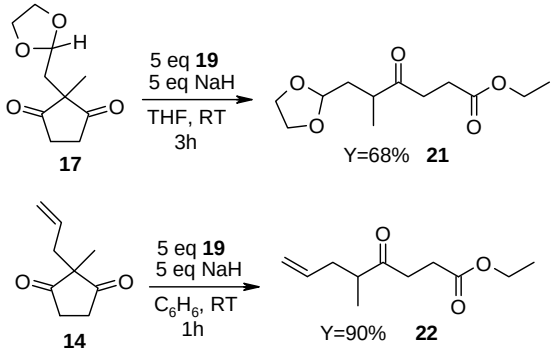
Further, *via* the transesterification procedure[85], the respective chiral HWE reagent, (1*R*,2*S*,5*R*)–8-phenylmenthyl ester **20**[86], was synthesized.

Then we tried to use the HWE reaction applying the prepared carbonyl substrates **16** and **17**, and chiral HWE reagent **20**. (Scheme 29)



Scheme 29. Attempted HWE reactions

Unfortunately, we observed that the chiral phosphonate **20** does not react with diketones **16** and **17**, neither in -20°C nor at room temperature. Thus, we tried to elucidate the proper reaction conditions using a simple achiral phosphonate **19**. (Scheme 30)



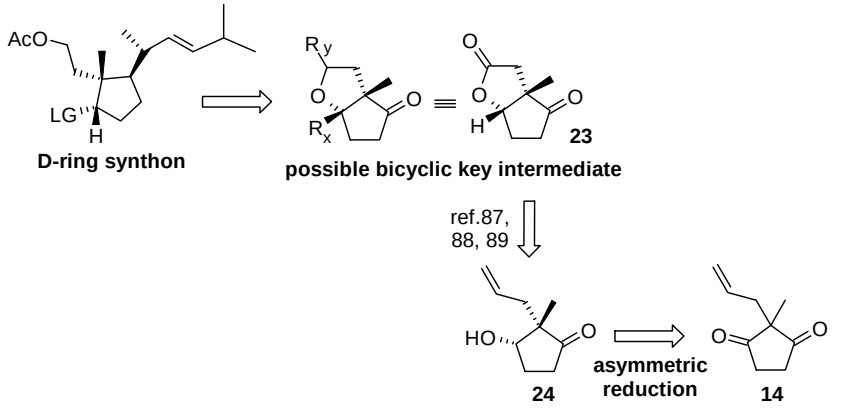
Scheme 30. Reactions of diketones **14** and **17** with phosphonate **19**

The reaction proceeds smoothly, however, instead of olefination of diketones **17** and **14**, the cleavage of the cyclopentane ring occurred, resulting in the unexpected products **21** and **22**, respectively. According to our knowledge it is a new reaction, thus we looked into that reaction in more detail. Indeed, the additional synthetic and NMR-experiments published in article III revealed that substrates 2,2-disubstituted 1,3-diketones **14** and **17** are very sensitive to the attack of intermolecular nucleophiles toward carbonyl group and tend to give the subsequent retro-aldol reaction and cleavage of cyclopentane ring. Thus, with the HWE reagent formed aliphatic substituted keto esters (**21** and **22** respectively) in up to 90% isolated yield.

The cleavage of the cyclopentane ring in 2,2-disubstituted-1,3-cyclopentanediones in HWE conditions forced us to proceed with other approaches.

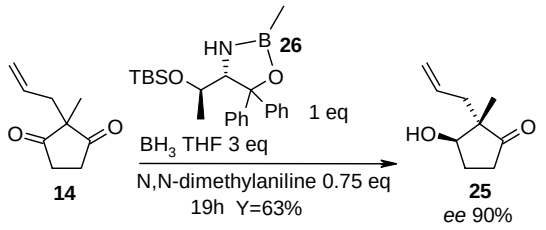
5.2.2 Desymmetrization of 1,3-diketone 14 *via* asymmetric reduction

The bicyclic intermediates provide usually a good starting point for diastereoselective modifications because of the nature of bicyclic rings that guarantee a certain arrangement of chains after ring cleavage. Therefore we considered the enantiomeric bicyclic intermediate **23**[87] as the promising precursors for the D-ring synthon. The compound **23** has the suitable substitution in the cyclopentane ring, including quaternary carbon atom with methyl group and two-carbon atom moiety. The rigid structure of bicyclic key intermediate **23** offers a good precondition to introduce the side-chain into cyclopentane moiety with high diastereoselectivity. (Scheme 31)



Scheme 31. The retrtosynthesis of bicycle **23**, *via* asymmetric reduction of 2-allyl-2-methylcyclopentanedione **14**

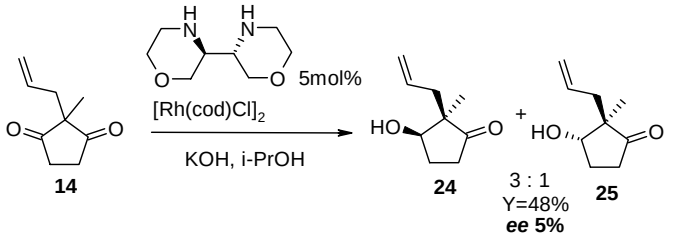
The synthesis of bicycle **23** has previously been realized in one step, through oxidative cleavage of the terminal double bond, starting from 2-allyl-3-hydroxy-2-methylcyclopentanone **24**.[88,89,90] The key step in this synthetic route is the enantioselective reduction of prochiral 2-allyl-2-methylcyclopentanedione **14**. Brooks *et al.*[88,89] have used the yeast-mediated reduction, which affords mainly (2*S*,3*S*)-3-hydroxy-2-allyl-2-methylcyclopentanone **24** in 98% *ee* together with its *trans*-diastereomer, (2*R*,3*S*)-3-hydroxy-2-allyl-2-methylcyclopentanone in a ratio 9:1, and in 75% overall yield. Shimizu *et al.*[91] have recently published the stereocontrolled reduction of 2-allyl-2-methylcyclopentane-1,3-dione **14** using chiral oxazaborolidine-BH_3 reagent **26**, affording (2*S*,3*R*)-3-hydroxy-2-allyl-2-methylcyclopentanone **25** in 90% *ee* and in 63% yield. (Scheme 32)



Scheme 32. The enantioselective reduction of 1,3-diketone **14**, by Shimizu, M. *et al.*[91]

However, the catalyst **26** is not commercially available and can be derived from L-threonine in five steps procedure.[92] The other method mentioned above includes the use of yeast-mediated reaction, which usually is not very convenient in large-scale production. Therefore, we tried to find new chiral catalysts for the reduction of prochiral 1,3-diketone **14**.

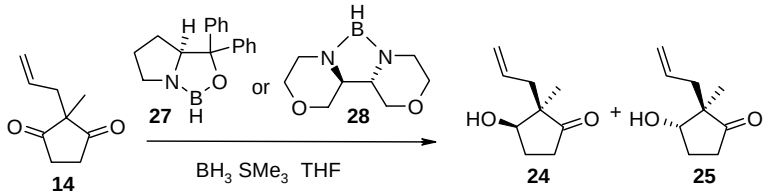
In our research group the (3*S*,3'*S*)-bimorpholine[93] has been synthesized and its use as a ligand in the transfer hydrogenation of ketones by rhodium-mediated catalysis have been studied.[94,95] Based on these results we wondered whether this type of catalysts can be applied in the reduction of 1,3-diketone **14**. (Scheme 33)



Scheme 33. Hydrogenation of 1,3-diketone **14** in Rh catalysis with (*S*,*S*)-3,3'-bimorpholine as a chiral ligand

We found that the stereoselectivity of reduction was in favor of *cis*-diastereomer (-)-(*R*,*R*)-**24** in *cis:trans* ratio 3:1. In order to determine the enantiomeric excess of the products, *cis*-diastereomer **24** was converted to *R*(-)-methoxymandelic acid derivative[96], and for *trans*-isomer **25** the *ee* of products was determined by chiral HPLC. However, the enantiomeric excess for both diastereomers was only 5%. The absolute configuration of major *cis*-isomer was determined through comparison of the retention times in chiral HPLC and optical rotation with literature data[89].

As the stereoselectivity of the Rh-catalysed transfer hydrogenation of the diketone **14** was very low, borane reduction with chiral catalysts **27** and **28**, were tried. (Scheme 34, Table 1)



Scheme 34. The reduction of 1,3-diketone **14** with complexes **27** and **28**

The oxazaborolidine **27**, the CBS catalyst (named after Corey, Bakshi, Shibata)[97], was prepared *in situ* from the corresponding L-proline derived amino alcohol and hydroborane sulfide complex.[98] The new catalyst, diazaborolidine **28** was prepared analogously to the latter from (3*S*,3'*S*)-bimorpholine[93].

Table 1. The catalysts and results of the reduction of 1,3-diketone **14** with borane complexes

Catalyst, amount	Reaction temperature	Isolated yield of **24**+**25**	*cis:trans* ratio[a]	Enantiomeric excess
27, 0.1 eq	0°C	32% (33% of recovered **14**)	5:1	racemic[b,c]
	-30-0°C	53% (13% of recovered **14**)		
27, 1 eq	-78°C	60%	2:1	25% for (*R*,*R*)(-)-**24**[d]; 23% for **25**[c]
28, 0.15 eq	-78°C	85%	7:1	racemic[c]

[a] Determined by GC analysis

[b] Determined for *cis*-diastereomer **24,** the through HPLC analysis of the corresponding *R*(-)-methoxymandelic acid esters.

[c] Determined for *trans*-isomer **25** by the HPLC analysis using chiral column Chiralcel OD-H.

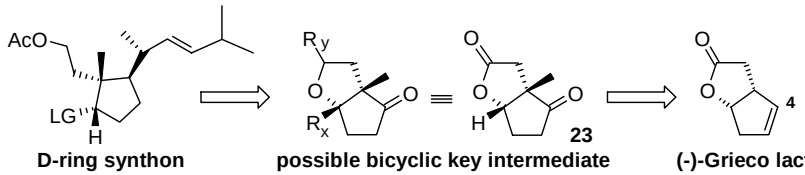
[d] Determined by the interpolation of optical rotation from the literature[89]

When 0.1-0.15 equivalents of the catalysts were used, racemic mixtures of hydroxyketones were obatined for both catalysts. (Table 1, lines 1, 3) The highest diastereoselectivity, the *cis:trans* ratio of 7:1, respectively, was obtained with bimorpholine derived catalyst **28** (Table 1, line 3). Slight enantiodifferentiation (*ee* 23%) of the prochiral faces of carbonyl groups in 1,3-diketone **14** was observed only when a stoichiometric amount of the oxazaborolidine **27** was used. (Table 1, line 2) Similarly, it has also found for another oxazaborolidine catalyst that a stoichiometric amount of the catalyst is needed in order to achieve high enantioselectity of the reduction of 1,3-diketone **14**, (Shimizu *et al.*[91]). (Scheme 32) This observation indicates the existence of a competing reduction of diketone **14** by the uncomplexed achiral hydroborane. Additionally, it is noteworthy that in all our reductions the formation of diols, the products of overreductions, was not a problem (<10% by GC). The obligatory need for a stoichiometric amount of the catalyst in this reaction

reduces the attraction of the approach for the preparative use. This forced us to look for alternative strategies.

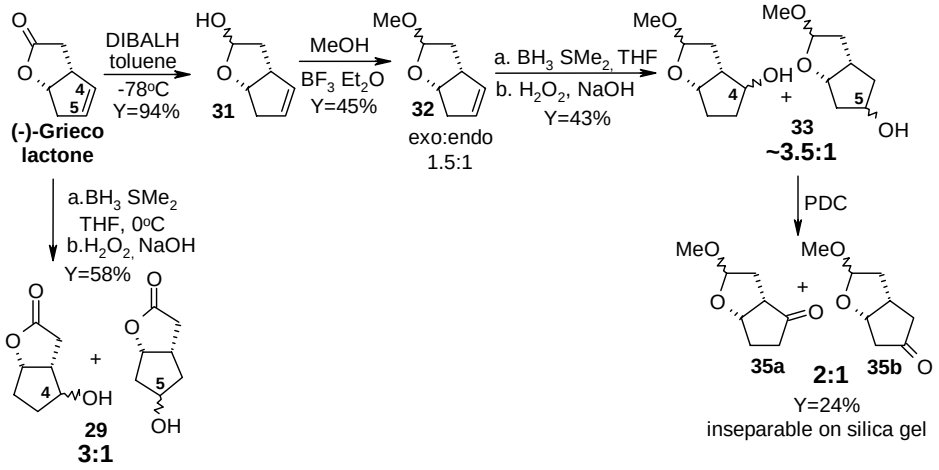
5.2.3 Derivatization of Grieco lactone

The functionalization of bicyclic enantiomerically pure starting materials (Section 5.1.1) encouraged us to consider an alternative approach toward the synthesis of enantiomeric bicyclic intermediate **23**. We chose the known (-)-Grieco lactone as a promising starting material. (Scheme 35)



Scheme 35. The (-)-Grieco lactone as the precursor for bicyclic key intermediate **23** of the D-ring synthon

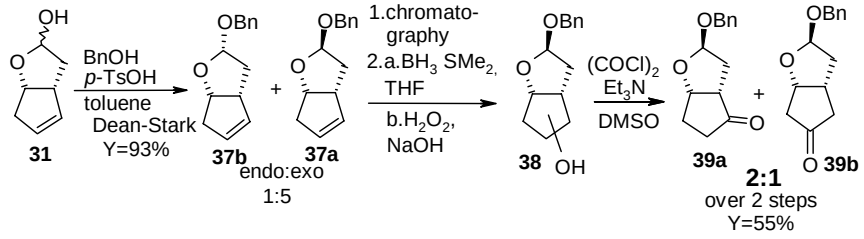
The Grieco lactone[99] is readily available in the multigram scale and has been prepared enantioselectively using microbial Baeyer-Villiger oxidations[100,101] and by the recrystallization of diastereomeric salts[102]. The introduction of two new functional groups into starting Grieco lactone, the oxo-moiety at the C-4 position and the angular methyl group, will provide bicycle **23**.



