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TETRAHEDRON: *ASYMMETRY*

Lipase mediated resolution of 1,3-butanediol derivatives: chiral building blocks for pheromone enantiosynthesis. Part 3†

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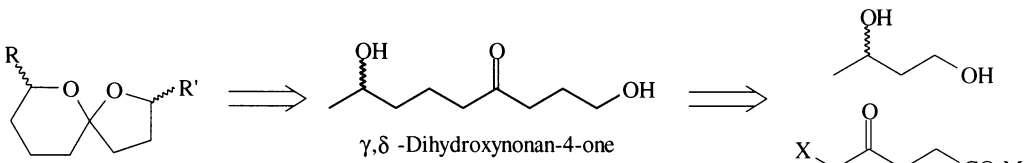
Abstract—(*R*,*S*)-1,3-Butanediol **5** was kinetically resolved by enzymatic acetylation with vinyl acetate under the presence of Chirazyme™ L-2, c–f, yielding (*S*)-1-*O*-acetyl-1,3-hydroxybutane **6** and (*R*)-1,3-di-*O*-acetyl-1,3-butanediol **7** with enantiomeric excesses of 91% ($E=67.3$). Compounds **6** and **7** were easily transformed into the corresponding (*S*)-3-*O*-(2-methoxyethoxymethyl)-3-hydroxybutanal **10** and (*R*)-3-benzyloxybutanal **19**, through a protection–deprotection and functional group interchange methodology. Subsequent reaction of **10** and **19** with 3-(methoxycarbonylpropionyl-methylene)triphenylphosphorane afforded methyl (*E*,*S*)-8-*O*-(2-methoxyethoxymethyl)-4-oxo-5-nonenoate **12** and (*E*,*R*)-8-benzyl-oxy-4-oxo-5-nonenoate **20**. The alkenes **19** and **20** were then catalytically hydrogenated to the corresponding saturated esters **13** and **21**. Treatment of **13** and **21** with 1,2-ethanedithiol/$F_3B{\cdot}OEt_2$ afforded dithioketals **14** and **22**, which were respectively reduced to (*S*)-1,8-dihydroxy-4-nonanone ethylidenedithioketal **15** and (*R*)-8-*O*-benzyl-1,8-dihydroxy-4-nonanone ethylidenedithioketal **23**. Finally, deprotection of **15** by catalytic hydrogenation under acidic conditions gave the expected (5*S*,7*S*)-(−)-7-methyl-1,6-dioxaspiro[4.5]decane **1**. The (5*R*,7*R*)-(+)-**1** enantiomer was analogously prepared from **23**. Both compounds were formed by this procedure with an e.e. of 91%.

1. Introduction

Since Francke et al.[2] initially identified mixtures of the 7-methyl- **1** (major component), 2-methyl- **2**, 7-ethyl-2-methyl- **3**, and 2-ethyl-7-methyl-1,6-dioxaspiro[4.5]-decane **4** analogues, together with 2-nonanone as the antiaggregation pheromone bouquet of workers of the common wasp *Vespula vulgaris* (F.), *V. germanica* (F.), and *Dolichovespula saxonica* (F.) in 1978 and 1979, little information about the stereochemistry of naturally occurring **1**–**4** has been communicated. Thus, only a comment in the paper by Weston et al.[3a] about the unpublished dissertation of G. Lübke,[3b] where (5*S*,7*S*) and (2*S*,5*S*,7*S*) configurations for **1** and **3** from the venom of *V. vulgaris* and *V. germanica* were respectively assigned, has been reported. In recent years, our group has been involved in the stereospecific synthesis and identification of semiochemicals,[4] and due to the extreme structure–activity relationship existing in the case of the pheromones,[5] we are interested in continuing our efforts in the highly stereoselective synthesis of some of the above spiroketals. To this end, we report herein on a new and simple procedure for the preparation of highly enantiopure samples of (5*S*,7*S*)-(−)- and (5*R*,7*R*)-(+)-**1**.



1 R = Me; R' = H
2 R = H; R' = Me
3 R = Et; R' = Me
4 R = Me; R' = Et

Scheme 1.

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† For Part 2, see Ref. 1.

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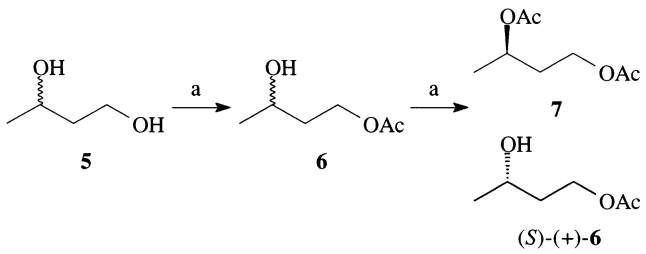


Scheme 2. (a) Chirazyme™ L-2, c–f/vinyl acetate/diethyl ether.

Several syntheses of (±)-**1** have been reported[3a,6] including stereoselective ones, involving alkylation of acetone *N*,*N*-dimethylhydrazone[7] and α-acyl-lactones[8] with chiral synthons, alkylation of chiral oxiranes[9] with acetylide, and finally enzymatic resolution procedures.[10] Retrosynthetic analysis of compound **1** (see Scheme 1) clearly demonstrated that chiral 1,3-butanediol and levulinic acid derivatives could be excellent and cheap starting materials for its stereoselective synthesis and with this particular aim new syntheses were planned by our group.

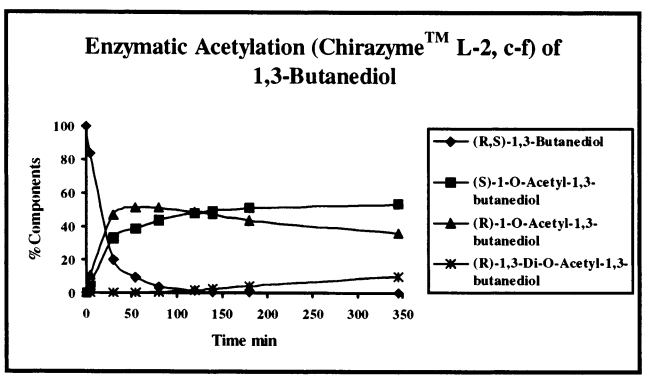
Preparation of both (*R*)- and (*S*)-1,3-butanediol has been previously reported. Mori et al.[11] either subjected poly(3-hydroxybutanoate) (PHB), produced by *Zoogloea ramigera*, to ethanolysis to afford ethyl (*R*)-3-hydroxybutanoate or reduced ethyl acetoacetate microbiologically (using baker's yeast) to the (*S*)-enantiomer. Both products were then reduced (LAH) to afford the corresponding enantiomeric 1,3-butanediols. More recently, Mori[12] obtained (*R*)-1,3-butanediol by enantiodegradation of the (*S*)-enantiomer by *Geotrichum* sp. WF9101 from a racemic mixture. A similar methodology to that described herein is that used by Eguchi et al.,[13] where a racemic mixture of 1,3-butanediol was resolved by acetylation with butyl acetate in the presence of a lipase, yielding (*R*)-1,3-diacetoxybutane. Eguchi's study showed SP382 (from *Candida* sp.) to be the most efficient resolving agent.

