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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of C_2-symmetric hexols from β,δ-diketosulfoxides

Guy Solladié,* Françoise Colobert and Donatienne Denni

Université Louis Pasteur (ECPM), Laboratoire de Stéréochimie associé au CNRS, 1 rue Blaise Pascal, 67008 Strasbourg, France

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Abstract

An enantioselective synthesis of (1,2*S*,4*S*,8*S*,10*S*,11)-hexahydroxyundecane, a C_2-symmetric hexol precursor of the alkaloid (−)-lythranidine, is described. This convergent synthesis was based on the stereoselective reduction of two different β,δ-diketosulfoxides.

1. Introduction

Following our previous results on the asymmetric synthesis of enantiomerically pure 2,6-disubstituted pyridines,[1] we were interested in the piperidine alkaloid (−)-lythranidine[2,3] which has never been synthesized in enantiomerically pure form.

A possible precursor of this macrocycle could be the tetrahydroxylated piperidine derivative **A** which can be obtained from the enantiomerically pure hexol **1** by the methodology we have already described[1] for the synthesis of simple piperidine derivatives. We report in this paper a convergent synthesis of the hexol **1** from the two diketosulfoxides **4** and **5** which can be made from (+)-(*R*)-menthyl *p*-toluenesulfinate or (−)-(*S*)-methyl-*p*-tolylsulfoxide (Scheme 1).

2. Results and discussion

The sulfinyl diketoester **5** was prepared from the diketoester **6** which was obtained in one step from commercially available dehydroacetic acid by a known procedure.[4] Condensation of the trianion of **6**, prepared in THF with 1 equiv. of NaH and 2 equiv. of *t*-BuLi at 0°C, to (+)-menthyl (*R*)-*p*-toluenesulfinate[5] afforded in 80% yield the (*S*)-diketosulfoxide **5** (Scheme 2).

* Corresponding author. Fax: 33 3 88 61 65 31; e-mail: solladie@chimie.u-strasbg.fr

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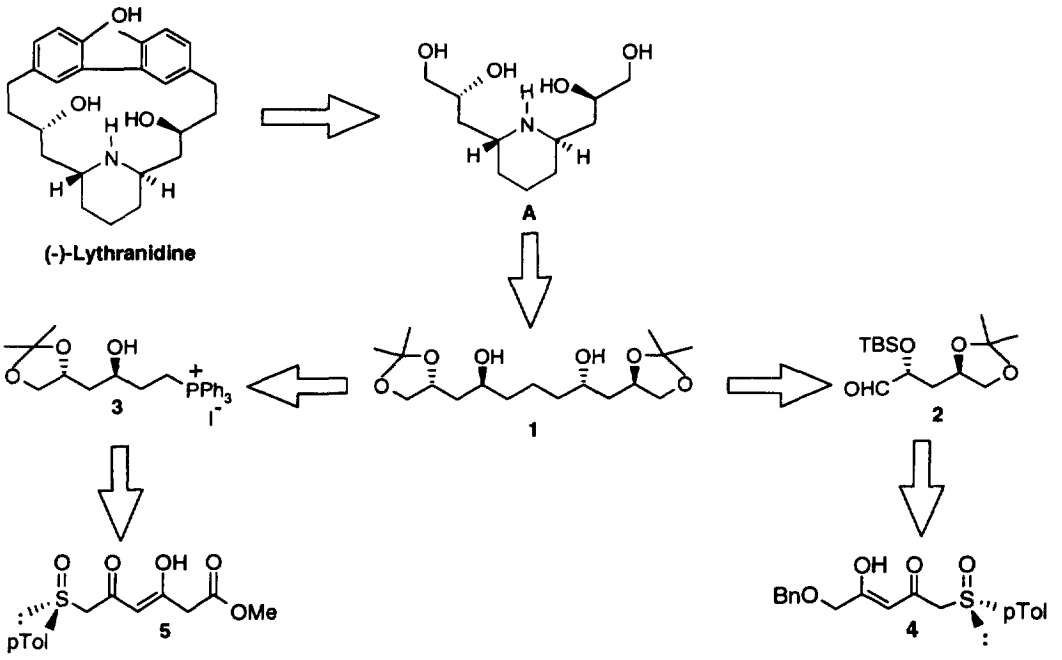
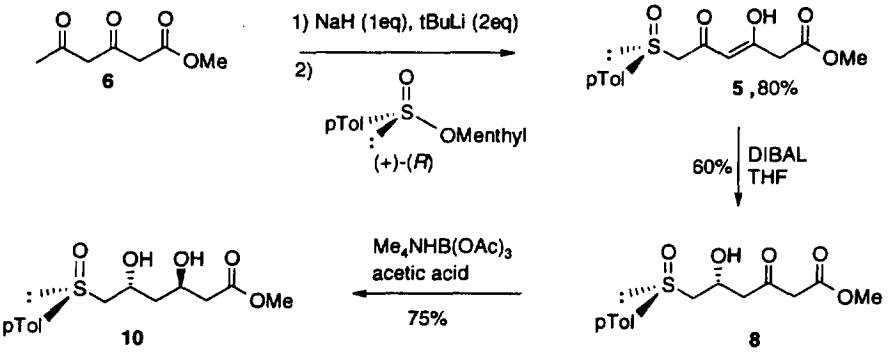


Scheme 1.

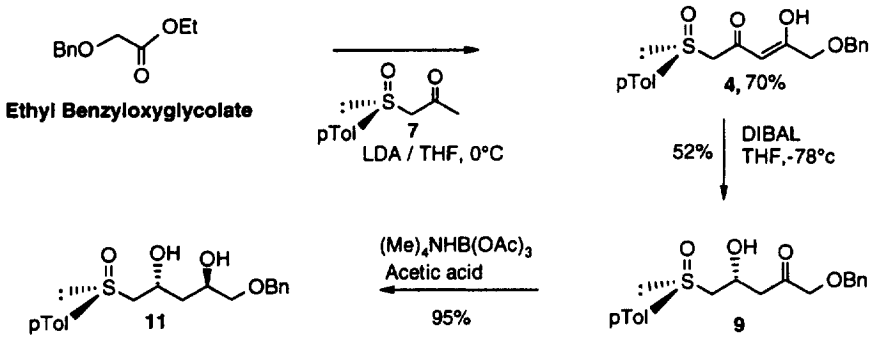


Scheme 2.

Similarly the (*S*)-diketosulfoxide **4** was prepared by condensation of the dianion of the β-ketosulfoxide[6] **7** (prepared from (−)-(*S*)-methyl-*p*-tolylsulfoxide and ethyl acetate in 90% yield) with the ethyl benzyloxyglycolate. The ^{1}H NMR spectrum of compounds **4** and **5** showed as expected[7] that only the δ-carbonyl was entirely enolized (Scheme 3).

Following our previous results,[7] the diastereoselective reduction of the β-carbonyl of the (*S*)-β,δ-dicarbonyl sulfoxides **4** and **5** was carried out with 2 equiv. of DIBAL in THF at −78°C. Only one diastereomer of the resulting β-hydroxy-δ-ketosulfoxides **8** and **9** was detected from the 200 MHz ^{1}H NMR spectrum of the crude product. The absolute configuration of the compounds **8** and **9** was deduced from our previous results.[7] The large non-equivalence ($\Delta\nu$=61 and 71 Hz) of the two methylenic protons α to the sulfinyl group was always observed for a (*SS*,3*R*) relative configuration. Yields of the isolated product (compared to our previous results[7]) were improved by using purification by crystallization followed by washing the solids **8** and **9** with ether instead of the usual purification by chromatography on metal-free silica gel which decomposed the products.

In the next step, the δ-carbonyl was reduced to the *anti*-diol with $(Me)_4NHB(OAc)_3$[8] in good yields:



Scheme 3.

75% for compound **10** and 95% for compound **11** (de >98%). The hydroxylic groups were protected with 2,2-dimethoxypropane (DMP) and the resulting acetonides **10a** and **11a** were submitted to a Pummerer rearrangement with acetic anhydride and sodium acetate (Scheme 4).

The intermediate **13** was reduced with lithium aluminium hydride in ether. The six-membered acetonide was then isomerized in an acidic medium to the thermodynamically more stable[9] five-membered ketal **15**.

