Asymmetric Synthesis of (*S*,*S*)- and (*R*,*R*)-2-Methylthreitol

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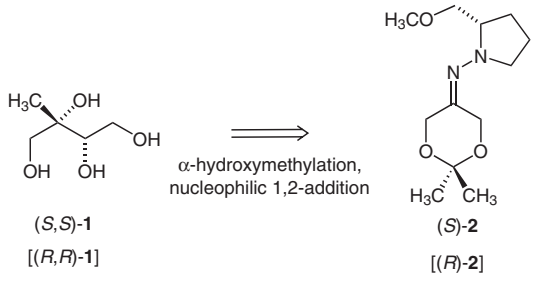
Abstract: The asymmetric synthesis of (*S*,*S*)- and (*R*,*R*)-2-methylthreitol was carried out, starting from the SAMP or RAMP hydrazone of 2,2-dimethyl-1,3-dioxan-5-one. The protocol involves an enantioselective α-alkylation as a key step. The second stereogenic center was installed by either nucleophilic 1,2-addition or diastereoselective epoxidation with bis(acetylacetonato)oxovanadium(IV) [$VO(acac)_2$] as catalyst. The title compounds were obtained in excellent diastereo- and enantiomeric excesses (≥98% de, 98% ee) and in good overall yields (40–61%).

Key words: asymmetric synthesis, epoxidation, tetrols, α-alkylation, SAMP/RAMP hydrazones, 1,2-addition

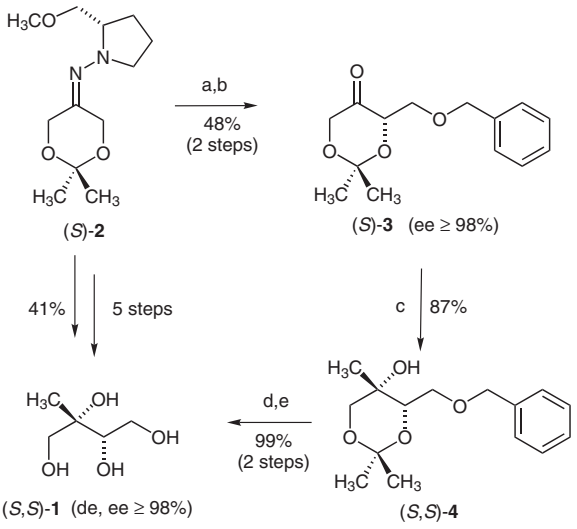
(+)-2-Methylerythritol plays an important role in the mevalonate-free, methylerythritol phosphate (MEP) pathway for the biosynthesis of terpenoids in algae, plant chloroplasts, and Gram-negative bacteria.[1] This could be a starting point for the development of new microbe-inhibiting drugs.[2,3] Up to now the effect of the other stereoisomers on the MEP pathway are unknown. In addition, the tetrols occur in the atmosphere, mainly above the rainforest, where they act as condensation nuclei and scatter sunlight.[4] They arise by photooxidation of isoprene, leading to a mixture of all four stereoisomers. Up to now only (+)-2-methylerythritol[3,5] and (+)-2-methylthreitol[3] have been synthesized by asymmetric synthesis with moderate enantiomeric excess. Very recently, a chemo-enzymatic synthesis of all four isomers was published.[6]

We envisaged a new diastereo- and enantioselective route to both enantiomers of the title 2-methylthreitol (**1**) based on α-hydroxymethylation of the SAMP- or RAMP-derived hydrazone of 2,2-dimethyl-1,3-dioxan-5-one [(*S*)- or (*R*)-**2**][7] and a nucleophilic 1,2-addition to generate the quaternary stereocenter as key steps (Scheme 1).



Scheme 1 Retrosynthetic analysis for 2-methylthreitol

SAMP-derived hydrazone (*S*)-**2**, easily obtained in multigram quantities by condensation of the chiral auxiliary SAMP and the corresponding dioxanone,[8,9] was metalated with *tert*-butyllithium, and the azaenolate was trapped with (benzyloxy)methyl chloride (BOMCl) (Scheme 2). Acidic hydrazone cleavage[10] gave the α-[(benzyloxy)methyl]-substituted dioxanone (*S*)-**3**, obtained in 48% yield over two steps. Dioxanone (*S*)-**3** was obtained in 98% ee (determined by CSP-GC analysis), indicating that the hydrazone alkylation occurred with virtually complete asymmetric induction and that the auxiliary was removed without any racemization. Next, ketone (*S*)-**3** was reacted with methyllithium to afford the tertiary alcohol (*S*,*S*)-**4** (Scheme 2), thus introducing the second and contiguous quaternary stereocenter. The nucleophilic 1,2-addition proceeded in good diastereoselectivity (84% de) and under optimized reaction conditions in 87% yield. The major diastereomer (*S*,*S*)-**4** could be efficiently separated (in ≥98% de) from its diastereomeric impurity by preparative HPLC. Finally, two deprotection steps were performed to obtain (*S*,*S*)-2-methylthreitol [(*S*,*S*)-**1**] (Scheme 2). The acetonide function was hydrolyzed under acidic conditions and the benzyloxy group was removed by hydrogenolysis, to afford the title compound almost quantitatively over these two steps.