2. Results and discussion

Reaction between (*R*,*S*)-1,3-butanediol **5** and vinyl acetate in ether in the presence of different lipases[14] was initially explored and on the basis of the obtained results, Chirazyme™ L-2, c–f was chosen. The choice was made on the following basis: GLC monitoring of the reaction on a chiral (β-DEX™) stationary phase (see Scheme 2, Fig. 1, and Section 4) demonstrated that Chirazyme™ L-2, c–f firstly acts in a fast and extremely chemoregio- but non-enantioselective manner to give (*R*,*S*)-1-*O*-acetyl-1,3-butanediol **6** (Fig. 1), which is then kinetically and highly enantioresolved, in a second step, to produce the corresponding (*R*)-(−)-1,3-di-*O*-acetyl derivative **7** and (*S*)-(+)-**6** each with an e.e. of 91% ($E=67.3$). The products, (*S*)-(+)-**6** and **7**, were easily separated by chromatography and identified on the basis of their optical and spectroscopic data.[15] These results improved those reached by Eguchi, where an e.e. of 85.8% ($E=22$) was obtained.

Compound (*S*)-(+)-**6** was readily transformed (see Scheme 3) into (*S*)-3-*O*-(2-methoxyethoxymethyl)-butanal **10**, through its initial protection as 3-*O*-MEM derivative **8**, followed by deacetylation to the corresponding partially protected alcohol **9** and finally PCC oxidation to the required aldehyde **10** (which has been previously reported[16]) for use in the next step of the synthesis.

Reaction of **10** with (3-methoxycarbonylpropionyl)methylenetriphenylphosphorane **11**[17] afforded methyl (*E*,*S*)-8-*O*-(2-methoxyethoxymethyl)-4-oxo-5-



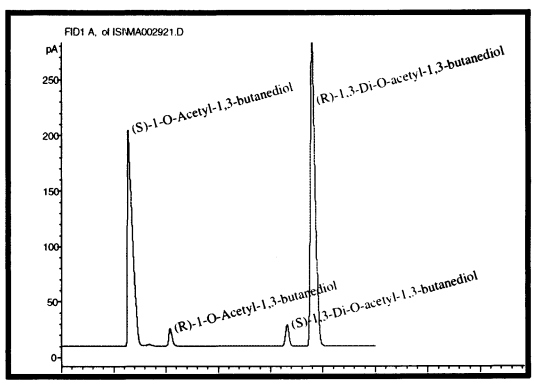
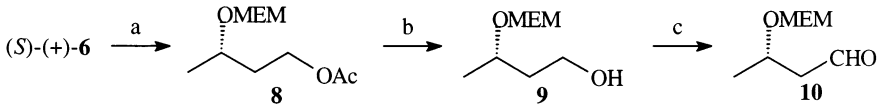


Figure 1. Kinetic data for enzymatically (Chirazyme™ L-2, c–f) catalyzed acetylation of **5** and GLC analysis (e.e.) on a β-DEX™ column.

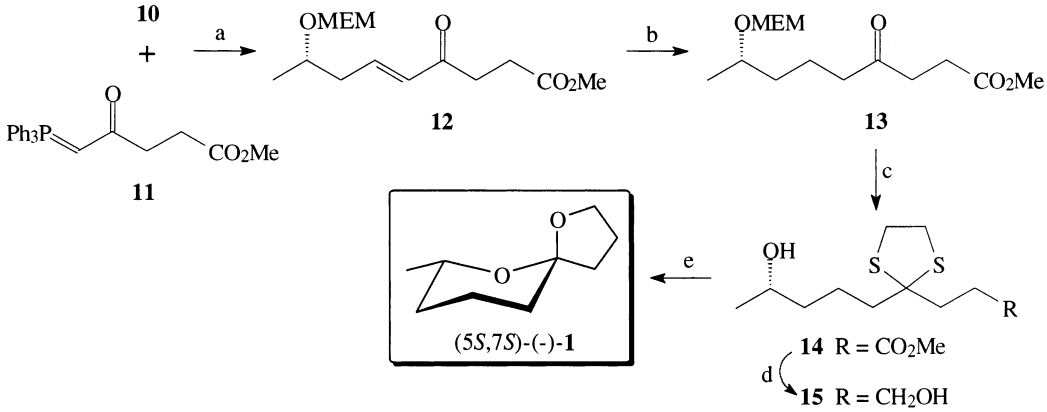


Scheme 3. (a) MEMCl/DIPEA/CH_2Cl_2; (b) NaOMe/MeOH; (c) PCC/4 Å MS/CH_2Cl_2.

nonenoate **12**, a key intermediate for the required chiral 1,8-dihydroxynonan-4-one skeleton of the target molecule. The (*E*)-configuration was assigned on the basis of the alkenic coupling constant ($J_{5,6}=16$ Hz) in the proton NMR spectrum of **12**. Catalytic hydrogenation on 10% Pd–C gave the saturated ester **13**, that contains the structural and functional features allowing it to be straightforwardly transformed into the target pheromone (−)-**1**. Thus, reaction of **13** with 1,2-ethanedithiol, catalyzed by $F_3B{\cdot}OEt_2$, caused deprotection at O-8 concomitant with the formation of the corresponding methyl (*S*)-8-hydroxy-4-oxononanoate ethylidenedithioketal **14**, that was subsequently $LiAlH_4$ reduced to (*S*)-1,8-dihydroxy-4-nonanone ethylidenedithioketal **15**. Finally, removal of the dithioketal protecting group of **15** under literature conditions gave rise to an intramolecular ketalation process to afford the expected (5*S*,7*S*)-7-methyl-1,6-dioxaspiro[4.5]-decane [(−)-**1**] (see Scheme 4), with 91% e.e., according to GLC analysis (A) on a chiral (β-DEX™) stationary phase (see Fig. 2). The high stereoselectivity observed during the formation of the new stereogenic center at C-(5) must be attributed to steric and stereoelectronic factors.[18]