Scheme 36. The hydroboration of (-)-Grieco lactone and its methyllactol derivative and oxidation of the latter

First, the direct hydroboration of (-)-Grieco lactone was applied. (Scheme 36) As a result, the chromatographically inseparable mixture of hydroxylated regioisomers **29** (C-4 hydroxylated and C-5 hydroxylated, in ratio 3:1,

respectively[b]) was isolated. Additionally, the formation of more polar triol **30**[c] (7%) was detected. Occurrence of these side products pointed to the sensitivity of the lactone carbonyl group toward the borane reagent. Therefore the (-)-Grieco lactone was reduced with diisobutylaluminium hydride into the corresponding lactol **31** and protected with methyl group. The volatile bicyclic methylacetals **32** were obtained in the mixture of *exo*- and *endo*-substituted diastereoisomers, in ratio 1.5:1, respectively. The hydroboration of diastereomeric mixture of **32** gave the 4- and 5-hydroxy methylacetals **33**, as the sum of 8 regio- and diastereoisomers (ratio of C4-OH:C5-OH regioisomers ~3.5:1, respectively), and also 4% of the 4*S*-hydroxylactol **34**[d]. The latter is formed due to the cleavage of protecting methyl group probably by the borane reduction. The 4- and 5-hydroxy methylacetals **33** were oxidized with pyridinium dichlorochromate into 4- and 5-ketones **35a** and **35b**, in ratio 2:1, respectively. Surprisingly, after oxidation diastereoselectively 17% of 4*S*-hydroxy bicycle **4*S*-33**[e] was recovered. Unfortunately, the regioisomers **35** were chromatographically inseparable. The regioselectivity of the hydroboration of Grieco lactone and its methyllactol as well as the reactions yields were quite low, due to the isolation problems caused by the hydrophility of the substances. Therefore, the more bulky and lipophilic substituent, the benzylgroup was chosen to protect lactol **31**. (Scheme 37)



Scheme 37. The hydroboration with borane and oxidation of *exo*-benzyllactol **38**

Acetalization of lactol **31** with benzylalcohol gave the benzyllactols **37a** and **37b** in ratio 5:1, respectively. The hydroboration of the major diastereomer and the following oxidation afforded the mixture of regioisomers, 4-oxo (**39a**) and 5-oxo (**39b**) substituted bicycles in ratio 2:1, respectively. Next, the bulkier hydroboration reagent 9-borabicyclo[3.3.1]nonane (9-BBN) was tried. (Scheme 38)

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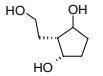
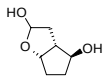
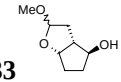
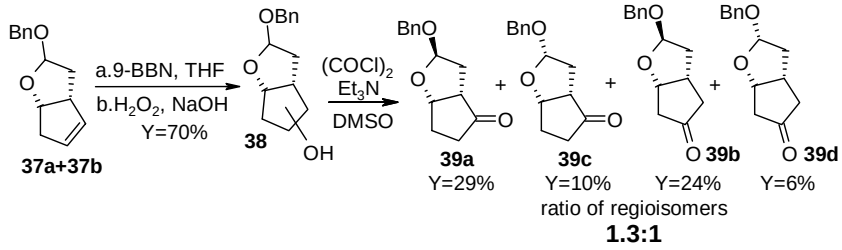
[b] Determined by NMR

[c]  **30**

[d]  **34**

[e] 4*S*-hydroxy bicycle **4*S*-33**  .

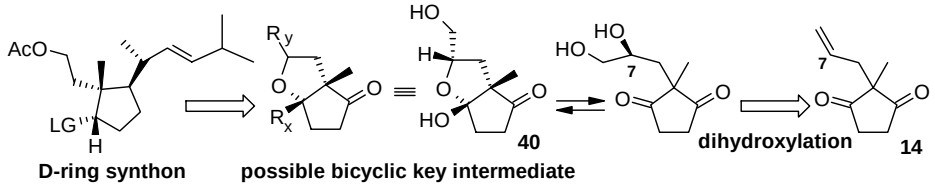


Scheme 38. The hydroboration of **37a+37b** with 9-borabicyclo[3.3.1]nonane and the following oxidation of benzyllactols **38**

The regioselectivity of hyroboration of the mixture of benzyllactols **37a** and **37b** with bulky 9-BBN (1.3:1) was even lower than with hydroborane dimethylsulfide complex (2:1) and also lower than the methyllactol hydroboration results (3:1). Also, the protection of lactol **31** with bulky TBS block was tried, unfortunately the yield of silylation was only 16% and the following hydroboration-oxidation sequence did not proceed with high selectivity. The stydied hydroboration reaction did not promise the satisfactory results in oxo-group insertion into the Grieco lactone derivatives. The epoxidation of Grieco lactone is an alternative approach for double bond oxidation, but it will require an extra step. Therefore, the idea to apply the Grieco lactone as a source of chirality in the construction of bicycle **23** (Scheme 35) was considered not promising.

5.2.4 Desymmetrization of 1,3-diketone **14** *via* dihydroxylation

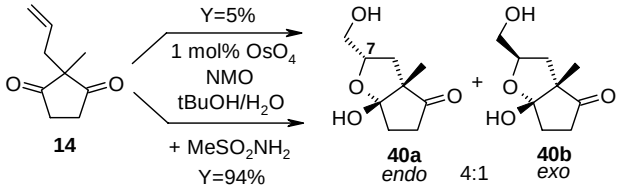
None of the attempted approaches described above fulfilled our requirements for possible preparative synthesis of the D-ring synthon intermediate and were therefore abandoned. The observation of spontaneous intramolecular *cis*-cyclisation in the case of hemiacetal **18** (Scheme 27, Section 5.2.1), derived from cyclopentanedione **14**, led us to an assumption, that 7-hydroxylated derivative of diketone **14** could also form an analogous bicyclic product. The latter could be considered as a new possible bicyclic intermediate **40** for the synthesis of 9,11-secosterol D-ring synthon. (Scheme 39)



Scheme 39. Synthetic strategy toward the D-ring synthon through possible bicyclic key intermediate **40** *via* dihydroxylation

The new bicyclic compound **40** is quite similar to the previously described bicycle **23**. (Scheme 31, Section 5.2.2) Compound **40** has also appropriately

1,2,3-substituted cyclopentane ring, including quaternary carbon atom with methyl group and alkyl chain, where the cleavage of the terminal carbon can easily be achieved through oxidation.
The dihydroxylation of 2-allyl-2-methyl-1,3-cyclopentanedione **14** was performed. (Scheme 40)



Scheme 40. Dihydroxylation of diketone **14**

First, as a result of dihydroxylation with 1 mol% of OsO_4, only 5% of expected dihydroxylated intramolecularly cyclizised diastereomeric hemiacetals **40a** and **40b,** (in ratio 4:1[f]) were isolated. (Scheme 40, upper arrow) The starting ketone **14** was mainly recovered. The low conversion of the starting material pointed to the difficulties in the turnover of the catalytic cycle. Therefore, the methylsulfoneamide[103] was used to speed up the hydrolysis of intermediate osmate esters and hence the catalytic turnover. (Scheme 40, lower arrow) $MeSO_2NH_2$ accelerated the reaction rate significantly, leading to the bicyclic compounds **40** in 94% of isolated yield, although the diastereomeric ratio remained the same.

The fact that $MeSO_2NH_2$ was essential to run the catalytic cycle shows that the intramolecular cyclization of the dihydroxylated product happens instantly in the reaction media and the osmate ester with "tertiary hydroxyl group" of hemiacetal is generated. The formation of *cis*-cyclisized compounds is in good agreement with established knowledge that the *cis*-oriented five-membered bicyclic compounds are more stable than the *trans*-oriented. Two possible explanations for the observed prevalence of *endo*-substituted isomer in the diastereomeric mixture could be suggested. First, the selectivity of cyclization is controlled by the diastereopreferential attack of 7-hydroxyl group to one of carbonyl groups. Second, the diastereoselectivity depends on the different conformational stability of the formed *exo*- and *endo*-hemiacetals, as usually hemiacetals are in equilibrium with each other. However, the NMR spectrum of isolated bicyclic compounds **40** does not show the presence of the corresponding open-ring dihydroxy isomer. On the basis of that we suppose that the dihydroxylation products exist only as hemiacetals and probably do not interchange between each other at room temperature. Unfortunately, the diastereomers of **40** are chromatographically inseparable and therefore the equilibrium between hemiacetals was not determined.

[f] Determined by NMR

These results show that in principle the desymmetrization of prochiral 2-allyl-2-methyl-1,3-cyclopentanedione **14** is possible through dihydroxylation. The new racemic bicyclic hemiacetals **40** has been synthesized and the optimization of standard conditions enhanced the yield of dihydroxylation from initial 7% to 94%. Several methodologies for enantioselective oxidation of olefins have been developed.[104] Among them, the Sharpless catalytic asymmetric dihydroxylation[105] of alkenes is a general and highly selective reaction toward chiral vicinal diols. Additionally, it is known that the stereoselectivity of dihydroxylation is higher in cases of internal olefins compared to the terminal ones. The concern over the use of toxic osmium catalyst, for example, for the synthesis of pharmaceuticals in industry could be relieved by the availability of immobilized OsO_4[106], which reduces the possible hazard.
Therefore the exploration of applying chiral catalyst as well as homologous 2-methyl-1,3-cyclopentanediones will be the nearest perspective in the synthesis of D-ring synthon intermediates.

5.3 Conclusions

Numerous different approaches toward the 9,11-secosterol D-ring synthon have been discussed in previous Sections. None of these demonstrate a complete solution for the synthesis of this synthon. The closely situated stereogenic carbon centres in a relatively small cyclopentane derivative demand an efficient and selective synthesis. The following conclusions toward the D-ring synthon can be drawn:

- Several new strategies toward synthesis of 1,2,3-substituted cyclopentanes suitable for the 9,11-secosterol D-ring synthon were studied:
  - the Horner-Wadsworth-Emmons reaction with 2-allyl-2-methyl-1,3-cyclopentanedione **14**;
  - asymmetric reduction of diketone **14**;
  - derivatization of chiral bicyclic Grieco lactone;
  - dihydroxylation of diketone **14**.

- A new nucleophilic reaction of ethyl 2-(diethylphosphono)propionate toward 2,2-disubstituted-1,3-cyclopentanediones was disclosed. The reaction results in 4-oxohexanoic acid ethyl esters derivative in up to 90% isolated yield.

- The reduction of 1,3-diketone **14**, applying a new catalyst **28** derived from (3*S*,3'*S*)-bimorpholine, resulted mainly in *cis*-3-hydroxy-2-allyl-2-methylcyclopentanone **24** (*dr* 7:1, racemic). The (3*S*,3'*S*)-bimorpholine/Rh-catalyzed transfer hydrogenation gave also *cis*-**24** (*dr* 3:1, *ee* 5%, in favour of (2*R*,3*R*)-**24**). The highest asymmetric induction was achieved by using the CBS catalyst, the oxazaborolidine **27** and the enantiomeric excess of product (2*R*,3*R*)-**24** was 23%.

- The regioselectivity of hydroboration of (-)-Grieco lactone and its derivatives was in favour of desired 6-hydroxy isomer, the highest ratio of regioisomers was 3.5:1 in the case of hydroboration of methyllactol **32**.

- The catalytic dihydroxylation of 1,3-diketone **14** afforded the new bicyclic hemiacetals **40** in 94% isolated yield. This promising strategy can provide a novel approach for the synthesis of 9,11-secosterol D-ring synthon.

