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Catalytic enantioselective annulation using phenylsulfanylmethyl vinyl ketone. An approach to *trans*-hydrindane building blocks for *ent*-vitamin D_3 synthesis

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Abstract

An enantioselective synthesis of the *ent*-vitamin D_3 northern portion building block is presented. The key step involves phenylalanine-catalyzed annulation of 2-methylcyclopent-2-en-1-one with phenylsulfanylmethyl vinyl ketone. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantioselective amino acid-catalyzed annulation of 2-methylcyclopenta-1,3-dione[1–3] (**3**, Scheme 1) or 2-methylcyclohexa-1,3-dione[4–6] with methyl vinyl ketone, affording optically active hydrindane or decaline derivatives, respectively, has made possible efficient total synthesis of several natural products and their analogues (some recent related studies are given in the bibliography[7–13]). Ethyl vinyl ketone and some alkyl vinyl ketones bearing a remote substituent in the alkyl group were also successfully employed in this reaction.[14–17] However, to date no α,β-unsaturated ketones with an activated methylene group have been examined (except for preliminary experiments with the Nazarov reagent[6]). As far as the catalysts are concerned, it has been generally accepted that homochiral proline or phenylalanine give the best results.[18,19]

In conjunction with research on the total synthesis of 1α,25-dihydroxy vitamin D_3 (**1**, Fig. 1) ongoing in our laboratory,[20,21] it was of interest to examine the application of the highly reactive (thiophenyl)methyl vinyl ketone (**2**, Scheme 1) as an electrophile[22] in reaction with dione **3** under asymmetric annulation conditions. Bicyclic sulfide **4a**, if formed, could be oxidized at sulfur to afford the corresponding sulfone **4b**. Since it was recently shown that the reduction of related α,β-unsaturated β-phenylsulfonyl ketones with lithium aluminum hydride occurs with deoxygenation and affords diastereoselectively

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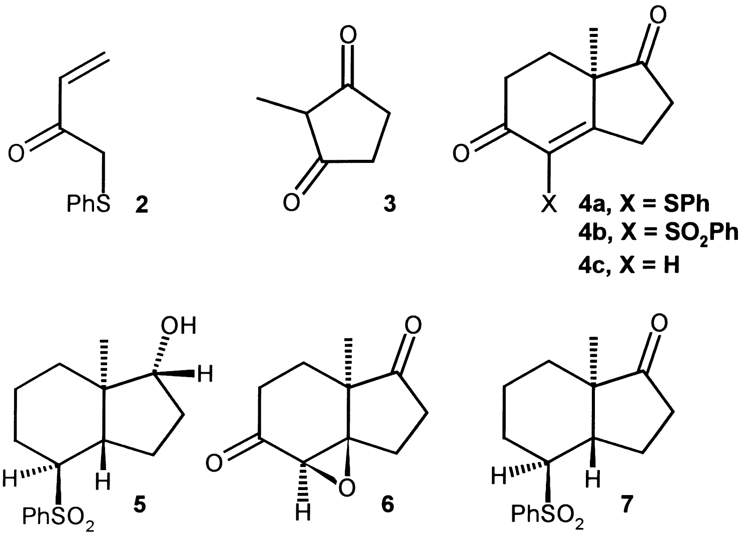


Scheme 1.

saturated sulfone with a *trans*-ring junction,[22,23] we expected that reduction of **4b** would yield hydroxy sulfone **5**. The hydroxy group in the latter could be further used to construct the vitamin D side chain. On the other hand, the phenylsulfonyl group could serve as a handle for the attachment of the ring A fragment.[24] As the synthesis target the CD side-chain portion of the *ent*-vitamin D_3 **11** was chosen.

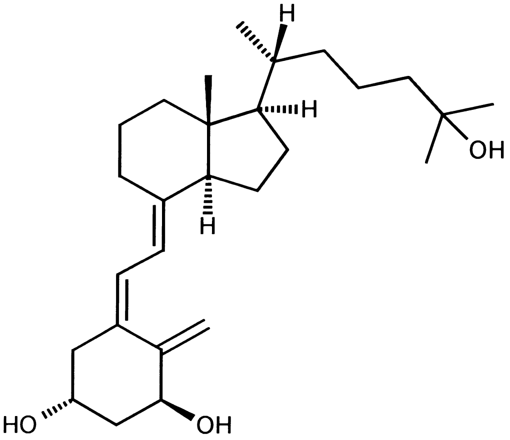


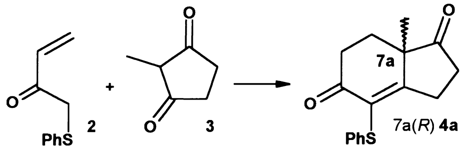
Figure 1.