In a similar strategy, compound **7** was catalytically (NaOMe/MeOH) deacylated to (*R*)-1,3-butanediol[19] **5**, which was chemoselectively tritylated at C-(1) to produce (*R*)-**16**.[19] Subsequent *O*-benzylation at C-(8) gave (*R*)-8-*O*-benzyl-1-*O*-trityl-1,3-butanediol **17**. Removal of the 1-*O*-trityl group followed by PCC oxidation afforded the desired (*R*)-3-*O*-benzyloxybutanal **19** in good yield (see Scheme 5).[20]

Reaction of **19** with phosphorane **11** also occurred with high stereoselectivity as above, giving methyl (*E*,*R*)-8-benzyloxy-4-oxo-5-nonenoate **20**, that was hydrogenated to the saturated ester **21**, and subsequently transformed (after dithioketalation to **22** and reduction) to (*R*)-8-*O*-benzyl-1,8-dihydroxy-4-nonanone ethylidenedithioketal **23**. Finally, dethioketalation of **23**, followed by the debenzylation of the not investigated



Scheme 4. (a) CH_2Cl_2; (b) H_2/10% Pd–C; (c) $HS(CH_2)_2SH/F_3B{\cdot}OEt_2$; (d) $LiAlH_4$/ether; (e) $HgCl_2/MeCN/H_2O$.

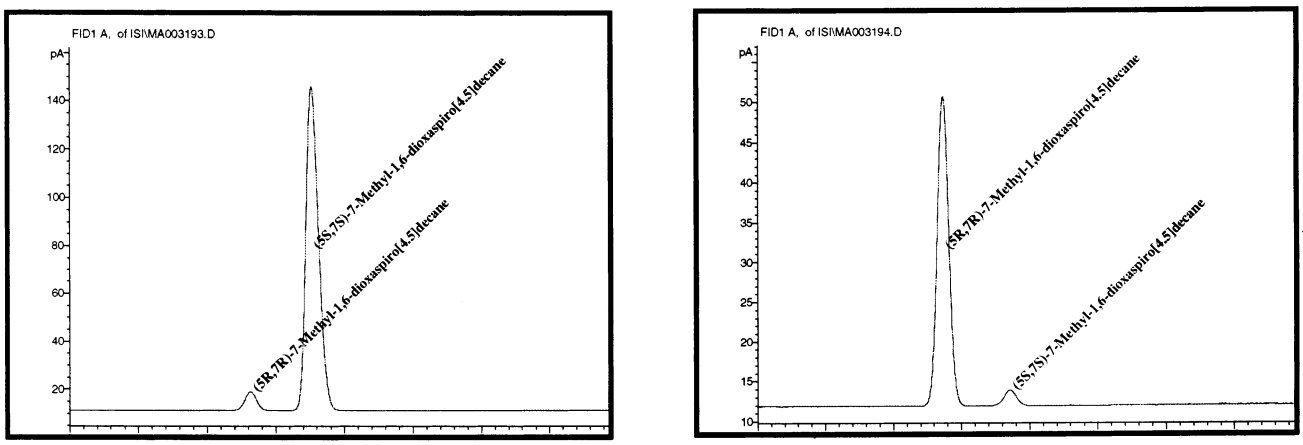
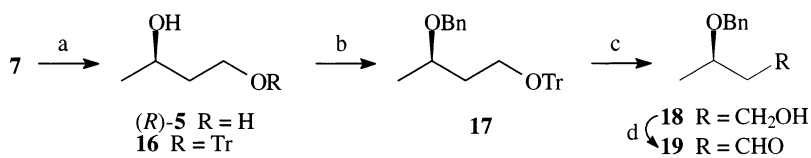
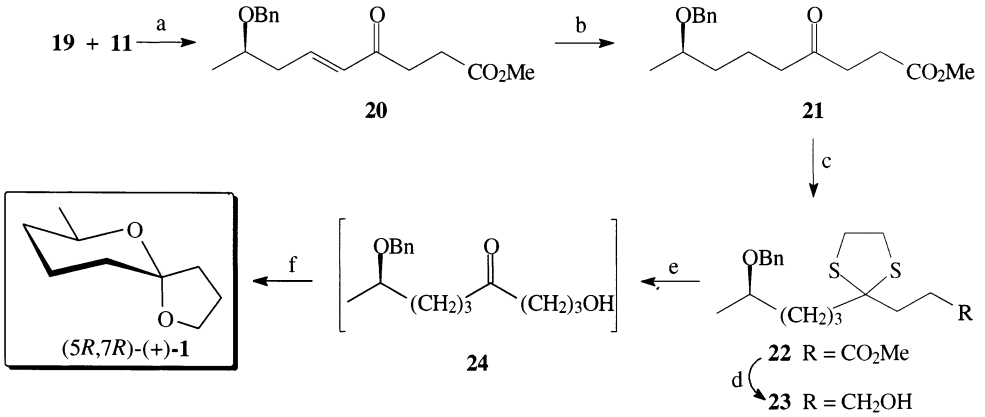


Figure 2. GLC analysis (e.e.) on a β-DEX™ column of (−)-**1** and (+)-**1**, respectively.



Scheme 5. (a) NaOMe/MeOH then $TrCl/Et_3N/CH_2Cl_2$; (b) NaH/THF then BnBr; (c) H_3O^+; (d) PCC/4 Å MS/CH_2Cl_2.



Scheme 6. (a) CH_2Cl_2; (b) H_2/10% Pd–C; (c) $HS(CH_2)_2SH/F_3B{\cdot}OEt_2$; (d) $LiAlH_4/Et_2O$; (e) $HgCl_2$/HgO/MeCN, H_2O; (f) 10% Pd–C/H_2, ether, H_3O^+, 24 h.

intermediate hydroxyketone **24**, caused internal spiroketalation to afford (5*R*,7*R*)-7-methyl-1,6-dioxaspiro-[4.5]decane [(+)-**1**] with a 91% e.e. (see Scheme 6 and Fig. 2).

3. Conclusion

On the basis of the above results, we can conclude that the use of cheap commercial racemic materials in conjunction with immobilized lipases is an excellent methodology for the enantiosynthesis of both enantiomers of complex chiral biologically active products from natural sources.

4. Experimental

4.1. General

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. GLC was performed on a Hewlett–Packard 6890 gas chromatograph equipped with split/splitless injector, a flame-ionization detector, and a β-DEX™ 325 (Supelco™) capillary column (30 m×0.25 mm i.d×0.25 μm film thickness) at: (A) 110°C or a capillary HP-5 column (30 m×0.25 mm i.d.×0.25 μm film thickness) at: (B) 5 min at 130°C, program to 250°C, 10°C/min; (C) 230°C; (D) 7 min at 100°C, program to 230°C, 10°C/min; (E) 4 min at 180°C, program to 250°C, 10°C/min. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275°C. TLC was performed on precoated silica gel 60 F_{254} aluminum sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, mass spectrum and HRMS.