References

1. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed.*, **2000**, *39*, 44-122.
2. Koljak, R.; Lopp, A.; Pehk, T.; Varvas, K.; Müürisepp, A.-M.; Järving, I.; Samel, N. *Tetrahedron*, **1998**, *54*, 179-186.
3. D´Auria, M. V.; Luigi, M.; Raffaele, R. *Chem. Rev.* **1993**, *93*, 1839-1895.
4. Enwall, E. L; Van der Helm, D.; Hsu, I. N.; Pattabhiraman, T.; Schmitz, F.J.; Spraggins, R.L.; Weinheimer, A. J. *J. Chem. Soc. Chem. Comm.* **1972**, 215-216.
5. Capon, R. J.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 4771-4773.
6. Dopeso, J.; Quiñoá, E.; Riguera, R.; Debitus, C.; Bergquist, P. R. *Tetrahedron*, **1994**, *50*, 3813-3828.
7. He, H.; Kulanthaivel, P.; Baker, B. J.; Kalter, K.; Darges, J.; Cofield, D.; Wolff, L.; Adams, L. *Tetrahedron*, **1995**, *51*, 51-58.
8. Morris, L. A.; Christie, E. M.; Jaspars, M.; van Ofwegen, L. P. *J. Nat. Prod.*, **1998**, *61*, 538-541.
9. Aiello, A.; Esposito, G.; Fattorusso, E.; Iuvone, T.; Luciano, P.; Menna, M. *Steroids*, **2003**, *68*, 719-723;
10. Migliuolo, A.; Piccialli, V.; Sica, D. *Steroids* **1992**, *57*, 334-347.
11. Koljak, R.; Pehk, T.; Järving, I.; Liiv, M.; Lopp, A.; Varvas, K.; Vahemets, A.; Lille, Ü.; Samel, N. *Tetrahedron Lett.*, **1993**, *34*, 1985-1986.
12. Lopp, A.; Pihlak, A.; Paves, H.; Samuel, K.; Koljak, R.; Samel, N. *Steroids*, **1994**, *59*, 274-281
13. Migliuolo, A.; Piccialli, V.; Sica, D. *Tetrahedron* **1991**, *47*, 7937-7950.
14. Jäälaid, R.; Järving, I.; Pehk, T.; Lille, Ü. *Proc. Estonian Acad. Sci. Chem.* **1998**, *47*, 39-43.
15. Jäälaid, R.; Järving, I.; Pehk, T.; Lille, Ü. *Proc. Estonian Acad. Sci. Chem.* **1998**, *47*, 196-199.
16. Jäälaid R.; Järving I.; Pehk T.; Parve O.; Lille, Ü. *Nat. Prod. Lett.*, **2001**, *15*, 221-228.
17. Kuhl, A.; Kreiser, W. *Tetrahedron Lett.* **1998**, *39*, 1145-1148.
18. Kuhl, A.; Kreiser, W. *Collect. Czech. Chem. C.* **1998**, *63*, 1007-1011.
19. Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948-10954.
20. Burckhardt, V.; Reichstein, T. *Helv. Chim. Acta*, **1942**, *25*, 821-832.
21. Review on Claisen rearangement: Castro, A. M. M., *Chem. Rev*, **2004**, *104*, 2939-3002.
22. Review on intramolecular ene-reactions: Snider, B.B. In *Comprehensive Organic Synthesis*: Trost, B.M., Fleming, I., Eds.: Pergamon: **1991**, Vol 5, 9-27.
23. Ley, S.V. in *Comprehensive Organic Synthesis*: Trost, B.M., Fleming, I., Eds.: Pergamon: **1991**, Vol 7, 128-135.
24. Pharmaceutical trademark Taxol® (Paclitaxel): www.taxol.com
25. Danishefsky, S. J.; Masters, J. J.; Young, W. B. *et al.*, *J. Am. Chem. Soc.* **1996**, *118*, 2843-2859.
26. Paquette, L. A.; Backhaus, D.; Braun, R.; Underiner, T. L.; Fuchs, K. *J. Am. Chem. Soc.* **1997**, *119*, 9662-9671.
27. Fitzpatrick F. A.; Moos P.; Mullally J. E., EP No. WO2004009023 Jan. 29, **2004**.

28. Batrachotoxinin-A 20-α-benzoate most recent application: Verleye, M.; André, N.; Heulard, I.; Gillardin, J.-M. *Brain Research,* **2004**, *1013,* 2, 249-255.
29. Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120,* 6627-6628.
30. Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115,* 6078-6093
31. Pezzuto, J. M.; McChesney, J. D.; Cuendet, M. A.; Helson, L.; US Patent No 20030149096, August 7, **2003**.
32. Kaczorowski G. J.; Tkacz J. S.; Goetz M. A.; Monaghan R. L.; Strohl W. R.; EP No WO03105868, Dec. 12, **2003**.
33. Smith, III, A. B.; Kingery-Wood, J.; Leenay, T.L.; Nolen, E.G.; Sunazuka, T. *J. Am. Chem. Coc.* **1992**, *114*, 1438-1449.
34. Wieland, P.; Miescher, K. *Helv. Chem. Acta* **1950**, *33*, 2215-2228.
35. Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16-17.
36. Rajagopal, D.; Moni, M. S.; Subramanian, S.; Swaminathan, S. *Tetrahedron Asymmetry* **1999**, *10*, 1631-1634.
37. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496-497.
38. Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.
39. Gutzwiller, J.; Buchschacher, P.; Fürst, A. *Synthesis* **1977**, 167-168.
40. Buchschacher, P.; Fürst, A.; Gutzwiller, in *J. Org. Synth. Coll. Vol.* Ed.: Freeman, J.P. Wiley & Sons: NewYork **1990**, *VII*, 368-372.
41. Synthesis of (*R*)-WM ketone: Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T. *Synthesis* **1990**, 53-56.
42. Rajagopal, D.; Rajagopalan, K.; Swaminathan, S. *Tetrahedron: Asymmetry*, **1996**, *7*, 2189-2190.
43. Bui, T.; Barbas III, C. F. *Tetrahedron Lett*, **2000**, *41*, 6951-6954.
44. Rajagopal, D.; Narayanan, R.; Swaminathan, S. *Tetrahedron Lett.* **2001**, *42*, 4887-4890.
45. Zhong, G.; Hoffmann, T.; Lerner, R. A.; Danishefsky, S.; Barbas III, C. F. *J. Am. Chem. Soc.* **1997**, *119*, 8131-8132.
46. Prelog, V.; Acklin, W. *Helv. Chim. Acta* **1956**, *39*, 748-757.
47. Fuhshuku, K.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000**, *65*, 129-135.
48. Hioki, H.; Hashimoto, T.; Kodama, M. *Tetrahedron: Asymmetry*, **2000**, *11*, 829-834.
49. Newkome, G. R.; Roach, L. C.; Montelaro, R. C.; Hill, R. K. *J. Org. Chem.* **1972**, *37*, 2098-2101.
50. Lo, L.-C.; Shie, J.-J.; Chou, T.-C. *J. Org. Chem.* **2002**, *67*, 282-285.
51. Ward D. E.; Rhee C. K.; Zoghalb W. M. *Tetrahedron Lett.* **1988**, *29*, 517-520.
52. Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *34*, 3205-3208.
53. Vanderhaeghe, H.; Katzenellenbogen, E. R.; Dobriner, K.; Gallagher, T. F. *J.Am.Chem. Soc.* **1952**, *74*, 2810-2813.
54. Cheung, W. S.; Wong, H. N. C. *Tetrahedron* **1999**, *55*, 11001-11016
55. Rychnovsky, S. D.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732-2736
56. Minnaard, A. J.; Stork, G. A.; Wijnberg, J. B.; Groot, A. *J. Org. Chem.* **1997**, *62*, 2344-2349
57. Holland, H. L., Auret, B. J. *Can. J. Chem.* **1975**, *53*, 2041-2044.
58. Hudlicky T. *Chem. Rev.* **1996**, *96*, 3-30.

59. Hutchinson, J. H.; Money, T. *J. Chem. Soc., Chem. Commun.* **1986**, 288-289.
60. Dadson, W. M.; Lam, M.; Money, T.; Piper, S. E. *Can. J. Chem.* **1983**, *61*, 343-346.
61. Nemoto, H.; Kurobe, H.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1986**, *51*, 5311-5320.
62. Tomioka, K.; Nagaoka, Y. in *Comperhensive Asymmetric Catalysis* III, Eds: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Springer, Berlin, **1999**, Chapter 31, 1105-1139.
63. Marczak, S.; Michalak, K.; Urbańczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218-2223.
64. Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293-5298.
65. Marczak, S.; Michalak, K.; Wicha, J. *Tetrahedron Lett.*, **1995**, *36*, 5425-5428.
66. Haynes, R. K.; Vonwiller, S. C.; Hambley, T. W. *J. Org. Chem.* **1989**, *54*, 5162-5170.
67. Welch, M. C.; Bryson, T. A. *Tetrahedron Lett.*, **1988**, *29*, 521-524.
68. Fukuzaki, K.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 3591-3594.
69. Takahashi, T.; Naito, Y.; Tsuji, J. *J. Am. Chem. Soc.*, **1981**, *103*, 5261-5263.
70. Funk, R. L.; Vollhardt, P. C. *J. Am. Chem. Soc.*, **1980**, *102*, 5253-5261.
71. Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399-2402.
72. Piers, E.; Renaud, J.; Rettig, S. J. *Synthesis*, **1998**, 590-602.
73. Denmark, S. E.; Germanas, J. P. *Tetrahedron Lett.*, **1984**, *25*, 1231-1234.
74. Quinkert, G.; Müller, T.; Königer, A.; Schultheis, O; Sickenberger, B, Düner, G. *Tetrahedron Lett.* **1992**, *33*, 3469-3472.
75. Haynes, R. K.; Stokes, J. P.; Hambley, T. W. *J. Chem. Soc., Chem. Commun.* **1991**, 58-60.
76. Stork, G.; Winkler, J. D.; Saccomano, N. A. *Tetrahedron Lett.* **1983**, *24*, 465-468.
77. Stork, G.; Saccomano, N. A. *New J. Chem.* **1986**, *10*, 677-679.
78. Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944-953.
79. Snider, B. B.; Lobera, M.; Marien, T. P. *J. Org. Chem.* **2003**, *68*, 6451-6454.
80. Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579-594.
81. Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994,** *59*, 5847-5849.
82. Billington, S.; Mann, J.; Quazi, P. *Tetrahedron* **1991**, *47*, 5231-5236.
83. Freeman, J. P. *Org. Synth. Coll. Vol.* Wiley & Sons: NewYork **1990**, Vol VII, 168-171.
84. Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.
85. Hatakeyama, S.; Satoh, K.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1987**, *28*, 2713-2716.
86. Rein, T.; Anvelt, J.; Soone, A.; Kreuder, R.; Wulff, C.; Reiser, O. *Tetrahedron Lett.* **1995**, *36*, 2303-2306.
87. Schwarz, S.; Carl, C.; Schick, H. *Z. Chem.* **1978**, *18*, 401-402.
88. Brooks, D. W.; Grothaus, P. G.; Irwin, W. L. *J. Org. Chem.* **1982**, *47*, 2820-2821.
89. Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223-3232.
90. Schick, H.; Ballschuh, S.; Welzel, H.-P. *J. prakt. Chem.* **1991**, 749-758.
91. Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tertahedron: Asymmetry* **2000**, *11*, 3883-3886.
92. Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265-10274.
93. Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry*, **2002**, *13*, 857-865.

94. Kriis, K.; Kanger, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry*, **2003**, *14*, 2271-2275.
95. Kriis, K.; Kanger, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry*, **2004**, *15*, 2687-2691.
96. O. Parve; Aidnik, M.; Lille, Ü.; Martin, I.; Vallikivi, I.; Vares, L.; Pehk, T. *Tetrahedron: Asymmetry* **1998**, *9*, 885-896.
97. Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.
98. Quallich, G. J.; Woodall, T. M. *Synlett*, **1993**, 929-930.
99. Grieco, P.A. *J. Org. Chem.* **1972**, *37*, 2363-2364.
100. Alphand, V.; Archelas, A.; Furstoss, R. *Tetrahedron Lett.* **1989**, *30*, 3663-3664.
101. Carnell A. J.; Roberts, S. M.; Sik, V.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2385-2389.
102. Corey, E.J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832-6833.
103. Gott, B. D.; Muxworthy, J. P.; Brown, M. US006054613A, Apr, 25, **2000**.
104. Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981-5021.
105. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547.
106. Choudary, B. M.; Chowdari, N. S.; Jyothi, K.; Kantam, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 5341-5349.

Abstract

Marine organisms provide one of the world's richest sources of polyoxygenated sterols. Among others, the 9,11-secosterols are a class of biologically active terpenoids, first isolated from gorgonian *Pseudopterogorgia americana* by E. L. Enwall *et al.* in 1972.
This thesis is focused on the synthesis of intermediates of the antiproliferative and cytotoxic 9,11-secosterols**,** which have been isolated from the White Sea soft coral *Gersemia fruticosa* by R. Koljak *et al*.

Our vision of the synthesis of 9,11-secosterol **1**, the 24-nor-9,11-seco-11-acetoxy-3β,6α-dihydroxy-cholest-7,22(E)-dien-9-one, is concentrated on the applying of the total synthesis concept. The retrosynthetic analysis of the 9,11-secosterol **1** consists of four–main steps: first, coming down to the precursor; second, dividing the sterol into two independent synthons, which could be easily coupled; third, the synthesis of A,B-ring synthon and fourth, the synthesis of D-ring synthon.

The synthesis of the A,B-ring synthon, the (3*S*,5*S*,6*S*,10*S*)-3,6-diacetoxy-10-methylbicyclo[4.4.0]decan-9-one was started from enantiopure (*S*)-Wieland-Miescher ketone and completed diastereoselectively in 8 steps and in overall yield of 25%.
Also, the oxidation of substituted bicyclo[4.4.0]decen-3-ones was studied and it was found that, as a result of oxidation of 10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-4-en-3-one and its derivative 10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-5-en-3-one under basic conditions, the regiocontrolled formation of either relevant γ-hydroxyenones and 1,4-diketones or 1,2-diketones is achieved.