Protection of the secondary OH with *tert*-butyl dimethylsilylchloride and debenzylation of the primary alcohol gave the compound **17** in 88% yield.

The other Pummerer intermediate **12** was desulfurized with Raney nickel and the resulting acetate was hydrolyzed under mild conditions (K_2CO_3) followed by thermodynamic isomerization of the acetonide in an acidic medium affording the alcohol **14** in 55% overall yield. The ester **14** was then transformed by reduction with lithium aluminium hydride into the corresponding diol **16**.

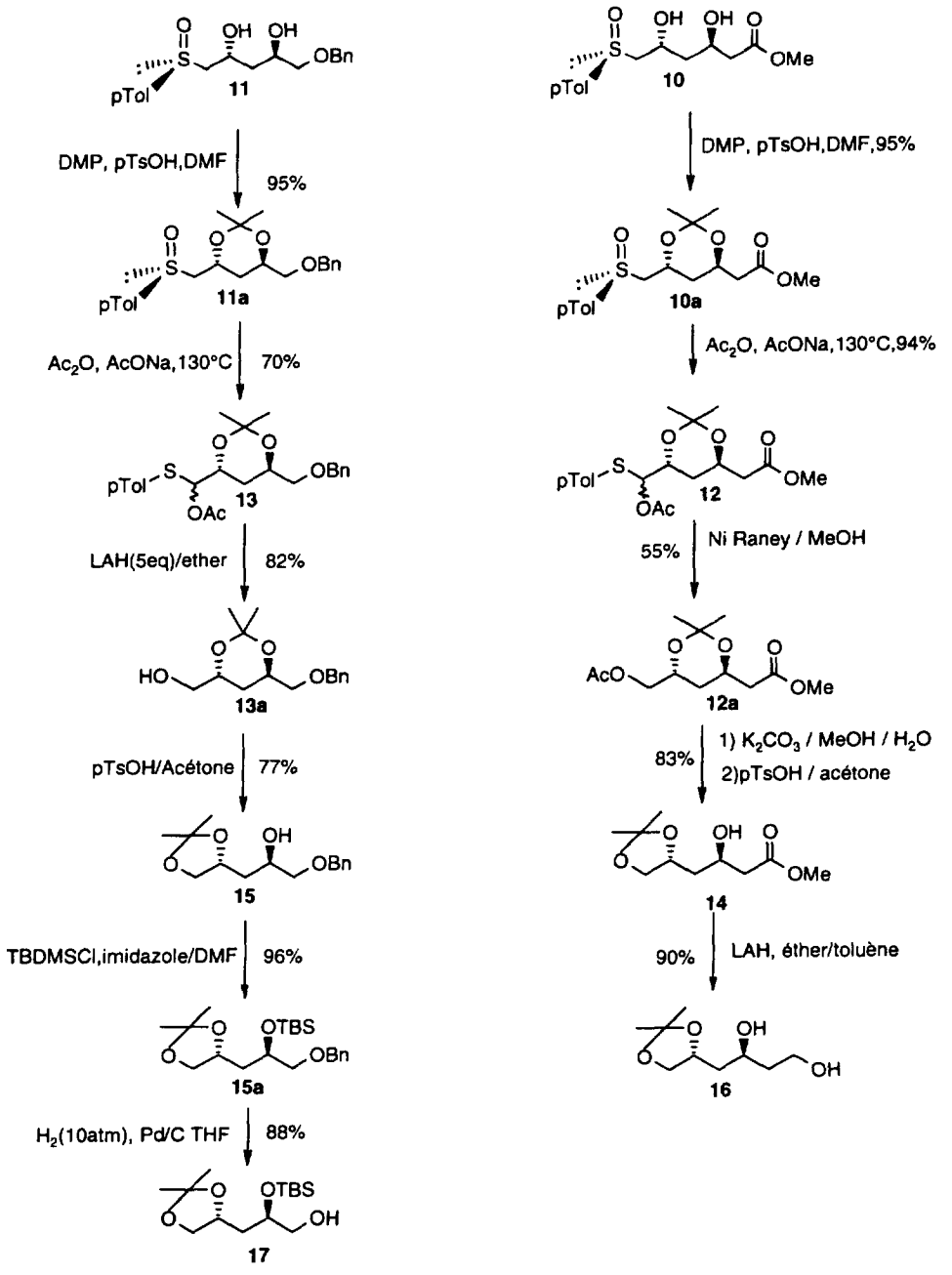
Finally, the two synthons **16** and **17** were modified for coupling via a Wittig reaction: the alcohol **16** was transformed into the phosphonium salt **3** in 60% yield, and the aldehyde **2** obtained from the alcohol **17** by a Swern oxidation (Scheme 5). The Wittig reaction between the phosphonium salt **3** and the aldehyde **2** was carried out in the presence of 2 equiv. of BuLi and lithium bromide to give the olefin **18** in 50% yield. Reduction of the double bond and deprotection of the silylated ether afforded the C_2-symmetric pure hexol **1** in 77% yield.

This procedure could be very easily applied to the preparation of all the other stereoisomers just by changing the absolute configuration of the starting sulfoxide and forming either the *syn*- or *anti*-diol by known procedures.[8,10]

3. Experimental

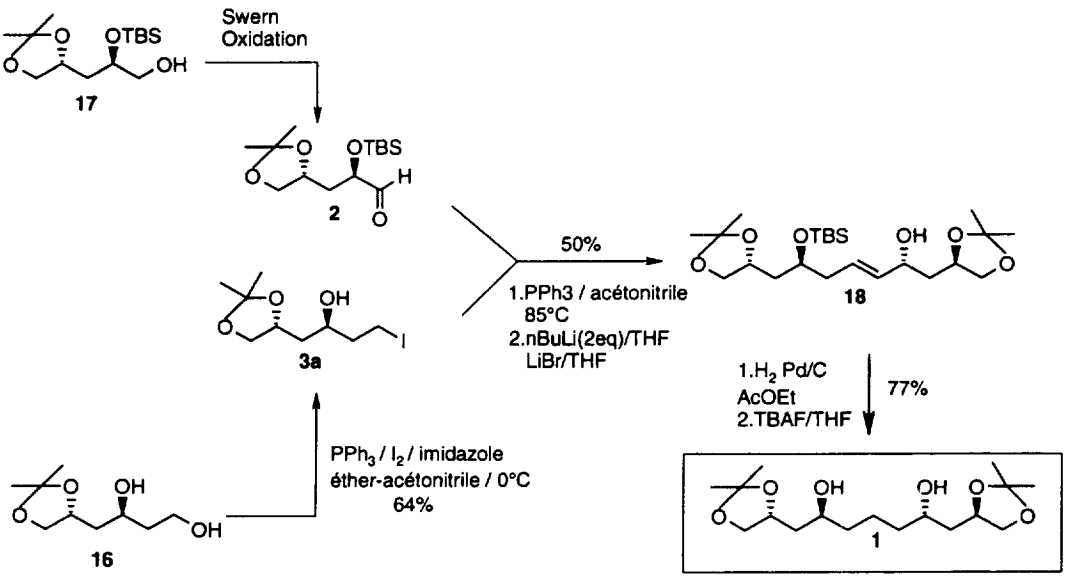
3.1. Ethyl benzyloxyglycolate

To a cold (0°C) solution of ethyl glycolate (7.3 ml, 76.84 mmol) in dry THF (120 ml) was added sodium hydrate (1.87 g, 77.86 mmol), tetrabutylammonium iodide (2.84 g, 7.864 mmol) and benzyl bromide (9.2 ml, 77.35 mmol). The reaction mixture was then stirred at room temperature until no more starting material was detected by TLC (hexane:AcOEt=6:1). The reaction mixture was then cooled and hydrolyzed with a saturated ammonium chloride solution (100 ml). The aqueous layer was extracted with AcOEt (3×100 ml). The combined organic layers were washed with brine (100 ml), dried ($MgSO_4$) and evaporated. Chromatography on silica gel of the residue (hexane and then gradient hexane/AcOEt) gave benzyloxyglycolate as a pale yellow oil (10.59 g, 71%); R_f 0.40 (hexane:AcOEt=6:1); ^{1}H NMR ($CDCl_3$,



Scheme 4.