Scheme 2 Asymmetric synthesis of (*S*,*S*)-2-methylthreitol. *Reagents and conditions*: (a) 1. *t*-BuLi, THF, –78 °C, 2. BOMCl, –100 °C to r.t.; (b) sat. aq oxalic acid, Et_2O, r.t.; (c) 1. MeLi, THF, –90 °C, 2. epimer separation (HPLC); (d) H^+, MeOH, r.t.; (e) Pd/C, H_2, MeOH, r.t.

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The absolute configuration was confirmed by an X-ray crystal structure analysis of the alcohol (*R*,*R*)-**4**,[11] which showed a *trans* orientation of the methyl and (benzyloxy)methyl groups (Figure 1). The *trans* orientation was additionally confirmed by NOE measurements carried out for alcohol (*S*,*S*)-**4**.

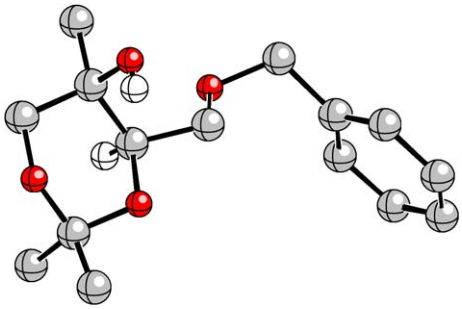
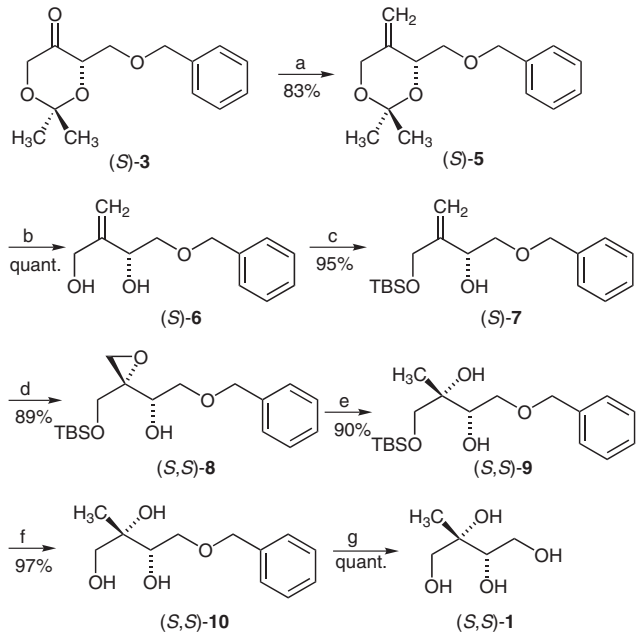


Figure 1 Crystal structure of alcohol (*R*,*R*)-**4**

The enantiomeric (*R*,*R*)-2-methylthreitol [(*R*,*R*)-**1**] was synthesized by the same procedure, from RAMP hydrazone (*R*)-**2** as starting material. Tetrol (*R*,*R*)-**1** was obtained in an overall yield of 40% as a single stereoisomer (98% de and ee), as determined by CSP-GC, HPLC, and NMR spectroscopy.

In addition, we have developed an alternative route to (*S*,*S*)-2-methylthreitol that preserves the ketone (*S*)-**3** as a key intermediate and involves a reductive epoxide ring-opening reaction (Scheme 3). Thus, Wittig olefination of ketone (*S*)-**3** to (*S*)-**5** followed by acetal hydrolysis afforded the alkene (*S*)-**6** in 83% yield over two steps. Selective protection of the primary alcohol as a silyl ether produced the allylic alcohol (*S*)-**7**. Screening of a series of epoxidation conditions showed allylic alcohol (*S*)-**8** to react efficiently in the presence of a catalytic amount of bis(acetylacetonato)oxovanadium(IV) and the terminal oxidant *tert*-butyl hydroperoxide. The epoxide product (*S*,*S*)-**8** was obtained in high yield (89%) and as a single diastereomer (≥98% de) (Scheme 3). Finally, the epoxide (*S*,*S*)-**8** could be ring-opened regio- and stereoselectively by reaction with Super-Hydride™, to install the tertiary alcohol group and quaternary stereocenter of alcohol (*S*,*S*)-**9**. The alcohol groups were deprotected by desilylation with tetrabutylammonium fluoride to give triol (*S*,*S*)-**10**, which was debenzylated with hydrogen and palladium on carbon to afford (*S*,*S*)-2-methylthreitol [(*S*,*S*)-**1**] in 61% overall yield (98% ee, ≥98% de) starting from ketone (*S*)-**3**.



