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Towards the total synthesis of 9,11-secosterol: Linking A,B- and D-rings with Michael addition to sulfone-activated cyclopentenone

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ABSTRACT

The application of Michael addition to the construction of the carbon skeleton of 9,11-secosterols has been investigated using the following Michael acceptor - sulfone 2-[(4-methylphenyl)sulfonyl]cyclopent-2-en-1-one, where the addition product was isolated in good yield and as a mixture of two diastereomers. Also, the diastereomers were separable by crystallization, and, based on NMR spectroscopic data, the relative configuration of the formed stereocentres of the isolated diastereomer matched the 9,11-secosterol found in nature. This study can be exploited to create a total synthesis scheme for 9,11-secosterols.

1. Introduction

The first 9,11-secosterol was isolated from soft coral *Pseudopterogorgia americana* in 1972 [1] and since then more than a hundred different members of the 9,11-secosterol family have been isolated. A variety of bioactivities have been attributed to this group of compounds, such as cytotoxic/antiproliferative [2–4], anti-inflammatory [5], immunosuppressive [6,7], antibacterial [8,9] and antifungal activities [10], as well as apoptosis induction [2] in cancer cells etc., which make 9,11-secosterols attractive for the development of new medical drugs.

The total chemical synthesis of steroids has been the focus of synthetic and medicinal chemistry throughout the 20th century. After the first chemical synthesis of the steroid equilenin in 1939 [11], a wide variety of steroid synthesis methods have been developed. Besides total synthesis, several semi-synthetic modifications of existing steroids have been developed [12,13]. The classical build-up of the steroid skeleton uses the Diels-Alder reaction [14], Michael addition [15] and Torgov reaction [16], transition metal-catalyzed reactions [17–20], organocatalytic approaches etc. [21,22] Also, several microbiological/enzymatic transformations [23,24], and biomimetic cyclization processes have been applied [25,26].

There are several semi-synthetic methods also for 9,11-secosterol synthesis [27–34] starting from natural sterols. However, despite extensive steroid synthesis studies a general total chemical synthesis scheme for 9,11-secosterols is still virtually undeveloped. Our aim is to develop a convenient synthetic scheme for the preparation of 9,11-secosterols with a key step of constructing the carbon bond between the C-8 and C-14 atoms.

2. Results and discussions

2.1. The possibilities of linking A,B- and D-rings

Already since the discovery of 9,11-secosterols **1**, our research group has been involved in the elaboration of chemical access to that family of compounds. First, in the beginning of the 21st century, a semi-synthetic approach was used [35–37]. A total synthesis route was started from the synthesis of the A,B-ring of 9,11-secosterols in 2000 [35]. Because of the continues interest in medicinal chemistry, we returned to this topic some years ago, elaborating a route to the enantioenriched 9,11-secosterol D-ring [36]. The general strategy for the synthesis of 9,11-secosterols was based on building a bond between the A,B-ring and the D-ring precursors according to retrosynthetic scheme (Scheme 1).

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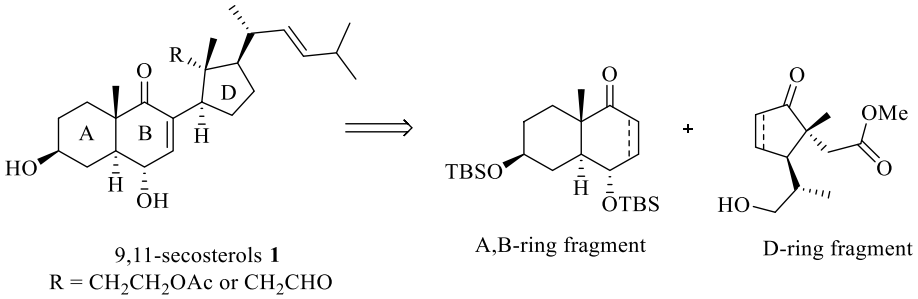