2. Results and discussion

Our first objective was to examine the transformation of thiophenyl enone **4a** into the saturated sulfone **5**. Hajos–Parrish–Wiechert ketone **4c** (Scheme 1) was oxidized[25] into epoxide **6** which was treated with thiophenol[26] to give sulfide **4a**. The latter was oxidized with *m*-chloroperbenzoic acid to give sulfone **4b**. Reduction of **4b** with lithium aluminum hydride provided stereoselectively the *trans*-hydrindane derivative **5** which, without isolation, was oxidized with the Jones reagent to give the keto sulfone **7**. The structure of **7** was confirmed by removing the phenylsulfonyl group (sodium amalgam in THF–methanol) which yielded known[27] *trans*-7a-methyl-octahydroinden-1-one.

After confirming our plans regarding the transformation of **4a** into **5** we turned our attention to the annulation reaction. Reaction of **2**, prepared immediately before use by oxidation of 1-thiophenyl-2-hydroxybut-3-ene[26] with the Dess–Martin reagent,[28] with **3** in aqueous acetic acid (the Hajos–Parrish conditions[29] for the Michael addition step) directly afforded the racemic bicyclic product **4a**. Monitoring the reaction progress by TLC indicated the presence of an intermediate, most likely the corresponding trione. However, all attempts to isolate this compound failed. When a solution of **2** and **3** in acetonitrile was treated with (*S*)-(−)-proline (3 mol%) and some perchloric acid, and the mixture was heated under reflux (the Schering procedure[3]), only a small amount of racemic **4a** was obtained. Using larger amounts of proline and carrying the reaction out at room temperature lead to a non-racemic product (Table 1). Use of DMF as the solvent provided **4a** in 60% yield, 56.6% ee (Table 1, entry 3). Further alternations of the classical procedures failed to improve the reaction outcome. Application of the method developed by Hagiwara and Uda and their coworkers[30,31] with (*S*)-(−)-phenylalanine as the catalyst, (1*S*)-(+)-camphorsulfonic acid (D-CSA) as the dehydrating agent and a gradual increase of the temperature gave the product **4a** in 69–71% yield and 86–89% ee (95–96% ee after one recrystallization from methanol) (Table 1, entry 4). Under analogous conditions, but with the (*R*)-(+)-phenylalanine the enantiomer of **4a** was obtained in 71% yield, 89.1% ee (Table 1, entry 5). Replacement of phenylalanine with proline in the Hagiwara procedure resulted in lowering the product yield and enantiomeric excess (Table 1, entry 6).

Table 1

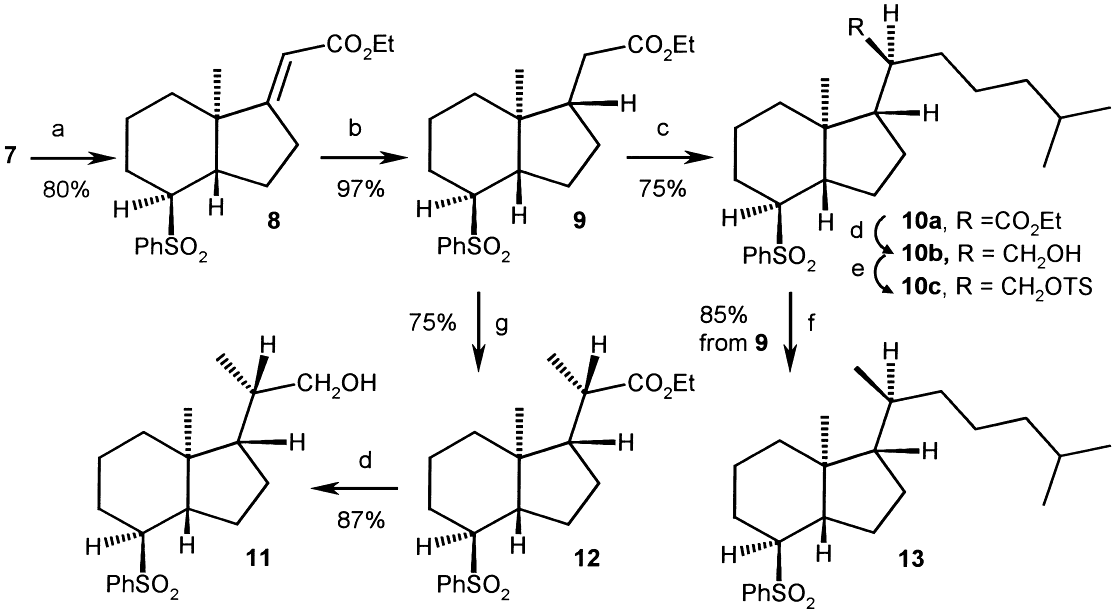


	Conditions	yield	$[\alpha]_D^{23}$*	ee (%)	C-7a conf.
1	*S*-(-)- proline/CH_3CN, rt, then H_2SO_4	44%	+ 29.1	10.2	(*S*)
2	S-(-)- proline/DMF, 70-75 °C, then H_2SO_4	52%	+65.6	45.4	(*S*)
3	S-(-)- proline/DMF, 70-75 °C,then rt H_2SO_4	60%	+81.4	56.6	(*S*)
4	S-(-)- phenylalanine/ Et_3N/D-CSA/DMF	69%	+183.1	86.2**	(*S*)
5	R-(+)-phenylalanine/ Et_3N/D-CSA/DMF	71%	-201.4	89.1	(*R*)
6	S-(-)-proline/ Et_3N/D-CSA/DMF	50%	+77.9	53.8	(*S*)

*c = 0.7-0.8.