Several approaches toward 9,11-secosterol D-ring synthon have been proposed. The derivatization of Grieco lactone was studied. The screening of desymmetrization possibilities for 2-allyl-2-methyl-1,3-cyclopentanedione and especially the application of dihydroxylation for synthesis of new bicyclic hemiacetal, the 6a-hydroxy-2-(hydroxymethyl)-3a-methylhexahydro-cyclopenta[b]furan-4-one promises to provide the novel approach toward the D-ring synthon.
Also, we established the new nucloephilic reaction of ethyl 2-(diethylphosphone)propionate toward 2,2-disubstituted 1,3-cyclopentanediones, which provided the 4-oxohexanoic acid ethyl ester derivatives up to 90% isolated yield.

9,11-SEKOSTEROOLIDE VAHEÜHENDITE SÜNTEES

Kokkuvõte

Mereorganismid on ühed rikkamad polüoksüdeerunud steroolide allikad. 9,11-sekosteroolid, kuuluvad bioaktiivsete terpenoidide klassi, mis eradati esmakordselt korkkorallist *Pseudopterogorgia americanast* E. L. Enwall *et al.* poolt 1972 aastal.
Käesolev doktoriväitekiri keskendub antiproliferatiivsete ja tsütotoksiliste 9,11-sekosteroolide vaheühendite sünteesile, nimetatud sekosteroolid eraldati Valge mere pehmest korallist *Gersemia fruticosast* R. Koljak *et al.* poolt.

Meie lähenemine 9,11-sekosterooli **1**, 24-nor-9,11-seko-11-atsetoksü-3β,6α-dihüdroksü-kolest-7,22(E)-dieen-9-oon sünteesiks on rajatud täiskeemilise sünteesi põhimõtetele. 9,11-sekosterooli retrosünteetiline analüüs koosneb neljast põhipunktist: esiteks, 9,11-secosterooli eellase saamine; teiseks, sterooli eellase struktuuri jagamine kaheks iseseisvaks süntoniks, mida oleks võimalik lihtsalt liita; kolmandaks, A,B-ringi süntoni süntees ja neljandaks, D-ringi süntoni süntees.

A,B-ringi sünton, (3*S*,5*S*,6*S*,10*S*)-3,6-diatsetoksü-10-metüülbitsüklo[4.4.0]-dekan-9-oon süteesiti enantiomeerselt puhtast (*S*)-Wieland-Miescheri ketoonist 8 etapiga, mille kogusaagis oli 25%.
Uuriti ka asendatud bitsüklo[4.4.0]detsen-3-oonide osüdeerimist ja leiti, et 10-metüül-9-*tert*-butüüldimetüülsilüüloksobitsüklo[4.4.0]dets-4-een-3-ooni ja selle derivaadi 10-metüül-9-*tert*-butüüldimetüülsilüüloksobitsüklo[4.4.0]dets-5-een-3-ooni oksüdeerimisel aluselistes tingimustes tekivad regioselektiivselt kas vastavad γ-hüdroksüenoonid ja 1,4-diketoonid või 1,2-diketoonid.

Pakuti välja mitmeid lähenemisi 9,11-sekosterooli D-ringi süntoni sünteesiks. Derivatiseeriti Grieco laktooni. Uuriti 2-allüül-2-metüül-1,3-tsüklopentaandiooni desümmetriseerimise võimalusi. Paljulubav lähenemine D-ringi süntoni sünteesil on dihüdroksüleerimise kasutamine uue bitsüklilise poolatsetaali, 6a-hüdroksü-2-(hüdroksümetüül)-3a-metüülheksahüdro-tsüklopenta[b]furan-4-ooni saamisel.
Lisaks sellele, avastati uus etüül 2-(dietüülfosfoon)propionaadi nukleofiilne reaktsioon 2,2-diasendatud 1,3-tsüklopentaandioonidega, mille abil on võimalik sünteesida 4-oksoheksaanhappe etüül esteri derivaate kuni 90% saagisega.

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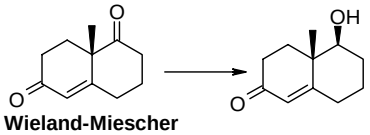
6 Experimental

All reactions, sensitive to moisture or oxygen were carried out under argon atmosphere and in oven-dried glassware. Commercial reagents were used as received. All solvents were distilled. THF was distilled over Na/benzophenone ketyl prior to use. Full assignment of ^{13}C- and ^{1}H-NMR chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX 500 instrument. Solvent peaks in ^{13}C- and ^{1}H-NMR and external 85% H_3PO_4 peak in ^{31}P-NMR were used as chemical shift references. The mass spectra were recorded on a Hitachi M80B spectrometer using electron ionization (EI) at 70 eV or chemical ionization (CI) with isobutane. IR spectra were recorded on Perkin-Elmer Spectrum BX FT-IR infrared spectrophotometer. The numeration of carbon skeleton of all compounds synthesized toward A,B-ring synthon is based on steroid nomenclature.



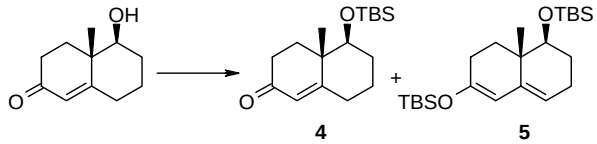
Wieland-Miescher ketone

(9*S*,10*S*)-10-Methyl-9-hydroxybicyclo[4.4.0]dec-4-en-3-one

A solution of 251 mg (1 eq) of Wieland-Miescher ketone in 60 mL (0.024M) of methanol/CH_2Cl_2 (1:1) was cooled in dry-ice/acetone bath to -78°C and then 237 mg (4.5 eq) of $NaBH_4$ was added. The mixture was stirred for 1 h 15 min then 3 mL of acetone was added and warmed to room temperature. Then 60 mL of 1N NaOH solution was added and aqueous phase was extracted 4 times with CH_2Cl_2, collected organic phases were dried over $MgSO_4$. Crude product was purified on SiO_2 (eluent 5%-12% acetone/CH_2Cl_2) and 247 mg (97%) of the corresponding alcohol was isolated. (Structure and configuration of OH-group was confirmed by NMR analysis.)

There is also a simpler way for reduction of this ketone, which is more convenient in larger scale:

A solution of 1.3 g (1 eq) of W-M ketone in 14 mL (0.5M) of ethanol was cooled in ice bath to 0°C and 100 mg (0.38 eq) of $NaBH_4$ was added. The mixture was stirred for 5 h, then 15 mL of H_2O was added and extracted 7 times with CH_2Cl_2, the organic phase was washed with brine and dried over $MgSO_4$. After purification on SiO_2, 1.07 g (81%) of alcohol **2** was isolated.



4 **5**

(9*S*,10*S*)-10-Methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-4-en-3-one (4)

1.22 g (3 eq) of imidazole was placed into 2-necked flask, equipped with reflux condenser and argon inlet, and dissolved in 2 mL of dry DMF (distilled in vacuum over CaH_2). 1.07 g (1 eq) of alcohol was dissolved in 4 mL DMF and was added to reaction flask. 0.9 g (1 eq) of TBDMSCl was dissolved in 2 mL DMF and added in portions during the first day. The reaction mixture was kept warm in oil bath (*ca* 40°C bath temperature), on the next day 0.2 g of TBDMSCl was added and the reaction mixture was held in 30°C over weekend. On the forth day 0.7 g of TBDMSCl (altogether 2 eq) was added in portions. On the fifth day the reaction was completed. 150 mL of water was added and the mixture was extracted 5 times with CH_2Cl_2, organic phase was washed with brine and dried over $MgSO_4$. Product was purified by flash chromatography on SiO_2 (eluent 0%-5% EtOAc/petroleum ether). 1.3 g (75%) of compound **4** as white-gray crystals was isolated along with 276 mg (12%) of disilylated compound **5** as colorless oil (decomposes easily).

4: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.70 (H-1α), 2.10 (H-1β), 2.39 (H-2), 5.76 (H-4), 2.18 and 2.31 (H-6), 1.36 and 1.84 (H-7), 1.70 (H-8), 3.36 (H-9α), 1.16 (C-10-CH_3), 0.89 (t-Bu), 0.04 and 0.05 (Si- CH_3).

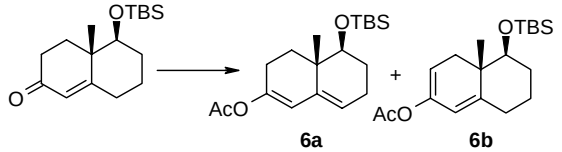
^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block): 34.70, 33.88, 199.74, 125.30, 168.83, 32.05, 22.93, 30.69, 78.85, 42.16, 15.49, -3.97, -4.95, 25.76, 17.99.

CIMS *m/z* 295 (MH^+), 237, 203, 163, 73, 55, 44.

5: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.23 (H-1α), 1.92 (H-1β), 2.05 (H-2α), 2.27 (H-2β), 5.32 (H-4), 5.11 (H-6), 2.18 (H-7), 1.65 (H-8α), 1.84 (H-8β), 3.51 (H-9α), 0.98 (C-10-CH_3), 0.87 (t-Bu), 0.04 and 0.06 (Si- CH_3) from the block at C-9; 0.87 (t-Bu), 0.15 and 0.16 (Si- CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-blocks): 33.45, 27.57, 151.28, 108.53, 139.85, 117.70, 24.90, 27.25, 76.49, 37.52, 17.19, -3.97, -4.85, -4.18, -4.42, 25.66, 25.88, 18.05, 18.08.

MS *m/z* 408 (M^+), 351, 276, 250, 147, 73.



6a **6b**

(9*S*,10*S*)-10-Methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-3,5-dien-3-ol acetate (6a)

The solution of 0.312 mmol (92 mg) of enone **4** in 3 mL isopropenylacetate in the presence of 0.011 mmol (0.6 μL) H_2SO_4, was refluxed for 1.5 h. The

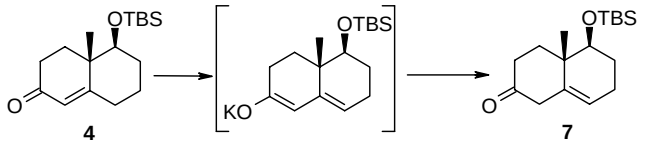
reaction mixture was quenched with saturated solution of $NaHCO_3$, extracted with CH_2Cl_2, the combined organic layers were washed with brine and dried over $MgSO_4$. The crude product was purified on silica gel and the inseparable mixture of dienolacetates **6a** and **6b**, in ratio 2:1, respectively (according to NMR), in yield of 53% (53.9 mg) was isolated.

6a: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.31 (H-1α), 1.96 (H-1β), 2.14 and 2.43 (H-2), 5.72 (H-4), 5.32 (H-6), 2.20 (H-7), 1.83 (H-8), 3.51 (H-9α), 1.00 (C-10-CH_3), 0.90 (t-Bu), 0.03 and 0.06 (Si- CH_3), 2.13 (Ac).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block, acetyl) 33.04, 24.62, 147.57, 116.56, 137.98, 123.19, 24.97, 27.03, 76.03, 37.50, 17.05, -4.04, -4.91, 25.80, 18.00, 18.08, 169.28, 21.04).

6b: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.31 (H-1), 5.22 (H-2), 5.38 (H-4), 2.06 and 2.26 (H-6), 1.34 and 1.71 (H-7), 1.55 and 1.65 (H-8), 3.52 (H-9α), 1.00 (C-10-CH_3), 0.88 (t-Bu), 0.03 and 0.04 (Si- CH_3), 2.13 (Ac).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block, acetyl) 36.20, 107.81, 147.40, 117.00, 144.60, 30.40, 23.11, 31.31, 80.40, 41.56, 14.71, -3.94, -4.91, 25.76, 18.00, 169.50, 20.93).



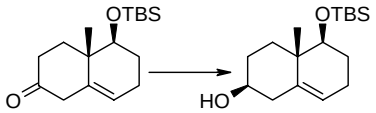
4 **7**

(9*S*,10*S*)-10-Methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-5-en-3-one (7)

15.12 g (8 eq) of *t*-BuOK was placed in to argon filled reaction flask, 200 mL of dry *t*-BuOH (distilled over Na) was added and the mixture was submitted to three freeze-pump-thaw cycles (degassing procedure- using freezing in vacuum, filling with argon and thawing). 4.96 g (1 eq) of enone **4** was dissolved in 80 mL of *t*-BuOH and added to the reaction mixture. After stirring for 2 hours at RT, the mixture was cooled to 0^{o}C and 240 mL of 10% acetic acid solution (cooled previously also to 0^{o}C) was rapidly added. Then 387 mL of saturated solution of $NaHCO_3$ (previously cooled) was added and the reaction mixture was extracted 4 times with Et_2O. Organic phase was dried fast by shaking with mixture of $MgSO_4$ and K_2CO_3 and filtering trough celite, and then traces of water were removed 3 times with toluene azeotrope. The crude product was immediately used in next step

7: ^{13}C NMR (125.7 MHz, C_6D_6), δ: (from C-1 to C-10, C-10-CH_3 and Si-block): 36.01, 37.30, 207.20, 47.94, 138.08, 121.95, 24.85, 27.81, 77.20, 40.10, 17.65, -3.97, -4.79, 25.98, 18.18.