200 MHz): δ 1.30 (t, 3H, H-4), 4.10 (s, 2H, OCH_2Ph), 4.24 (q, 2H, H-3), 4.65 (s, 2H, H-1), 7.36 (m, 5H, H arom.); ^{13}C NMR ($CDCl_3$): δ 14.15 (C-4), 60.80 (C-3), 67.18 (OCH_2Ph), 73.27 (C-1), 127.95, 128.02, 128.43 (C-H arom.), 137.07 (C_q arom.), 170.28 (C-2); IR ($CHCl_3$) 2860–2980, 1720–1760, 1630–1600, 1520–1490 cm^{-1}. Anal. calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.16; H, 7.28.



Scheme 5.

3.2. (−)-S(S) 5-Benzyloxy-2,4-dioxo-1-(p-tolylsulfinyl) pentane, 4

To a solution of LDA (161.7 mmol) in THF (290 ml) cooled at 0°C, was added a solution of (−)-(*S*)-1-(*p*-tolylsulfinyl)-2-propanone[6] **7** (15.62 g, 79.5 mmol) in THF (190 ml). After stirring for 30 min at 0°C this solution was dropwise added to a solution of ethyl benzyloxyglycolate (4.98 g, 25.67 mmol) in THF (190 ml) cooled at 0°C. The reaction mixture was stirred at room temperature for 30 min, hydrolyzed with water (150 ml) and acidified to pH 3–4 with an aqueous 5% H_2SO_4 solution. The aqueous layer was extracted with AcOEt (3×200 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on metal-free silica gel (gradient hexane:AcOEt=8:1 to hexane:AcOEt=5:5) to afford the (−)-S(*S*)-5-benzyloxy-2,4-dioxo-1-(*p*-tolylsulfinyl) pentane as an orange oil (6.19 g, 70%); R_f 0.44 (AcOEt 100%); $[\alpha]_D$=−208 (c 2.0, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.40 (s, 3H, Me *p*-Tol), 3.68 (AB, 2H, J_{AB}=0.06 Hz, Δν=0.38 Hz, H-1), 4.07 (s, 2H, OCH_2Ph), 4.21 (s, 2H, H-5), 5.88 (s, 1H, H-3), 7.5 (m, 9H, H arom.); ^{13}C NMR ($CDCl_3$): δ 19.01 (Me *p*-Tol), 62.63 (C-1), 68.71 (OCH_2Ph), 72.46 (C-5), 97.08 (C-3), 121.64, 125.42, 125.62, 126.10, 127.58 (C-H arom.), 134.58, 137.34, 139.77 (C_q arom.), 177.80 (C-4), 191.80 (C-2); IR ($CHCl_3$) 3690, 2840–3020, 1695, 1038 cm^{-1}. Anal. calcd for $C_{19}H_{20}O_4S$: C, 66.25; H, 5.85. Found: C, 66.35; H, 6.02.

3.3. (−)-[2(R),S(S)]-5-Benzyloxy-2-hydroxy-4-oxo-1-(p-tolylsulfinyl) pentane, 9

To a solution of the β,δ-diketosulfoxide **4** (3.24 g, 9.4 mmol) in THF (300 ml) was dropwise added at −78°C a solution of DIBAL-H (18.3 ml of a 1 M solution in toluene; 18.8 mmol). Stirring was continued for 30 min before adding MeOH (150 ml) and then the solution was stirred for 30 min at room temperature. The solvent was evaporated and the residue was dissolved in AcOEt (200 ml), and saturated disodium L-tartrate dihydrate (200 ml) was added. The stirring was continued until a clear phase-separation occurred. The aqueous layer was acidified to pH=5–6 with a 10% solution of HCl and extracted with AcOEt (3×200 ml). The combined organic layers were washed with brine (200 ml), dried ($MgSO_4$), and concentrated to afford a solid residue. The crude product was washed with ether (4×20

ml) to afford the β-hydroxy-δ-ketosulfoxide **9** as an ivory solid (1.66 g, 51%); R_f 0.48 (AcOEt 100%); $[\alpha]_D=-176$ (c 2.0, acetone); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.41 (s, 3H, Me *p*-Tol), 2.62 (d, 2H, H-3), 2.90 (AB of ABX, 2H, J_{AB}=13.8 Hz; J_{AX}=3.2 Hz; J_{BX}=9.7 Hz, Δν=61.2 Hz, H-1), 4.05 (s, 2H, OCH_2Ph), 4.28 (d, 1H, OH), 4.55 (s, 2H, H-5), 4.60 (m, 1H, H-2), 7.53 (m, 9H, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.53 (Me *p*-Tol), 45.37 (C-3), 61.49 (C-1), 63.22 (C-2); 73.50 (C-6), 75.44 (C-5), 127.09, 128.02, 128.19, 128.64, 130.22 (C–H arom.), 136.99, 139.46, 141.82, 207.57 (C_q arom.); IR ($CHCl_3$) 3400, 2860–2980, 1700–1720, 1595–1570, 1460–1510 cm^{-1}. Anal. calcd for $C_{19}H_{22}O_4S$: C, 65.87; H, 6.40. Found: C, 65.95; H, 6.60.

3.4. (−)-[2(R),4(R),S(S)]-5-Benzyloxy-2,4-dihydroxy-1-(p-tolylsulfinyl) pentane, 11

A solution of tetramethylammonium triacetoxyborohydride (10.10 g, 38.33 mmol) in anhydrous acetic acid (67 ml) was stirred at ambient temperature for 30 min. The mixture was cooled at 0°C, and a solution of β-hydroxy-δ-ketosulfoxide **9** (1.66 g, 4.80 mmol) in acetic acid (80 ml) was added via cannula. The mixture was stirred at room temperature for 2 h. The reaction was quenched at 0°C with water (100 ml) and the aqueous layer was extracted with dichloromethane (3×100 ml). The combined organic layers were washed with a saturated solution of sodium hydrogenocarbonate, brine, dried ($MgSO_4$), and concentrated to afford a solid residue. The crude product was washed with ether to afford the β,δ-dihydroxysulfoxide **11** as an ivory solid (1.59 g, >95%); R_f 0.29 (AcOEt 100%); $[\alpha]_D=-134$ (c 0.5, DMSO); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.60 (m, 2H, H-3), 2.42 (s, 3H, Me *p*-Tol), 2.92 (AB of ABX, 2H, J_{AB}=13.6 Hz; J_{AX}=9.6 Hz; J_{BX}=2.1 Hz, Δν=88.5 Hz, H-1), 3.42 (AB of ABX, 2H, J_{AB}=9.4 Hz; J_{AX}=7.2 Hz; J_{BX}=4.0 Hz, Δν=21.2 Hz, H-5), 4.04 (m, 1H, H-4), 4.50 (m, 1H, H-2), 4.52 (s, 2H, OCH_2Ph), 7.40 (m, 9H, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.43 (Me *p*-Tol), 39.26 (C-1), 61.03 (C-3), 64.81 (C-4), 67.58 (C-2), 73.39 (OCH_2Ph), 74.15 (C-5), 124.04, 127.76, 128.49, 130.13 (C–H arom.), 137.80, 139.00, 141.65 (C_q arom.); IR ($CHCl_3$) 3330, 2840–2900, 1020 cm^{-1}. Anal. calcd for $C_{19}H_{24}O_4S$: C, 65.5; H, 7.28. Found: C, 65.36; H, 6.90.

3.5. Methyl 3,5-dioxohexanoate, 6

Magnesium turnings (7.8 g, 0.32 mol) were dissolved in 1.5 l methanol and dehydroacetic acid (36 g, 0.21 mol) in methanol (300 ml) was added. The reaction mixture was heated under reflux for 10 h, after which the solvent was distilled under reduced pressure. The residue was dissolved in ethyl acetate and acidified with aqueous 1 M HCl (650 ml) and extracted with ethyl acetate (5×200 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was distilled under reduced pressure (91°C/0.6 mmHg) to afford a colorless liquid (27 g, 80%); R_f 0.82 (AcOEt:CH_2Cl_2=5:5). The ^{1}H NMR spectrum indicated the presence of 83% of an enol form, ^{1}H NMR ($CDCl_3$, 200 MHz): enol, δ 2 (s, 3H, H-6), 3.27 (s, 2H, H-2), 3.66 (s, 3H, OMe), 5.54 (s, 1H, H-4); ketone: 2.17 (s, 3H, H-6), 3.50 (s, 2H, H-2), 3.66 (s, 3H, OMe), 3.68 (s, 2H, H-4); ^{13}C NMR ($CDCl_3$): enol, δ 23.4 (C-6), 44.1 (C-2), 51.5 (OMe), 99.9 (C-4), 167.3 (C-1), 186.9 (C-5), 189.5 (C-3); ketone: 29.9 (C-6), 48.5 (C-2), 51.5 (OMe), 56.4 (C-4), 166.8 (C-1), 196.7 (C-5), 201.4 (C-3).

