Proceedings of the Estonian Academy of Sciences,
2024, **73**, 3, 223–227
https://doi.org/10.3176/proc.2024.3.06
Available online at www.eap.ee/proceedings

ASYMMETRIC SYNTHESIS

The applicability of sulfoxide Michael acceptor – 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one in constructing the carbon skeleton of 9,11-secosterols

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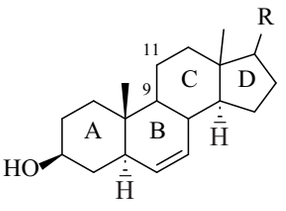
Received 23 August 2023, accepted 2 November 2023, available online 16 August 2024

Abstract. A possibility of use of the Michael addition reaction of the A,B-ring fragment enolate to sulfoxide 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one for constructing the main skeleton of 9,11-secosterols was studied. The reaction was conducted with the racemic or the enantiomerically enriched sulfoxide as the acceptor, affording a mixture of five or three main diastereomers, respectively. It was shown that the diastereoselectivity of that addition reaction is relatively low and does not afford a competitive new route for the total synthesis of secosterols.

Keywords: Michael addition, sulfoxides, 9,11-secosterols.

INTRODUCTION

Secosterols are compounds of the sterol family that bear a cleaved ring in the steroid tetracyclic nucleus. 9,11-Secosterols are a subtype of sterols that have a cleaved bond between the 9th and the 11th carbon in the C-ring.



Sterols

Scheme 1. The structure of sterols.

9,11-Secosterols were first discovered at the beginning of the 1990s [1–3]. Secosterol **1** was isolated from the soft coral *Gersemia fruticosa* by the Lille research team at the same time [4]. In fact, the majority of these secosteroids have been isolated from marine organisms, such as sponges, gorgonians and soft corals [5]. 9,11-Secosterols exhibit various biological activities, such as cytotoxic, antiproliferative [4,6,7], apoptosis induction [7,8], anti-inflammatory [9–11], antihistaminic [12], antibacterial [13,14] and antifungal [15] ability. These properties make them attractive lead compounds for the development of new drug candidates.

The first semi-synthetic pathway to secosterols, starting from natural sterols, was elaborated by the Sica group [16]. Later, Lille and several other research groups have developed a number of semi-synthetic schemes [17–24]. Recently, we used a whole-cell-catalysis-assisted synthesis of 9,11-secosterols [25]. With the ever-growing number of new 9,11-secosterol structures and with the need to test these structures, a more general total synthesis pathway was required. Therefore, we have recently developed a

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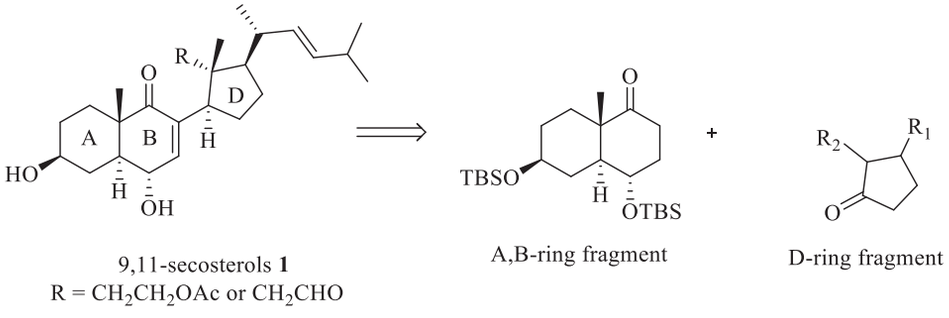
general total synthesis scheme for 9,11-secosterols [26]. Our strategy consists of preparing the A,B-ring and D-ring fragments separately and then connecting them by an appropriate addition reaction, as it is presented in Scheme 2.

The syntheses of the A,B-ring and D-ring fragments were solved successfully some years ago [27,28]. The connection of these two substituted fragments, however, was not a straightforward task. The problem was finally solved by using sulfone-activated cyclopentanones [26]. Now we have turned our attention to the works of Posner and colleagues, who have demonstrated that enantiomeric cyclopentenone sulfoxides **3** can also act as Michael acceptors, allowing, in certain cases, the generation of a new C-C bond in good yield and stereoselectivity [29–31]. The requisite enantiomerically enriched sulfoxide **3** can be prepared from the corresponding sulfide by using the titanium(IV)isopropoxide (Ti(*i*PrO)$_4$)/(+)-diethyl L-tartrate ((+)-DET)/tert-butyl hydroperoxide (TBHP) complex, according to Modena et al. [32,33], resulting in (+)-**3** with *ee* 99% after recrystallization.