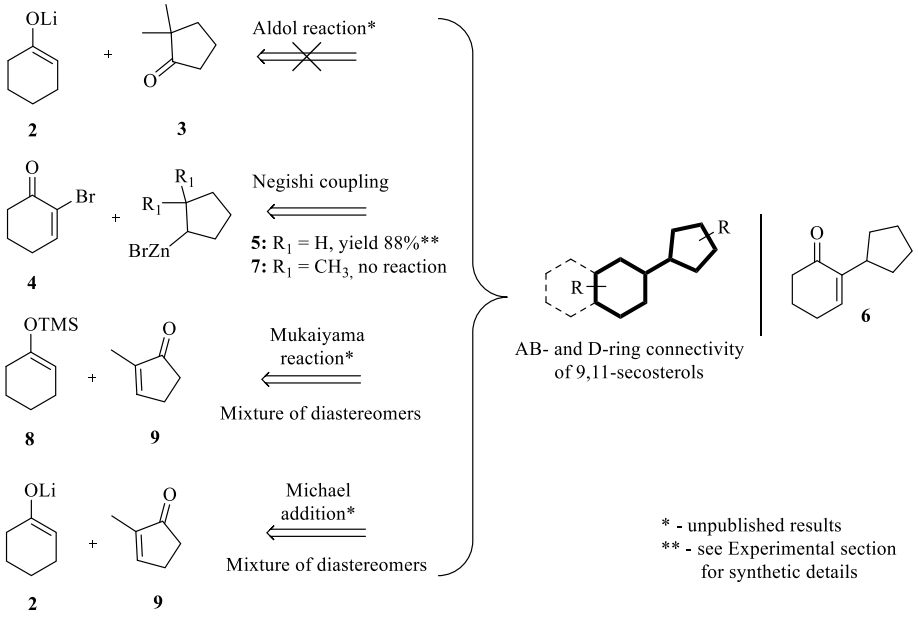
Scheme 1. Retrosynthetic approach to 9,11-secosterols.

In order to connect these rings, possibilities of connecting the A,B- and D-ring fragments using different model reactions were tested (Scheme 2). First, a simple aldol reaction between cyclohexanone enolate **2** and 2,2-dimethyl cyclopentanone **3** was applied. Instead of direct addition, the cyclohexanone Li-enolate acts as a base deprotonating the cyclopentanone **3**. Thus, the following 1,2-addition reaction occurred in the opposite direction affording an addition to the cyclohexanone carbonyl group. Negishi coupling in the presence of Pd catalyst and Q-Phos ligand, which was effective for 2-bromocyclohex-2-en-1-one **4** and ZnBr-derivative of a non-substituted bromocyclopentane **5** forming a product **6** with a yield of 88% (details in Experimental section), failed to react with the ZnBr-derivative of α,α-disubstituted cyclopentane **7**.

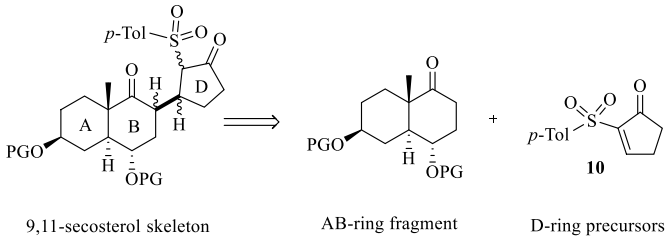
Then we turned to cyclopentenone addition reactions. The Mukaiyama reaction with cyclohexanone trimetylsilyl ether **8** (65% from cyclohexanone) and 2-methylcyclopent-2-en-1-one **9** in the presence of tritylium hexachloroantimonate $TrSbCl_6$ afforded the coupling reaction product in 51% yield as a mixture of diastereomers. The application of the Mukaiyama reaction in the synthesis of steroids has been described in the literature [38,39], where it was stated that the coupling of 6-methoxytetralone TMS-enol ether to 2-methyl-2-cyclopent-2-en-1-one **9** occurred in excellent (90%) yield, affording a mixture of diastereomers. However, the problems arose during the secondary alkylation (to generate the D-ring substituents), as desilylation (resilylation) occurred in the very first reaction. It was concluded that the Mukaiyama approach is not usable in this case in building the upper chains of sterols.

For the Michael addition reaction with the model compounds, cyclohexanone lithium enolate **2** was generated in the presence of LDA *in situ* from DIPA and *n*BuLi. The addition reaction proceeded in 32% yield resulting in a mixture of diastereomers. From that result we proposed that the Michael acceptor needs higher activation.