Scheme 3 Asymmetric synthesis of (*S*,*S*)-2-methylthreitol by epoxidation. *Reagents and conditions*: (a) 1. $[Ph_3PMe]^+Br^-$, *t*-BuOK, THF, 0 °C, 2 h; 2. (*S*)-**3**, 3 h; (b) ion-exchange resin, MeOH, r.t.; (c) 1. imidazole, THF, 0 °C, 15 min; 2. TBSCl, 1 h, 0 °C, then r.t., overnight; (d) 1. $VO(acac)_2$, 4-Å MS, CH_2Cl_2, 0 °C, 10 min; 2. *t*-BuOOH, 0 °C, 1 h, then r.t., 20 h; (e) Super-Hydride™, THF, 0 °C, 3 h; (f) TBAF, THF, r.t., 1 h; (g) Pd/C, H_2, MeOH, r.t., 2 h.

In summary, we have developed two different routes for the efficient enantio- and diastereoselective syntheses of the tetrol (*S*,*S*)-2-methylthreitol and its enantiomer (*R*,*R*)-2-methylthreitol.

All reagents were of commercial quality and were used from freshly opened containers. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled under argon from Na/Pb alloy, CH_2Cl_2 was freshly distilled under argon from CaH_2, and 15% *t*-BuLi in *n*-pentane was purchased from Merck (Darmstadt). Standard Schlenk techniques were used for conducting the reactions under argon. Preparative flash chromatography was carried out on Merck silica gel 60 (particle size 0.040–0.063 mm; 230–240 mesh). Analytical TLC analyses were performed on silica gel 60 F_{254} plates from Merck (Darmstadt). Visualization of the developed chromatograms was performed by UV irradiation (254 nm) or staining with acidic $(NH_4)_2MoO_4$ and $KMnO_4$. Optical rotation values were measured on a Perkin-Elmer P241 polarimeter; solvents used were of Merck UVASOL quality. Microanalyses were obtained with an Elementar Vario EL instrument. Mass spectra were acquired on Varian MAT 212 (EI, 70 eV, 1 mA) and on Finnigan MAT SSQ 7000 (CI, 100 eV) spectrometers. HRMS data were obtained on a Finnigan MAT, MAT 95 instrument. IR spectra were measured on a Perkin-Elmer FT/IR 1760 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini 300, Varian Inova 400, or Varian Unity 500 spectrometers, and all measurements were performed with TMS as internal standard. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument. Melting points were determined on a Tottoli melting point apparatus and are uncorrected. The chiral auxiliaries SAMP and RAMP and the corresponding dioxanone hydrazones (*S*)- and (*R*)-**2** were prepared from (*S*)- and (*R*)-proline according to literature procedures.[12]

(4*S*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one [(*S*)-3]

To a soln of (*S*)-**2** (1.21 g, 5 mmol) in THF (20 mL) at –78 °C was added 1.5 M *t*-BuLi in pentane (3.7 mL, 5.5 mmol). After stirring for 2 h, the mixture was cooled to –100 °C and BOMCl (0.86 g, 5.5 mmol) diluted with THF (1 mL) was added dropwise. The mixture was stirred at the same temperature for 2 h and then allowed to slowly warm to r.t. overnight. The mixture was quenched by the addition of pH 7 buffer, diluted, and extracted with Et_2O (4 × 10 mL). The organic phase was washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 2:1) gave the alkylated hydrazone as a

pure yellow oil. The purified hydrazone was dissolved in Et_2O (50 mL), sat. aq oxalic acid (20 mL) was added, and the mixture was vigorously stirred. After 2 h, the mixture was extracted with Et_2O (10 mL) and the organic phase was washed with pH 7 buffer (2 × 10 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo to give pure (*S*)-**3** as a clear, colorless liquid in 98% ee.

Yield: 0.64 g (48%, over 2 steps); $[\alpha]_D^{31}$ –150.1 (*c* 1.1, $CHCl_3$).