CIMS: *m/z* 295($M+H^+$), 237, 163, 75.



7 **(3*S*)-8**

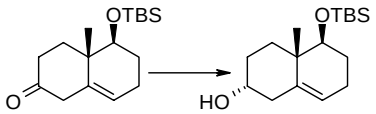
(3*S*,9*S*,10*S*)- 10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-5-en-3-ol ((3*S*)-8)

To 10.5 g (2.5 eq) of $LiAl(OtBu)_3H$ under argon atmosphere 40 mL of dry THF was added, the mixture was cooled to 0°C and 4.8 g (1 eq) of keto-ene **7** (crude) dissolved in 30 mL of THF (cooled) was added during 30 min period. After 2 hours 4 mL of H_2O was added, the mixture was warmed to RT and dried over $MgSO_4$. Product was purified by flash chromatography on SiO_2 (eluent 5%-10% acetone/petroleum ether) and 4.3 g (86% for two steps) of alcohol **(3*S*)-8** was isolated.

This two-step procedure was carried out in one day, to avoid oxidative side-reactions.

(*3S*)-8: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.08 (H-1α), 1.94 (H-1β), 1.52 (H-2β), 1.87 (H-2α), 3.52 (H-3α), 2.18 (H-4β), 2.34 (H-4α), 5.28 (H-6), 2.04 (H-7), 1.56 (H-8α), 1.72 (H-8β), 3.43 (H-9α), 1.04 (C-10-CH_3), 0.90 (t-Bu), 0.04 and 0.06 (Si- CH_3);

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block,): 36.57, 31.47, 71.75, 41.67, 140.06, 120.94, 24.79, 27.56, 78.41, 39.49, 17.55, -3.98, -4.88, 25.85, 18.05.



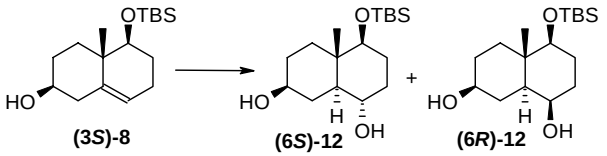
7 **(3*R*)-8**

(3*R*,9*S*,10*S*)-10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]dec-5-en-3-ol ((3*R*)-8)

A solution of 75.8 mg (0.257 mmol) of keto ene **7** in 2 mL of dry THF under argon atmosphere was cooled in dry-ice/acetone bath to –78°C, then 1 mL (4 eq) of 1M solution of L-Selectride® in THF was added dropwise. Reaction mixture was stirred for 30 min and quenched with THF/H_2O 1:1 mixture. The reaction mixture was warmed to RT and extracted 4 times with EtOAc, the organic layers were washed with brine and dried on $MgSO_4$. After solvent evaporation, the product was purified on silica gel with 5% EtOAc in petroleum ether. 37 mg (49%) of alcohol **(*3R*)-8** (containing 4% of diastereoisomer **(*3S*)-8,** according to GC analysis) along with 6.7 mg (9%) of starting enone **4** were isolated.

(*3R*)-8: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.44 (H-1α), 1.73 (H-1β), 1.73 (H-2), 4.04 (H-3β), 2.12 and 2.51 (H-4), 2.34 (H-4α), 5.33 (H-6), 2.04 (H-7), 1.57 (H-8α), 1.71 (H-8β), 3.54 (H-9α), 1.05 (C-10-CH_3), 0.90 (t-Bu), 0.05 and 0.06 (Si-CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block) 32.38, 28.69, 67.07, 39.23, 138.02, 123.00, 24.80, 27.54, 78.43, 40.28, 16.88, -3.99, -4.83, 25.87, 18.07.



(3*S*,5*S*,6*S*,9*S*,10*S*)-10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]deca-3,6-diol ((6*S*)-12)

A solution of 9.3 g (31.3 mmol) of alcohol **(*3S*)-8** in 200 mL of dry THF under inert gas atmosphere was cooled in ice bath (0^{o}C). 5.94 mL (62.6 mmol) of BH_3·SMe_2 was dropwise added and the mixture was refluxed for 3 h. The mixture was cooled in ice bath, then 75 mL of water, 70 mL of 3M NaOH solution and 17 mL (6 eq) of 30% H_2O_2 was added and stirred for 30 min. The mixture was extracted 3 times with Et_2O, washed with brine and dried over $MgSO_4$. After purification on silica gel (acetone/hexane) 7.48 g (76%) of **(6*S*)-12** as a white solid was isolated along with traces of **(6*R*)-12**.

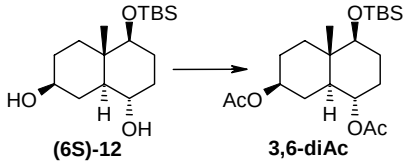
(6*S*)-12: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.81 (H-1α), 1.63 (H-1β), 1.23 (H-2α), 1.61 (H-2β), 3.33 (H-3α), 0.98 (H-4β), 1.89 (H-4α), 0.80 (H-5α), 3.18 (H-6β), 1.09 (H-7α), 1.77 (H-7β), 1.43 (H-8), 3.03 (H-9α), 0.66 (C-10-CH_3), 0.70 (t-Bu), -0.14 and -0.15 (Si- CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block) 36.38, 29.92, 70.44, 31.37, 48.21, 68.29, 33.14, 29.12, 78.69, 38.77, 10.73, -4.51, -5.34, 25.38, 17.63.

(6*R*)-12: EIMS *m/z* 314 (M^+), 299, 257, 221, 147, 75.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.85 (H-1α), 1.68 (H-1β), 1.36 (H-2α), 1.72 (H-2β), 3.50 (H-3α), 1.49 (H-4β), 1.53 (H-4α), 1.03 (H-5α), 3.60 (H-6α), 1.73 (H-7α), 1.50 (H-7β), 1.39 (H-8α), 1.80 (H-8β), 3.10 (H-9α), 0.97 (C-10-CH_3), 0.81 (t-Bu), -0.03 and –0.05 (Si- CH_3).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Si-block) 37.62, 30.76, 71.17, 33.99, 45.12, 70.43, 31.78, 26.14, 79.82, 38.67, 13.01, -4.19, -5,07, 25.64(x3), 17.89.



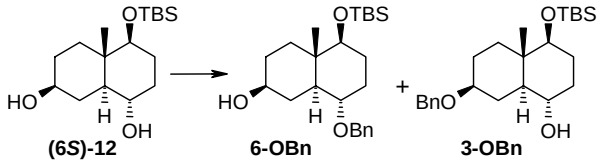
(3*S*,5*S*,6*S*,9*S*,10*S*)-3,6-diacetoxy-10-methyl-9-*tert*-butyldimethylsilyloxobicyclo[4.4.0]decane (3,6-diAc)

To a solution of 10.36 g (1 eq) of **(6*S*)-12** in 100 mL of pyridine was added 18.64 mL of acetic acid anhydride and 80 mg (0.02 eq) of DMAP and the mixture was stirred at RT for 2 h. Et_2O was added and washed 4 times with water, water phase was extracted once with ether, organic layers were washed

with brine and dried over $MgSO_4$. After purification on silica gel 12.48 g (95%) of diester **3,6-diAc** was isolated.

3,6-diAc: ^{1}H NMR (500 MHz, C_6D_6), δ: 1.06 (H-1α), 1.85 (H-1β), 1.84 (H-2α), 1.51 (H-2β), 4.65 (H-3α), 1.27 (H-4β), 1.84 (H-4α),1.31 (H-5α), 4.65 (H-6β), 1.31 (H-7α), 2.02 (H-7β), 1.78 1.64 (H-8), 3.22 (H-9α), 0.90 (C-10-CH_3), 2.030 and 2.033 (Ac), 0.87 (t-Bu), 0.02 and 0.03 (Si- CH_3).

^{13}C NMR (125.7 MHz, C_6D_6), δ: (from C-1 to C-10, C-10-CH_3 , Si- block and Ac): 36.15, 26.83, 71.71, 28.27, 45.61, 73.00, 30.00, 28.98, 78.38, 39.33, 11.01, -4.06, -4.88, 25.79, 17.98, 170.55, 170.81, 21.21, 21.39.



(6*S*)-12 **6-OBn** **3-OBn**

Benzylation

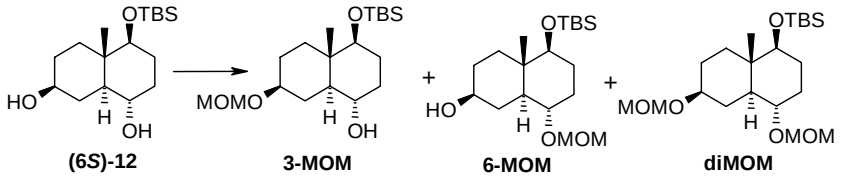
To the suspension of 25 mg (1.04 mmol) of NaH in 1 mL of THF was dropwise added the solution of 60 mg (0.191 mmol) of **(6*S*)-12** in 1 mL of THF and the mixture was stirred at RT for 25 min. At the end of this period 2 mg (0.005 mmol) of Bu_4NI and 130 mg (0.763 mmol) of benzylbromide was dropwise added and stirred at RT overnight. Then the additional 7 mg of Bu_4NI was added and the mixture was refluxed for 1 day. The products were extracted, dried over $MgSO_4$ and purified on silica gel. The main products of the reaction were isolated as the mixture of monobenzylated alcohols **6-OBn** and **3-OBn** 20.9 mg (27%) in ratio 1.6:1, respectively.

6-OBn: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.05 (bs, 6H); 0.85 (s, 3H); 0.9 (s, 9H); 0.99 (m, 1H); 1.18 (m, 1H); 1.21 (m, 1H); 1.26 (m, 1H); 1.40 (m, 1H); 1.53 (m, 1H); 1.68 (m, 1H);1.80, (m, 1H); 1.83 (m, 1H); 2.17 (m, 1H); 2.31 (m, 1H); 3.18 (m, 1H); 3.20 (m, 1H); 3.57 (m, 1H); 7.28 (m, 1H); 7.32-7.35 (m, 4H).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: -4.03, -4.84, 18.01, 25.82, 29.24, 29.95, 30.70, 32.20, 36.60, 39.19, 47.22, 71.2, 76.53, 78.95, 127.49, 127.67 (x2), 128.32 (x2), 138.80.

3-OBn: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.05 (bs, 6H); 0.85 (s, 3H); 0.9 (s, 9H); 0.98 (m, 1H); 0.99 (m, 1H); 1.25 (m, 1H); 1.27 (m, 1H); 1.49 (m, 1H); 1.62 (m, 2H); 1.83, (m, 1H); 1.94 (m, 1H); 1.98 (m, 1H); 2.30 (m, 1H); 3.21 (m, 1H); 3.32 (m, 1H); 3.43 (m, 1H); 7.27 (m, 1H); 7.33-7.38 (m, 4H).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: -4.03, -4.84, 18.01, 25.82, 27.76, 28.83, 29.35, 33.99, 36.65, 39.39, 48.65, 69.20, 77.83, 78.95, 127.37, 127.55 (x2), 128.32 (x2), 139.05.



Methoxymethylation

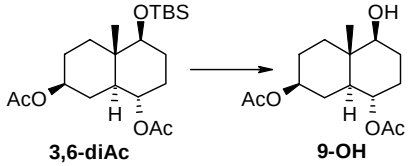
To the solution of 23.7 mg (0.075 mmol) of **(6*S*)-12** in 1.5 mL of DME was added 169 mg (1.13 mmol) of NaI, 267 μL (1.53 mmol) of diisopropylethylamine and 110 μL (1.45 mmol) of MOMCl in tree portions over 2 days period and heated at 55°C on the first day and at 80°C on the second day. The mixture was extracted with diethyl ether, the combined organic layers were washed with solution of $Na_2S_2O_3$ and brine, dried over $MgSO_4$ and purified on silica gel. As a result 3 mg (9%) of **diMOM** and 9 mg (34%) of mixture of monoalkylated **3-MOM** and **6-MOM** were isolated.

diMOM: ^{13}C NMR (125.7 MHz, $CDCl_3$), *δ*: -4.02, -8.86, 11.21, 18.02, 25.83 (x3) 28.06, 29.21, 29.43, 30.91, 36.59, 39.38, 47.21, 55.13, 55.44, 74.81, 76.11, 78.81, 94.53, 95.44.

^{1}H NMR (500 MHz, $CDCl_3$), *δ*: 0.023 (s, 3H), 0.03 (s, 3H), 0.853 (s, 3H), 0.875 (s, 9H), 0.5-1.2 (m, 2H), 1.1-1.2 (m, 3H), 1.2-1.3 (m, 4H), 1.4-1.5 (m, 2H), 3.195 (dd, *J*=10.8/5.1Hz, 1H), 3.33 (m, 1H), 3.365 (s, 3H), 3.368 (s, 3H), 3.48 (m, 1H), 4.56 (d, *J*=4.6Hz, 1H), 4.59-4.72 (m, 3H).