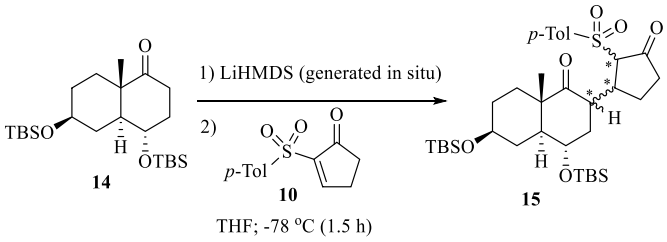
We turned our attention to the works of Posner et al., who demonstrated that the substituted cyclopentenone sulfoxides, which are more powerful Michael acceptors, afforded addition products in good yield and excellent stereoselectivity with 1-tetralones [40–42]. In a preliminary experiment the racemic Posner cyclopentenone sulfoxide afforded the addition product in 51% yield as a mixture of 5 diastereomers. The related α,β-unsaturated sulfones, which are widely used as building blocks in synthetic organic chemistry, would be even more active Michael acceptors than sulfoxides. Thus, we studied the application of the sulfone 2-[(4-methylphenyl)sulfonyl]-2-cyclopenten-1-one **10** in Michael addition reactions according to the retrosynthetic pathway outlined in Scheme 3. When A,B- and D-rings are linked (shown as a bold bond in Scheme 3), the formed sulfone can be transformed into natural 9,11-secosterol substituents and side chains according to known procedures (e.g. Refs. [41–43], and references cited therein).



Scheme 2. Model reactions for A,B- and D-ring linking.



Scheme 3. A,B- and D-ring linking with cyclopentenone sulfone **10**.



Scheme 6. The key intermediate **15** from Michael addition reaction of **14** to **10**.

2.2. Synthesis of the D-ring precursor for the Michael addition

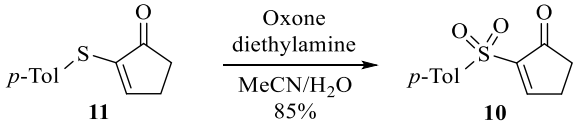
Thus, sulfone 2-[(4-methylphenyl)sulfonyl]cyclopent-2-en-1-one **10** was synthesized from sulfide **11** according to Scheme 4. There is a known two-step procedure for the synthesis of sulfone **10** from sulfide **11** in order to avoid oxidation of the double bond. We found that sulfone **10** can be more easily synthesized from sulfide **11** in one step in 85% yield using Oxone as an oxidant [44], so that the double bond was not affected.

A Michael donor **12** has been synthesized according to the procedure described by us earlier [35]. The acetyl protecting groups in **12** were not suitable for enolate generation with LiHMDS, so these were changed to the TBS groups (Scheme 5). Thus, the acetyl groups were removed in acid-catalyzed hydrolysis to give the diol **13**, because the basic hydrolysis in the presence of K_2CO_3 in methanol afforded a complex mixture of several by-products together with the target compound. Diol **13** was silylated according to a standard procedure to afford disilylated product **14** in 63% total yield for two steps. When the diol **13** was isolated and the reactions performed separately, the yields were 75% and 87%, respectively not giving any big advantages.

2.3. Linking the A,B- and D-rings

When both the suitable Michael donor **14** and the acceptor **10** were in hand, we performed the Michael addition reaction under standard conditions: LiHMDS was generated *in situ* from *n*-BuLi and HMDS, the reaction was started at −78 °C for 1.5 h and continued at room temperature overnight (Scheme 6).

Sulfone **10** reacted readily with the enolate generated from **14**, affording **15** in 74% yield as a mixture of the two main diastereomers with a ratio of 1:1. To our delight the diastereomers were separable by crystallization from an EtOAc : hexane mixture. Furthermore, the diastereomeric purity (determined by ^{1}H NMR)



Scheme 4. Activated Michael acceptor **10** from sulfide **11**.

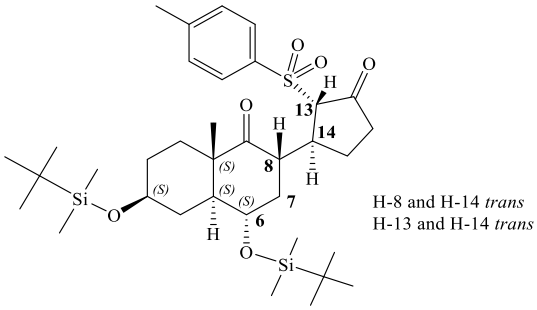
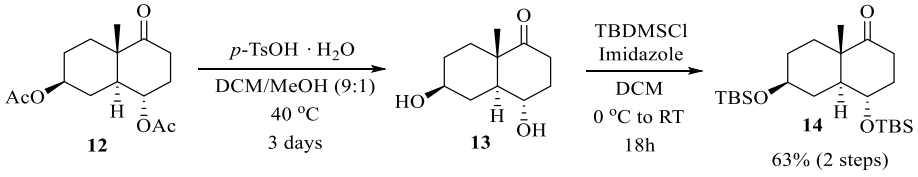


Fig. 1. Relative configuration of **15**.

can be increased by recrystallization - after recrystallization the isolated diastereomer was separated in at least 95% purity.

