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Synthesis of 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one, a D-ring precursor of 9,11-secosterols

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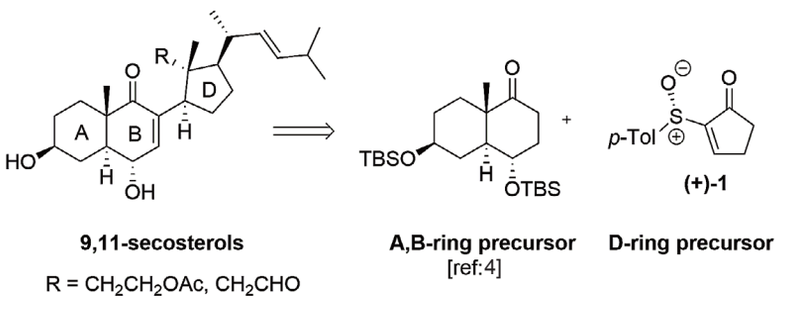
Abstract. The asymmetric oxidation of a key intermediate for 9,11-secosterol synthesis, 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** with a Ti(*i*PrO)$_4$/(+)-DET/TBHP complex was studied. The kinetic resolution of racemic 2-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** by oxidation with the same Ti-complex was also carried out. In both cases enantioenriched 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** was obtained in satisfactory yields and sufficient enantiomeric purity for further enantioenrichment by recrystallization. The obtained results afford simple access to the D-ring precursor of 9,11-secosterols.

Keywords: asymmetric oxidation of sulfide, titanium-catalytic oxidation, enantiomeric sulfoxide, 9,11-secosterols.

INTRODUCTION

Since the discovery of highly bioactive 9,11-secosterols [1–3], our research group has been involved in the elaboration of the chemical access to that family of compounds [4–8]. In eighties of the last century Posner et al. demonstrated that substituted cyclopentenone sulfoxides can be used as Michael acceptors for 1-tetralone enolates [9–11]. Therefore, we envisioned using the title compound 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** in constructing A,B- and D-ring connections of 9,11-secosterols in a stereochemically appropriate form (Scheme 1). As demonstrated below, the chiral-activated cyclopentenone **1** would act as a D-ring precursor and chiral auxiliary, allowing us to construct the D-ring of 9,11-secosterols in stereoselective manner.

Synthesis of the chiral nonracemic sulfoxides can be performed by using the asymmetric oxidation of sulfides



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

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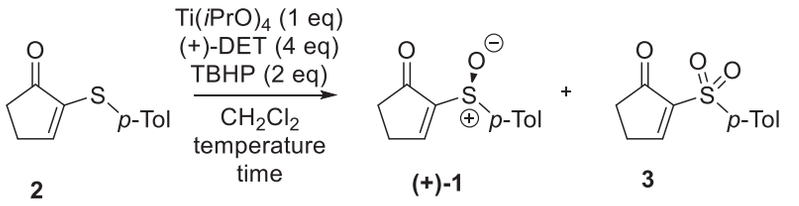
Table 1. Oxidation of 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** with Ti(*i*PrO)$_4$/(+)-DET/TBHP complex



Entry	Additives	Temperature °C and time	**2**, recovered, %	Yield, %; (*ee*)	
				1	**3**
1	–	–20; 24 h	100	–	–
2	4Å MS	–20; 72 h	75	18; (22)	–
3	4Å MS	[a]	–	24; (48)	41
4	4Å MS	[b]	21	33; (62)	26
5	4Å MS	[c]	50	20; (13)	–

[a] Temperature –20 °C for 24 h, then r.t. for 24 h;
[b] Temperature –20 °C for 0.5 h, then +4 °C for 98 h;
[c] Temperature –20 °C for 0.5 h, then –5 °C for 75 h.

or by the kinetic resolution of racemic sulfoxides which can be acquired from sulfides by a simple single step. For the stereoselective asymmetric oxidation of sulfur a titanium catalyst complex with enantiomeric C_2-symmetrical diol ligand (most frequently tartaric esters) with peroxy-oxidant is commonly used [12–17]. The biological approaches for the same reaction generally include the usage of various monooxygenases (e.g. prazole sulfide monooxygenase [18], cyclohexanone monooxygenase [19] and Baeyer–Villiger monooxygenase [20]) and sulfoxide reductases [21–23]. Both aforementioned biochemical approaches have limited scope in total chemical synthesis, thus the oxidation of other substrates than aryl methyl or prazole sulfides is still a challenge.