** After one recrystallization from MeOH, 95.6% ee; $[\alpha]_D^{23}$ = + 190.8

Having in hand diketo sulfide **4a** of high enantiomeric purity, we followed the above described procedure to transform it into the enantiomeric keto sulfone **7**. The latter product was treated with triethylphosphonoacetate and sodium ethoxide in ethyl alcohol.[32] To our disappointment, **7** resisted any changes under standard conditions for 17-oxo steroid transformation. Ultimately, the Horner–Wadsworth–Emmons reaction was executed by treatment of **7** (Scheme 2) with triethylphosphonoacetate and sodium hydride in DMF containing HMPA to give **8** in 80% yield (when DMPU was used instead of HMPA, **8** was obtained in 58% yield). The unsaturated ester **8** was hydrogenated using palladium catalyst to afford **9**.



Scheme 2. Reagents and conditions: (a) NaH–$(EtO)_2POCH_2CO_2Et$/DMF–HMPA; (b) H_2–10% Pd on carbon/EtOH; (c) LDA–1-iodo-4-methylhexane/THF–HMPA; (d) DIBAH/CH_2Cl_2–toluene; (e) TsCl–Et_3N–DMAP/CH_2Cl_2; (f) L-Selectride®/THF

Next, we aimed at selective alkylation of **9** to the carboethoxy group in the presence of the phenylsulfonyl group α to the carboethoxy group. It was thought that steric shielding of the phenylsulfonyl group activated proton would be beneficial. We were pleased to find that treatment of **9** with LDA and then with isohexyl iodide and some HMPA provided ester **10a** in 67% yield after chromatography (ca. 10% of the unchanged **9** was recovered). Alkylation of **9** with methyl iodide under analogous conditions afforded **12** (75% yield). No diastereomers of the alkylation products could be detected.

Reduction of the carboethoxy group in **10a** with DIBAH followed by tosylation of alcohol **10b** and reduction of the tosylate **10c** (L-Selectride®) afforded **13**. This compound may be used for the synthesis of *ent*-vitamin D_3 which has not been described until now. Similarly, reduction of ester **12** with DIBAH yielded alcohol **11** which may also be used for the synthesis of vitamin D stereo-analogues.

In conclusion, an enantioselective synthesis of building blocks **13** and **11** for vitamin D analogue construction has been developed using asymmetric annulation.

3. Experimental

Melting points were determined on a Kofler hot-stage melting point apparatus. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ on a Varian Gemini 200 MHz spectrometer and multiplicities were assigned using DEPT sequence. Mass spectra were determined at an ionizing voltage of 70 eV; (*m/z*) relative intensity are given in brackets. Optical rotations were measured on a Perkin–Elmer, model 141 polarimeter in chloroform solutions at concentration (g/100 ml), unless otherwise indicated. HPLC analyses were performed using a Shimadzu LC-8A chromatograph provided with a SPD-6A variable λ detector and fitted with a Chiralcel® OD-H column (25×0.46 cm) with the eluent 2-propanol:hexane, 1:1, flow 0.3 ml/min; detection at λ=254 nm. Air-sensitive reactions were performed in oven- or flame-dried glassware under argon. Organic extracts were dried over Na_2SO_4 and solvents were evaporated on a rotary evaporator.

3.1. *1-Phenylsulfanyl-but-3-en-2-one* ***2***

To a solution of 1-phenylsulfanyl-but-3-en-2-ol[26] (3.488 g, 19.38 mmol) in DMSO (1.5 ml), stirred at 15°C, *o*-iodoxybenzoic acid (7.645 g, 29.07 mmol) in DMSO (19.5 ml) was added. The mixture was stirred at 15°C for 1 h and then set aside at rt for 2.5 h and then diluted with cold water and filtered through a pad of Celite (ca. 1 cm layer). The filtrate was extracted with diethyl ether and the Celite was washed with diethyl ether. The combined ethereal solutions were washed with water and the solvent was evaporated. The residue was chromatographed on SiO_2 (125 g, hexane:EtOAc, 20:1 to 5:1) to give ketone **2** (2.815 g, 82%).

3.2. *(1*R*,4a*R*,7a*R*)-4a-Methyl-tetrahydro-1-oxa-cyclopropa[*d*]indene-2,5-dione* ***6***[25]

To a solution of endione[29] **4c** ($[\alpha]_D^{23}$=−349, c=1.0, toluene) (1.0 g, 6 mmol) in MeOH (15 ml) H_2O_2 (30%, 2 ml, 24 mmol) was added followed, after cooling to 0°C, by 4 N NaOH (750 μl, 3 mmol). The mixture was set aside at rt for 5 h and then diluted with water. The product was extracted with $CHCl_3$. The extract was evaporated. Epoxide **6** was obtained (99 mg, 92% yield), mp 75–77°C.