IR (film): 3063 (w), 3031 (w), 2990 (s), 2936 (m), 2871 (s), 1799 (s), 1747 (vs), 1600 (w), 1497 (w), 1454 (m), 1379 (s), 1322 (w), 1224 (vs), 1160 (m), 1101 (vs), 989 (m), 913 (m), 848 (m), 744 (s), 700 (s), 608 (m), 535 (w), 465 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.74 (dd, *J* = 6, 11 Hz, 1 H, CHC*H*H), 3.88 (dd, *J* = 3, 11 Hz, 1 H, CHCH*H*), 3.96 [d, *J* = 16.8 Hz, 1 H, C*H*HC(O)], 4.29 [dd, *J* = 1.6, 16.9 Hz, 1 H, CH*H*C(O)], 4.46 (dd, *J* = 1.5, 3.0 Hz, 1 H, OCH), 4.58 (s, 1 H, C*H*HC$_6$H$_5$), 4.59 (s, 1 H, CH*H*C$_6$H$_5$), 7.25–7.35 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.55 (CH_3), 24.12 (CH_3), 66.74 [*C*H$_2$C(O)], 67.90 (CH*C*H$_2$), 73.62 (*C*H$_2$C$_6$H$_5$), 75.27 (OCH), 100.93 [*C*(CH$_3$)$_2$], 127.69 (*p*CH^{Ph}), 128.36 (*o*CH^{Ph}), 128.43 (*m*CH^{Ph}), 137.89 (C^{Ph}), 207.44 (CO).

MS (EI, 70 eV): *m*/*z* (%) = 250 (1) [M]$^+$, 162 (10), 149 (12), 129 (10), 107 (18), 92 (10), 91 (100), 72 (23), 59 (11).

MS (CI, 100 eV, methane): *m*/*z* (%) = 251 (7) [M$^+$ + 1], 249 (10), 207 (25), 161 (16), 147 (12), 143 (24), 123 (10), 117 (44), 107 (60), 105 (40), 91 (100).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.89; H, 7.24.

(4*R*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxan-5-one [(*R*)-3]

By the procedure described for its *S*-enantiomer, hydrazone (*R*)-**4** (4.85 g, 20 mmol) was alkylated with BOMCl (3.45 g, 22 mmol). After hydrolytic removal of the auxiliary, ketone (*R*)-**3** was obtained as a clear, colorless liquid in 98% ee.

Yield: 2.86 g (57%, over 2 steps); $[\alpha]_D^{31}$ +146.3 (*c* 1.3, $CHCl_3$).

All spectroscopic data were consistent with those of the *S*-enantiomer.

(4*S*,5*S*)-4-[(Benzyloxy)methyl]-2,2,5-trimethyl-1,3-dioxan-5-ol [(*S*,*S*)-4]

To a soln of (*S*)-**3** (1.73 g, 6.9 mmol) in THF (70 mL) at –90 °C was slowly added 1.6 M MeLi in Et_2O (17.4 mL, 13.8 mmol). After stirring at the same temperature for 3 h, the mixture was quenched by the addition of sat. aq NH_4Cl (70 mL), warmed to r.t., and extracted with Et_2O (3 × 48 mL). The organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 1:1) gave (*S*,*S*)-**4** as a colorless solid in 84% de.

The diastereomers could be separated by preparative HPLC (LiChrosorb Si60, 7 μm, 250 mm × 25 mm; *n*-pentane–Et_2O, 1:1; flow rate: 25 mL/min; t_R = 12.8 min and 18.9 min); this gave the major diastereomer in ≥98% de.

Yield: 1.37 g (75%); mp 40 °C; $[\alpha]_D^{25}$ +8.9 (*c* 1.0, $CHCl_3$).

IR ($CHCl_3$): 3953 (w), 3571 (s), 3493 (s), 3241 (w), 3062 (m), 3030 (m), 2990 (vs), 2937 (vs), 2873 (vs), 2718 (w), 1722 (m), 1604 (w), 1497 (w), 1454 (s), 1379 (vs), 1292 (s), 1261 (s), 1201 (vs), 1159 (s), 1111 (vs), 1073 (vs), 994 (m), 974 (w), 938 (m), 899 (w), 847 (s), 745 (vs), 699 (s), 602 (m), 526 (m), 471 (w) cm^{-1}.

^1H NMR (300 MHz, DMSO): δ = 0.96 (s, 3 H, COHC*H*$_3$), 1.31 [s, 3 H, C(CH$_3$)$_2$], 1.36 [s, 3 H, C(CH$_3$)$_2$], 3.30 (d, *J* = 11.6 Hz, 1 H, CH*H*COH), 3.37 (dd, *J* = 6.4, 10.9 Hz, 1 H, CHC*H*H), 3.67 (d, *J* = 11.8 Hz, 1 H, C*H*HCOH), 3.68 (dd, *J* = 3.5, 10.6 Hz, 1 H, CHCH*H*), 3.85 (dd, *J* = 3.5, 6.4 Hz, 1 H, OCH), 4.47 (s, 2 H, C*H*$_2$C$_6$H$_5$), 7.28–7.38 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (75 MHz, DMSO): δ = 19.56 [C(CH$_3$)$_2$], 21.53 (COH*C*H$_3$), 29.23 [C(*C*H$_3$)$_2$], 66.11 (COH), 69.74 (CHCH$_2$), 69.93 (*C*H$_2$COH), 72.62 (*C*H$_2$C$_6$H$_5$), 75.35 (OCH), 98.48 [*C*(CH$_3$)$_2$], 127.87 (*p*CH^{Ph}), 128.07 (*o*CH^{Ph}), 128.71 (*m*CH^{Ph}), 138.98 (C^{Ph}).