3-MOM: ^{13}C NMR (125.7 MHz, $CDCl_3$), *δ*: -4.87, -4.04, 11.17, 18.00, 25.80 (x3), 28.11, 29.26, 29.32, 34.01, 36.61, 39.20, 48.71, 55.15, 69.19, 75.98, 78.88, 94.45.

6-MOM: ^{13}C NMR (125.7 MHz, $CDCl_3$), *δ*: -4.87, -4.04, 11.24, 18.04, 25.80 (x3), 29.21, 30.79, 30.88, 32.22, 36.57, 42.5?, 47.13, 55.45, 71.21, 74.73, 78.79, 95.43.

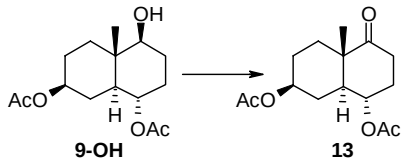


(3*S*,5*S*,6*S*,9*S*,10*S*)-3,6-diacetoxy-10-methylbicyclo[4.4.0]decan-9-ol (9-OH)

To a solution of 12.48 g (31.32 mmol, 1 eq) of diester **3,6-diAc** in 75 mL of dry THF was added 75 mL (2.4 eq) of 1M Bu_4NF in THF, under inert gas atmosphere. The mixture was stirred at 35-40°C for 7 h. After completion of reaction the THF was partially evaporated, water was added, the mixture was extracted with EtOAc and dried over $MgSO_4$. After purification on silica gel 7,8 g (88%) hydroxy-diacetate was isolated.

9-OH: ^{1}H NMR (500 MHz, $CDCl_3$), *δ*: 1.16 (H-1α), 1.89 (H-1β), 1.86 (H-2α), 1.51 (H-2β), 4.66 (H-3α), 1.26 (H-4β), 1.84 (H-4α),1.32 (H-5α), 4.65 (H-6β), 1.34 (H-7α), 2.04 (H-7β),1.78 (H-8α), 1.62 (H-8β), 3.30 (H-9α), 0.93 (C-10-CH_3), 2.02 and 2.03 (Ac).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Ac) 35.64, 26.65, 71.54, 28.16, 45.53, 72.80, 30.02, 28.56, 77.93, 38.76, 10.72, 170.52, 170.76, 21.14,21.32

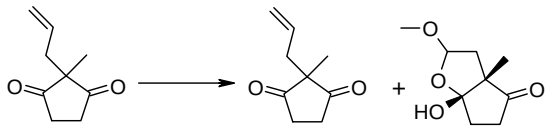


9-OH **13**

(3*S*,5*S*,6*S*,10*S*)-3,6-diacetoxy-10-methylbicyclo[4.4.0]decan-9-one (13)

To a solution of 7.8 g (27.4 mmol, 1 eq) hydroxy-diacetate (**9-OH**) in 91.4 mL of freshly distilled (over P_2O_5) CH_2Cl_2 under argon atmosphere was added 8.86 g (41.1 mmol, 1.5 eq) of PCC and *ca* 1 g of molecular sieves in powder. After 7 h the mixture was filtered through celite and the product was purified on silica gel. 7.29 g (94%) of keto-diacetate **8** was isolated.

13: White crystals with m.p. 111-114^{o}C; $[\alpha]^{22}_{546}$ -89^o (c 1, MeOH)
CIMS *m/z* 283 (MH^+), 163.
^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.55 (H-1α), 1.78 (H-1β), 1.92 (H-2α), 1.49 (H-2β), 4.62 (H-3α), 1.40 (H-4β), 1.97 (H-4α),1.75 (H-5α), 5.06 (H-6β), 1.65 (H-7α), 2.33 (H-7β),2.33 (H-8α), 2.76 (H-8β), 1.20 (C-10-CH_3), 2.03 and 2.06 (Ac).
^{13}C NMR (125.7 MHz, $CDCl_3$), δ: (from C-1 to C-10, C-10-CH_3 and Ac) 30.93, 26.32, 71.93, 28.29, 45.95, 70.01, 30.86, 35.00, 212.45, 46.39, 16.67, 170.38, 170.70, 21.09, 21.28.



14 **15** **18**

6a-Hydroxy-2-methoxy-3a-methyl-hexahydro-cyclopenta[b]furan-4-one (18)

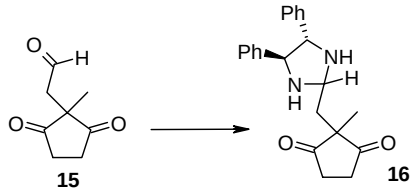
The title compound was prepared according to the procedure for *in situ* acetalization of aldehydes during ozonation[83] as follows: Ozonolysis of 2-allyl-2-methyl-1,3-cyclopentanedione **14** 100 μL (0.675 mmol) at –78^{o}C in 2.2 mL of methanole was performed, then 12.5 mg (0.07 mmol) of *p*-TsOH was added and stirred at RT for 1.5 h. The mixture was neutralized with 57 mg (0.679 mmol) of $NaHCO_3$ and quenched with 97 μL (1.32 mmol) of dimethylsulfide and stirred additionally for 3 h. After solvent evaporation and purification on silica gel 21.5 mg (17%) of intramolecular hemiacetals **18** as the mixture of *exo*- and *endo*-methoxy diastereomers (in ratio 1.3:1, respectively), along with 47.6 mg (46%) of aldehyde **15** were isolated.

18-exo: ^{13}C NMR (125.7 MHz, $CDCl_3$+C_6H_6), δ: 15.75, 27.84, 35.36, 42.89, 54.39, 56.28, 104.04, 115.14, 218.52.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.57 (s, 3H); 2.28 (m, 1H), 2.42 (dd, J=5.5/13.2Hz, 1H), 2.775 (m, 1H), 2.80 (m, 1H), 2.85 (m, 1H), 2.976 (m, 1H), 3.845 (s, 3H), 5.37 (d, J=5.5Hz, 1H).

18-endo: ^{13}C NMR (125.7 MHz, $CDCl_3$+C_6H_6), δ: 15.39, 26.69, 35.17, 41.99, 55.85, 58.54, 105.33, 113.84, 218.62.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.54 (s, 3H), 2.22 (m, 1H), 2.39 (dd, J=4.4/13.8Hz, 1H), 2.76 (m, 1H), 2.80 (m, 1H), 2.83 (m, 1H), 3.16 (dd, J=6.4/13.8Hz, 1H), 3.87 (s, 3H), 5.31 (dd, J=4.4/6.3Hz, 1H).



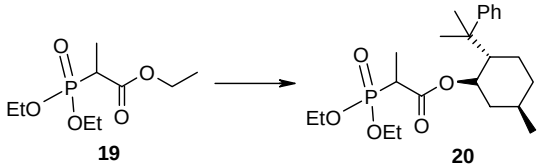
15 **16**

2-((4S,5S)-4,5-Diphenyl-imidazolidin-2-ylmethyl)-2-methyl-cyclopentane-1,3-dione (16)

A solution of 191 mg (1 eq) of 1,2-diphenyl-ethane-1,2-diamine and 126 mg (1 eq) of crude aldehyde **15** in 2.7 mL of CH_2Cl_2 was stirred in presence of molecular sieves overnight. After evaporation of solvent and flash chromatography (eluent: 15% Et_2O in petroleum ether + 1% Et_3N) 210 mg of aminal **16** (yield starting from **14** 68%), as white crystals was isolated.

16: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.10 (s, 3H); 1.77 (s, 3H); 2.17 (s, 3H); 2.25 (dd, 1H); 2.43 (dd, 1H); 2.6-2.75 (m, 2H); 2.85-2.95 (m, 1H); 3.11-3.19 (m, 1H); 3.2 (t, 1H); 3.75 (d, 1H); 3.86 (d, 1H); 6.99 (d, 2H); 7.15 (d, 2H); 7.2-7.27 (m, 4H); 7.32 (d, 2H).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 22.20, 34.15, 34.73, 35.58, 37.11, 39.62, 50.72, 73,18, 76.90, 85.64, 126.73, 127.29, 127.89, 128.13, 128.23, 128.44, 130.01, 138.02, 139.03, 213.93, 216.62.



19 **20**

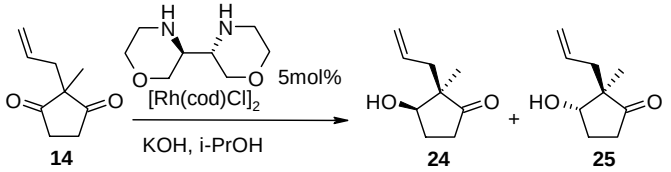
(1'*R*,2'*S*,5'*R*)–8'-phenylmenthyl 2-(diethylphosphono)propionate (20)

A solution of 652 mg (2.8 mmol) of 8-phenylmenthole, 2 g (8.4 mmol) of phosphonate **19** and 342 mg (2.8 mmol) of 4-DMAP in 7 mL of toluene was refluxed overnight in Dean-Stark apparatus. The solvent was evaporated and crude product purified on silica gel, affording 707 mg (60%) of diastereomeric mixture of phosphonates **20**[86].

Major-20: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 11.09 (d, J_{CP}=5.9Hz), 16.23, (d, J_{CP}=5.7Hz), 16.25 (d, J_{CP}=6.0Hz), 21.72, 23.19, 26.24, 29.15, 31.17, 34.48, 38.16 (d, J_{CP}=129.8Hz), 39.42, 41.16, 62.32 (d, J_{CP}=5.8Hz), 62.35 (d,

J_{CP}=6.8Hz), 74.88, 124.99, 125.22 (x2), 127.72 (x2), 151.98, 168.77 (d, J_{CP}=5.1Hz).

Minor-20: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 11.57 (d, J_{CP}=6.4Hz), 16.33, (d, J_{CP}=5.7Hz), 16.38 (d, J_{CP}=5.7Hz), 21.68, 23.19, 26.27, 29.15, 31.24, 34.40, 39.84 (d, J_{CP}=138.9Hz), 39.88, 41.33, 62.40 (d, J_{CP}=6.2Hz), 62.49 (d, J_{CP}=6.4Hz), 75.96, 125.15, 125.54 (x2), 127.92 (x2), 151.18, 168.96 (d, J_{CP}=2.8Hz).



Rh-catalyzed transfer hydrogenation of diketone 14

To 13 mg (0.027 mmol, 0.05 eq) of $[Rh(cod)Cl]_2$ is added a 0.027M solution of 19 mg (0.108 mmol, 20 mol%) of (3*S*, 3'*S*)-bimorpholine in dry degassed *i*-PrOH and 2.95 mL (0.161 mmol, 30mol%) of KOH as a 0.55M solution in *i*-PrOH, under argon atmosphere. The mixture was stirred at RT for 1 h, then a 0.14M solution of 82 mg (0.539 mmol, 1 eq) of 2-allyl-2-methyl-1,3-cyclopentanedione **14** in *i*-PrOH was added and the mixture was stirred for 48 h at RT. Et_2O was added and the catalyst removed by filtration through a pad of Celite®. The filtrate was concentrated in vacuum and crude product purified by flash chromatography on silica gel. 15 mg of hydroxyketone **24**, 10 mg of hydroxyketone **25** and 15 mg of mixture of **24** and **25** (altogether 48%, the ratio of **24**:**25** was 3:1, respectively, determined by GC), along with 14 mg (17%) of starting diketone were isolated.

The enantiomeric excess 5.9% for **25** was determined by chiral HPLC analysis (column: Chiralcel OD-H, detector 206 nm, 97.5:2.5 Hexane:*i*PrOH, *er* 55.9:44.1). The enantiomeric excess for **24** (*ee* 5%) was determined through derivatization with *R*-(-)-methoxymandelic acid, prepared as described by O. Parve *et al.*[96]. The ratio of formed diastereomers was determined by HPLC analysis (47.4:52.6, *de* 5%)

24: MS *m/z* 154(M^+), 136, 121, 110, 94, 79, 67, 55, 41, 28, 15.

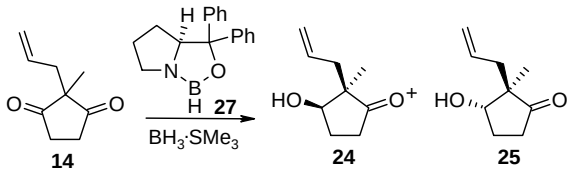
^{1}H NMR (500 MHz, $CDCl_3$), δ: 0.98 (s, 3H); 1.95 (m, 1H); 2.14-2.36 (m, 5H); 2.45 (m, 1H); 4.1 (t, *J*=2x3.6Hz, 1H); 5.09 (dp, *J*=17Hz, 1H); 5.12 (dp, *J*=10Hz, 1H); 5.85 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 19.57, 27.69, 33.93, 35.29, 53.10, 77.25, 118.02, 134.26, 220.79.

25: MS *m/z* 154(M^+), 121, 110, 109, 94, 79, 67, 55, 41, 28, 14.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.02 (s, 3H); 1.65 (bd, *J*=4Hz, 1H); 1.87 (m, 1H); 2.13-2.30 (m, 4H); 2.48 (m, 1H); 4.23 (m, 1H); 5.1-5.14 (m, 2H); 5.77 (m, 1H).