The crystallized diastereomer **15** was further studied by NMR spectroscopy to determine its relative configuration. The configuration of the all-*S* isomer (Fig. 1) was determined after the structural analysis from NMR spectra (^{1}H and ^{13}C, ^{1}H COSY, ^{1}H−^{13}C HSQ and HMBC). ^{1}H NOESY spectra were interpreted by UFF MM calculations (ArgusLab 4.0.1). Spin-spin coupling information from H-8 to H-7$_{axial}$ showed a value of 14.0 Hz, indicating its axial (β) orientation, which is also confirmed by a strong NOESY correlation peak from the C-10 methyl protons. The *S*-configuration of C-8 limited the number of remaining candidates for the separated isomer from C-8 to C-14. Geometry optimization of these isomers afforded two, with C−8H to C−14H dihedral angles close to 180° (one with *cis*- and another with *trans*-orientation of H-13 and H-14 in the five-membered ring). The observed three-bond vicinal coupling constant between H-8 and H-14 was 3.8 Hz, which suggests a close to gauche dihedral angle. The final choice between all-*S* and 14-*epi* (14-*R*) isomers was made based on a NOESY experiment, in which strong correlation peaks were observed between H-13 and H-7$_{axial}$ and 7$_{equatorial}$ (7-α and 7-β) protons. This corresponds to an all-*S* configuration of the separated isomer. The excluded 14-*epi* isomer was thermodynamically the most unstable from the 8 calculated isomers of this secosterol.

Further synthesis towards the compounds of 9,11-secosterols family will involve the substitution of the sulfone group with appropriate alkyl groups and side chain synthesis at the C-17 position, both of which have been described previously (e.g Refs. [41–43]) and are ongoing in our laboratory.



Scheme 5. Synthesis of Michael donor **14**.

3. Conclusions

These results prove that the use of sulfone **10** as a strong Michael acceptor in the appropriate coupling reaction is feasible for constructing the A,B- and D-ring link in 9,11-secosterols, giving two diastereomers, which are easily separable by crystallization. These results can be considered a formal total synthesis of 9,11-secosterols as the following manipulations of the D-ring are known from sterol chemistry [41–43]. We also confirmed have the separated diastereomer has the relative configurations corresponding to the 9,11-secosterol stereochemistry at positions C-8 and C-14.

4. Experimental section

Pre-coated silica gel 60 F_{254} plates were used for TLC, and for column chromatography silica gel ThoMar Kieselgel 60 extra fine (40–63 μm) was used. Reactions were conducted under an argon atmosphere in oven-dried glassware. Anhydrous CH_2Cl_2, acetone and EtOAc were freshly distilled from P_2O_5. Anhydrous THF was distilled from sodium/benzophenone under argon before use. Dichloromethane was kept on 4 Å molecular sieves until use. The petroleum ether used had a boiling point range of 40–60 °C. Other solvents and commercial reagents were used as received.

Full assignment of ^{1}H and ^{13}C chemical shifts were based on the 1D and 2D FT NMR spectra measured with a Bruker Avance III 400 MHz or a Bruker Avance III 800 MHz instrument. Residual solvent signals were used ($CDCl_3$: δ = 7.26 ^{1}H NMR, δ = 77.2 ^{13}C NMR) as internal standards. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500. IR spectra were obtained using a PerkinElmer Spectrum BX FT-IR spectrometer. High-resolution mass spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass QTOF LC/MS spectrometer by using ESI ionization. Mass spectra were recorded on Shimadzu GCMS-QP2010 spectrometer using EI ionization (70 eV). Gas chromatographic analysis has been performed with a Shimadzu GC-2010 FID instrument, using Agilent DB-5 capillary column (25 m × 0.25 mm, film thickness 0.25 μm).