4.2. (*S*)-1-*O*-Acetyl- 6 and (*R*)-1,3-di-*O*-acetyl-1,3-butanediol 7

(a) To a gently stirred solution of (*R*,*S*)-1,3-butanediol (**5**, 18 mL, 0.2 mol) in ether (300 mL), vinyl acetate (26 mL, 0.4 mol) and Chirazyme™ L-2, c–f (300 mg) were added at room temperature. Progress of the reaction was monitored by GLC analysis (A) which indicated that, after 125 min, the starting material was completely consumed and two products had formed (found to be (*S*)-(+)- and (*R*)-(−)-**6**, t_R 7.3 and 7.9 min, respectively). The reaction was continued for a further 220 min when the transformation of (*R*)-(−)-**6** into (*R*)-(−)-**7** (10%, t_R 10.9 min) could only be observed (see below and Fig. 1). In order to increase the rate of the latter process additional enzyme (100 mg) was added and the reaction was left to reach completion (30 h). The reaction was quenched by filtering off the enzyme, which was thoroughly washed with ether. The combined filtrate and washings were concentrated to a residue (30.25 g). An aliquot (3 g) was chromatographed (gradient elution: ether/hexane, 3:1→ether) to afford first (*R*)-(−)-**7** (1.52 g, 87.4%), e.e. 91%, $E=67.3$; $[\alpha]_D^{27}$ −27 (*c* 1) [lit.[15] $[\alpha]_D^{27}$ −23.5 (*c* 1)]; ν_{max}^{film} 1747, 1744 and 1740 cm^{-1} (OAc). The second fraction was (*S*)-(+)-**6** (1.15 g, 87%), e.e. 91% $E=67.3$; $[\alpha]_D^{27}$ +17.5 (*c* 1.2); ν_{max}^{film} 3434 (OH), 1744 and 1741 cm^{-1} (OAc).

Conventional acetylation of (*S*)-(+)-**6** (135 mg, 1 mmol) in dry dichloromethane (2 mL) with triethylamine (0.2 mL) and acetic anhydride (0.2 mL) gave, after work-up and column chromatography (ether/hexane, 1:3), (*S*)-(+)-**7** (100 mg, 56%): t_R 10.2 min (A); $[\alpha]_D^{24}$ +29 (*c* 0.9) [lit.[15] $[\alpha]_D^{25}$ +27.6 (*c* 4)].

(b) When the enzymatic acetylation of **5** (0.18 mL, 2 mmol) in ether (3 mL) with vinyl acetate (0.35 mL, 3.8 mmol) was carried out in the presence of the same enzyme (40 mg), its optimal conversion into (*S*)-(+)-**6** and (*R*)-(−)-**7** was achieved in 200 min, with the same enantioselectivity.

4.3. (*S*)-1-*O*-Acetyl-3-*O*-(2-methoxyethoxymethyl)-1,3-butanediol 8

To a stirred solution of (*S*)-(+)-**6** (6.33 g, 48 mmol) in dry dichloromethane (40 mL) and *N*,*N*-diisopropylethylamine (12.5 mL, 72 mmol) a solution of 2-methoxyethoxymethyl chloride (MEMCl, 8.3 mL, 72 mmol) in the same solvent (20 mL) was added dropwise at room temperature and the mixture left for 3 h. TLC (ether/hexane, 1:1) then revealed the presence of a new compound of higher mobility. Usual work-up of the reaction mixture afforded the crude MEM ether **8** (9.68 g, 92%) as a mobile oil. An aliquot (500 mg) was chromatographed (ether/hexane, 1:4) to yield pure **8** (420 mg): $[\alpha]_D^{25}$ +34.5 (*c* 1.3). Physical and spectroscopic data were in accordance with those reported in the literature[21] for the racemic compound. Mass spectrum (LSIMS): *m*/*z*: 243.12071 (M^++Na) for $C_{10}H_{20}NaO_5$ 243.12084 (deviation 0.6 ppm).

4.4. (*S*)-3-*O*-(2-Methoxyethoxymethyl)-1,3-butanediol 9

To a solution of **8** (9.2 g, 41.8 mmol) in anhydrous methanol (50 mL) was added a catalytic amount of sodium methoxide and the mixture was kept at room temperature for 3 h. TLC (ether/hexane, 3:1) then showed one product of higher polarity. The mixture was neutralized with acetic acid, concentrated and the residue was dissolved in dichloromethane (30 mL), and the resulting solution was washed with water and concentrated to afford crude **9** (6.7 g, 90%). An aliquot (1.57 g) was chromatographed (gradient elution: ether/hexane, 3:2→ether→ether/methanol, 10:1) to yield pure **9** as mobile oil (1.1 g): GLC (B) t_R 6.49 min; $[\alpha]_D^{24}$ +96 (*c* 1.3); ν_{max}^{film} 3506 cm^{-1} (OH). NMR data: ^{1}H, 4.79 and 4.67 (2 d, 2H, J=7.1 Hz, OCH_2O), 3.99 (ddq, 1H, $J_{2a,3}$=4, $J_{2b,3}$=8.7 Hz, H-3), 3.80 (m, 2H, H-1a,1b), 3.64–3.53 (m, 4H, O(CH_2)$_2$O), 3.38 (s, 3H, OCH_3), 2.42 (bs, 1H, HO), 1.79–1.60 (m, 2H, H-2a,2b), and 2.30 (d, 3H, $J_{3,4}$=6.2 Hz, H-4,4,4); ^{13}C, 93.26 (OCH$_2$O), 71.82 and 67.01 (O(CH_2)$_2$O), 70.76 (C-3), 59.46 (C-1), 59.08 (OCH_3), 39.46 (C-2), and 19.44 (C-4). Mass spectrum (LSIMS): *m*/*z*: found 201.1 (M^++Na).

4.5. Methyl (*E*,*S*)-8-*O*-(2-methoxyethoxymethyl)-4-oxo-5-nonenoate 12

To a stirred solution of **9** (746 mg, 4.19 mmol) in dry dichloromethane (15 mL), molecular sieves (4 Å, powder, 2 g) and PCC (2 g) were added at room temperature. After 20 min, GLC (B) then revealed the absence of **9** and the presence of a new compound (t_R 5.38 min). The mixture was diluted with ether (30 mL), filtered through a silica gel pad, thoroughly washed with ether, and the combined filtrate and washings concentrated to a clear mobile oil, presumably (*S*)-3-*O*-(2-methoxyethoxymethyl)-3-hydroxylbutanal **10** that was not investigated but used in the next step.