3.3. *(7a*R*)-7a-Methyl-4-phenylsulfanyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione* ***4a***

To a mixture of epoxide **6** (90 mg, 5 mmol), EtOH (2 ml) and 15% aqueous KOH (0.09 ml), stirred at 0°C, thiophenol (0.51 ml, 5 mmol) in THF (1.5 ml) was added within 30 min. The mixture was set aside at 0° to +5°C for 24 h and then diluted with water (10 ml). The product was extracted using a mixture of diethyl ether and toluene (1:1). The organic extract was washed with brine. The solvent was evaporated and the residue (1.36 g) was chromatographed on SiO_2 (34 g, hexane:EtOAc, 9:1). Sulfide **4a** was obtained (1.17 g, 86% yield): mp 152–154°C (MeOH); $[\alpha]_D^{23}$=−201.8, (c=0.75, toluene); IR (KBr) 1743, 1668, 1600 cm^{-1}; UV (1.29 mg/10 ml EtOH) λ_{max}=193 nm, ε=22139; λ_{max}=248 nm, ε=13943; ^1H NMR 7.31–7.09 (m, 5H), 3.41–3.20 (m, 1H), 2.94–1.85 (m, 7H), 1.38 (s, 3H); ^{13}C NMR 215.82 (0), 192.90 (0), 175.14 (0), 135.36 (0), 129.00 (1), 128.77 (0), 128.04 (1), 126.06 (1), 51.20 (0), 35.39 (2), 33.41 (2), 28.06 (2), 27.20 (2), 21.42 (3); EI MS 272 (M^+, 76), 230 (5), 215 (4), 163 (100), 139 (6), 135 (14), 121 (31), 110 (23), 105 (6), 93 (12), 77 (13), 65 (5), 51 (6), 41 (4), 39 (5). Anal. calcd for $C_{16}H_{16}O_2S$ (272.37): C, 70.55; H, 5.92. Found: C, 70.33; H, 6.08.

3.4. *(7a*R*)-4-Benzenesulfonyl-7a-methyl-2,3,7,7a-tetrahydro-6*H*-indene-1,5-dione* ***4b***

To a solution of sulfide **4a** (1.0 g, 3.7 mmol) in CH_2Cl_2 (15 ml), stirred at 0°C, *m*-CPBA (634 mg, 3.7 mmol) was added and the mixture set aside in rt for 12 h before another portion of *m*-CPBA (634 mg, 3.7 mmol) was added. After 12 h the mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous $Na_2S_2O_3$ and water, and then dried. The solvent was evaporated and the residue was chromatographed on SiO_2 (10 g, hexane:EtOAc, 9:1) to give sulfone **4b** (1.08 g, 97% yield): mp 177–179°C (MeOH); $[\alpha]_D^{23}$=−88.2 (c=0.75); UV (0.75 mg/10 ml EtOH), λ_{max}=200 nm, ε=7082; λ_{max}=218 nm, ε=6099; IR (KBr) 1750, 1674, 1595, 1307, 1148 cm^{-1}; ^1H NMR 8.05–7.96 (m, 2H), 7.65–7.45 (m, 3H), 4.31–4.14 (m, 1H), 3.50–3.25 (m, 1H), 3.05–1.70 (m, 6H), 1.41 (s, 3H); ^{13}C NMR 213.97 (0), 190.89 (0), 178.73 (0), 141.09 (0), 134.63 (0), 133.46 (1), 128.66 (1), 128.26 (1), 52.07 (0), 34.59 (2), 33.58 (2), 26.70 (2), 25.83 (2), 22.69 (3); EI MS 304 (M^+, 54), 276 (63), 261 (4), 240 (12), 212 (8), 197 (10), 185 (11), 183 (8), 163 (100), 135 (27), 121 (12), 105 (9), 93 (20), 91 (38), 77 (38), 65 (9), 51 (15), 39 (8). EI MS HR: calcd for $C_{16}H_{16}O_4S$ (M^+): 304.07693. Found: 304.07795.

3.5. *(3a*S*,4*S*,7a*R*)-4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-one* **7**

To a solution of sulfone **4b** (90 mg, 2.96 mmol) in THF (10 ml), stirred under argon, $LiAlH_4$ (1 M in THF) (11.8 ml, 11.8 mmol) was added and the mixture was heated at reflux for 30 min. After cooling, the excess reagent was decomposed with MeOH and the mixture was poured into a 10% aqueous tartaric acid solution. The product was extracted with CH_2Cl_2. The extract was dried and the solvent was evaporated. The residue (alcohol **5**, 87 mg) was dissolved in acetone (10 ml) and the Jones reagent was added dropwise until a brown color persisted. After 30 min the excess reagent was decomposed with propan-2-ol and the mixture diluted with water. The product was isolated with CH_2Cl_2 and chromatographed (SiO_2, 30 g, hexane:EtOAc, 19:1) to give ketone **7** (69 mg, 80% yield): mp 201–203°C (MeOH); $[\alpha]_D^{23}=-68.5$ (c=0.25); IR (KBr) 1737, 1304, 1145 cm^{-1}; ^{1}H NMR 7.95–7.85 (m, 2H), 7.76–7.52 (m, 3H), 3.28–3.10 (m, 1H), 2.60–1.05 (m, 11H), 0.91 (s, 3H); ^{13}C NMR 218.36 (0), 137.59 (0), 133.73 (1), 129.13 (1), 128.66 (1), 62.63 (1), 48.88 (0), 44.22 (1), 35.00 (2), 30.63 (2), 27.56 (2), 23.34 (2), 20.29 (2), 13.77 (3); EI MS 292 (M^+, 9), 167 (20), 151 (100), 133 (86), 109 (81), 91 (19), 81 (34), 67 (34), 55 (12), 51 (4), 41 (11). EI MS HR: calcd for $C_{16}H_{20}O_3S$ (M^+): 292.11331. Found: 292.11301.