4.1. 2-Cyclopentylcyclohex-2-en-1-one **6**

To a stirred suspension of zinc dust (374 mg, 5.71 mmol, 4 eq) in THF (3.2 mL), two drops of 1,2-dibromoethane were added. The mixture was heated for 20 min at 60 °C, then three drops of Me_3SiCl were added and the mixture was stirred for an additional 20 min at 60 °C. The bromocyclopentane **5** (0.31 mL, 2.86 mmol, 2 eq) was added dropwise, and the mixture was stirred overnight at 50 °C. The unreacted zinc was allowed to settle down, the solution of zinc reagent was syringed away from the excess zinc and was added to a separate flask containing bromocyclohex-2-en-1-one **4** (250 mg, 1.43 mmol, 1 eq), Pd_2 (dba)$_3$ (8.2 mg, 0.014 mmol, 0.01 eq) and Q-Phos (20.3 mg, 0.029 mmol, 0.02 eq) in THF (1.4 mL). The resulting mixture was stirred at 50 °C for 24 h. The reaction was quenched by the addition of saturated NH_4Cl solution (3 mL) and subsequently extracted with EtOAc (2 × 8 mL and then 1 × 5 mL). The extracts were dried (Na_2SO_4) and the solvents were evaporated. The residue was purified by flash column chromatography (silica gel, 10% acetone/petroleum ether) yielding 206.8 mg product **6** (88%) as a red-orange oil (contaminated with Q-Phos, GC purity 90%).

Note 1: According to the ^{1}H NMR analysis of the reaction mixture, the conversion of compound **4** is 95%.

Note 2: In the case of 2-bromo-1,1-dimethylcyclopentane, no reaction occurred and starting compounds were detected in the mixture.

R_f = 0.73 (10% acetone/petroleum ether; UV, *p*-anisaldehyde); IR (neat film) ν_{max} (cm^{-1}): 2950, 2868, 1675, 1454, 1381, 1250, 1173, 1108, 903; MS *m/z* (EI): 164 (M^+), 149, 135, 121, 108, 95, 79, 67, 53, 43; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.71 (t, *J* = 4.3 Hz, 1H), 2.93–2.79 (m, 1H), 2.42 (dd, *J* = 7.5, 5.9 Hz, 2H), 2.35 (tdd, *J* = 5.9, 4.2, 1.4 Hz, 2H), 1.96 (dq, *J* = 8.0, 6.1 Hz, 2H), 1.89–1.80 (m, 2H), 1.76–1.54 (m, 4H), 1.33–1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.7, 143.3, 142.2, 39.0, 38.9, 32.0 (2xCH_2), 26.1, 25.1 (2xCH_2), 23.1; GC: t_R 11.305 min (temperature program: rate 12 °C/min, from 60 °C (2 min hold isothermally) to 250 °C; carrier gas He).

4.2. 2-[(4-methylphenyl)sulfonyl]-2-cyclopenten-1-one **10**

To a well-stirred solution of thioether **11** (1.13 g, 5.51 mmol, 1 eq) and diethylamine (80.6 mg, 1.10 mmol, 0.2 eq) in acetonitrile (14 mL) was added a solution of Oxone (5.9 g, 9.65 mmol, 1.75 eq) in water (26 mL). Stirring was continued and the reaction was monitored by TLC. Upon completion of the reaction (ca 1.5 h), the mixture was diluted with cold water. The resultant sulfone **10** was filtered, washed with water and dried, affording the pure sulfoxide as pale yellow solid (1.11 g, 85%). The spectral data matched those found in literature [40,45–47].

R_f = 0.57 (40% acetone/petroleum ether; UV, *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.46 (t, *J* = 2.7 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.80 (dt, *J* = 7.5, 2.7 Hz, 2H), 2.56–2.52 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.1, 170.5, 147.3, 145.3, 136.1, 129.8, 128.8, 36.0, 26.8, 21.8.

4.3. (4S,4aS,6S,8aS)-4,6-dihydroxy-8a-methyloctahydronaphthalen-1(2H)-one **13**

The diacylated A,B-fragment **12** (985 mg, 3.49, 1 eq) was dissolved in CH_2Cl_2/MeOH (9:1, 23.4 mL) and then *p*-TsOH·H_2O (1.33 g, 6.98 mmol, 2 eq) was added. The resulting mixture was stirred overnight at 40 °C. After the reaction was completed, the mixture was poured into a separation funnel and washed with aqueous $NaHCO_3$ (10 mL). The water layer was extracted with EtOAc (9 × 8 mL) and the collected organic phase was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The product **13** was purified by flash column chromatography (silica gel, 50% acetone/petroleum ether) yielding 521.9 mg (75%) of product **13** as a colorless oil.