Crude **10** (640 mg, 3.63 mmol) was dissolved in dichloromethane (10 mL) and treated with a solution of (3-methoxycarbonylpropionyl)methylenetriphenylphosphorane[17] **11** (1.8 g, 4.6 mmol) in the same solvent (10 mL), and the mixture refluxed for 5 h. TLC (ether/hexane, 3:1) then showed the presence of a faster-running compound. The reaction mixture was supported on silica gel and chromatographed (ether/hexane, 2:1) to yield the title compound **12** as a syrup (850 mg, 71% from **9**): GLC (C) t_R 4.98 min; $[\alpha]_D^{23}$ −5.5, $[\alpha]_{405}^{23}$ −21 (*c* 1.1); ν_{max}^{film} 1743, 1740, 1678 and 1635 cm^{-1} (C=O and C=C). NMR data: ^{1}H, 6.86 (dt, 1H, $J_{5,6}$=16, $J_{6,7}$=$J_{6,7'}$=7.3 Hz, H-6), 6.16 (dt, 1H, $J_{5,7}$=$J_{5,7'}$=1.4 Hz, H-5), 4.76 and 4.70 (2 d, 2H, J=7.2 Hz, OCH$_2$O), 3.89 (sext., 1H, $J_{7,8}$=$J_{7',8}$=$J_{8,9}$=6 Hz, H-8), 3.72–3.63 (m, 2H, O(CH$_2$)$_2$O), 3.66 (s, 3H, CO$_2$CH$_3$), 3.53 (t, 2H, J=4.6 Hz, O(CH$_2$)$_2$O), 3.37 (s, 3H, OCH$_3$), 3.87 (t, 2H, $J_{2,3}$=6.7 Hz, H-3,3), 2.61 (t, 2H, H-2,2), 2.41 (m, 2H, H-7,7′) and 1.18 (d, 3H, H-9,9,9); ^{13}C, 197.92 (C-4), 173.41 (C-1), 143.80 (C-6), 132.08 (C-5), 93.85 (OCH$_2$O), 71.82 and 67.07 (O(CH$_2$)$_2$O), 71.77 (C-8), 59.13 (OCH$_3$), 51.86 (CO$_2$CH$_3$), 39.95 and 34.62 (C-3,7), 27.85 (C-2), and 20.27 (C-9). Mass spectrum (LSIMS): *m*/*z*: 311.14699 (M^++Na) for $C_{14}H_{24}NaO_6$ 311.14706 (deviation 0.2 ppm).

4.6. Methyl (*S*)-8-*O*-(2-methoxyethoxymethyl)-4-oxononanoate 13

Compound **12** (5.1 g, 17.7 mmol) in methanol (40 mL) was hydrogenated with 10% Pd–C (250 mg) at 65 psi for 30 min. GLC analysis (C) then revealed that **12** was completely consumed and a new compound (t_R 4.65 min) had formed. The catalyst was filtered off, washed with methanol and the combined filtrate and washings concentrated to crude saturated ester **13** (4.72 g, 92%). Column chromatography (ether/hexane, 2:1) of an aliquot (200 mg) afforded pure **13** as a mobile oil (180 mg): $[\alpha]_D^{23}$ +11 (*c* 1.7); ν_{max}^{film} 1743 and 1717 cm^{-1} (C=O). NMR data: ^{1}H, 4.65 and 4.58 (2 d, 2H, J=7.1 Hz, OCH$_2$O), 3.58 (m, 3H, H-8 and O(CH$_2$)$_2$O), 3.55 (s, 3H, CO$_2$CH$_3$), 3.43 (t, 2H, J=4.7 Hz, O(CH$_2$)$_2$O), 3.27 (s, 3H, OCH$_3$), 2.60 (t, 2H, $J_{2,3}$=6.5 Hz, H-3,3), 2.46 (t, 2H, H-2,2), 2.36 (t, 2H, $J_{5,6}$=7.2 Hz, H-5,5), 1.62–1.22 (m, 4H, H-6,6′,7,7′) and 1.04 (d, 3H, $J_{8,9}$=6.2 Hz, H-9,9,9); ^{13}C, 207.90 (C-4), 173.06 (C-1), 93.59 (OCH$_2$O), 72.52 (C-8), 71.61 and 66.65 (O(CH$_2$)$_2$O), 58.80 (OCH$_3$), 51.55 (CO$_2$CH$_3$), 42.36 (C-5), 36.82 and 36.13 (C-3,7), 27.50 (C-2), 19.93 (C-9), and 19.54 (C-6). Mass spectrum (LSIMS): *m*/*z*: found 313.2 (M^++Na).

4.7. Methyl (*S*)-8-hydroxy-4-oxononanoate ethylidenedithioketal 14

To an ice-water cooled and stirred mixture of **13** (290 mg, 1 mmol) and ethanedithiol (0.22 mL, 2.64 mmol), $F_3B{\cdot}OEt_2$ (0.11 mL, 0.88 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to reach room temperature. After 15 min GLC

(C) revealed that **13** had disappeared and that a new product was formed (t_R 7.01 min). The reaction mixture was diluted with ether and washed with aqueous 10% sodium hydroxide, water and concentrated. Column chromatography (ether/hexane, 1:1) of the residue afforded **14** as a colorless mobile oil (195 mg, 70%): $[\alpha]_D^{25}$ +7, $[\alpha]_{405}^{26}$ +15.5 (*c* 1.3); ν_{max}^{film} 3441 (OH) and 1739 cm^{-1} (C=O). NMR data: ^1H, 3.85 (sext., 1H, $J_{7,8}=J_{7',8}=J_{8,9}=$ 6.1 Hz, H-8), 3.70 (s, 3H, OCH_3), 3.29 (s, 4H, $S(CH_2)_2S$), 2.63 (dd, 2H, $J=7.5$, $J=11$ Hz, H-3,3′), 2.24 (dd, 2H, H-2,2′), 2.03–1.88 (m, 2H, H-5,5′), 1.75–1.38 (m, 4H, H-6,6′,7,7′) and 1.22 (d, 3H, H-9,9,9); ^{13}C, 173.93 (C-1), 70.90 (C-4), 67.86 (C-8), 51.75 (OCH_3), 40.10 ($S(CH_2)_2S$), 44.47, 39.25 and 37.65 (C-3,5,7), 31.54 (C-2), 23.63 (C-9), and 23.09 (C-6). Mass spectrum (LSIMS): *m/z*: 301.09111 (M^++Na) for $C_{12}H_{22}NaO_3S_2$ 301.09081 (deviation −1.0 ppm).