MS (EI, 70 eV): *m*/*z* (%) = 266 (1) [M]$^+$, 190 (14), 147 (11), 115 (17), 107 (10), 91 (100), 72 (13), 59 (35), 58 (25).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 68.08; H, 8.62.

(4*R*,5*R*)-4-[(Benzyloxy)methyl]-2,2,5-trimethyl-1,3-dioxan-5-ol [(*R*,*R*)-4]

By the procedure described for its *S*-enantiomer, ketone (*R*)-**3** (2.86 g, 11.4 mmol) was treated with 1.6 M MeLi in Et_2O (22.0 mL, 34.2 mmol); after purification the corresponding alcohol (*R*,*R*)-**4** was obtained as a colorless solid in 98% ee and 84% de.

The diastereomers could be separated by preparative HPLC (LiChrosorb Si60, 7 μm, 250 mm × 25 mm; *n*-pentane–Et_2O, 1:1; flow rate: 25 mL/min; t_R = 12.8 min and 18.9 min); this gave the major diastereomer in ≥98% de.

Yield: 2.13 g (70%); mp 40 °C; $[\alpha]_D^{27}$ –9.0 (*c* 1.1, $CHCl_3$)

All spectroscopic data were consistent with those of the *S*-enantiomer.

(4*S*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-5-methylene-1,3-dioxane [(*S*)-5]

A 1 M soln of *t*-BuOK in THF (50 mL, 50 mmol) was added slowly to a cooled (0 °C) soln of [Ph$_3$PMe]$^+$Br$^-$ (17.9 g, 50 mmol) in THF (180 mL). The yellow reaction mixture was stirred at the same temperature for 2 h, and then a soln of (*S*)-**3** (2.50 g, 10 mmol) in THF (17 mL) was added dropwise. After 3 h, the mixture was quenched by the addition of H_2O (30 mL), warmed to r.t., and extracted with Et_2O (3 × 50 mL). The organic phase was washed with brine (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 6:1) gave (*S*)-**5** as a colorless liquid in 98% ee.

Yield: 2.06 g (83%); $[\alpha]_D^{25}$ –51.0 (*c* 1.0, $CHCl_3$).

IR (film): 3065 (w), 3030 (m), 2989 (s), 2936 (s), 2903 (s), 2860 (s), 1657 (w), 1496 (m), 1454 (s), 1416 (w), 1375 (s), 1258 (m), 1222 (vs), 1162 (s), 1097 (vs), 1047 (m), 1028 (m), 905 (s), 860 (m), 833 (m), 740 (s), 699 (s), 611 (w), 517 (w), 459 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 3.65 (dd, *J* = 6, 10.4 Hz, 1 H, CHC*H*H), 3.73 (dd, *J* = 4.7, 10.2, 1 H, CHCH*H*), 4.25 [m, 2 H, C*H*$_2$C(CH$_2$)], 4.57–4.65 (m, 3 H, C*H*$_2$C$_6$H$_5$, OCH), 4.89 (m, 2 H, CCH$_2$), 7.25–7.35 (m, 5 H, C$_6$H$_5$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.99 (CH_3), 27.26 (CH_3), 64.09 [*C*H$_2$C(CH$_2$)], 70.14 (OCH), 71.22 (CH*C*H$_2$), 73.34 (*C*H$_2$C$_6$H$_5$), 99.45 (*C*(CH$_3$)$_2$), 107.40 [*C*(CH$_2$)], 127.46 (*p*CH^{Ph}), 127.58 (*o*CH^{Ph}), 128.17 (*m*CH^{Ph}), 137.88 (C^{Ph}), 143.05 (C(*C*H$_2$)].

MS (EI, 70 eV): *m*/*z* (%) = 190 (11), 160 (12), 127 (92), 92 (10), 91 (100), 85 (12), 69 (34), 59 (21).

MS (CI, 100 eV, methane): *m*/*z* (%) = 249 (7) [M$^+$ + 1], 191 (10), 131 (13), 129 (17), 127 (56), 91 (100), 83 (23).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.58; H, 8.10.