3.6. *Annulation reactions*

The annulation reactions were carried out under an argon atmosphere, with magnetic stirring, using ca. 2 mmol of phenylsulfanylmethyl vinyl ketone **2**, 150 mol% 2-methyl-1,3-cyclopentadione **3** and the appropriate amino acid. The reaction was monitored by TLC (hexane:EtOAc, 2:1). Product (**4a** and its enantiomer) was isolated with CH_2Cl_2 and filtered through SiO_2 (ca. 10 g, hexane:EtOAc, 9:1). Yields, specific rotations and ee values (determined by HPLC on a Chiracel column) are given in Table 1.

Reaction of **2** and **3** in water containing acetic acid at rt gave *rac*-**4a** in a 75% yield. The starting material was consumed in ca. 4 h. An intermediate was detected on TLC (hexane:EtOAc, 1:1), but all attempts to isolate this compound failed. Reaction of **2** and **3** in CH_3CN containing *S*-(−)-proline (3 mol%) and $HClO_4$ at reflux temperature under conditions described by the Schering workers[3] gave *rac*-**4a** in a 29% yield.

A mixture of **2** (390 mg, 2.2 mmol), **3** (370 mg, 3.3 mmol), *S*-(−)-proline (126 mg, 1.1 mmol) and CH_3CN (4 ml) was stirred at rt for 18 h (the starting material was consumed). 96% H_2SO_4 (0.07 ml) was then added and the mixture was heated at 90°C for 16 h. Product **4a** (262 mg, 44%), $[\alpha]_D^{23}=+29.1$ (c=0.14) was obtained; 10.2% ee by HPLC.

A mixture of **2** (180 mg, 1 mmol), **3** (170 mg, 1.5 mmol), *S*-(−)-proline (58 mg, 0.5 mmol) and DMF (3 ml) was stirred at 70–75°C for 18 h. 96% H_2SO_4 (0.035 ml) was then added and the mixture was stirred at 90°C for 48 h. Product **4a** (143 mg, 52%), $[\alpha]_D^{23}=+65.6$ (c=0.81) was obtained; 45.4% ee.

A mixture of **2** (180 mg, 1 mmol), **3** (170 mg, 1.5 mmol), *S*-(−)-proline (58 mg, 0.5 mmol) and DMF (3 ml) was stirred at 70–75°C for 18 h. The mixture was allowed to cool to rt and then 96% H_2SO_4 (0.035 ml) was added. Stirring at rt was continued for 4 days. Product **4a** (165 mg, 60%), $[\alpha]_D^{23}=+81.4$ (c=0.80) was obtained; 56.6% ee.

Reaction under the conditions developed by Hagiwara and Uda.[31] To a mixture of **2** (348 mg, 1.96 mmol), **3** (328 mg, 2.9 mmol) and DMF (4 ml) was added triethylamine (0.048 ml, 0.2 mmol). The mixture was stirred at rt for 7 h (the starting material was consumed, TLC). Then *S*-(−)-phenylalanine (323 mg, 1.96 mmol) and D-CSA (227 mg, 0.98 mmol) were added. The mixture was stirred at rt for 24 h, and the temperature was raised by 10°C in every 24 h for 3 days (up to 55°C). After cooling, the mixture was poured into saturated aqueous $NaHCO_3$ and the product was isolated with CH_2Cl_2. Product **4a** (367 mg, 69%), $[\alpha]_D^{23}$=+183.1 (c=0.75) was obtained; 86.2% ee. Recrystallization of the crude product from MeOH gave material of 95.6% ee.

In an analogous experiment with use of *R*-(+)-phenylalanine and D-CSA, product **4a** (71% yield, 89.1% ee) was obtained.

In an analogous experiment with use of *S*-(−)-proline and D-CSA, product **4a** (50% yield, 53.8% ee) was obtained.