4.8. (*S*)-1,8-Dihydroxy-4-nonanone ethylidenedithioketal 15

To a stirred solution of **14** (154 mg, 0.54 mmol) in anhydrous ether (10 mL), $LiAlH_4$ (40 mg) was added portionwise and the mixture was heated under reflux for 5 h. TLC (ether/hexane, 3:1) then showed the presence of a more polar product. The reaction mixture was quenched by cautious addition of aqueous 10% ammonium chloride, the organic phase separated and the aqueous extracted with ether (3×15 mL). The combined extracts were concentrated and the residue chromatographed (ether) to yield **15** (110 mg, 94%): GLC (C) t_R 6.57 min; $[\alpha]_D^{27}$ +11 (*c* 1); ν_{max}^{film} 3364 cm^{-1} (OH). NMR data: ^1H, 3.86 (sext., 1H, $J_{7,8}=J_{7',8}=J_{8,9}=6.1$ Hz, H-8), 3.71 (t, 2H, $J_{1,2}=6.3$ Hz, H-1,1), 3.31 (s, 4H, $S(CH_2)_2S$), 2.06–1.94, 1.86–1.76, and 1.74–1.43 (3 m, 12H, H-2,2′,3,3′,5,5′,6,6′,7,7′, OH-1,8), and 1.23 (d, 3H, H-9,9,9); ^{13}C, 71.38 (C-4), 67.92 (C-8), 62.90 (C-1), 39.77 ($S(CH_2)_2S$), 43.75, 39.65 and 39.28 (C-3,5,7), 30.19 (C-2), 23.68 (C-9), and 23.17 (C-6). Mass spectrum (LSIMS): *m/z*: 273.09602 (M^++Na) for $C_{11}H_{22}NaO_2S_2$ 273.09589 (deviation −0.5 ppm).

4.9. (5*S*,7*S*)-7-Methyl-1,6-dioxaspiro[4.5]decane 1

To a stirred solution of **15** (1.55 g, 6.2 mmol) in 4:1 v/v acetonitrile/water (40 mL) was added mercuric chloride (2.1 g, 7.75 mmol) and the mixture stirred at room temperature for 24 h. TLC (ether/hexane, 3:1) then revealed the presence of a less polar compound. The mixture was filtered and the filtrate extracted with *n*-pentane (4×25 mL) and the combined extracts were washed with aqueous 10% sodium hydrogen carbonate, then concentrated in a water–ice bath to a residue that was chromatographed (ether/*n*-pentane, 1:10) to afford pure (−)-**1** (830 mg, 86%): GLC analysis (D) t_R 6.36 min, (A) t_R 6.88 min, e.e. 91%; $[\alpha]_D^{26}$ −87 (*c* 1, *n*-pentane), [lit.[8b] $[\alpha]_D^{22}$ −95.5 (*c* 1,14, *n*-pentane); lit.[10b] $[\alpha]_D^{23}$ −92.9 (*c* 0.59, *n*-pentane)]. Physical and spectroscopic data were in agreement with those reported in the literature.[8b,10b]

4.10. (*R*)-1,3-Butanediol (*R*)-5

To a solution of **7** (6.8 g, 39 mmol) in anhydrous methanol (40 mL) was added 0.5 N sodium methoxide (2 mL) and the mixture kept at room temperature for 2 h. TLC (ether) then showed one product of slightly lower mobility. The mixture was neutralized with acetic acid, and the crude diol was supported on silica gel and chromatographed (ether→ether/methanol, 10:1) to give (*R*)-**5** (3.13 g, 90%): $[\alpha]_D^{22}$ −26 (*c* 1, ethanol), [lit.[19] $[\alpha]_D^{21.5}$ −30.7 (*c* 1.47, ethanol)].

4.11. (*R*)-1-*O*-Trityl-1,3-butanediol 16

To an ice-water and stirred solution of (*R*)-**5** (2.73 g, 30.3 mmol) and triethylamine (5.4 mL) in dry dichloromethane (50 mL) a solution of trityl chloride (8.8 g, 30.6 mmol) in the same solvent (20 mL) was added dropwise, and the mixture was allowed to reach room temperature and kept for 6 h. TLC (ether) then revealed a less polar compound. Methanol (2 mL) was added and after 30 min the mixture was concentrated to a residue that was partitioned in ether–water. The ethereal extracts were concentrated to a residue that was chromatographed (ether/hexane, 1:5) to yield pure **16** (9.7 g, 96%): $[\alpha]_D^{25}$ +1 (*c* 1, ethanol), $[\alpha]_D^{24}$ +21 (*c* 1), [lit.[19] $[\alpha]_D^{22}$ −2.5 (*c* 1.12, ethanol)]; ν_{max}^{film} 3420 (OH), 3089, 3057 and 3032 cm^{-1} (aromatic). NMR data: ^1H, 7.45–7.21 (m, 15H, aromatic), 3.98 (ddq, 1H, $J_{2,3}=9.6$, $J_{2',3}=3.4$ Hz, H-3), 3.37 (ddd, 1H, $J_{1,1'}=9.4$, $J_{1,2}=8.2$, $J_{1,2'}=4.4$ Hz, H-1), 3.22 (ddd, 1H, $J_{1',2}=5.6$, $J_{1',2'}$ 4.7 Hz, H-1′), 2.86 (bs, 1H, OH), 1.85–1.65 (m, 2H, H-2,2′) and 1.16 (d, 3H, $J_{3,4}=6.2$ Hz, H-4,4,4); ^{13}C, 147.97, 128.67, 127.98, and 127.16 (Ph_3C), 87.34 (Ph_3C), 67.51 (C-3), 62.57 (C-1), 38.54 (C-2), and 23.35 (C-4). Mass spectrum (LSIMS): *m/z*: 355.16725 (M^++Na) for $C_{23}H_{24}NaO_2$ 355.16740 (deviation 0.4 ppm).

4.12. (*R*)-3-*O*-Benzyl-1-*O*-trityl-1,3-butanediol 17

To a stirred solution of **16** (9.7 g, 29.2 mmol) in dry DMF (50 mL) 80% oil dispersion of sodium hydride (1.3 g, 44 mmol) was added. After 15 min the mixture was cooled (ice-water) and a solution of benzyl bromide (7 mL, 58.4 mmol) in the same solvent (10 mL) was added dropwise and the stirring was maintained overnight. TLC (ether/hexane, 1:2) then showed the presence of a less polar compound. The hydride excess was destroyed by cautious addition of methanol and the mixture concentrated to a residue that was partitioned in ether–water, the organic phase was separated, then concentrated. Column chromatography (ether/hexane, 1:10) afforded **17** as a syrup (11.7 g, 94%): $[\alpha]_D^{22}$ −8 (*c* 1); ν_{max}^{film} 3087, 3063, and 3033 cm^{-1} (aromatic). NMR data: ^1H, 7.45–7.42 and 7.31–7.21 (2 m, 20H, aromatic), 4.53 and 4.39 (2 d, 2H, $J=11.6$ Hz, $PhCH_2$), 3.80 (bsext. 1H, H-3), 3.28–3.15 (m, 2H, H-1,1′), 1.95 (ddt, 1H, $J_{2,3}=5.8$, $J_{1,2}=7.5$, $J_{2,2'}=13.6$ Hz, H-2), 1.77 (m, 1H, H-2′) and 1.17 (d, 3H, $J_{3,4}=6.2$ Hz, H-4,4,4); ^{13}C, 144.47, 139.01, 128.78, 128.33, 127.81, 127.70, 127.40, and 126.94 (Ph_3C and $PhCH_2$), 86.5 (Ph_3C), 72.37 (C-3), 70.56 ($PhCH_2$), 60.43 (C-1), 37.40 (C-2), and 20.01 (C-4). Mass spectrum (LSIMS): *m/z*: found 445.2 (M^++Na).