3.6. (−)-S(S) Methyl 3,5-dioxo-6-(p-tolylsulfinyl) hexanoate, 5

To a suspension of NaH (1.82 g, 75.8 mmol) in dry THF (250 ml) at 0°C was added dropwise a solution of methyl 3,5-dioxohexanoate (11.86 g, 75 mmol) in THF (50 ml). The mixture rapidly became a thick white suspension. At 0°C, *tert*-butyllithium (100 ml of a 1.5 M pentane solution; 0.15 mol) was then

quickly added with a cannula over a period of 15 min. The solution turned yellow, orange, and finally deep red as the addition progressed. The (+)-menthyl (*R*)-*p*-toluenesulfinate[5] (11.04 g, 37.5 mmol) in solution in THF (45 ml) was then added dropwise within 20 min. Stirring at 0°C was continued for 2 h until all the sulfinate was consumed (TLC). The reaction was quenched with a saturated solution of NH_4Cl (120 ml), diluted with AcOEt (100 ml), and then acidified to pH 3 with a 10% solution of H_2SO_4. The aqueous layer was extracted with AcOEt (4×200 ml). The combined organic layers were washed with brine (200 ml), dried over $MgSO_4$, and filtered before being concentrated. The crude oily residue was purified by rapid chromatography on metal-free silica gel (hexane and CH_2Cl_2) to give an orange oil which was crystallized (diethyl ether) to afford (−)-S(*S*) methyl 3,5-dioxo-6-(*p*-tolylsulfinyl) hexanoate **5** as pale yellow prisms (7.8 g, 70%); R_f 0.42 (AcOEt:CH_2Cl_2=5:5); $[\alpha]_D$=−262 (c 1, $CHCl_3$); mp=51–53°C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.39 (s, 3H, Me *p*-Tol), 3.34 (s, 2H, H-2), 3.62 (AB of ABX, 2H, J_{AB}=8 Hz, Δν=17 Hz, H-6), 3.71 (s, 3H, OMe), 5.64 (s, 1H, H-4), 7.40 ($(AB)_2$, 4H, J_{AB}=8 Hz, Δν=39 Hz, H arom.), 14.4 (s, 1H, H enol); ^{13}C NMR ($CDCl_3$): δ 21.4 (Me *p*-Tol), 45.1 (C-2), 52.5 (OMe), 64.7 (C-6), 102.7 (C-4), 123.99, 130 (C–H arom.), 139.5, 142.3 (C_q arom.), 167.3 (C-1), 179.5 (C-3), 188.8 (C-5).

3.7. (−)-[5(R)S(S)] Methyl 5-hydroxy 3-oxo-6-(p-tolylsulfinyl) hexanoate, 8

To a solution of the β,δ-diketosulfoxide **5** (1 g, 3.39 mmol) in THF (100 ml) at −78°C was added dropwise a solution of DIBAL-H (6.77 ml of a 1 M solution in toluene, 6.78 mmol). Stirring was continued for 30 min before adding MeOH (30 ml) and then the solution was stirred 30 min at room temperature. The solvent was evaporated and the residue was dissolved in AcOEt (30 ml), and saturated disodium L-tartrate dihydrate (30 ml) was added. The stirring was continued until a clear phase-separation occurred. The aqueous layer was acidified to pH=5–6 with a 10% solution of HCl and extracted with AcOEt (3×50 ml). The combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), and concentrated to afford a solid residue. The crude product was washed with ether (4×10 ml) to afford the β-hydroxy-δ-ketosulfoxide **8** as an ivory solid (0.61 g, 60%); R_f 0.44 (AcOEt 100%); $[\alpha]_D$=−202 (c 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.43 (s, 3H, Me *p*-Tol), 2.74 (A of ABX, 1H, J_{AB}=13.6 Hz; J_{AX}=2.5 Hz, Δν=70.9 Hz, H-6), 2.81 (d, 2H, H-4), 3.07 (B of ABX, 1H, J_{AB}=13.6 Hz; J_{BX}=9.5 Hz, Δν=70.9 Hz, H-6), 3.48 (s, 2H, H-2), 3.72 (s, 3H, OMe), 4.21 (d, 1H, OH), 4.63 (m, 1H, H-5), 7.44 (AB, 4H, J_{AB}=8.2 Hz, Δν=34.1 Hz, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.52 (Me *p*-Tol), 49.09 (C-2), 49.67 (C-4), 52.58 (OMe), 60.53 (C-6), 63.57 (C-5), 124.07, 130.25, (C-arom.), 139.26, 141.76 (C_q arom.), 173.65 (C-1), 201.60 (C-3); IR ($CHCl_3$) 1700–1735, 2940–3020, 3400 cm^{-1}. Anal. calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 5.78. Found: C, 56.33; H, 5.78.

3.8. (−)-[5(R)3(R)S(S)] Methyl-3,5-dihydroxy 6-(p-tolylsulfinyl) hexanoate, 10

A solution of tetramethylammonium triacetoxyborohydride (6.35 g, 24.13 mmol) in anhydrous acetic acid (44 ml) was stirred at ambient temperature for 30 min. The mixture was cooled at 0°C, and a solution of β-hydroxy-δ-ketosulfoxide **8** (900 mg, 3.02 mmol) in acetic acid (45 ml) was added via cannula. The mixture was stirred at room temperature for 2 h. The reaction was quenched at 0°C with water (100 ml). The aqueous layer was extracted with dichloromethane (3×100 ml). The combined organic layers were washed with a saturated solution of sodium hydrogenocarbonate and with brine, dried ($MgSO_4$), and concentrated to afford a solid residue. The crude product was washed with ether to afford the β,δ-dihydroxysulfoxide **10** as an ivory solid (680 mg, 75%); R_f 0.18 (AcOEt 100%); $[\alpha]_D$=−172 (c 1.0, DMSO); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.60–1.74 (m, 2H, H-4), 2.42 (s, 3H, Me *p*-Tol), 2.50 (m, 2H,

H-2), 2.93 (AB of ABX, 2H, J_{AB}=13.4 Hz; J_{AX}=9.9 Hz; J_{BX}=2.1 Hz, Δν=71.1 Hz, H-6), 3.69 (s, 3H, H-5), 3.77 (d, 1H, J=3.53 Hz, MeO), 4.33 (m, 1H, OH), 4.52 (m, 1H, H-5), 4.65 (d, 1H, J=3.4 Hz), 7.43 ($(AB)_2$, 4H, J_{AB}=8.1 Hz, Δν=34.4 Hz, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.44 (Me *p*-Tol), 41.30 (C-4), 42.44 (C-2), 51.80 (OMe), 61.88 (C-6), 64.01 (C-3), 64.93 (C-5), 124.04, 130.17 (C–H arom.), 139.26, 147.77 (C_q arom.), 172.66 (C-1); IR ($CHCl_3$) 3420, 2960–3040, 1725 cm^{-1}. Anal. calcd for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71. Found: C, 55.92; H, 6.70.