R_f = 0.38 (50% acetone/petroleum ether; *p*-anisaldehyde); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.85 (td, *J* = 10.3, 4.4 Hz, 1H), 3.52 (tt, *J* = 10.1, 4.6 Hz, 1H), 2.87 (br, 2H), 2.72 (td, *J* = 15.2, 6.8 Hz, 1H), 2.35–2.24 (m, 2H), 2.20 (ddd, J = 9.6, 4.5, 2.2 Hz, 1H), 1.92–1.81 (m, 1H), 1.73–1.54 (m, 2H), 1.54–1.27 (m, 4H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 214.3, 70.4, 67.9, 49.3, 46.4, 35.6, 35.0, 32.3, 31.4, 31.1, 17.0.

4.4. (4S,4aS,6S,8aS)-4,6-bis((tert-butyldimethylsilyl)oxy)-8a-methyloctahydronaphthalen-1(2H)-one **14**

A solution of diol **13** (510 mg, 2.57 mmol, 1 eq) and imidazole (1.05 g, 15.43 mmol, 6 eq) in CH_2Cl_2 (10.3 mL) was cooled to 0 °C and then TBDMSCl (1.56 g, 10.29 mmol, 4 eq) was added in three portions over a 30 min interval under argon atmosphere. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and stirred overnight. Water (21 mL) was added, CH_2Cl_2 layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 13 mL). The combined extracts were washed with brine (13 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (silica gel, 10% acetone/petroleum ether) to give target compound **14** as a white solid (958.4 mg, 87%).

R_f = 0.67 (15% acetone/petroleum ether; *p*-anisaldehyde); ^{1}H

NMR (400 MHz, $CDCl_3$): δ (ppm) 3.81 (td, J = 10.2, 4.7 Hz, 1H), 3.48 (tdd, J = 10.5, 7.4, 4.8 Hz, 1H), 2.70 (td, J = 14.7, 6.6 Hz, 1H), 2.26 (ddd, J = 15.0, 5.4, 2.6 Hz, 1H), 2.14 (ddtd, J = 15.5, 12.9, 4.8, 2.5 Hz, 2H), 1.75 (ddt, J = 12.6, 5.0, 2.3 Hz, 1H), 1.64 (dddd, J = 14.4, 7.6, 6.1, 3.5 Hz, 2H), 1.52–1.37 (m, 2H), 1.34–1.21 (m, 2H), 1.13 (s, 3H), 0.89 (d, J = 5.1 Hz, 18H), 0.06 (dd, J = 11.5, 2.6 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 214.5, 71.6, 68.9, 49.6, 46.6, 35.7, 35.5, 33.3, 31.7, 31.1, 26.0 (3xCH_3), 25.9 (3xCH_3), 18.4, 18.2, 17.2, −4.0, −4.5, −4.6, −4.7; HRMS: for $C_{23}H_{46}O_3Si_2$, $[M+H]^+$ calculated 427.3058, found 427.3052.

Note: Deacylation and disilylation can be performed sequentially without purifying the intermediate diol **13**. In this case, the overall yield of **14** is 63% (1.10 g) starting from 1.15 g of diacylated A,B-fragment **12**.

4.5. (4S,4aS,6S,8aS)-4,6-bis((tert-butyldimethylsilyl)oxy)-8a-methyl-2-(3-oxo-2-tosyl-1λ^3,2λ^3-cyclopentyl) octahydronaphthalen-1(2H)-one **15**

Into a dry flask was placed HMDS (0.24 mL, 1.16 mmol, 1.1 eq) and THF (3 mL). The solution was cooled to −78 °C and treated dropwise with *n*-BuLi (2.5 M in hexanes, 0.46 mL, 1.16 mmol, 1.1 eq). Stirring was continued at −78 °C for 30 min, the mixture was warmed to room temperature and then cooled back to −78 °C. To recooled mixture, A,B-fragment **14** (450.7 mg, 1.06 mmol, 1 eq) solution in THF (1.5 mL + 0.5 mL for rinsing) was added dropwise. After being stirred for 1.5 h at −78 °C, sulfone **10** (274.5 mg, 1.16 mmol, 1.1 eq) solution in THF (2.5 mL + 0.5 mL for rinsing) was added, then mixture was warmed to room temperature and left to stir overnight. Saturated NH_4Cl solution (1 mL) was added and then extracted with DCM (3 × 1 mL). The organic extract was dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, gradient 5%–40% acetone/petroleum ether) to give target compound **15** as a white solid (519,7 mg, 74%) as mixture of two diastereomers (ca 1:1 by NMR). The diastereomers can be separated by recrystallization - the compound is dissolved in a minimal amount of EtOAc, then an equal amount of *n*-hexane is added and the mixture is cooled to +4 °C for 24 h. The separated crystals of **15** are analyzed.