2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** is usually acquired by the Andersen method, which involves a reaction between a chiral sulfinate ester and a cyclic organometallic compound [9,24–27]. The described multi-step procedure however leads to the formation of unstable vinyl anion intermediates and is therefore experimentally inconvenient. In the present work we explored the synthesis of (*S*)-**1** by a direct Ti-catalyzed asymmetric oxidation of sulfide **2**, or by a kinetic resolution of racemic sulfoxide *rac*-**1**.

RESULTS AND DISCUSSION

Synthesis of enantioenriched 2-(*S*)-[(4-methylphenyl) sulfinyl]-2-cyclopenten-1-one 1 by asymmetric oxidation of 2-[(4-methylphenyl)thio]-cyclopenten-1-one 2

The starting sulfide 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** was synthesized according to known procedures [28, 29]. In our hands the best yield of sulfide **2** was only 38%, although the published yields are around 65%.

The asymmetric oxidation of sulfide **2** was performed with Ti(*i*PrO)$_4$/(+)-DET/TBHP in a ratio of 1:4:2 by using the known procedure [8]. The obtained results are presented in Table 1.

The typical known procedure [15] did not afford the expected sulfoxide **1**, and the starting sulfide **2** remained unreacted (Table 1, entry 1). This result indicates that the asymmetric oxidation of sulfides is, as expected, quite substrate-specific: for each substrate, a suitable reagent system and the suitable reaction conditions must be adopted. When 4Å molecular sieves were added to the same reagent system sulfoxide **1** was formed in 18% yield, with *ee* 22% (Table 1, entry 2). However, even after 72 h a considerable amount of the starting material remained unreacted. Therefore, a combined temperature regime – the first 24 hours at –20 °C, followed by 24 hours at room temperature – was applied (Table 1, entry 3). In these conditions, no sulfide **2** remained unreacted and the yield of sulfoxide **1** increased to 24% with 48% *ee*. In this case, a substantial amount of overoxidized product, sulfone **3** (41%), formed. To avoid overoxidation, we reduced the main reaction temperature to +4 °C, which led to the reaction mixture containing all three compounds: **1**, **2** and **3**. The yield of the target compound – sulfoxide **1** (*ee* 62%), was slightly higher than that of sulfone **3** (Table 1, entry 4). When the reaction temperature was reduced to –5 °C, no sulfone **3** was formed, however, the yield of sulfoxide **1** was also lower (20%) and, surprisingly, the enantioselectivity of the oxidation reaction also decreased (*ee* 13%; Table 1, entry 5). These unsatisfactory results forced us to explore the use of other

oxidants and chiral ligands. So, we changed the oxidant/Ti ratio and checked cumene hydroperoxide (CHP) as an oxidation agent [30] for the asymmetric oxidation of sulfide **2**. The results are presented in Table 2.

Using one equivalent of TBHP, sulfoxide **1** was formed in 28% yield and 78% *ee* (Table 2, entry 1). With two equivalents of TBHP, the yield of sulfoxide **1** slightly increased, but the selectivity decreased (33% with 62% *ee*; Table 2, entry 2). In both cases overoxidized product **3** formed in substantial amounts (19% and 26%, respectively). With a reduced amount of oxidant, more sulfide **2** remained unreacted (21% vs 36%). Although it is well known that the chlorinated solvents dichloromethane (CH_2Cl_2) and 1,2-dichloroethane are suitable for the asymmetric oxidation of sulfides [31], we got slightly better yields of both sulfoxide **1** (yield 35%; *ee* 64%) and sulfone **3** (yield 26%) with no change in selectivity (Table 2, entry 3) using toluene (with one equivalent of TBHP). This result is in good agreement with the observations that toluene does not significantly affect the outcome of the reaction [32].