4.13. (*R*)-3-*O*-Benzyl-1,3-butanediol 18

A solution of **17** (11.2 g, 26.5 mmol) in water/acetic acid/methanol 3:4:3 (100 mL) was heated at 50°C for 2.5 h. TLC (ether/hexane, 1:4) indicated that a more polar product had formed. The mixture was concentrated and repeatedly co-distilled with water. The distillation residue was further purified by chromatography (ether/hexane, 1:5) to afford **18** as a colorless syrup (3.35 g, 70%): $[\alpha]_D^{24}$ −57.5 (*c* 1); ν_{max}^{film} 3421 (OH), 3066, and 3031 cm^{-1} (aromatic). NMR data: ^1H, 7.33 (bs, 5H, *Ph*CH_2), 4.62 and 4.43 (2 d, 2H, J = 11.6 Hz, PhCH_2), 3.76 (m, 3H, H-1,1′,3), 1.77 (m, 2H, H-2,2′) and 1.25 (d, 3H, $J_{3,4}$ = 6.1 Hz, H-4,4,4); ^{13}C, 138.44, 128.52, 127.78, and 127.74 (*Ph*CH_2), 74.63 (C-3), 70.48 (Ph*C*H_2), 60.87 (C-1), 38.82 (C-2), and 19.41 (C-4). Mass spectrum (LSIMS): m/z: found 203.1 (M^++Na).

4.14. Methyl (*E*,*R*)-8-benzyloxy-4-oxo-5-nonenoate 20

To a stirred solution of **18** (1.44 g, 8 mmol) in dry dichloromethane (20 mL), molecular sieves (4 Å, powder, 3.5 g) and PCC (3.5 g) were added at room temperature. After 30 min, GLC (E) then revealed the absence of **18** (t_R 3.95 min) and the presence of a new compound (t_R 3.45 min). The mixture was diluted with ether (50 mL), filtered through a silica gel pad, thoroughly washed with ether, and the combined filtrate and washings concentrated to a residue that was percolated (ether/hexane, 1:2) to afford presumably (*R*)-3-*O*-benzyl-3-hydroxylbutanal **19** as a clear mobile oil (1.02 g, 72%): $[\alpha]_D^{24}$ −35 (*c* 1.4) [lit.[20a] $[\alpha]_D$ −29.8 (*c* 1.36, dichloromethane), lit.[20b] $[\alpha]_D^{25}$ −36.5 (*c* 1)]; ν_{max}^{film} 1726 cm^{-1} (CO).

Compound **19** (1 g, 5.62 mmol) was dissolved in dichloromethane (15 mL) and treated with a solution of (3-methoxycarbonylpropionyl)methylenetriphenylphosphorane[17] (**11**, 2.5 g, 6 mmol) in the same solvent (15 mL), and the mixture stirred under reflux for 3 d. GLC (E) then showed the presence of a new compound (t_R 12.0 min). The reaction mixture was supported on silica gel and chromatographed (ether/hexane, 1:3) to yield the title compound **20** as a syrup (1.32 g, 80%): GLC analysis (C) t_R 7.80 min; $[\alpha]_D^{25}$ −5.7 (*c* 1); ν_{max}^{film} 1745, 1734, 1699, 1679 and 1635 cm^{-1} (C=O and C=C). NMR data: ^1H, 7.33 (m, 5H, *Ph*CH_2), 6.75 (dt, 1H, $J_{5,6}$ = 16, $J_{6,7}$ = $J_{6,7'}$ = 7.3 Hz, H-6), 6.15 (dt, 1H, $J_{5,7}$ = $J_{5,7'}$ = 1.4 Hz, H-5), 4.58 and 4.47 (2 d, 2H, J = 11.8 Hz, PhCH_2), 3.68 (s, 3H, CO_2Me), 3.67 (sext., 1H, $J_{7,8}$ = $J_{7',8}$ = $J_{8,9}$ = 6.1 Hz, H-8), 2.87 (t, 2H, $J_{2,3}$ = 6.7 Hz, H-3,3), 2.62 (t, 2H, H-2,2), 2.49 (dddd, 1H, H-7), 2.4 (dddd, 1H, $J_{7,7'}$ = 12.8 Hz, H-7′), and 1.23 (d, 3H, H-9,9,9); ^{13}C, 198.00 (C-4), 173.41 (C-1), 144.04 (C-6), 131.97 (C-5), 138.52, 129.03, 128,48, and 127.73 (*Ph*CH_2), 73.56 (C-8), 70.58 (Ph*C*H_2), 51.85 (CO_2*C*H_3), 39.65 and 34.48 (C-3,7), 27.85 (C-2), and 19.76 (C-9). Mass spectrum (LSIMS): m/z: 313.14105 (M^++Na) for $C_{17}H_{22}NaO_4$ 313.14158 (deviation 1.7 ppm).

4.15. Methyl (*R*)-8-benzyloxy-4-oxononanoate 21

Hydrogenation of **20** (1.3 g, 4.48 mmol) in methanol (20 mL) with 10% Pd–C (60 mg) as above gave **21** (1.21 g, 92.4%), after column chromatography (ether/hexane, 1:2): GLC analysis (C) t_R 7.09 min; $[\alpha]_D^{26}$ −16 (*c* 1); ν_{max}^{film} 1743 and 1716 cm^{-1} (C=O). NMR data: ^1H, 7.39–7.26 (m, 5H, *Ph*CH_2), 4.60 and 4.46 (2 d, 2H, J = 11.7 Hz, PhCH_2), 3.70 (s, 3H, CO_2Me), 3.54 (sext., 1H, $J_{7,8}$ = $J_{7',8}$ = $J_{8,9}$ = 6.1 Hz, H-8), 2.72 (t, 2H, $J_{2,3}$ = 6.3 Hz, H-3,3), 2.60 (t, 2H, H-2,2), 2.47 (t, 2H, $J_{5,6}$ = 7.2 Hz, H-5,5), 1.78–1.41 (m, 4H, H-6,6′,7,7′), and 1.22 (d, 3H, H-9,9,9); ^{13}C, 208.88 (C-4), 173.33 (C-1), 139.09, 128.40, 127.74, and 127.49 (*Ph*CH_2), 74.59 (C-8), 70.42 (Ph*C*H_2), 51.83 (CO_2*C*H_3), 42.71, 37.09 and 36.14 (C-3,5,7), 27.81 (C-2), 19.91 (C-6), and 19.60 (C-9). Mass spectrum (LSIMS): m/z: found 315.2 (M^++Na).