3.9. (−)-[2(R)4(R)S(S)]-5-Benzyloxy-2,4-(isopropylidenedioxy)-1-(p-tolylsulfinyl)-pentane, ***11a***

The dihydroxysulfoxide **11** (1.46 g, 4.20 mmol) and catalytic *p*-TsOH (80 mg, 0.42 mmol) were dissolved in dimethylformamide (154 ml) and dimethoxypropane (6.20 ml). Stirring at room temperature was continued until all starting material disappeared (TLC). The reaction mixture was diluted in AcOEt (50 ml) and saturated $NaHCO_3$ (50 ml) was added. The reaction was stirred at room temperature to obtain a white precipitate. The aqueous layer was extracted with AcOEt (3×50 ml). The combined organic layers were washed with a saturated solution of NH_4Cl (50 ml) and with brine (50 ml), dried over $MgSO_4$, and filtered before being concentrated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:AcOEt=6:4) to give a yellow oil (1.55 g, 95%); R_f 0.50 (CH_2Cl_2:AcOEt=6:4); $[\alpha]_D$=−110 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43 (s, 3H, Me acetal), 1.49 (s, 3H, Me acetal), 1.60 (m, 2H, H-3), 2.40 (s, 3H, Me *p*-Tol), 2.78 (AB of ABX, 2H, J_{AB}=13.2 Hz; J_{AX}=9.1 Hz; J_{BX}=4.0 Hz, Δν=19.3 Hz, H-1), 3.48 (AB of ABX, 2H, J_{AB}=10.3 Hz; J_{AX}=4.5 Hz; J_{BX}=6.2 Hz, Δν=23.6 Hz, H-5), 4.09 (m, 1H, H-4), 4.45 (m, 1H, H-2), 4.57 (AB, 2H, J_{AB}=12 Hz, Δν=11.9 Hz, OCH_2Ph), 7.31 (m, 9H, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.28 (Me *p*-Tol), 24.54–24.82 (C-8 and C-7), 33.98 (C-1), 60.95 (C-4), 64.01 (C-3), 66.12 (C-2), 72.30 (OCH_2Ph), 73.27 (C-5), 101.06 (C-6), 123.68, 127.54, 127.58, 128.26, 129.66 (C arom.), 136.04, 141.26, 141.42 (C_q arom.); IR ($CHCl_3$) 2840–2910, 1010 cm^{-1}. Anal. calcd for $C_{22}H_{28}O_4S$: C, 68; H, 7.21. Found: C, 67.9; H, 7.21.

3.10. [2(R)4(R)]-1-Acetoxy-5-benzyloxy-2,4-(isopropylidenedioxy)-1-(p-tolylthio)-pentane, ***13***

Anhydrous sodium acetate (0.15 g, 1.81 mmol) was added to the preceding sulfoxide (58.5 mg, 0.15 mmol). Acetic anhydride (5 ml) was then added, and the mixture was refluxed (135°C) until all the sulfinate was consumed (TLC). After cooling, the solvent was removed by azeotropic distillation with toluene to obtain a deep brown solid which was diluted in CH_2Cl_2 and filtered through Celite. The crude product was purified by column chromatography on silica gel (hexane:AcOEt=9:1) to afford **13** as a yellow oil (45.4 mg, 70%), a mixture of the two isomers at the C_1 position which were not separated. ^{1}H NMR ($CDCl_3$, 200 MHz): major isomer, δ 1.36 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.77 (m, 2H, H-3), 2.07 (s, 3H, MeCOO), 2.33 (s, 3H, Me *p*-Tol), 3.46 (m, 2H, H-5), 4.08 (m, 2H, H-2 and H-4), 4.58 (AB, 2H, J_{AB}=12.3 Hz, Δν=11 Hz, OCH_2Ph), 7.26 (m, 9H, H arom.); minor isomer, δ 1.36 (s, 3H, H-7), 1.40 (s, 3H, H-8), 1.77 (m, 2H, H-3), 2.05 (s, 3H, MeCOO), 2.33 (s, 3H, Me *p*-Tol), 3.46 (m, 2H, H-5), 4.08 (m, 2H, H-5), 4.58 (AB, 2H, J_{AB}=12.3 Hz, Δν=11 Hz, OCH_2Ph), 7.26 (m, 9H, H arom.); ^{13}C NMR ($CDCl_3$): δ 19.69 (Me *p*-Tol), 21.32 (MeOAc), 24.64, 24.96 (C-7 and C-8), 31.48 (C-3), 66.46 (C-4), 68.33 (C-2), 72.43 (OCH_2Ph), 73.59 (C-5), 82.11 (C-1), 101.27 (C-6), 127.83, 128.51, 129.94, 133.87, 134.04, 134.40 (C arom.), 138.26, 138.63, 138.72, 169.89 (C_q arom.); IR ($CHCl_3$) 2880–3000, 1750, 1015 cm^{-1}. Anal. calcd for $C_{24}H_{30}O_5S$: C, 66.95; H, 7.02. Found: C, 67.10; H, 7.20.

3.11. [2(R)4(R)]-5-Benzyloxy-2,4-(isopropylidenedioxy)-pentanol, **13a**

To a solution of the acetoxy **13** (31.7 mg, 0.07 mmol) in dry ether (2.4 ml) at 0°C was added $LiAlH_4$ (14 mg, 0.37 mmol). The reaction mixture was stirred at room temperature until all the starting material was consumed (TLC). After quenching with a saturated solution of Na_2SO_4, the reaction was stirred at room temperature to obtain a white suspension. The mixture was dried over $MgSO_4$, filtered over Celite, washed with hot ether and the solvent flash evaporated. The crude product was purified by column chromatography on silica gel (ether:hexane=8:2) to give a pale yellow oil (15.3 mg, 82%); R_f 0.47 (CH_2Cl_2:AcOEt=6:4); $[\alpha]_D$=+28 (c 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 6H, H-7 and H-8), 1.61 (m, 2H, H-3), 2.03 (m, 1H, OH), 3.56 (m, 4H, H-1 and H-5), 4.01 (m, 2H, H-2 and H-4), 4.58 (AB, 2H, J_{AB}=12.2. Hz, Δν=10.5 Hz, OCH_2Ph), 7.31 (m, 5H, H arom.); ^{13}C NMR ($CDCl_3$): δ 24.96–25.05 (C-7 and C-8), 30.01 (C-3), 65.46 (C-1), 66.36 (C-2), 67.55 (C-4), 72.61 (OCH_2Ph), 73.44 (C-5), 100.72 (C-6), 127.74, 127.79, 128.47 (C arom.), 138.31 (C_q arom.); IR ($CHCl_3$) 3600, 2880–3000, 1015 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.39. Found: C, 67.61; H, 8.39.

3.12. [2(R)4(R)]-5-Benzyloxy-4-hydroxy-1,2-(isopropylidenedioxy)-pentane, **15**

To a solution of the preceding acetonide **13a** (988 mg, 3.79 mmol) in acetone (172 ml) was added at room temperature *p*-toluenesulfinic acid (36 mg, 0.19 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. After quenching with a saturated solution of $NaHCO_3$, the aqueous layer was extracted with AcOEt (3×100 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2:AcOEt=6:4) to afford a colorless oil (939 mg, 93%); R_f 0.46 (CH_2Cl_2:AcOEt=6:4); $[\alpha]_D$=−5 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H, H-7), 1.39 (s, 3H, H-8), 1.67 (m, 2H, H-3), 2.93 (s, 1H, OH), 3.41 (AB of ABX, 2H, J_{AB}=9.5 Hz; J_{AX}=7.2 Hz; J_{BX}=3.8 Hz, Δν=65.9 Hz, H-5), 3.53 (A of ABX, 1H, J_{AB}=7.9 Hz; J_{AX}=7.7 Hz, Δν=225.1 Hz, H-1), 3.97 (X of ABX, m, 1H, H-4), 4.06 (B of ABX, 1H, J_{AB}=7.9 Hz; J_{BX}=6.0 Hz, Δν=225.1 Hz, H-1), 4.29 (X of ABX, m, 1H, H-2); 4.53 (s, 2H, OCH_2Ph), 7.32 (m, 5H, H arom.); ^{13}C NMR ($CDCl_3$): δ 25.68–26.91 (C-7 and C-8), 36.77 (C-3), 67.77 (C-2), 69.68 (OCH_2Ph), 73.25 (C-5), 73.39 (C-4), 74.41 (C-1), 108.63 (C-6), 127.67, 127.72, 128.39 (C arom.), 137.89 (C_q arom.); IR ($CHCl_3$) 3570, 2840–2980, 1059 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.27. Found: C, 67.50; H, 8.27.