^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 14.94, 27.48, 34.82, 39.82, 52.92, 75.44, 118.69, 133.54, 219.73.



Reduction of diketone 14 with borane CBS complex at 0°C

The CBS catalyst **27** was prepared a day before from diphenyl-pyrrolidin-2-yl-methanol and $BH_3 \cdot SMe_2$ as described by E. J. Corey[97].

To a 0.3M solution of 182 mg (1.2 mmol, 1 eq) of diketone **14** in dry THF, under argon atmosphere, at 0°C 0.12 mmol (0.1 eq) of CBS catalyst **27** in 1.5 mL toluene was added. Then 68 μL (0.72 mmol) of $BH_3 \cdot SMe_2$ was added in two portions with interval of 2 h. The mixture was stirred at 0°C overnight, quenched with MeOH, extracted and dried over $MgSO_4$. The crude product was purified on silica gel and 17 mg of **24**, 9 mg of **25**, 23 mg of mixture of **24** and **25** (altogether 32%, the ratio of **24**:**25** 5:1, determined by GC) was isolated along with 50 mg (33%) of starting diketone. Both hydroxyketones **24** and **25** were racemic, the determination of enantiocomposition was analogous to previous example.

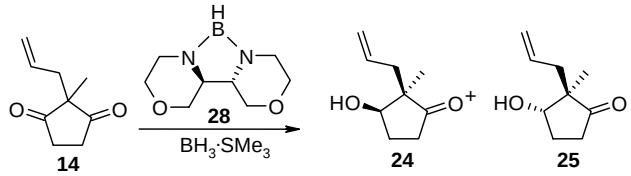
Reduction of diketone 14 with borane CBS complex at -30°C

To a 0.03M solution of 50 mg (0.2 mmol, 0.1 eq) diphenyl-pyrrolidin-2-yl-methanol in dry THF was added 323 μL (3.4 mmol) of $BH_3 \cdot SMe_2$ and the mixture was stirred under argon atmosphere at RT overnight. Then 7 mL of THF was added and the mixture cooled to -30°C. 2M solution of 308 mg (2 mmol, 1 eq) of diketone **14** in THF was added dropwise during 40 min to the borane complex. The reaction was quenched with 3 mL of MeOH, most of the solvents were evaporated, Et_2O was added and the mixture extracted with 5% HCl solution, the water layers extracted additionally with CH_2Cl_2 and dried over $MgSO_4$. The crude product was purified on silica gel. 70 mg of **24**, 25 mg of **25** and 70 mg of the mixture of **24** and **25** (altogether 53%, the ratio of **24**:**25** 5:1, determined by GC) were isolated along with 41 mg (13%) of starting diketone. Both hydroxyketones **24** and **25** were racemic, the determination of enantiocomposition was analogous to previous example.

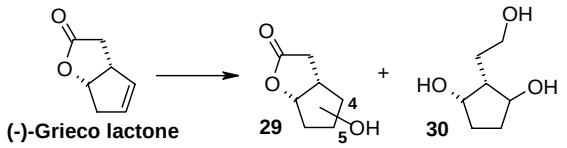
Reduction of diketone 14 with borane CBS complex at -78°C

To a 0.1M solution of 1 mmol (253 mg, 1 eq) of diphenyl-pyrrolidin-2-yl-methanol in dry THF was added 5 mmol (475 μL) of $BH_3 \cdot SMe_2$ and the mixture was stirred under argon atmosphere at RT overnight. The solvent was evaporated in vacuum, 7 mL of THF added and cooled to -78°C in dry-ice/acetone bath. 148 μL (1 mmol, 1 eq) of diketone **14** was added at once and stirred for 10 min. The mixture was quenched with 1.5 mL of MeOH and warmed to RT. Solvents were evaporated, CH_2Cl_2 added and extracted with 2M HCl solution, dried over $MgSO_4$. The crude product was purified on silica gel and 51 mg of **24**, 19 mg of **25**, 22 mg of mixture of **24** and **25** (altogether 60%, the ratio of **24**:**25** 2:1, determined by GC) were isolated.

The enantiomeric excess 23% for **25** was determined by chiral HPLC analysis (column: Chiralcel OD-H, detector 206 nm, 97.5:2.5 Hexane:*i*PrOH, *er* 62:38) The enantiomeric excess 25% for **24** was determined by interpolation of optical rotation[89] ($[\alpha]_D^{20}$ -20° (c 0.03, $CHCl_3$))

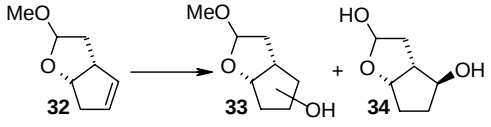


Reduction of diketone 14 with borane diazaborolidine complex 28 at -78°C
To a 0.014M solution of 17 mg (0.1 mmol, 0.15 eq) of (3*S*,3'*S*)-bimorpholine[93] in dry THF was added 66 μL (0.7 mmol) of $BH_3{\cdot}SMe_2$ and the mixture was stirred under argon atmosphere at RT overnight. The mixture was cooled to -78°C in dry-ice/acetone bath, 100 μL (0.67 mmol, 1 eq) of diketone **14** was added at once and stirred for 1 h. 33 μL (0.35 mmol) of $BH_3{\cdot}SMe_2$ was additionally added and stirred for 2.5 h. Then the mixture was quenched with 1.5 mL of MeOH and warmed to RT. Solvents were evaporated, CH_2Cl_2 was added, the mixture was extracted with 2M HCl solution and dried over $MgSO_4$. The crude product was purified on silica gel and 55 mg of **24**, 16 mg of **25**, 15 mg of mixture of **24** and **25** (altogether 85%, the ratio of **24**:**25** 7:1, determined by GC) were isolated. By the chiral HPLC analysis was determined that hydroxyketone **25** was racemic.

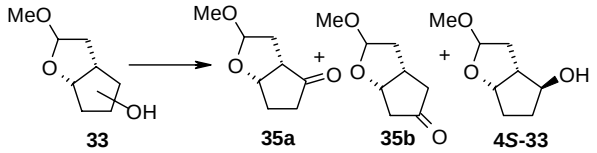


4-Hydroxy-hexahydro-cyclopenta[b]furan-2-one and 5-hydroxy-hexahydro-cyclopenta[b]furan-2-one (29)
To a solution of 199 mg (1.605 mmol, 1 eq) of (-)-Grieco lactone in 4.5 mL of dry THF under argon atmosphere at 0°C was dropwise added the solution of 101.5 μL (1.07 mmol, 0.67 eq) of $BH_3{\cdot}SMe_2$ in 1 mL THF. The mixture was stirred for 6 h, then 0.5 mL of 3M NaOH and 0.5 mL of 30% H_2O_2 were added and stirred additionally for 1h. The mixture was acidified with 50% solution of HCl and then the saturated solution of Na_2SO_3 (prepared from 0.4g of Na_2SO_3) was added. The mixture was neutralized with $NaHCO_3$ and dried over $MgSO_4$. 106 mg of total 159 mg of crude product was purified on silica gel and 62 mg (58%) of hydroxylated Grieco lactones **29**, as the mixture of diastereo- and regioisomers (according to NMR analysis, ratio of regioisomers was in favor of 4-hydroxylated lactone ~3:1), along with 8 mg (7%) reduced derivative **30** was isolated.
Major isomer of 29–4*S*-OH: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 30.44, 31.89, 32.97, 47.12, 78.90, 85.60, 117.28.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.78 (m, 2H), 1.96 (m, 1H), 2.17 (m, 1H), 2.31 (d, 1H), 2.83 (m, 1H), 2.86 (m, 1H), 4.12 (bs, 1H), 5.12 (t, 1H).
30: ^{13}C NMR (125.7 MHz, $CDCl_3$+MeOD), δ: 26.56, 32.50 (2C), 47.58 (2C), 61.09, 74.81.
^{1}H NMR (500 MHz, $CDCl_3$+MeOD), δ: 1.56 (m, 1H), 1.78 (m, 2H), 1.82 (m, 4H), 3.64 (t, *J*=2x6.2Hz, 2H), 4.07 (bs, 2H).



2-Methoxy-hexahydro-cyclopenta[b]furan-4-ol and 2-methoxy-hexahydro-cyclopenta[b]furan-5-ol (33)
The synthesis was carried out analogously to the procedure of hydroboration of Grieco lactone, only without addition of HCl. Obtained alcohols were extracted with EtOAc before drying over $MgSO_4$. From 0.99 mmol (138 mg) of methyllactol **32** 67 mg (43%) of mixture of alcohols **33**, along with 6 mg (4%) hydroxylactols **2*R*,4*S*-34** and **2*S*,4*S*-34** were isolated (4:1, respectively).
Major isomers of 33 - 2*S*,4*S*-33: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 32.05, 33.31, 37.76, 51.42, 54.2, 79.79, 85.84, 106.10.
^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.65 (m, 1H), 1.82 (m, 1H), 1.89 (m, 1H), 2.06 (m, 1H), 2.20 (m, 1H), 2.25 (m, 1H), 2.53 (m, 1H), 3.28 (s, 3H), 4.24 (m, 1H), 4.78 (t, 1H), 4.96 (d, 1H).
2*R*,4*S*-33: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 30.13, 31.91, 37.67, 50.60, 54.15, 78.94, 83.15, 105.64.
^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.5 (m, 1H), 1.65 (m, 1H), 1.81 (m, 1H), 1.83 (m, 1H), 2.03 (m, 1H), 2.20 (dd, 1H), 2.73 (m, 1H), 3.30 (s, 3H), 4.06 (m, 1H), 4.70 (t, 1H), 4.99 (d, 1H).
3*R*,6*S*-34: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 30.18, 31.87, 38.23, 50.36, 78.83, 83.58, 99.25.
^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.52 (m, 1H), 1.65 (d, *J*=13.2Hz, 1H), 1.83 (m, 2H), 2.05 (m, 1H), 2.22 (dd, *J*=9.9/13.2Hz, 1H), 2.80 (q, *J*=3x8.2Hz, 1H), 4.06 (d, *J*=3.5Hz, 1H), 4.87 (t, *J*=2x6.2Hz, 1H), 5.54 (d, *J*=4.8Hz, 1H).
3*S*,6*S*-34: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 32.07, 33.24, 38.40, 51.70, 79.71, 85.63, 99.55.
^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.59 (m, 1H), 1.85 (m, 1H), 1.90 (m, 1H), 2.10 (m, 1H), 2.28 (m, 2H), 2.54 (t, *J*=2x8.5Hz, 1H), 4.28 (m, 1H), 4.74 (t, *J*=6.1Hz, 1H), 5.47 (bd, *J*=2/4.8Hz, 1H).



2-Methoxy-hexahydro-cyclopenta[b]furan-4-one and 2-methoxy-hexahydro-cyclopenta[b]furan-5-one (35)

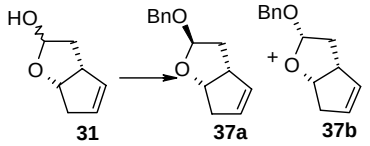
To a suspension of 106.5 mg (0.28 mmol) of PDC in 1 mL of CH_2Cl_2 was dropwise added the solution of 30 mg (0.189 mmol) of the mixture of alcohols **33**. The reaction mixture was stirred at RT for 2 days and filtered through celite. After solvent evaporation and purification on silica gel 7 mg (24%) of regioisomeric ketones **35**, in ratio 2:1 in favor of 4-oxo isomer **35a**, along with 5 mg (17%) of recovered alcohol **4*S*-33** were isolated.

35a: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 28.35, 35.21, 38.32, 49.97, 53.95, 82.71, 104.64, 220.38.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.15 (m, 1H), 2.16 (m, 1H), 2.26 (m, 1H), 2.28 (m, 1H), 2.33, (bd, *J*=13.3Hz, 1H), 2.56 (m, 1H), 2.66 (bt, 1H), 3.27 (s, 3H), 4.91 (t, *J*=2x5.9Hz, 1H), 4.98 (d, *J*=4.8Hz, 1H).

35b: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 37.85, 40.82, 43.94, 44.49, 54.99, 78.89, 105.81, 217.32.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.02 (m, 1H), 2.03 (m, 1H), 2.25 (bd, *J*=13.6Hz, 1H), 2.52 (bd, 2H), 2.57 (d, *J*=19.3Hz, 1H), 2.99 (m, 1H), 3.38 (s, 3H), 4.75 (t, *J*=2x3.6Hz, 1H), 5.13 (dd, *J*=2.1/5.3Hz, 1H).



2-Benzyloxy-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan (37)

A solution of 302 mg (2.38 mmol) of lactol **31**, 269 μL (2.86 mmol) of benzylalcohol and 2 mg of *p*-TsOH in 12 mL of dry toluene was refluxed in Dean-Stark apparatus for 2h. The saturated solution of $NaHCO_3$ was added, the mixture was extracted with EtOAc and dried over $MgSO_4$. After solvent evaporation and purification on silica gel, 480 mg (93%) of benzyllactols **37a** and **37b** (as the mixture of *exo*- and *endo*-isomers, in ratio 5:1 respectively), were isolated.