*3.7. (*Z*,3a*S*,4*S*,7a*R*)-(4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-ylidene)-acetic acid ethyl ester **8***

Sodium hydride (50% in mineral oil, 0.34 g, 14 mmol) was washed with THF and suspended in DMF (3 ml). The suspension was cooled to −20°C and then triethyl phosphonoacetate (1.26 g, 5.6 mmol) in DMF (1 ml) was added followed, after 30 min, by HMPA (1 g, 5.6 mmol). The mixture was allowed to warm to rt and ketone **7** (218 mg, 0.7 mmol) in DMF (2 ml) was added. The whole was set aside for 12 h and then diluted with water. The product was extracted with diethyl ether. The extract was washed with water and dried. The solvent was evaporated and the residue (0.32 g) was chromatographed on SiO_2 (2 g, hexane:EtOAc, 9:1). Ester **8** was obtained (213 mg, 80% yield): $[\alpha]_D^{23}$=+14.0 (c=0.56); IR (film) 1651, 1306, 1146 cm^{-1}; ^1H NMR 7.92–7.82 (m, 2H), 7.70–7.48 (m, 3H), 5.57–5.53 (m, 1H), 4.15 (q, 2H, J=7.14 Hz), 3.20–3.03 (m, 1H), 2.95–2.82 (m, 2H), 2.40–2.22 (m, 1H), 1.85–1.40 (m, 8H), 1.25 (t, 3H, J=7.14 Hz), 0.86 (s, 3H); ^{13}C NMR 172.89 (0), 166.80 (0), 137.64 (0), 133.49 (1), 128.94 (1), 128.87 (1), 109.35 (1), 63.04 (1), 59.55 (2), 47.57 (1), 45.82 (0), 34.27 (2), 29.88 (2), 27.43 (2), 25.67 (2), 20.79 (2), 18.38 (3), 14.25 (3); EI MS 362 (M^+, 10), 317 (3), 275 (2), 221 (25), 205 (2), 193 (8), 175 (24), 159 (2), 147 (100), 133 (12), 119 (8), 105 (17), 91 (14), 77 (8), 67 (5), 55 (6), 41 (6). EI MS HR: calcd for $C_{16}H_{26}O_4S$ (M^+): 362.15518. Found: 362.15734.

*3.8. (1*S*,3a*S*,4*S*,7a*S*)-(4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-yl)-acetic acid ethyl ester **9***

A mixture of compound **8** (78 mg, 0.2 mmol), EtOH (5 ml) and 10% palladium on carbon (15 mg) was stirred under hydrogen for 16 h and then filtered through Celite. The Celite was washed with EtOH and the combined filtrate was evaporated to give **9** (76 mg, 97% yield): $[\alpha]_D^{23}$=+16.1 (c=0.13); IR (KBr) 1725, 1140 cm^{-1}; ^1H NMR 7.92–7.82 (m, 2H), 7.70–7.49 (m, 3H), 4.11 (q, 2H, J=7.14 Hz), 3.11–2.95 (m, 1H), 2.42–0.96 (m, 14H), 1,24 (t, 3H, J=7.14 Hz), 0.62 (s, 3H); ^{13}C NMR 173.16 (0), 137.99 (0), 133.37 (1), 128.91 (1), 128.71 (1), 63.71 (1), 60.28 (2), 47.25 (1), 45.99 (1), 44.11 (0), 36.31 (2), 35.11 (2), 27.76 (2), 27.46 (2), 25.71 (2), 20.87 (2), 14.24 (3), 12.42 (3); EI MS 319 (3), 223 (33), 177 (12), 149 (22), 136 (11), 135 (100), 119 (2), 107 (6), 93 (9), 79 (6), 67 (6), 55 (4), 41 (3). EI MS HR: calculated for $C_{18}H_{23}O_3S$ $(M-OC_2H_5)^+$: 319.13679. Found: 319.13608. Calcd for $C_{14}H_{23}O_2$ $(M-SO_2Ph)^+$: 223.16981. Found: 223.16944.

3.9. (2S)-2-[(1S,3aS,4S,7aS)-4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-yl]-6-methyl-heptanoic acid ethyl ester ***10a***

To a solution of LDA prepared from diisopropylamine (63 μl, 0.44 mmol), *n*-BuLi (230 μl, 0.44 mmol, 1.94 M in hexane) and THF (0.5 ml), stirred at −78°C, a solution of ester **9** (81 mg, 0.22 mmol) in THF (0.75 ml)–HMPA (0.15 ml) was added. The mixture was stirred for 1 h and then 1-iodo-4-methylhexane (95 μl, 0.44 mmol) in HMPA (100 μl) was added. The whole was stirred at −30 to −20°C for 3 h, and then left aside at rt for 16 h. Water was added and the product was extracted with diethyl ether. The extract was washed with water and brine, and then dried and evaporated. The residue was chromatographed on SiO_2 (5 g, hexane:EtOAc, 19:1) to give compound **11** (65 mg, 67% yield) and unchanged **9** (6 mg, eluted with hexane:EtOAc, 10:1): $[\alpha]_D^{23}$=+8.3 (c=0.08); IR (film) 1727, 1305, 1146 cm^{-1}; ^1H NMR 7.90–7.79 (m, 2H), 7.70–7.48 (m, 3H), 4.08 (q, 2H, J=7.14 Hz), 3.09–2.94 (m, 1H), 2.3–0.96 (m, 20H), 1,24 (t, 3H, J=7.14 Hz), 0.84 (d, 3H, J=6.59 Hz), 0.83 (d, 3H, J=6.59 Hz), 0.71 (s, 3H); ^{13}C NMR 175.95 (0), 138.12 (0), 133.41 (1), 128.96 (1), 128.77 (1), 63.67 (1), 59.82 (2), 51.69 (1), 47.48 (1), 47.31 (1), 44.20 (0), 38.74 (2), 36.56 (2), 32.20 (2), 27.77 (1), 27.39 (2), 26.77 (2), 24.93 (2), 22.70 (3), 22.33 (3), 20.99 (2), 14.20 (3), 12.04 (3); EI MS 307 (28), 261 (7), 233 (38), 177 (3), 149 (7), 135 (100), 121 (7), 107 (8), 81 (15), 67 (11), 55 (9), 41 (8). EI MS HR: calcd for $C_{10}H_{15}$ $(M-SO_2Ph–HCOOC_2H_5–C_7H_{14})^+$: 135.11738. Found: 135.11910.