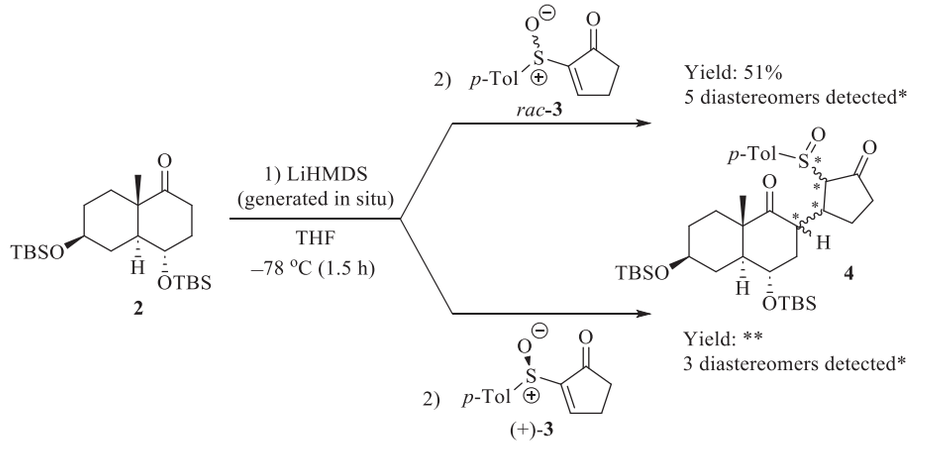
Thus, we decided to use the enantiomerically enriched A,B-ring precursor **2** and both the racemic and enantiomerically enriched D-ring precursor 2-[(4-methylphenyl) sulfinyl]-2-cyclopenten-1-one (*rac*-**3** and (+)-**3**) in constructing the 9,11-secosterol skeleton.

RESULTS AND DISCUSSION

Both the racemic sulfoxide *rac*-**3** and enantiomerically enriched sulfoxide (+)-**3** were prepared according to [33]. The Michael addition reaction was performed according to Scheme 3 by using standard conditions from [26]. The reaction of *rac*-**3** gave Michael addition product **4** in 51%



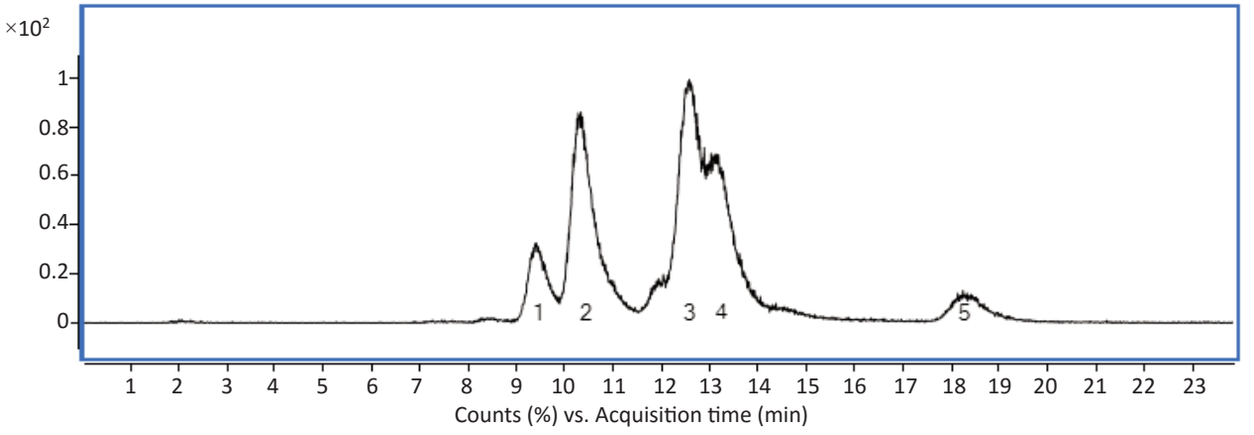
Scheme 2. Retrosynthetic analysis of the total synthesis of 9,11-secosterols.



* according to HPLC-HRMS

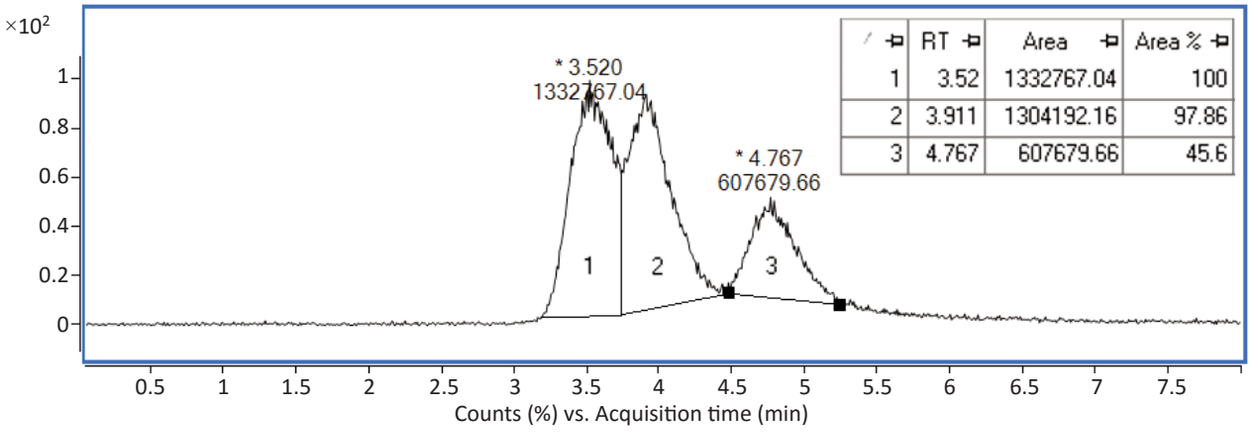
** according to HPLC-HRMS analysis, the crude mixture contained compounds **2**, (+)-**3** and **4** with 53%, 5% and 41%, respectively

Scheme 3. The Michael addition reactions of **2** with *rac*-**3** and with (+)-**3** gave Michael product **4**.