3.13. [2(R)4(R)]-5-Benzyloxy-4-(tert-butyldimethylsilyloxy)-1,2-(isopropylidenedioxy)-pentane, **15a**

To a solution of the alcohol **15** (49.6 mg, 0.19 mmol) in DMF (1 ml) was added at 0°C imidazole (38 mg, 0.56 mmol) and *tert*-butyldimethylsilyl chloride (56.2 mg, 0.37 mmol). The reaction mixture was stirred at room temperature overnight and hydrolyzed with a saturated solution of NH_4Cl. After extraction with ether (3×50 ml), the organic layers were washed with brine (50 ml) and dried over $MgSO_4$. After evaporating the solvent, the crude product was purified by column chromatography on silica gel (CH_2Cl_2:AcOEt=6:4) to afford a colorless oil (68 mg, 96%); R_f 0.39 (hexane:AcOEt=9:1); $[\alpha]_D$=+9 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.09 (s, 3H, Me_2Si), 0.12 (s, 3H, Me_2Si), 0.92 (s, 9H, *t*-BuSi), 1.36 (s, 3H, H-7), 1.42 (s, 3H, H-8), 1.74 (m, 2H, H-3), 3.41 (AB of ABX, 2H, J_{AB}=9.6 Hz; J_{AX}=5.5 Hz; J_{BX}=2.2 Hz, Δν=48.5 Hz, H-5), 3.51 (A of ABX, 1H, J_{AB}=7.7 Hz; J_{AX}=7.7 Hz, Δν=231.1 Hz, H-1), 4.05 (B of ABX, 1H, J_{AB}=7.7 Hz; J_{BX}=7.7 Hz, Δν=231.1 Hz, H-1), 4.11 (m, 1H, H-4); 4.25 (m, 1H, H-2), 4.53 (s, 2H, OCH_2Ph), 7.34 (m, 5H, H arom.); ^{13}C NMR ($CDCl_3$): δ −4.83 ($(CH_3)_2Si$), −4.34 ($(CH_3)_2Si$), 16.12 (C-3), 25.62 (C-7 and C-8), 25.90 ($C(CH_3)_3Si$), 27.06 ($C(CH_3)_3Si$),

36.63 ($C(CH_3)_3Si$), 66.72 (C-2), 69.95 (C-5), 72.66 (C-4), 73.30 (OCH_2Ph), 75.06 (C-1), 106.55 (C-6), 126.32, 127.55, 127.62 (C arom.), 136.32 (C_q arom.); IR ($CHCl_3$) 2960–2840, 1100 cm^{-1}. Anal. calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 66.14; H, 9.69.

3.14. *[2(R)4(R)]-4-(*tert*-Butyldimethylsilyloxy)-1,2-(isopropylidenedioxy)-5-pentanol,* **17**

A solution of the preceding benzyl ether **15a** (245 mg, 0.65 mmol) and 5% Pd/C (one spatula) in tetrahydrofuran (20 ml), under a hydrogen atmosphere (10 atm), was stirred at room temperature for 5 h. The catalyst was then removed by filtration over Celite, washed with tetrahydrofuran and the solvent evaporated. The crude product was purified by column chromatography (hexane:AcOEt=9:1) to afford a colorless oil (0.16 g, 88%); R_f 0.46 (hexane:AcOEt=9:1); $[\alpha]_D$=+5 (c 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.10 (s, 6H, Me_2Si), 0.90 (s, 9H, *t*-BuSi), 1.34 (s, 3H, H-7), 1.39 (s, 3H, H-8), 1.72 (m, 2H, H-3), 2.07 (t, 1H, OH), 3.49 (A of ABX, 1H, J_{AB}=7.7 Hz; J_{AX}=7.7 Hz, Δν=118.5 Hz, H-1), 3.59 (m, 2H, H-5), 3.95 (m, 1H, H-2), 4.05 (B of ABX, 1H, J_{AB}=7.7 Hz; J_{BX}=7.7 Hz, Δν=118.5 Hz, H-1), 4.17 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$): δ −4.45 ($(CH_3)_2Si$), −4.66 ($(CH_3)_2Si$), 18.13 (C-3), 25.90 (C-7 and C-8), 27.10 ($C(CH_3)_3Si$), 38.36 ($C(CH_3)_3Si$), 67.20 (C-1), 69.90 (C-5), 70.43 (C-2), 72.84 (C-4), 109.00 (C-6); IR ($CHCl_3$) 3450–3540, 2870–3000 cm^{-1}. Anal. calcd for $C_{14}H_{30}O_4Si$: C, 57.89; H, 10.41. Found: C, 57.92; H, 10.35.

3.15. *[2(R)4(R)]-4-*tert*-Butyldimethylsilyloxy)-1,2-(isopropylidenedioxy)-5-pentanal,* **2**

To a stirred solution of oxalyl chloride (0.14 ml, 1.58 mmol) in dichloromethane (3 ml) at −78°C was added dimethyl sulfoxide (0.23 ml, 3.17 mmol). After 15 min, a solution of alcohol **17** (0.15 mg, 0.53 mmol) in CH_2Cl_2 (3.7 ml) was slowly added to the reaction mixture via a cannula. After stirring at −78°C during 1.5 h, triethylamine was added (0.88 ml, 6.33 mmol). After stirring at −78°C for 30 min and at 0°C for 1 h, the reaction was quenched with a saturated solution of NH_4Cl (10 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent flash evaporated. The crude product was purified by column chromatography (hexane:AcOEt=9:1) to afford a colorless oil (0.13 g, 82%); R_f 0.39 (hexane:AcOEt=9:1); $[\alpha]_D$=+18 (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.095 (s, 3H, Me_2Si), 0.10 (s, 3H, Me_2Si), 0.93 (s, 9H, *t*-BuSi), 1.34 (s, 3H, H-7), 1.39 (s, 3H, H-8), 1.78 (m, 2H, H-3), 3.54 (AB of ABX, 2H, J_{AB}=7.7 Hz; J_{AX}=7.7 Hz; J_{BX}=5.9 Hz, Δν=106.7 Hz, H-1), 4.06 (A of ABX, 1H, J_{AB}=7.7 Hz; J_{AX}=7.7 Hz, Δν=106.7 Hz, H-1), 4.23 (m, 2H, H-2 and H-4); ^{13}C NMR ($CDCl_3$): δ −5.05 ($(CH_3)_2Si$), −4.55 ($(CH_3)_2Si$), 18.26 ($C(CH_3)_3Si$), 25.81 (C-7 and C-8), 27.09 ($C(CH_3)_3Si$), 36.19 (C-3), 69.60 (C-1), 71.78 (C-2), 75.30 (C-4), 109.04 (C-6.); IR ($CHCl_3$) 2920–3040, 2860–2900, 1750 cm^{-1}.

3.16. *(−)-[3(R)5(R)S(S)]-3,5-(Isopropylidenedioxy)-6-(*p*-tolylsulfinyl)methyl hexanoate,* **10a**

The dihydroxysulfoxide **10** (1.5 g, 5.33 mmol) and catalytic *p*-TsOH (0.11 g, 0.53 mmol) were dissolved in acetone (270 ml) and dimethoxypropane (27 ml). Stirring at room temperature was continued until all starting material disappeared (TLC). The reaction mixture was diluted in AcOEt (100 ml) and saturated $NaHCO_3$ (100 ml) was added. The reaction was stirred at room temperature to obtain a white precipitate. The aqueous layer was extracted with AcOEt (3×100 ml). The combined organic layers were washed with a saturated solution of NH_4Cl (100 ml) and with brine (100 ml), dried over $MgSO_4$, and filtered before being concentrated. The crude product was purified by column chromatography on silica gel (AcOEt:CH_2Cl_2=6:4) to give a yellow oil (1.72 g, 95%); R_f 0.44 (AcOEt:CH_2Cl_2=6:4); $[\alpha]_D$=−119 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 3H, H-8), 1.44 (s, 3H, H-9), 1.71 (m, 2H, H-4),

2.39 (s, 3H, Me *p*-Tol), 2.51 (AB of ABX, 2H, J_{AB}=15.87 Hz; J_{AX}=5.6 Hz; J_{BX}=7.9 Hz, Δν=33 Hz, H-6), 2.78 (m, 2H, H-2), 3.66 (s, 3H, MeO), 4.35 (m, 1H, H-3), 4.42 (m, 1H, H-5), 7.42 ($(AB)_2$, 4H, J_{AB}=8 Hz, Δν=42.4, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.37 (Me *p*-Tol), 24.36–24.61 (C-8 and C-9), 37.07 (C-4), 40.31 (C-2), 51.66 (MeO), 60.94 (C-3), 63.33 (C-5), 64.05 (C-6), 101.43 (C-7), 123.77, 129.99 (C arom.), 141.41 (C_q arom.), 171.15 (C-1); IR ($CHCl_3$) 3000–2860, 1720 cm^{-1}. Anal. calcd for $C_{17}H_{24}O_5S$: C, 59.97; H, 7.11. Found: C, 60.17; H, 6.98.