R_f = 0.55 (20% acetone/petroleum ether; UV, *p*-anisaldehyde); ^{1}H NMR (800 MHz, $CDCl_3$): δ (ppm) 7.75–7.67 (m, 2H), 7.39–7.33 (m, 2H), 3.87 (td, J = 10.3, 10.3, 4.6 Hz, 1H), 3.50–3.43 (m, 2H), 3.27 (ddd, J = 14.0, 5.8, 3.2 Hz, 1H), 3.20 (dtd, J = 8.7, 7.0, 6.4, 3.2 Hz, 1H), 2.45 (s, 3H), 2.44–2.40 (m, 2H), 2.37–2.30 (m, 1H), 2.14 (ddd, J = 12.9, 5.8, 3.2 Hz, 1H), 2.11 (ddt, J = 12.4, 4.8, 2.5 Hz, 1H), 1.78–1.71 (m, 1H), 1.57 (dd, J = 10.1, 2.8 Hz, 1H), 1.55–1.45 (m, 2H), 1.44–1.36 (m, 3H), 1.31–1.25 (m, 1H), 1.13 (s, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.10 (d, J = 4.3 Hz, 6H), 0.04 (d, J = 3.3 Hz, 6H); ^{13}C NMR (201 MHz, $CDCl_3$): δ (ppm) 213.9, 206.4, 145.5, 134.6, 130.0, 129.4, 72.4, 71.4, 68.7, 50.3, 46.8 (2x), 39.4, 38.2, 37.1, 33.2, 31.5, 31.1, 26.0 (2x), 23.8, 21.9, 18.4, 18.2, 17.5, −4.0, −4.5, −4.6, −4.7; HRMS: for $C_{35}H_{58}O_6SSi_2$, $[M+H]^+$ calculated 663.3565, found 663.3551; $[\alpha]^{25}_D$ = +37.7633 (*c* 0.424, $CHCl_3$).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] E.L. Enwall, D. van der Helm, I.N. Hsu, T. Pattabhiraman, F.J. Schmitz, R.L. Spraggins, A.J.J.C.S. Weinheimer, Chem. Commun. (J. Chem. Soc. Sect. D) (1972) 215–216.
[2] R. Koljak, A. Lopp, T. Pehk, K. Varvas, A.-M. Müürisepp, I. Järving, N. Samel, Tetrahedron 54 (1998) 179–186.
[3] R. Koljak, T. Pehk, I. Järving, M. Liiv, A. Lopp, K. Varvas, A. Vahemets, Ü. Lille, N. Samel, Tetrahedron Lett. 34 (1993) 1985–1986.
[4] A. Lopp, A. Pihlak, H. Paves, K. Samuel, R. Koljak, N. Samel, Steroids 59 (1994) 274–281.
[5] H. He, P. Kulanthaivel, B.J. Baker, K. Kalter, J. Darges, D. Cofield, L. Wolff, L. Adams, Tetrahedron 51 (1995) 51–58.
[6] Y.-C. Chang, T.-L. Hwang, L.-M. Kuo, P.-J. Sung, Mar. Drugs 15 (2017) 11–21.
[7] Y.-C. Chang, T.-L. Hwang, C.-H. Chao, P.-J. Sung, Molecules 22 (2017) 393–400.
[8] I. Yang, H. Choi, S.-J. Nam, H. Kang, Arch Pharm. Res. (Seoul) 38 (2015) 1970–1974.
[9] I. Yang, H. Choi, D.H. Won, S.-J. Nam, H. Kang, Bull. Kor. Chem. Soc. 35 (11) (2014) 3360–3362.
[10] H. Li, S. Matsunaga, N. Fusetani, Experientia 50 (1994) 771–773.
[11] W.E. Bachmann, W. Cole, A.L. Wilds, J. Am. Chem. Soc. 61 (1939) 974–975.
[12] Z. Wang, C. Hui, Org. Biomol. Chem. 19 (2021) 3791–3812.
[13] C.F. Nising, S. Bräse, Angew. Chem. Int. Ed. 47 (2008) 9389–9391.
[14] E.G. Mackay, M.S. Sherburn, Synthesis 47 (1) (2015) 1–21.
[15] N.R. Cichowicz, W. Kaplan, Y. Khomutnyk, B. Bhattarai, Z. Sun, P. Nagorny, J. Am. Chem. Soc. 137 (45) (2015) 14341–14348.
[16] Y.-Y. Yeung, R.-J. Chein, E. Corey, J. *J. Am. Chem. Soc.* 129 (34) (2007) 10346–10347.