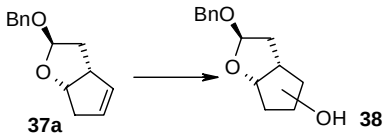
37: MSCI: *m/z* 217(MH^+), 199, 717, 133, 109, 91.

37a: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.85 (dt, *J*=13.2/2x5.2Hz, 1H), 2.24 (m, 1H), 2.52 (d, *J*=18.2Hz, 1H), 2.65 (m, 1H), 3.43 (m, 1H), 4.49 (d, *J*=11.8Hz, 1H), 4.75 (d, *J*=11.8Hz, 1H), 4.82 (t, *J*=2x6.3Hz, 1H), 5.25 (d, *J*=5.3Hz, 1H), 5.62 (m, 1H), 5.63 (m, 1H), 7.28-7.38 (m, 5H).

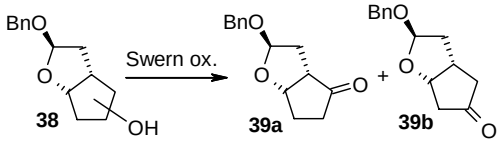
^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 38.13, 39.10, 48.54, 68.63, 81.12, 103.45, 127.51, 127.92 (x2), 127.93, 128.35 (x2), 133.35, 138.18.

37b: ^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.04 (d, *J*=13.2Hz, 1H), 2.13 (m, 1H), 2.55 (d, *J*=17.5Hz, 1H), 2.69 (dd, *J*=18.6/6.6Hz, 1H), 3.36 (t, *J*=2x7Hz, 1H),

4.41 (d, *J*=12.1Hz, 1H), 4.70 (d, *J*=12.1Hz, 1H), 4.90 (t, *J*=2x6.5Hz, 1H), 5.19 (d, *J*=5.2Hz, 1H), 5.65-5.73 (m, 2H), 7.25-7.34 (m, 5H).
^{13}C NMR (125.7 MHz, $CDCl_3$), δ:37.79, 41.72, 48.93, 68.73, 83.35, 103.66, 127.29, 127.67 (x2), 128.08, 128.24 (x2), 133.14, 138.44.

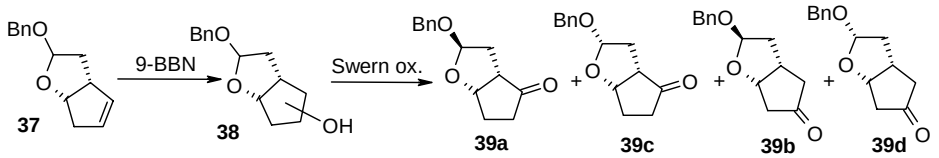


2-Benzyloxy-hexahydro-cyclopenta[b]furan-4-ol and 2-benzyloxy-hexahydro-cyclopenta[b]furan-5-ol (38)
To a 0.3M solution of 96 mg (0.44 mmol) of *exo*-benzyllactol **37a** in dry THF at 0^{o}C under argon atmosphere was added 296 μL (0.269 mmol) of BH_3 (1M solution in THF). The mixture was stirred at 0^{o}C for 3 h. Then 250 μL of 3M NaOH solution was added, followed by 250 μL of 30% H_2O_2 and stirred for 15 min at RT. After extraction with Et_2O, drying over $MgSO_4$ and evaporation of solvents, 101 mg of crude alcohols **38** were isolated.
38:GC-MS: *m/z* 234(M^+), 212, 194, 167, 152, 105, 91, 77, 51.
GC-MS: *m/z* 234(M^+), 176, 170, 147, 127, 109, 91.



2-Benzyloxy-hexahydro-cyclopenta[b]furan-4-one and 2-benzyloxy-hexahydro-cyclopenta[b]furan-5-one (39)
To a 0.2M solution of 55 μL (0.632 mmol) of $(COCl)_2$ in dry CH_2Cl_2 was added 3.3M solution of 97 μL (1.366 mmol) of DMSO in CH_2Cl_2, at -78^{o}C and stirred for 30min. Then the 0.2M solution of 101 mg (0.43 mmol) of crude alcohols **38** in CH_2Cl_2 was added. The mixture was stirred for 1 h, and then 300 μL (2.15 mmol) of Et_3N was added and the reaction mixture was warmed to the RT. 10 mL of H_2O was added, extracted with CH_2Cl_2 and dried over $MgSO_4$. After purification on silica gel 39 mg (37%) of ketone **39a** and 18 mg (18%) of ketone **39b** were isolated.
39a: MS: *m/z* 232(M^+), 125, 107, 91.
^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 25.50, 34.87, 37.39, 50.89, 69.14, 80.27, 103.85, 127.65, 127.84 (x2), 128.38 (x2), 137.70, 220.46.
^{1}H NMR (500 MHz, $CDCl_3$+C_6D_6), δ: 2.13 (m, 1H), 2.26-32.35 (m, 4H), 2.43 (m, 1H), 2.79 (m, 1H), 4.48 (d, *J*=11.8Hz, 1H), 4.74 (d, *J*=11.8Hz, 1H), 4.86 (t, *J*=2x4.8Hz, 1H), 5.25 (dd, *J*=2/4.8Hz, 1H), 7.27-7.38 (m, 5H).
39b: MS: *m/z* 232(M^+), 188, 141, 125, 108, 92, 91.
^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 37.86, 40.83, 43.93, 44.43, 69.21, 79.02, 103, 86, 127.64, 127.86 (x2), 128.39 (x2), 137.82, 217.27.

^{1}H NMR (500 MHz, $CDCl_3$+C_6D_6), δ: 2.00-2.06 (m, 2H), 2.35 (m, 1H), 2.54 (d, *J*=3.9Hz, 2H), 2.58 (dd, *J*=9.9/19.3Hz, 1H), 3.01 (m, 1H), 4.50 (d, *J*=12.0Hz, 1H), 4.76 (d, *J*=12.0Hz, 1H), 4.81 (q, *J*=5.9/2x3.7Hz, 1H), 5.34 (dd, *J*=5.3/1.8Hz, 1H), 7.28-7.38 (m, 5H).



2-Benzyloxy-hexahydro-cyclopenta[b]furan-4-one and 2-benzyloxy-hexahydro-cyclopenta[b]furan-5-one (39)

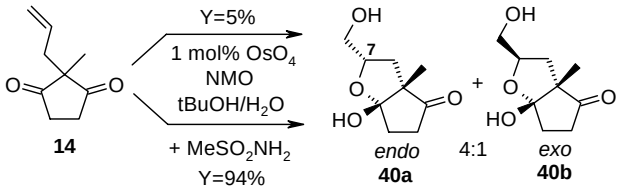
To a 0.7M solution of 261 mg (1.07 mmol) of 9-BBN in dry THF was added 154 mg (0.71 mmol) of benzyllactols **33**, under argon atmosphere. After stirring for 5 h at RT 286 mg (1.1 mmol) of 9-BBN was added and the mixture was stirred over week-end. Then 0.5 mL of 3M solution of NaOH was added at 0°C, followed by 0.5 mL of 30% H_2O_2 and stirred for 20 min at RT. After extraction with Et_2O, drying over $MgSO_4$, evaporation of solvents and purification on silica gel 117 mg (70%) of alcohols **38**, as a mixture of regio- and diastereoisomers, were isolated. Then Swern oxidation of alcohols was performed as described above and 39 mg (29%) of **39a**, 11 mg (10%) of **39c**, 27 mg (24 %) of **39b** and 7 mg (6%) of **39d** were isolated.

39c: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 28.43, 35.41, 38.34, 50.11, 68.14, 82.89, 102.64, 127.34 (x2), 127.47, 128.36 (x2), 137.58, 220.17.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.2-2.3 (m, 4H), 2.41 (d, *J*=13.1Hz, 1 H), 2.53 (m, 1H), 2.70 (dd, *J*=9.2/6.1Hz, 1H), 4.46 (d, *J*=11.8Hz, 1H), 46.8 (d, *J*=11.8Hz, 1H), 4.94 (t, *J*=2x5.5Hz, 1H), 5.17 (d, *J*=4.8Hz, 1H), 7.22-7.38 (m, 5H).

39d: ^{13}C NMR (125.7 MHz, $CDCl_3$), δ: 37.47, 40.24, 44.00, 46.75, 69.18, 81.65, 104.34, 127.60, 127.93 (x2), 128.37 (x2), 137.64, 217.69.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.09 (d, *J*=13.4Hz, 1H), 2.24 (m, 1H), 2.53-2.60 (m, 4H), 3.05 (p, *J*=4x7.9Hz, 1H), 4.39 (d, *J*=11.8Hz, 1H), 4.68 (d, *J*=11.8Hz, 1H), 4.89-4.93 (m, 1H), 5.25 (d, *J*=5.2Hz, 1H), 7.27-7.36 (m, 5H).



6a-Hydroxy-2-hydroxymethyl-3a-methyl-hexahydro-cyclopenta[b]furan-4-one (40)

To a 34 mg of anchored homogenous catalyst OsO_4 Fibre Cat®[g] 3003 (contain 7.5% of OsO_4, 0.01 mmol) and 152 mg (1.3 mmol) of NMO was added 6 mL of H_2O/*t*-BuOH (1/3) and 148 μL (1 mmol) of diketone **14**. The reaction mixture was heated at 60°C for 48h. The catalyst was filtered, washer with EtOAc and crude product purified on silica gel. 9 mg (5 %) of bicycles **40a** and **40b** (inseparable on silica gel), in ratio (4:1, respectively) were isolated.

To a solution of 252 mg (3 mmol) of $MeSO_2NH_2$ and 152 mg (1.3 mmol) of NMO in 6 mL of H_2O/*t*-BuOH (1/3) was added 131 μL (0.01 mmol) of OsO_4 solution in *t*-BuOH (2.5 wt%), followed by 148 μL (1 mmol) of diketone **14**. The mixture was stirred overnight at RT, and then 515 mg of Na_2SO_3 and $MgSO_4$ was added. The crude product was filtered and purified on silica gel. 175 mg (94%) of bicycles **40a** and **40b** (in ratio 4:1, respectively), were isolated.

40: GC-MS: *m/z* 186(M^+),168, 155, 127, 95, 69.

IR: 3370, 2935, 2876, 1740, 1569, 1457, 1406, 1375, 1266, 1192, 1071, 890.

40a: ^{13}C NMR (125.7 MHz, $CDCl_3$), *δ*: 15.78, 29.24, 34.46, 35.32, 59.28, 63.25, 78.55, 110.87, 220.22.

^{1}H NMR (500 MHz, $CDCl_3$), *δ*: 1.03 (s, 3H), 1.86 (m, 1H), 2.09 (m, 1H), 2.28-2.5 (m, 4H), 3.43 (d, 1H), 3.70 (d, 1H), 4.09 (m, 1H).

40b: ^{13}C NMR (125.7 MHz, $CDCl_3$), *δ*: 16.14, 30.01, 35.78, 36.92, 60.43, 64.64, 77.85, 111.90, 120.53.

^{1}H NMR (500 MHz, $CDCl_3$), *δ*: 1.04 (s, 3H), 1.95-2.12 (m, 3H), 2.30-2.47 (m, 3H), 3.33 (m, 1H), 3.49 (m, 1H), 4.29 (m, 1H).

[g] Donated by Johnson Matthey.

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List of publications

1. R. Aav, T. Kanger, T. Pehk, M. Lopp, Unexpected Reactivity of Ethyl 2-(diethylphosphono)-propionate toward 2,2-Disubstituted-1,3-cyclopentanediones. *Phosphorus, Sulfur, and Silicon and the Related Elements*, in press, accepted 26.08.**2004**

2. R. Aav, T. Kanger, T. Pehk, M. Lopp. Oxidation of Substituted Bicyclo [4.4.0]decen-3-ones. *Proc. Estonian Acad. Sci. Chem.* **2001**, *50*, 138-146.

3. R. Aav , T. Kanger, T. Pehk, M. Lopp. Synthesis of the AB-Ring of 9,11-Secosterols. *Synlett*, **2000**, *4*, 529-531.

4. S. Pache, E. P. Kundig, R. Aav, A. Tomassini, A. Alexakis. Synthesis of Planar Chiral o-substituted Benzaldehyde Chromium Complexes via Enantio- and Diastereoselective Lithiation. Fall Meeting of the New Swiss Chemical Society in Lausanne, 2000. *CHIMIA* **2000**, *54*, No. 7/8.

5. R. Aav, O. Parve, T. Pehk, A. Claesson, I. Martin. Preparation of highly enantiopure stereoisomers of 1-(2,6-dimethylphenoxy)-2-aminopropane (mexiletine). *Tetrahedron: Asymmetry*, **1999**, *10*, 3033-3038.

6. A. Orav, T. Kailas, M. Liiv, R. Aav. Capillary Gas Chromatographic Analysis of the Monoterpenoid Fraction of Estonian Conifer Needle Oil. *Proc. Estonian Acad. Sci. Chem.,* **1995**, *44*, 2/3, 149-155.

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Diplomitöö teema – „Uut tüüpi antikonvulsandi D-23129 keemiline süntees", juhendaja keemiatead. kand. I. Martin

Teadustöö põhisuunad

Asümmeetrilise sünteesi meetodite rakendamine looduslike ühendite sünteesil. (9,11-sekosterooli totaalsüntees)