When CHP was used as an oxidant, the yield of sulfoxide **1** remained low with both one and two equivalents of the oxidant. Additionally, the amount of overoxidation was similar to that with TBHP. Although, the enantioselectivity was quite high with two equivalents of CHP (Table 2, entry 4), the separation of sulfoxide **1** from the reaction mixture was complicated because of the similar chromatographic behaviors of cumyl alcohol and sulfoxide **1**.

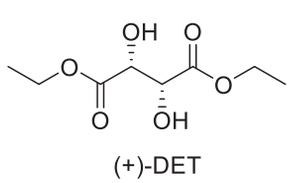
The asymmetric oxidation of sulfides is known to be sensitive to the presence of water. Pitchen et al. have found that the use of one equivalent of water increases the stereoselectivity of the reaction [12–14]. Therefore, we performed the reaction in the presence of water, molecular sieves and with other chiral ligands. The results are presented in Table 3.

Using the Ti(*i*PrO)$_4$/(+)-DET catalytic system and one or two equivalents of TBHP, one equivalent (eq.) of water or 4Å molecular sieves were added. The data reveals that the reaction did not proceed well with either one eq. of H_2O, or in dry condition with 4Å molecular sieves, affording almost no sulfoxide **1** (Table 3, entries 1 and 2). Furthermore, with (*R*)-BINOL the formation of sulfoxide **1** was not observed – we were able to isolate traces of the

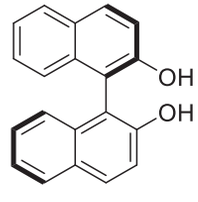
Table 2. Asymmetric oxidation of 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** with TBHP and CHP in Ti(*i*PrO)$_4$/(+)-DET system[a]

Entry	Oxidant; eq.	**2**, recovered, %	Yield, %; (*ee*)	
			1	**3**
1	TBHP; 1	36	28; (78)	19
2	TBHP; 2	21	33; (62)	26
3[b]	TBHP; 1	29	35; (64)	26
4	CHP; 2	–	19; (70)	21
5	CHP; 1	12	9; (46)	22

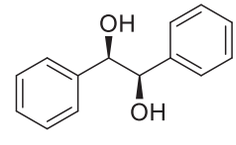
[a] Reaction conditions: Ti(*i*PrO)$_4$/(+)-DET, 1/4; at –20 °C for 30 min, then at 4 °C for 72–98 h; solvent: CH_2Cl_2;
[b] Solvent: toluene.



(+)-DET



(*R*)-(+)-BINOL



(*R*,*R*)-(+)-HB

Table 3. Oxidation of 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** in CH_2Cl_2 with different ligands

Entry	Ligand, eq.	Additives, eq.	Temperature and time	**2**, recovered %	Yield, %; (*ee*)	
					1	**3**
1	(+)-DET, 2[a]	H_2O, 1	[c]	31	4; (6)	–
2	(+)-DET, 2[b]	4Å MS	[d]	27	–	1
3	(*R*)-(+)-BINOL, 2	H_2O, 2	[e]	1	–	16
4	(*R,R*)-(+)-HB, 2	H_2O, 1	[f]	30	49; (–38)	21

[a] Ti(*i*PrO)$_4$ (1 eq.), oxidant TBHP (1 eq.);
[b] Ti(*i*PrO)$_4$ (1 eq.), oxidant TBHP (2 eq.);
[c] Temperature r.t. 0.4 h, then –20 °C for 3 h, then +4 °C for 69 h;
[d] Temperature –20 °C for 0.5 h, then +4 °C for 91 h;
[e] Temperature r.t. for 1 h, then –20 °C for 0.5 h, then +4 °C for 67 h;
[f] Temperature r.t. for 1 h, then 0 °C for 2 h, then +4 °C for 44 h.

starting sulfide **2** (1%) and a small amount of sulfone **3** (16%) (Table 3, entry 3). Using the titanium complex with (*R*,*R*)-hydrobenzoin as the chiral ligand a fast reaction was observed, leading to a moderate yield of sulfoxide **1** (49%) and sulfone **3** (21%). However, the stereoselectivity of the oxidation reaction was quite low, and the stereoisomer had opposite optical rotation (*ee* –38%; Table 3, entry 4).