3.17. (−)-[3(R)5(R)S(S)]-6-Acetoxy-3,5-(isopropylidenedioxy)-6-(p-tolylthio)-methyl hexanoate, ***12***

Anhydrous sodium acetate (1.45 g, 17.62 mmol) was added to the preceding sulfoxide **10a** (500 mg, 1.47 mmol). Acetic anhydride (100 ml) was then added, and the mixture was refluxed (135°C) until all the sulfoxide was consumed (TLC). After cooling, the solvent was removed by azeotropic distillation with toluene to obtain a deep brown solid which was dissolved in CH_2Cl_2 and filtered on Celite. The crude product was purified by column chromatography on silica gel (hexane:AcOEt=8:2) to afford **12** as a yellow oil (528 mg, 94%), a mixture of the two isomers at the C_6 position which were not separated. ^{1}H NMR ($CDCl_3$, 200 MHz): major isomer, δ 1.28 (s, 3H, H-8), 1.34 (s, 3H, H-9), 1.69 (m, 2H, H-4), 1.96 (s, 3H, MeCOO), 2.37 (s, 3H, Me *p*-Tol), 2.58 (m, 2H, H-2), 3.66 (s, 3H, MeO), 4.00 (m, 1H, H-3), 4.23 (m, 1H, H-5), 6.03 (m, 1H, H-6), 7.23 (AB, 4H, J_{AB}=8 Hz, Δν=55.5 Hz, H arom.); minor isomer, 1.37 (s, 3H, H-8), 1.41 (s, 3H, H-9), 1.69 (m, 2H, H-4), 1.92 (s, 3H, MeCOO), 2.37 (s, 3H, Me *p*-Tol), 2.58 (m, 2H, H-2), 3.66 (s, 3H, MeO), 4.00 (m, 1H, H-3), 4.23 (m, 1H, H-5), 6.03 (m, 1H, H-6), 7.23 (AB, 4H, J_{AB}=8 Hz, Δν=55.5 Hz, H arom.); ^{13}C NMR ($CDCl_3$): δ 21.02 (MeCOO), 24.56 (Me *p*-Tol), 34.53 (C-4), 40.35 (C-2), 51.66 (MeO), 63.42 (C-3), 67.74 (C-5), 81.90 (C-6), 101.26 (C-7), 129.85, 133.95 (C arom.), 138.54, 138.63 (C_q arom.), 169.68 (COMe), 171.06 (C-1). Anal. calcd for $C_{19}H_{26}O_6S$: C, 59.67; H, 6.85. Found: C, 59.74; H, 6.78.

3.18. (+)-[3(R)5(R)] Methyl-6-acetoxy-3,5-(isopropylidenedioxy) hexanoate, ***12a***

Raney nickel was added in portions to a solution of compound **12** (1.8 g, 207 mmol) in MeOH (25 ml). The reaction was stirred at room temperature for 25 h. The mixture was carefully filtered through Celite and the solid washed with MeOH. After evaporating the solvent, the product was purified by rapid chromatography on silica gel (hexane:AcOEt=8:2) to afford a colorless oil (527 mg, 75%); R_f 0.41 (hexane:AcOEt=6:4); $[\alpha]_D$=+17 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.27 (s, 3H, H-8), 1.30 (s, 3H, H-9), 1.61 (m, 2H, H-4), 2.00 (s, 3H, MeCOO), 2.44 (AB of ABX, 1H, J_{AB}=15.7 Hz; J_{AX}=7.7 Hz; J_{AX}=5.5 Hz, Δν=25.9 Hz, H-2), 3.61 (s, 3H, H-6 and H-3), 45.22 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 20.88 (CH_3COO), 24.49, 24.54 (C-8 and C-9), 33.67 (C-2), 40.38 (C-4), 51.65 (CH_3OCO), 63.26 (C-3), 64.84 (C-5), 66.13 (C-6), 100.88 (C-7), 170.91 (C-1), 171.13 (CH_3COO); IR ($CHCl_3$) 2940–2980, 1725 cm^{-1}. Anal. calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.44; H, 7.97.

3.19. [3(R)5(R)] Methyl 3,5-(isopropylidenedioxy)-3-hydroxy-hexanoate, ***14***

(1) An aqueous solution of K_2CO_3 (1.56 g, 11.28 mmol/72 ml) was added dropwise to a stirred solution of the preceding acetoxyester **12a** (1.174 g, 4.51 mmol) in MeOH (144 ml). The reaction mixture was stirred at room temperature for 20 min and then hydrolyzed with a saturated solution of NH_4Cl (100 ml). The aqueous layer was extracted with AcOEt (3×100 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated.

(2) To a solution of the resulting crude hydroxyester in acetone (90 ml) was added *p*-toluenesulfonic acid (85.77 mg, 0.45 mmol). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of $NaHCO_3$ (50 ml). The aqueous layer was extracted with AcOEt (3×50 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel (hexane:AcOEt=5:5) to afford a yellow oil (817 mg, 83%); R_f 0.38 (hexane:AcOEt=5:5); $[\alpha]_D=-12$ (c 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H, H-8), 1.39 (s, 3H, H-9), 1.73 (t, 2H, H-2), 2.51 (m, 2H, H-4), 3.37 (A of ABX, 1H, J_{AB}=8 Hz; J_{AX}=7.7 Hz, Δν=111.8 Hz, H-6), 3.70 (s, 3H, CH_3OCO), 3.90 (B of ABX, 1H, J_{AB}=8 Hz; J_{BX}=6.1 Hz, Δν=111.8 Hz, H-6), 4.22 (m, 2H, H-5 and H-3); ^{13}C NMR ($CDCl_3$): δ 25.73, 26.97 (C-8 and C-9), 40.40 (C-4), 41.40 (C-2), 51.76 (MeO), 65.51 (C-3), 69.52 (C-6), 74.49 (C-5), 108.81 (C-7), 172.92 (C-1); IR ($CHCl_3$) 3730, 3030–2930, 1750 cm^{-1}. Anal. calcd for $C_{10}H_{18}O_5$: C, 55.83; H, 8.31. Found: C, 55.89; H, 8.39.

3.20. (+)-[3(R)5(S)]-5,6-(Isopropylidendioxy)-1,3-hexanediol, ***16***

To a solution of lithium aluminium hydride (195.4 mg, 5.15 mmol) in ether (76 ml) at −25°C was added a solution of the ester **14** (1.12 g, 5.15 mmol) in ether (7.6 ml) at −25°C. The reaction mixture was stirred at −25°C until all the starting material was consumed (TLC). The reaction was quenched with a saturated solution of sodium sulfate, filtered over Celite and the solvent flash evaporated. The crude product was purified by silica gel chromatography (AcOEt 100%) to afford a colorless oil (833 mg, 85%); R_f 0.21 (AcOEt 100%); $[\alpha]_D=+3$ (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.36 (s, 3H, H-9), 1.42 (s, 3H, H-8), 1.76 (m, 4H, H-4), 2.67 (m, 1H, OH), 3.31 (m, 1H, OH), 3.58 (td, 2H, H-1), 3.58 (A of ABX, 1H, J_{AB}=8 Hz; J_{AX}=7.5 Hz, Δν=104 Hz, H-6), 3.94 (m, 1H, H-6), 3.86 (m, 2H, H-1), 4.09 (m, 2H, H-6 and H-3), 4.27 (m, 1H, H-5); ^{13}C NMR ($CDCl_3$): δ 25.72, 26.96 (C-8 and C-9), 38.82 (C-1), 40.54 (C-2), 61.06 (C-4), 68.63 (C-5), 69.55 (C-6), 73.50 (C-3), 108.89 (C-7); IR ($CHCl_3$) 3730–3660, 3030–2920 cm^{-1}. Anal. calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.78; H, 9.56.