* HPLC: Agilent C18, 88% MeOH:H_2O(0.05% HCOOH) 88:12, 0.2 mL/min, 230 nm: 1. diastereomer 9.4 min, 2. diastereomer 10.3 min, 3. diastereomer 12.5 min, 4. diastereomer 13.0 min, 5. diastereomer 18.2 min.

Fig. 1. HPLC chromatogram* of the mixture of diastereomers obtained when using *rac*-**3**.



	RT	Area	Area %
1	3.52	1332767.04	100
2	3.911	1304192.16	97.86
3	4.767	607679.66	45.6

* HPLC: Zorbax Eclipse Plus C18 Rapid Resolution HD, 85% MeOH:H_2O(0.05% HCOOH) 85:15, 0.2 mL/min, 210 nm: 1. diastereomer 3.5 min, 2. diastereomer 3.9 min, 3. diastereomer 4.8 min.

Fig. 2. HPLC chromatogram* of the diastereomers obtained from the reaction with (+)-**3**.

yield as a mixture of five main diastereomers according to HPLC-HRMS (Fig. 1). The structure of the main isomers was confirmed by ^{1}H and ^{13}C NMR spectra of the mixture, considering the spectra of the corresponding sulfones from our previous publication [28]. It was not possible to determine the exact ratio of the diastereomers due to overlapping peaks in both the chromatogram and the NMR spectra. It was concluded that the process is partly diastereoselective, but the stereoselectivity is not sufficient.

The same reaction with the enantioenriched sulfoxide (+)-**3** (*ee* 97%) resulted in a mixture of three diastereomers with approximate ratios 2:2:1, according to HPLC-HRMS (Fig. 2), and in 41% yield. The ^{1}H and ^{13}C spectra were similar to those obtained from the previous reaction. Additionally, the crude mixture contained the unreacted starting materials **2** (in 53%) and (+)-**3** (in 5%). The stereoinduction of the sulfoxide group is not sufficient to afford a stereoselective Michael addition reaction.

CONCLUSIONS

We demonstrated that sulfoxide **3** as a Michael acceptor is not superior to the corresponding sulfone in the connection reaction of the A,B- and D-rings in 9,11-seco-

sterols due to the low stereoselectivity. In fact, sulfoxide **3** does not offer any benefit. At the same time, the use of sulfones affords a mixture of two easily separable diastereomers in good yield, and, as a result, a simple method for the total synthesis of 9,11-secosterols is achieved, as described in our recent article [28].

NOTES

1. 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 instrument. Residual solvent signals were used ($CDCl_3$: δ = 7.26 ^{1}H NMR, δ = 77.2 ^{13}C NMR) as internal standards. HPLC-HRMS spectra were recorded with an Agilent Technologies 6540 UHD Accurate-Mass QTOF LC/MS spectrometer by using ESI ionization. (4*S*,4*αS*,6*S*,8*αS*)-4,6-*bis*((*tert*-butyldimethylsilyl)oxy)-8α-methyl-2-(3-oxy-2-(*p*-tolylsulfinyl)cyclopentyl) octahydronaphtalene-1(2H)-one **4** was obtained as a yellow solid. It was identified as a mixture of five diastereomers by HPLC-HRMS. For $C_{35}H_{58}O_5SSi_2$, $[M+H]^+$ calculated 647.3896, found 647.3616. R_f = 0.46 (20% acetone/petroleum ether; UV 254, *p*-anisaldehyde). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 210.57, 209.71, 202.86, 131.96, 130.89, 130.33, 130.20, 123.92, 73.99, 71.34, 68.54, 68.28, 50.35, 49.67, 47.63, 47.41, 46.81, 40.57, 35.44, 32.08, 31.65, 31.06, 30.43, 29.51, 26.01, 25.98, 25.92, 25.90, 22.84, 20.26, 18.39, –4.00, –4.11, –4.53, –4.66.

ACKNOWLEDGMENTS

We thank the Estonian Ministry of Education and Research (grants No. PRG657 and No. PRG1031), the Centre of Excellence in Molecular Cell Engineering (grant No. 2014-2020.4.01.15e0013) and the European Regional Development Fund (grant No. 2014-2020.4.02.16-0050) for supporting this work. The publication costs of this article were covered by the Estonian Academy of Sciences.

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