As the direct asymmetric oxidation of sulfide **2** with different chiral ligands afforded a moderate yield and stereoselectivity, we decided to explore the possibility of kinetic resolution of racemic sulfoxide **1** by a stereoselective overoxidation of sulfur with the Ti(*i*PrO)$_4$/(+)-DET/TBHP complex.

Kinetic resolution of *rac*-2-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one 1

It is known that the oxidative kinetic resolution often exhibits stereoselectivity similar to the asymmetric oxidation of sulfide [33,34], and the maximum yield of sulfoxide cannot be higher than 50%. The racemic sulfoxide **1** (1 eq.) was subjected to oxidation with Ti(*i*PrO)$_4$/(+)-DET/TBHP system. The reaction was performed in the presence of 4Å molecular sieves in CH_2Cl_2 (*rac*-**1**/Ti(*i*PrO)$_4$/(+)-DET/TBHP 1/1/4/1.2). Fortunately, after 48 h of reaction, the oxidative kinetic resolution resulted in enantioenriched sulfoxide (+)-**1** with an *ee* value of 76% in 31% yield, and sulfone **3** in 43%. The obtained result is similar to that for the asymmetric oxidation of sulfide **2**; however, the isolation of the product by chromatography is simpler.

The enantiopurity of sulfoxide **1** can be considerably increased by recrystallization. We performed recrystallizations from the mixture of EtOAc/Et_2O (1:1) at +4 °C. The obtained results are presented in Table 4.

As demonstrated in Table 4, enantioenrichment occurred when the initial *ee* of sulfoxide **1** was above 64% (Table 4, entries 2 and 3). By using recrystallization, it was possible to increase the *ee* of sulfoxide **1** up to 99%. Sulfoxide **1** with a lower *ee* (51%) did not afford any enrichment by recrystallization. Additionally, recrystallization at –20 °C instead of +4 °C afforded sulfoxide **1** in 84% yield and 90% *ee* (Table 4, entry 2).

Table 4. Enantioenrichment of sulfoxide **1** by recrystallization

Entry	Starting crystals	After first recrystallization	
	ee, %	*ee*, %	Yield, %
1	51	31	2
2[a]	76	90	84
3	64	97	17
4	78	99	20

[a] Recrystallization at –20 °C

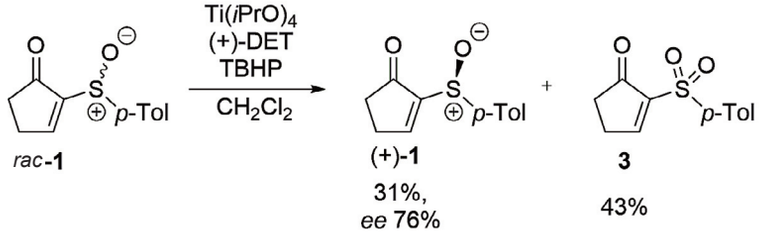
The absolute configuration of the sulfoxide **1** was established by specific rotation: according to Posner et al., the (*S*)-enantiomer of (+)-**1** has the specific rotation $[\alpha]_D^{25}$ +148 (*c* 0.11, $CHCl_3$) [9]. We obtained the value $[\alpha]_D^{25}$ +134 (*c* 0.368, $CHCl_3$). The same sign of the specific rotation allows to state that the kinetic resolution of *rac*-**1** and the asymmetric oxidation of sulfide **2** both afforded the expected (+)-enantiomer of 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1**.

CONCLUSION

We have shown that the asymmetric oxidation of 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** and the kinetic resolution of racemic sulfoxide **1** with Ti(*i*PrO)$_4$/(+)-DET/TBHP complex both afford enantioenriched sulfoxide (*S*)-**1**. These approaches can be considered as alternatives to the Andersen method. In the best cases, the obtained enantiopurity was sufficient for further enantioenrichment of sulfoxide **1** by recrystallization. The obtained results afford simple access to the D-ring precursor for 9,11-secosterol synthesis.