3.21. (−)-[3(R)5(S)]-1-Iodo-5,6-(isopropylidenedioxy)-3-hexanol, ***3a***

A solution of diol **16** (100 mg, 0.53 mmol) in ether (2.4 ml) and acetonitrile (1 ml) at 0°C was treated with imidazole (78.73 mg, 1.16 mmol), triphenylphosphine (151.66 mg, 0.58 mmol) and iodine (146.76 mg, 0.58 mmol). The reaction mixture was stirred at room temperature until no more starting material was detected by TLC (hexane:AcOEt=5:5). A saturated solution of $NaHCO_3$ (2 ml) was added and the mixture stirred for 10 min. To the resulting mixture was added iodine in small portions until a persistent red-colored organic layer was obtained. Stirring was continued for another 10 min. After addition of a sodium thiosulfate solution (2 ml), the mixture was extracted with ether (3×10 ml) and the combined organic layers washed with brine prior to drying ($MgSO_4$) and solvent evaporation. Silica gel chromatography of the residue (hexane:AcOEt=5:5) provided (−)-[3(*R*)5(*S*)]-1-iodo-5,6-(isopropylidenedioxy)-3-hexanol as a colorless oil (102 mg, 64%); R_f 0.53 (hexane:AcOEt=5:5); $[\alpha]_D=-23$ (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.35 (s, 3H, H-9), 1.41 (s, 3H, H-8), 1.72 (t, 2H, H-4), 1.95 (m, 2H, H-2), 2.71 (d, 1H, OH), 3.29 (td, 2H, H-1), 3.58 (A of ABX, 1H, J_{AB}=8 Hz; J_{AX}=7.5 Hz, Δν=104 Hz, H-6), 3.94 (m, 1H, H-5), 4.07 (B of ABX, 1H, J_{AB}=8 Hz; J_{BX}=6 Hz, Δν=104 Hz, H-6), 4.30 (m, 1H, H-3); ^{13}C NMR ($CDCl_3$): δ 2.55 (C-1), 25.65, 26.93 (C-8 and C-9), 39.39 (C-2), 40.91 (C-4), 68.93 (C-5), 69.32 (C-6), 73.36 (C-3), 109.10 (C-7). Anal. calcd for $C_9H_{17}O_3I$: C, 36; H, 5.71. Found: C, 35.92; H, 5.70.

3.22. (+)-[2(R)4(R)8(S)10(R)]-4-(tert-Butyldimethylsilyloxy)-1,2-10,11-(diisopropylidenedioxy)-8-hydroxy-5-undecene, 18

(1) [3(*R*)5(*S*)]-(5,6-(Isopropylidenedioxy)-3-hexanyl)-phosphonium iodide, **3**: A solution of the preceding iodide **3a** (0.27 g, 0.91 mmol) and triphenylphosphine (1.2 g, 4.57 mmol) in dry toluene (10 ml) was refluxed until no more starting material was detected by TLC (hexane:AcOEt=5:5). After evaporating the solvent, the phosphonium salt **3** was obtained as a white solid by precipitation from dry ether, filtration and washing with ether (quantitative yield). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 3H, H-8), 1.31 (s, 3H, H-9), 1.81 (m, 4H, H-4 and H-2), 3.50 (A of ABX, 1H, J_{AB}=8 Hz; J_{AX}=8 Hz, Δν=116.4 Hz, H-6), 3.88 (m, 1H, H-3), 4.09 (B of ABX, 1H, J_{AB}=8 Hz; J_{BX}=6 Hz, Δν=116.4 Hz, H-6), 4.26 (m, 3H, H-5 and H-1), 7.50 (m, 15H, H arom.).

(2) To a slurry of **3** (500 mg, 0.89 mmol) in THF (4 ml) at 0°C was added a solution of *n*-butyllithium (1.15 ml, 1.79 mmol, 1.55 M in hexane) dropwise over 2 min. The resulting yellow–orange solution was stirred vigorously at 0°C for 20 min and then at room temperature for 10 min, after which a solution of lithium bromide (77.21 mg, 0.89 mmol) in THF (4 ml) was added. The mixture was cooled to −45°C, and a solution of **2** (171 mg, 0.59 mmol) in THF (4 ml) was added. The reaction mixture was stirred at −30°C until all the aldehyde was consumed (TLC hexane:ether=6:4). After quenching with a saturated solution of NH_4Cl, the reaction was acidified to pH=5–6 with a 5% solution of HCl. The aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and the solvent flash evaporated. The crude product was purified by column chromatography on silica gel (hexane:ether=6:4) to give a colorless oil (105.4 mg, 50%); R_f 0.54 (hexane:ether=5:5); $[\alpha]_D$=+4 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.02 (s, 3H, $(CH_3)_2Si$), 0.05 (s, 3H, $(CH_3)_2Si$), 0.87 (s, 9H, $C(CH_3)_3Si$), 1.33 (s, 3H, H-14), 1.35 (s, 3H, H-15), 1.38 (s, 3H, H-17), 1.40 (s, 3H, H-18), 1.70 (m, 4H, H-3 and H-9), 2.23 (m, 2H, H-7), 2.58 (s, 1H, OH), 3.50 (m, 2H, H-1 and H-11), 3.75 (m, 2H, H-2 and H-10), 4.05 (m, 2H, H-1 and H-11), 4.23 (m, 2H, H-4 and H-8), 5.56 (m, 2H, H-5 and H-6); ^{13}C NMR ($CDCl_3$): δ −4.70 ($(CH_3)_2Si$), −4.05 ($(CH_3)_2Si$), 18.25 ($C(CH_3)_3Si$), 25.96 (C-13, C-14, C-16 and C-17), 27.00 ($C(CH_3)_3Si$), 39.86 (C-7), 40.83, 42.46 (C-3 and C-9), 68.02, 71.46 (C-10 and C-2), 69.92 (C-11 and C-1), 73.12, 73.84 (C-8 and C-4), 108.90 (C-12 and C-15), 125.97 (C-6), 137.86 (C-5). Anal. calcd for $C_{23}H_{44}O_6Si$: C, 57.95; H, 9.3. Found: C, 57.7; H, 9.24.

3.23. [2(R)4(R)8(S)10(R)]-1,2-10,11-(Diisopropylidenedioxy)-4,8-dihydroxy-undecane, 1

(1) A solution of the unsaturated compound **18** (141 mg, 0.32 mmol) and 10% Pd/C (44 mg) in AcOEt (6 ml), under a hydrogen atmosphere (5 atm), was stirred at room temperature for 5 h. The catalyst was removed by filtration over Celite, washed with AcOEt and the solvent evaporated. The crude compond was purified by silica gel chromatography (hexane:ether=5:5) to afford a colorless oil (138.6 mg, 97%); R_f 0.54 (hexane:ether=5:5); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.05 (s, 3H $(CH_3)_2Si$), 0.08 (s, 3H $(CH_3)_2Si$), 0.88 (s, 9H, $C(CH_3)_3Si$), 1.15 (m, 6H, H-5, H-6 and H-7), 1.3 (s, 3H, H-acetonide), 1.35 (s, 3H, H-acetonide), 1.38 (s, 3H, H-acetonide), 1.40 (s, 3H, H-acetonide), 1.42 (m, 4H, H-3 and H-9), 3.53 (m, 2H, H-1 and H-11), 3.86 (m, 2H, H-1, H-11 and H-8), 4.38 (m, 1H, H-4).

(2) To a solution of the preceding silyloxy derivative (60.9 mg, 0.14 mmol) in THF (2 ml) was added, at 0°C, tetrabutylammonium fluoride (0.34 ml of a 1 M solution in THF, 0.34 mmol). The reaction mixture was stirred at room temperature for 2 days and the solvent evaporated. The residue was dissolved in AcOEt (5 ml) and acidified with a 10% solution of HCl. The aqueous layer was extracted with AcOEt (3×5 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel chromatography (ether:AcOEt=8:2) to afford

a white solid (42.8 mg, 92%); R_f 0.22 (ether:AcOEt=8:2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35 (s, 6H, H-acetonide), 1.40 (s, 6H, H-acetonide), 1.50 (m, 6H, H-5, H-6 and H-79), 1.63 (m, 4H, H-3 and H-9), 3.58 (A of ABX, 1H, J_{AB}=7.5 Hz; J_{AX}=5 Hz, Δν=107.2 Hz, H-1 and H-11), 3.79 (B of ABX, 1H, J_{AB}=7.5 Hz; J_{BX}=7.5 Hz, Δν=107.2 Hz, H-6), 4.33 (m, 2H, H-4 and H-8).

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