3.10. (2S)-2-[(1S,3aS,4S,7aS)-4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-yl]-6-methyl-heptan-1-ol ***10b***

To a solution of **10a** (33 mg, 0.07 mmol) in CH_2Cl_2 (1 ml) DIBAH (20% in toluene, 60 μl, 0.29 mmol) was added at −20°C. The mixture was stirred at rt for 30 min and then the reaction was quenched with EtOAc (1 ml), and diluted with water. The product was extracted with EtOAc. The organic extract was washed consecutively with 2% H_2SO_4, water and brine, and dried. The solvent was evaporated and the residue was chromatographed on SiO_2 (1 g, hexane:EtOAc, 4:1). Alcohol **10b** was obtained (29 mg, 97%): $[\alpha]_D^{23}$=+6.8 (c=0.99); IR (film) 3520, 1304, 1143 cm^{-1}; ^1H NMR 7.92–7.82 (m, 2H), 7.70–7.48 (m, 3H), 3.75–3.58 (m, 2H), 3.12–2.97 (m, 1H), 2.18–0.98 (m, 21H), 0.86 (d, 6H, J=6.59 Hz), 0.71 (s, 3H); ^{13}C NMR 138.19 (0), 133.35 (1), 128.93 (1), 128.75 (1), 63.64 (1), 62.76 (2), 49.58 (1), 48.07 (1), 44.46 (0), 42.07 (1), 39.44 (2), 38.03 (2), 29.57 (2), 27.99 (1), 27.44 (2), 27.07 (2), 25.29 (2), 24.21 (2), 22.75 (3), 22.58 (3), 21.11 (2), 12.21 (3); EI MS 265 (39), 247 (80), 233 (10), 219 (1), 205 (1), 191 (8), 165 (15), 149 (39), 137 (100), 136 (10), 121 (38), 109 (34), 95 (80), 67 (36), 55 (37), 43 (27). EI MS HR: calcd for $C_{18}H_{33}O$ $(M-SO_2Ph)^+$: 265.25314. Found: 265.25274. Calcd for $C_{18}H_{31}$ $(M-SO_2Ph–H_2O)^+$: 247.24258. Found: 247.24549.

3.11. (1S,3aS,4S,7aS)-4-Benzenesulfonyl-1-[(1S)-1,5-dimethyl-hexyl]-7a-methyl-octahydro-indene ***13***

To a solution of alcohol **10b** (25 mg, 0.062 mmol) in CH_2Cl_2 (0.5 ml) containing Et_3N (4 μl, 0.031 mmol) and DMAP (0.8 mg, 0.0062 mmol) TsCl (35 mg, 0.186 mmol) was added. The mixture was set aside for 15 h and then saturated aqueous $NaHCO_3$ (2 ml) was added. The product was extracted with CH_2Cl_2. The organic extract was washed with water and brine, and dried. The solvent was evaporated to give crude tosylate **10c** (33 mg). This product was dissolved in THF (1 ml) and L-Selectride® (1 M in THF, 44.8 mg, 0.236 mmol) at 0 to +5°C. The mixture was set aside at rt for 5 h and then the reaction was quenched with water (2 ml). The product was extracted with diethyl ether. The organic extract was washed with water and brine, and dried. The solvent was evaporated and the residue was chromatographed on SiO_2 (1 g, hexane:EtOAc, 49:1) to give compound **13** (23 mg, 88% from **10b**): $[\alpha]_D^{23}$=+6.0 (c=0.17); ^{1}H NMR 7.90–7.81 (m, 2H), 7.70–7.48 (m, 3H), 3.12–2.90 (m, 1H), 2.18–0.98 (m, 20H), 0.90 (d, 3H, J=7.0 Hz), 0.86 (d, 3H, J=6.7 Hz), 0.86 (d, 3H, J=6.6 Hz), 0.69 (s, 3H); ^{13}C NMR 138.37 (0), 133.32 (1), 128.93 (1), 128.77 (1), 63.84 (1), 55.12 (1), 48.16 (1), 44.68 (1), 39.44 (1), 38.76 (2) 36.09 (2), 35.56 (2), 27.96 (1), 27.40 (2), 25.39 (2), 23.75 (2), 22.79 (3), 22.54 (3), 21.16 (2), 18.74 (3), 11.88 (3); EI MS 249 (67), 233 (10), 193 (26), 165 (24), 151 (24), 137 (57), 123 (57), 109 (77), 95 (100), 81 (71), 71 (56), 57 (71), 43 (53). EI MS HR: calcd for $C_{18}H_{33}$ $(M-PhSO_2)^+$: 249.25823. Found: 249.25929.