EXPERIMENTAL

Pre-coated silica gel 60 F254 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, Et_2O and



Scheme 2. Kinetic resolution of racemic sulfoxide 1.

EtOAc were freshly distilled from P_2O_5. Dichloromethane was kept on 4Å molecular sieves until use. The petroleum ether used had 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 was 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. Chiral HPLC was performed using Lux 3u Amylose-2 (250 x 4.6 mm) column. Optical rotations were obtained using an Anton Paar GWB Polarimeter MCP 500.

*Preparation of starting material sulfide **2***

A mixture of cyclopentanone (4.31 mL, 48.7 mmol, 2.4 eq.) and *p*-tolyl disulfide (5 g, 20.3 mmol, 1 eq.) were dissolved in DMSO (81 mL) at 80 °C in a flask, then iodine (520 mg, 2.0 mmol, 0,1 eq.) was added. The reaction mixture was stirred under air atmosphere for three days. The solution was diluted with EtOAc (162 mL), washed with H_2O (3 x 162 mL), and then the organic layer was separated and concentrated under vacuum. The crude product was purified by column chromatography (20% acetone/petroleum ether) to provide 2-[(4-methylphenyl) thio]-2-cyclopenten-1-one **2** (3.16 g, 38%). The spectral data matched those found in the literature [20,21].

2-[(4-methylphenyl)thio]-2-cyclopenten-1-one 2

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45–7.33 (m, 2H), 7.19 (d, J=7.9 Hz, 2H), 6.85 (t, J=3.0 Hz, 1H), 2.63–2.56 (m, 2H), 2.56–2.47 (m, 2H), 2.36 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 205.0, 154.3, 143.9, 139.0, 134.0, 130.4, 127.2, 34.8, 27.4, 21.3.

Asymmetric oxidation – standard procedure

In an oven-dried reaction flask, 4Å molecular sieves (200 mg) were suspended in CH_2Cl_2 (3 mL) under argon atmosphere at room temperature. The suspension was cooled to –20 °C and Ti(*i*PrO)$_4$ (0.29 mL, 1 mmol, 1 eq.), (+)-DET (0.67 mL, 4 mmol, 4 eq.), TBHP (5.5M solution in decane, 0.18 mL, 1 mmol, 1 eq.) and a solution of 2-[(4-methylphenyl)thio]-2-cyclopenten-1-one **2** (200 mg, 1 mmol, 1 eq.) in CH_2Cl_2 (2 mL) were added. The reaction mixture was kept at –20 °C for 0.5 hours and then at +4 °C for 98 hours. Now the reaction was quenched with a 5% aqueous solution of Na_2SO_3 (1.5 mL), CH_2Cl_2 was removed in vacuo, and 10 mL of EtOAc was added. After separation, the water layer was extracted with EtOAc (3 mL). The combined organic layers were washed with brine (3 mL) and dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient 20% to 35% acetone in petroleum ether) to give 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** (90 mg, 28%, *ee* 78%) and sulfone **3** (43 mg, 19%), both as white crystalline solids. Starting material **2** was recovered in 36% yield (72 mg). The spectral data matched those found in literature [3–9,27,35,36].

Note 1: If water (1 eq.) was used, then it was added before sulfide **2**.

Note 2: When using (*R*,*R*)-HB and (+)-BINOL, two equivalents of the corresponding ligands were used. Water was added before sulfide **2** and oxidant TBHP (2 eq.) was added at the end.

Note 3: For enantioenrichment by crystallization sulfoxide **1** was dissolved in minimal amount of solvent Et_2O/EtOAc (1:1) and kept at –20 °C until the formation of crystals.

2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one (+)-1

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14 (t, J=2.8 Hz, 1H), 7.71–7.60 (m, 2H), 7.30 (d, J=7.9 Hz, 2H), 2.91–2.79 (m, 1H), 2.79–2.66 (m, 1H), 2.65–2.56 (m, 1H), 2.55–2.44 (m, 1H), 2.39 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 202.2, 163.4, 152.0, 142.3, 139.3, 130.1, 125.1, 36.5, 27.6, 21.6.
HPLC: Lux 3u Amylose-2, Hex:iPrOH 85:15, 1 mL/min, 230 nm, minor 42.8 min, major 57.3 min.
Specific rotation: $[\alpha]^{25}_D$ = +134 (c 0.368, $CHCl_3$).