[17] R. Skoda-Földes, L. Kollár, Chem. Rev. 103 (10) (2003) 4095–4130.
[18] M. Kotora, F. Hessler, B. Eignerová, Eur. J. Org. Chem. (2012) 29–42.
[19] H.R. Khatri, N. Carney, R. Rutkoski, B. Bhattarai, P. Nagorny, Eur. J. Org. Chem. (2020) 755–776.
[20] D. Czajkowska-Szczykowska, J.W. Morzycki, A. Wojtkielewicz, Steroids 97 (2015) 13–44.
[21] K.S. Halskov, B.S. Donslund, S. Barfüsser, K.A. Jørgensen, Angew. Chem. Int. Ed. 53 (2014) 4137–4141.
[22] F.C.E. Sarabèr, A. de Groot, Tetrahedron 62 (2006) 5363–5383.
[23] M. Donova, Microorganisms 10 (2022) 53–59.
[24] L. Fernández-Cabezón, B. Galán, J.L. García, Front. Microbiol. 9 (2018) 958.
[25] R.A. Yoder, J.N. Johnston, Chem. Rev. 105 (12) (2005) 4730–4756.
[26] J.F. Quílez del Moral, Á. Pérez, A.F. Barrero, Phytochemistry Rev. 19 (2020) 559–576.
[27] R. Jäälaid, I. Järving, T. Pehk, Ü. Lille, Proc. Est. Acad. Sci., Chem. 47 (1998) 196–199.
[28] R. Jäälaid, I. Järving, T. Pehk, O. Parve, Ü. Lille, Nat. Prod. Lett. 15 (2001) 221–228.
[29] A. Migliuolo, V. Piccialli, D. Sica, Tetrahedron 47 (37) (1991) 7937–7950.
[30] R. Adinolfi, A. Migliuolo, V. Piccialli, D. Sica, J. Nat. Prod. 57 (9) (1994) 1200–1226.
[31] A. Kuhl, W. Kreiser, Tetrahedron Lett. 39 (1998) 1145–1148.
[32] A. Kuhl, W. Kreiser, Collect. Czech Chem. Commun. 63 (1998) 1007–1011.
[33] B. Kongkathip, A. Hasakunpaisarn, S. Boonananwong, N. Kongkathip, Steroids 75 (2010) 834–847.
[34] F. Noack, R.C. Heinze, P. Heretsch, Synthesis 51 (2019) (A-S).
[35] R. Aav, T. Kanger, T. Pehk, M. Lopp, Synlett 4 (2000) 529–531.
[36] M. Kõllo, R. Aav, S. Tamp, J. Jarvet, M. Lopp, Tetrahedron 70 (38) (2014) 6723–6727.
[37] M. Kõllo, M. Kasari, V. Kasari, T. Pehk, I. Järving, M. Lopp, A. Jõers, T. Kanger, Beilstein J. Org. Chem. 17 (2021) 581–588.
[38] F.C.E. Sarabèr, S. Dratch, G. Bosselaar, B.J.M. Jansen, A. de Groot, Tetrahedron 62 (2006) 1717–1725.
[39] F.C.E. Sarabèr, A. Baranovsky, B.J.M. Jansen, M.A. Posthumus, A. de Groot, Tetrahedron 62 (2006) 1726–1742.
[40] G.H. Posner, J.P. Mallamo, M. Hulce, L.L. Frye, J. Am. Chem. Soc. 104 (1982) 4180–4185.
[41] G.H. Posner, C. Switzer, J. Am. Chem. Soc. 108 (1986) 1239–1244.
[42] G.H. Posner, Acc. Chem. Res. 20 (1987) 72–78.
[43] B.B. Shingate, B.G. Hazra, Chem. Rev. 114 (2014) 6349–6382.
[44] R.V. Kupwade, S.S. Khot, U.P. Lad, U.V. Desai, P.P. Wadgaonkar, Res. Chem. Intermed. 43 (2017) 6875–6888.
[45] M. Hulce, J.P. Mallomo, L.L. Frye, T.P. Kogan, G.H. Posner, Org. Synth. 64 (1986) 196.
[46] N. Mase, Y. Watanabe, Y. Ueno, T. Toru, J. Org. Chem. 62 (1997) 7794–7800.
[47] J.L.G. Ruano, C. Fajardo, A. Fraile, M.R. Martín, J. Org. Chem. 70 (2005) 4300–4306.