3.12. (2S)-2-[(1S,3aS,4S,7aS)-4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-yl]-propionic acid ethyl ester **12**

To a solution of LDA prepared from diisopropylamine (49 μl, 0.344 mmol), *n*-BuLi (170 μl, 0.344 mmol, 2.03 M in hexane) and THF (0.5 ml), stirred at −78°C, a solution of ester **9** (57 mg, 0.156 mmol) in THF (0.5 ml)–HMPA (0.1 ml) was added. The mixture was stirred for 1 h and then methyl iodide (17 μl, 0.188 mmol) in HMPA (50 μl) was added. The whole was stirred at −78°C for 5 h, and then left aside at rt. After 16 h, water was added and the product was extracted with diethyl ether. The extract was washed with water and brine, and then dried and evaporated. The residue was chromatographed on SiO_2 (3 g, hexane:EtOAc, 19:1) to give the methyl derivative **12** (44 mg, 75% yield): $[\alpha]_D^{23}$=+13.6 (c=0.27); IR (film) 1728, 1144, 1305 cm^{-1}; ^{1}H NMR 7.92–7.80 (m, 2H), 7.70–7.48 (m, 3H), 4.07 (q, 2H, J=7.14 Hz), 3.10–2.91 (m, 1H), 2.50–0.80 (m, 13H), 1,24 (t, 3H, J=7.14 Hz), 1.11 (d, 3H, J=6.8 Hz), 0.71 (s, 3H); ^{13}C NMR 176.62 (0), 138.12 (0), 133.41 (1), 128.96 (1), 128.77 (1), 63.68 (1), 60.03 (2), 52.34 (1), 47.56 (1), 44.17 (0), 41.04 (1), 36.61 (2), 27.36 (2), 26.40 (2), 24.88 (2), 20.99 (2), 17.29 (3), 14.12 (3), 12.15 (3); EI MS 333 (1), 249 (2), 237 (18), 223 (3), 207 (1), 191 (8), 177 (2), 163 (27), 160 (9), 136 (10), 135 (100), 121 (3), 107 (8), 93 (9), 81 (26), 57 (7), 55 (9), 41 (7). EI MS HR: calcd for $C_{19}H_{25}O_3S$ $(M-OC_2H_5)^+$: 333.15244. Found: 333.15203. Calcd for $C_{15}H_{25}O_2$ $(M-SO_2Ph)^+$: 237.18546. Found: 237.18729.

3.13. (2S)-2-[(1S,3aS,4S,7aS)-(4-Benzenesulfonyl-7a-methyl-octahydro-inden-1-yl)]-propan-1-ol **11**

To a solution of ester **12** (24 mg, 0.063 mmol) in CH_2Cl_2 (1 ml) DIBAH (20% in toluene, 45 μl, 0.222 mmol) was added at −20°C. The mixture was set aside for 1 h at rt and then reaction was quenched with EtOAc (1 ml). Water was added and the product was extracted with EtOAc. The organic extract was washed consecutively with 2% H_2SO_4, water and brine, and then dried and evaporated. The residue was chromatographed on SiO_2 (1 g, hexane:EtOAc, 4:1) to give alcohol **11** (18.5 mg, 87%): $[\alpha]_D^{23}$=+15.3 (c=0.31); IR (film) 3475, 1304, 1143 cm^{-1}; ^{1}H NMR 7.91–7.80 (m, 2H), 7.70–7.48 (m, 3H), 3.57 (2H, part AB of ABM system, part A, δ=3.68 ppm, J=10.6, 3.9 Hz; part B, δ=3.46 ppm, J=10.6, 6.6 Hz), 3.03 (dt, 1H, J=11.4, 3.3 Hz), 2.18–0.76 (m, 14H), 0.96 (d, 3H, J=6.64 Hz), 0.71 (s, 3H); ^{13}C NMR 138.28 (0), 133.39 (1), 128.97 (1), 128.78 (1), 66.83 (1), 63.73 (2), 51.39 (1), 48.07 (1), 44.94 (0), 38.07 (2), 37.42 (1), 27.41 (2), 26.90 (2), 25.25 (2), 21.08 (2), 16.56 (3), 12.34 (3); EI MS 195 (50), 177 (94), 163 (13), 149 (5), 137 (100), 133 (5), 121 (37), 107 (26), 95 (95), 81 (73), 67 (33), 55 (38), 43 (15), 41 (28). EI MS HR: calcd for $C_{13}H_{23}O$ $(M-PhSO_2)^+$: 195.17489. Found: 195.17441.

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