4.16. Methyl (*R*)-8-benzyloxy-4-oxononanoate ethylidenedithioketal 22

To an ice-water cooled and stirred mixture of **21** (1.21 g, 4.14 mmol) and ethanedithiol (0.92 mL, 10.9 mmol), $F_3B{\cdot}OEt_2$ (0.45 mL, 3.6 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 30 min GLC (C) revealed that **21** was completely consumed and a new product had formed (t_R 11.68 min). The reaction mixture was diluted with ether and washed with aqueous 10% sodium hydroxide, water and then concentrated. Column chromatography (ether/hexane, 1:7) of the residue afforded **22** as a colorless mobile oil (1.33 g, 87%): $[\alpha]_D^{25}$ −13 (*c* 1); ν_{max}^{film} 1740 cm^{-1} (C=O). NMR data: ^1H, 7.39–7.26 (m, 5H, *Ph*CH_2), 4.60 and 4.49 (2 d, 2H, J = 11.8 Hz, PhCH_2), 3.70 (s, 3H, CO_2Me), 3.55 (sext., 1H, $J_{7,8}$ = $J_{7',8}$ = $J_{8,9}$ = 6.1 Hz, H-8), 3.28 (s, 4H, S(CH_2)$_2$S), 2.63 (bt, 2H, H-3,3′), 2.24 (bt, 2H, H-2,2′), 1.92 (bt, 2H, H-5,5′), 1.73–1.43 (m, 4H, H-6,6′,7,7′), and 1.23 (d, 3H, H-9,9,9); ^{13}C, 173.92 (C-1), 139.14, 128.40, 127.77, and 127.47 (*Ph*CH_2), 70.93 (C-4), 70.66 (C-8), 70.46 (Ph*C*H_2), 51.71 (CO_2*C*H_3), 40.08 (S(CH_2)$_2$S), 44.64, 37.66 and 36.72 (C-3,5,7), 31.55 (C-2), 22.87 (C-6), and 19.74 (C-9). Mass spectrum (LSIMS): m/z: 391.13776 (M^++Na) for $C_{19}H_{28}NaO_3S_2$ 391.13776 (deviation 0.0 ppm).

4.17. (*R*)-8-*O*-Benzyl-1,8-dihydroxy-4-nonanone ethylidenedithioketal 23

To a stirred suspension of $LiAlH_4$ (280 mg, 7.37 mmol) in anhydrous ether (10 mL) a solution of **22** (1.3 g, 3.53 mmol) in the same solvent (20 mL) was added dropwise and the mixture refluxed for 1 h. TLC (ether/hexane, 1:2) then showed the presence of a more polar product. The reaction mixture was quenched by cautious addition of aqueous 10% ammonium chloride, the organic phase separated and the aqueous extracted with ether (3×20 mL). The combined extracts were concentrated and the residue chromatographed (ether/hexane, 1:1) to yield **23** (1.1 g, 92%): $[\alpha]_D^{26}$ −12 (*c* 1); ν_{max}^{film} 3421 cm^{-1} (OH). NMR data: ^1H, 7.38–7.29 (m, 5H, *Ph*CH_2), 4.60 and 4.44 (2 d, 2H, J = 11.8 Hz, PhCH_2), 3.68 (t, 2H, $J_{1,2}$ = 6.4 Hz, H-1,1), 3.56 (sext., 1H, $J_{7,8}$ = $J_{7',8}$ = $J_{8,9}$ = 6.1 Hz, H-8), 3.30 (s, 4H, S(CH_2)$_2$S), 2.03–1.44 (3 m, 11H, H-2,2′,3,3′,5,5′,6,6′,7,7′, OH), and 1.24 (d, 3H, H-9,9,9); ^{13}C, 139.17, 128.41, 127.76, and 127.49

(*Ph*CH_2), 74.76 (C-8), 71.40 (C-4), 70.46 (Ph*C*H_2), 62.90 (C-1), 39.74 (S$(CH_2)_2$S), 43.94, 39.64 and 36.74 (C-3,5,7), 30.23 (C-2), 23.00 (C-6), and 19.77 (C-9). Mass spectrum (LSIMS): m/z: 363.14254 (M^++Na) for $C_{18}H_{28}NaO_2S_2$ 363.14284 (deviation 0.8 ppm).

4.18. (5*R*,7*R*)-7-Methyl-1,6-dioxaspiro[4.5]decane 1

To a stirred solution of **23** (1.07 g, 3.14 mmol) in 4:1 v/v acetonitrile/water (20 mL) was added mercuric chloride (1.1 g, 4.05 mmol) and mercuric oxide (1 g, 4.61 mmol) and the mixture kept at room temperature for 24 h. TLC (ether) then revealed the presence of a more polar product. The mixture was filtered and the filtrate was concentrated to a residue that was dissolved in ether and washed with aqueous 10% potassium iodide and water, then concentrated to yield the corresponding ketone **24** (790 mg, IR evidence 1714 cm^{-1}) that was subsequently hydrogenated in ether (20 mL) with 10% Pd–C (300 mg) and conc. HCl (0.1 mL) at 70 psi overnight. TLC (ether/hexane, 3:1) then revealed the presence of a faster-running compound. The catalyst was filtered off, and the filtrate washed with aqueous 10% sodium hydrogen carbonate, then concentrated in a water–ice bath to a residue that was chromatographed (ether/*n*-pentane, 1:10) to afford pure (+)-**1** (480 mg, 98%): GLC analysis (D) t_R 6.36 min, (A) t_R 6.68 min, e.e. 91%; $[\alpha]_D^{26}$ +81 (*c* 1, *n*-pentane), [lit.[7b] $[\alpha]_D^{23}$ +87.8 (neat); lit.[8b] $[\alpha]_D^{22}$ +98 (*c* 1.1, *n*-pentane)]. Physical and spectroscopic data were in agreement with those reported in the literature.[8b,10b]

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