2-[(4-methylphenyl)sulfonyl]-2-cyclopenten-1-one 3

^{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.

Preparation of racemic sulfoxide rac-***1***

A solution of *m*-chloroperbenzoic acid (*m*-CPBA purity 70–77%, 1.29 g, 6.54 mmol, 1 eq.) in CH_2Cl_2 (20 mL) was dropwise added to a solution of sulfide **2** (1.34 g, 6.54 mmol, 1 eq.) in CH_2Cl_2 (29 mL) at 0 °C. After stirring at 0 °C for 30 min, the mixture was left stirring at room temperature for an additional hour. If TLC analysis showed that the starting material remained, then the mixture was re-cooled to 0 °C and more *m*-CPBA in two portions (201.4 mg and then 84 mg, 285 mg in total) was added. After stirring at 0 °C for 30 min, the mixture was left stirring at room temperature for an additional hour and poured onto saturated aqueous $NaHCO_3$ (20 mL). The

organic layer was washed with brine (20 mL) and dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with 20% acetone in petroleum ether as eluent resulting in racemic sulfoxide *rac*-**1** (1.2 g, 82%).

Kinetic resolution

In an oven-dried reaction flask, molecular sieves (296.5 mg) were suspended in CH_2Cl_2 (4.0 mL) under argon atmosphere at room temperature. Then the suspension was cooled to –20 °C and Ti(*i*PrO)$_4$ (0.40 mL, 1.35 mmol, 1 eq.), (+)-DET (0.92 mL, 5.38 mmol, 4 eq.), TBHP (5.5M solution in decane, 0.29 mL, 1.62 mmol, 1.2 eq.) and a solution of racemic 2-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one **1** (*rac*-**1**) (296.5 mg, 1 eq.) in CH_2Cl_2 (2.69 mL) were added. The reaction mixture was kept at –20 °C for 0.5 hours and then at +4 °C for 48 hours. Then the reaction was quenched with a 5% aqueous solution of Na_2SO_3 (4.75 mL). After separation, the water layer was extracted with EtOAc (3 mL). The combined organic layers were washed with brine (3 mL) and dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with a gradient of 20% to 35% acetone in petroleum ether to give 2-(*S*)-[(4-methylphenyl)sulfinyl]-2-cyclopenten-1-one (+)-**1** (90.7 mg, 31%, *ee* 76%) and sulfone **3** (136.0 mg, 43%), both as white crystalline solids.

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9,11-sekosteroolide D-ringi prekursori 2-(*S*)-[(4-metüülfenüül)sulfinüül]-2-tsüklopenteen-1-ooni süntees

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Uuriti 9,11-sekosterooli sünteesi peamise lähteühendi 2-(*S*)-[(4-metüülfenüül)sulfinüül]-2-tsüklopenteen-1-ooni **1** saamisvõimalusi 2-[(4-metüülfenüül)tio]-2-tsüklopenteen-1-ooni **2** asümmeetrilisel oksüdatsioonil ja *rac*-2-[(4-metüülfenüül)sulfinüül]-2-tsüklopenteen-1-ooni **1** kineetilisel lahutamisel, kasutades vahendina asümmeetrilist Sharplessi Ti(*i*PrO)$_4$/(+)-DET/TBHP kompleksi. Mõlemal juhul saadi piisava enantioselektiivsusega 2-(*S*)-[(4-metüülfenüül)sulfinüül]-2-tsüklopenteen-1-oon **1** nii, et edasine enantiomeerne rikastamine oli võimalik ümberkristallimise teel. Saadud tulemused tagavad lihtsa võimaluse 9,11-sekosterooli D-ringi eellase saamiseks ja avavad tee sekosteroolide täiskeemiliseks sünteesiks.