(4*R*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-5-methylene-1,3-dioxane [(*R*)-5]

By the procedure described for its *S*-enantiomer, ketone (*R*)-**3** (0.98 g, 3.9 mmol) underwent a Wittig reaction with [Ph$_3$PMe]$^+$Br$^-$

(6.96 g, 19.5 mmol) and 1 M *t*-BuOK in THF (19.5 mL, 19.5 mmol); after purification, the corresponding alkene (*R*)-**5** was obtained as a colorless liquid in 98% ee.

Yield: 0.80 g (83%); $[\alpha]_D^{26}$ +58.3 (*c* 1.2, $CHCl_3$).

All spectroscopic data were consistent with those of the *S*-enantiomer.

(3*S*)-4-(Benzyloxy)-2-methylenebutane-1,3-diol [(*S*)-6]

Ion-exchange resin (DOWEX™ 50X2-200, 2.0 g) was added to a soln of (*S*)-**5** (1.21 g, 4.9 mmol) in MeOH (24 mL) at r.t. After 3 h the resin was removed by filtration and washed with MeOH, and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 1:2) gave pure (*S*)-**6** as a colorless liquid.

Yield: 1.0 g (100%); $[\alpha]_D^{24}$ –18.5 (*c* 1.1, $CHCl_3$).

IR (film): 3409 (vs), 3087 (w), 3064 (w), 3030 (m), 2866 (s), 1654 (m), 1496 (m), 1454 (s), 1363 (m), 1319 (w), 1207 (m), 1076 (vs), 1028 (vs), 913 (s), 816 (w), 740 (vs), 700 (s), 646 (w), 609 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.54 (dd, *J* = 9.6, 21.8 Hz, 1 H, CHC*H*H), 3.56 (dd, *J* = 9.6, 18.6 Hz, 1 H, CHCH*H*), 4.10 (d, *J* = 19 Hz, 1 H, C*H*HOH), 4.14 (d, *J* = 19 Hz, 1 H, CH*H*OH), 4.44 (dd, *J* = 4, 7.4 Hz, 1 H, C*H*OH), 4.55 (s, 2 H, $CH_2C_6H_5$), 5.16 [m, 2 H, $C(CH_2)$], 7.27–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.80 (CH_2OH), 72.16 (CHOH), 73.45 ($CH_2C_6H_5$), 73.73 (CHCH$_2$), 113.39 [$C(CH_2)$], 127.88 (pCH^{Ph}), 127.93 (oCH^{Ph}), 128.52 (mCH^{Ph}), 137.61 (C^{Ph}), 147.24 [$C(CH_2)$].

MS (EI, 70 eV): *m*/*z* (%) = 99 (11), 92 (35), 91 (100), 87 (25), 69 (18), 65 (14).

MS (CI, 100 eV, methane): *m*/*z* (%) = 209 (9) [M^+ + 1], 145 (13), 143 (11), 131 (17), 129 (16), 92 (11), 91 (100), 83 (12).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}O$ [M^+ – CH_5O_2]: 159.08099; found: 159.08092.

(3*R*)-4-(Benzyloxy)-2-methylenebutane-1,3-diol [(*R*)-6]

By the procedure described for its *S*-enantiomer, the acetal of the alkene (*R*)-**5** (0.99 g, 4.0 mmol) was cleaved to give the corresponding diol (*R*)-**6** as a colorless liquid in 98% ee after purification.

Yield: 0.82 g (100%); $[\alpha]_D^{24}$ +18.0 (*c* 1.0, $CHCl_3$).

All spectroscopic data were consistent with those of the *S*-enantiomer.

(3*S*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2-methylenebutan-3-ol [(*S*)-7]

A soln of (*S*)-**6** (0.27 g, 1.3 mmol) in THF (4 mL) was added to a cooled (0 °C) soln of imidazole (0.20 g, 3.1 mmol) in THF (4 mL). After the mixture had stirred at the same temperature for 15 min, TBSCl (0.23 g, 1.5 mmol) dissolved in THF (3 mL) was added slowly. The mixture was stirred at the same temperature for 1 h, and then allowed to warm to r.t. overnight. It was then filtered over Celite, washed with Et_2O, and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 5:1) gave (*S*)-**7** as a pure, colorless oil.

Yield: 0.42 g (95%); $[\alpha]_D^{25}$ –8.2 (*c* 1.0, $CHCl_3$).

IR (film): 3436 (s), 3065 (w), 3031 (w), 2932 (vs), 2858 (vs), 1655 (w), 1465 (s), 1389 (m), 1362 (m), 1316 (w), 1255 (s), 1211 (m), 1080 (vs), 910 (m), 842 (vs), 778 (s), 740 (m), 698 (m), 672 (m), 615 (w), 465 (w) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.06 [s, 6 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 3.52 (d, *J* = 7.9 Hz, 1 H, CHCH*H*), 3.62 (dd, *J* = 4, 9.6 Hz, 1 H, CHC*H*H), 4.20 (m, 2 H, $SiOCH_2$), 4.41 [m, 1 H, C*H*(OH)], 4.57 (s, 2 H, $CH_2C_6H_5$), 5.18 [m, 2 H, $C(CH_2)$], 7.25–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.45 [$Si(CH_3)_2$], 18.26 [$SiC(CH_3)_3$], 25.87 [$SiC(CH_3)_3$], 64.33 ($SiOCH_2$), 71.97 [CH(OH)], 73.35 ($CH_2C_6H_5$), 73.73 (CHCH$_2$), 111.95 [$C(CH_2)$], 127.80 (pCH^{Ph}), 127.90 (oCH^{Ph}), 128.45 (mCH^{Ph}), 137.87 (C^{Ph}), 146.89 [$C(CH_2)$].

MS (EI, 70 eV): *m*/*z* (%) = 201 (10), 157 (14), 91 (100), 75 (12), 73 (11).

MS (CI, 100 eV, methane): *m*/*z* (%) = 323 (57) [M^+ + 1], 305 (30), 289 (12), 287 (12), 247 (10), 215 (20), 213 (10), 173 (39), 157 (19), 145 (17), 143 (11), 131 (20), 129 (48), 119 (12), 91 (100), 83 (12).

Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.76; H, 9.40.

(3*R*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2-methylenebutan-3-ol [(*R*)-7]

By the procedure described for its *S*-enantiomer, diol (*R*)-**6** (1.14 g, 1.3 mmol) was mono-TBS-protected to give the corresponding allyl alcohol (*R*)-**7** as a colorless liquid after purification.

Yield: 1.68 g (90%); $[\alpha]_D^{25}$ +8.1 (*c* 1.1, $CHCl_3$).

All spectroscopic data were consistent with those of the *S*-enantiomer.

(1*S*)-2-(Benzyloxy)-1-[(2*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]-methyl}oxiran-2-yl]ethanol [(*S*,*S*)-8]

A soln of (*S*)-**7** (0.59 g, 1.8 mmol) in CH_2Cl_2 (9.5 mL) was added to a cooled (0 °C) soln of $VO(acac)_2$ (29 mg, 6 mol%) and 4-Å MS (180 mg) in CH_2Cl_2 (11.5 mL). After the mixture had stirred at the same temperature for 10 min, *t*-BuOOH (0.54 mL, 2.8 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h, allowed to warm to r.t., and stirred for 20 h; it was then quenched by the addition of sat. aq NH_4Cl (5.5 mL) and extracted with CH_2Cl_2 (3 × 7 mL). The organic phase was washed with brine (4 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–Et_2O, 3:1) gave pure (*S*,*S*)-**8** as a colorless liquid in 98% ee.

Yield: 0.55 g (89%); $[\alpha]_D^{25}$ –2.2 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3458 (s), 3063 (m), 3031 (m), 2930 (vs), 2858 (vs), 1723 (m), 1498 (w), 1465 (s), 1390 (m), 1362 (m), 1255 (vs), 1211 (m), 1102 (vs), 1029 (w), 1006 (w), 938 (m), 911 (m), 841 (vs), 779 (s), 741 (s), 699 (s), 670 (m), 615 (w) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 3 H, $Si(CH_3)_2$], 0.04 [s, 3 H, $Si(CH_3)_2$], 0.87 [s, 9 H, $SiC(CH_3)_3$], 2.66 (br s, 1 H, OH), 2.72 [d, *J* = 5 Hz, 1 H, C(C*H*HO)], 2.89 [d, *J* = 5 Hz, 1 H, C(CH*H*O)], 3.60 (dd, *J* = 6.1, 10.2 Hz, 1 H, CHC*H*H), 3.67 (dd, *J* = 3.9, 10.2 Hz, 1 H, CHCH*H*), 3.69 (d, *J* = 11.8 Hz, 1 H, SiOCH*H*), 3.88 (d, *J* = 11.6 Hz, 1 H, SiOC*H*H), 4.05 [m, C*H*(OH)], 4.56 (s, 2 H, $CH_2C_6H_5$), 7.25–7.34 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.58 [$Si(CH_3)_2$], 18.19 [$SiC(CH_3)_3$], 25.76 [$SiC(CH_3)_3$], 48.00 [$C(CH_2O)$], 59.68 [$C(CH_2O)$], 63.93 ($SiOCH_2$), 68.99 [CH(OH)], 70.88 ($CH_2C_6H_5$), 73.33 (CHCH$_2$), 127.54 (pCH^{Ph}), 127.68 (oCH^{Ph}), 128.21 (mCH^{Ph}), 137.69 (C^{Ph}).

MS (EI, 70 eV): *m*/*z* (%) = 143 (12), 105 (10), 91 (100), 75 (12).

MS (CI, 100 eV, methane): *m*/*z* (%) = 339 (3) [M^+ + 1], 215 (14), 213 (24), 207 (12), 171 (37), 159 (11), 143 (12), 91 (100).

Anal. Calcd for $C_{18}H_{30}O_4Si$: C, 63.87; H, 8.93. Found: C, 63.68; H, 9.02.

(1*R*)-2-(Benzyloxy)-1-[(2*R*)-2-{[(*tert*-butyldimethylsilyl)oxy]-methyl}oxiran-2-yl]ethanol [(*R*,*R*)-8]

By the procedure described for its *S*-enantiomer, allyl alcohol (*R*)-**7** (0.97 g, 3.0 mmol) was epoxidized in the presence of cat. $VO(acac)_2$ (47 mg, 6 mol%) and *t*-BuOOH (0.90 mL, 4.7 mmol);

this gave epoxide (*R*,*R*)-**8** as a colorless liquid in 98% ee after purification.

Yield: 0.88 g (87%); $[\alpha]_D^{25}$ +2.4 (*c* 1.1, $CHCl_3$).

All spectroscopic data were consistent with those of the (*S*,*S*)-**8** enantiomer.

(2*S*,3*S*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2-methylbutane-2,3-diol [(*S*,*S*)-9]

To a cooled (0 °C) soln of epoxide (*S*,*S*)-**8** (0.40 g, 1.1 mmol) in THF (12.9 mL), a 1.0 M soln of Super-Hydride™ in THF (3.2 mL, 3.3 mmol) was slowly added. The mixture was stirred at the same temperature for 3 h and then quenched by the addition of H_2O (6.5 mL) and extracted with Et_2O (3 × 13 mL). The organic phase was washed with brine (6 mL), dried ($MgSO_4$), and concentrated in vacuo; this gave crude (*S*,*S*)-**9** as a colorless liquid. Further purification by flash chromatography was not possible.

Yield: 0.34 g (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.04 [s, 3 H, $Si(CH_3)_2$], 0.05 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.22 (s, 3 H, $COHCH_3$), 3.44 (d, *J* = 10.1 Hz, 1 H, SiOCH*H*), 3.52 (d, *J* = 10.0 Hz, 1 H, SiOC*H*H), 3.54 (d, *J* = 5.4 Hz, 1 H, $CHCH_2$), 4.39 [m, C*H*(OH)], 4.55 (s, 1 H, $CHHC_6H_5$), 4.58 (s, 1 H, $CHHC_6H_5$), 7.29–7.34 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.54 [$Si(CH_3)_2$], 18.18 [$SiC(CH_3)_3$], 18.46 ($COHCH_3$), 25.78 [$SiC(CH_3)_3$], 69.82 ($SiOCH_2$), 70.23 ($CH_2C_6H_5$), 73.44 ($CHCH_2$), 78.97 [CH(OH)], 82.64 ($COHCH_3$), 127.62 (pCH^{Ph}), 128.32 (oCH^{Ph}), 128.36 (mCH^{Ph}), 137.04 (C^{Ph}).

(2*R*,3*R*)-4-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-2-methylbutane-2,3-diol [(*R*,*R*)-9]

By the procedure described for its (*S*,*S*)-enantiomer, epoxide (*R*,*R*)-**8** (0.65 g, 1.7 mmol) was ring-opened with 1.0 M Super-Hydride™ in THF (5.2 mL, 5.2 mmol) to give the corresponding diol (*R*,*R*)-**9** as a colorless liquid. Further purification by flash chromatography was not possible.

Yield: 0.52 g (89%).

All spectroscopic data were consistent with those of the (*S*,*S*)-enantiomer.

(2*S*,3*S*)-4-(Benzyloxy)-2-methylbutane-1,2,3-triol [(*S*,*S*)-10]

(a) From (*S*,*S*)-**4**: Ion-exchange resin (DOWEX™ 50X2-200, 2.0 g) was added to a soln of alcohol (*S*,*S*)-**4** (1.16 g, 4.4 mmol) in MeOH (9 mL) at r.t. After 1 h, the resin was removed by filtration and washed with MeOH, and the filtrate was concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–EtOAc, 1:5) gave pure (*S*,*S*)-**10** as a colorless liquid in 98% ee.

Yield: 0.98 g (100%).

(b) From (*S*,*S*)-**9**: A 1 M soln of TBAF in THF (1.8 mL, 1.8 mmol) was added dropwise to a soln of (*S*,*S*)-**9** (0.20 g, 0.6 mmol) in THF (3.0 mL) at r.t. After 4 h, the mixture was quenched by the addition of pH 7 buffer (6.0 mL) and extracted with EtOAc (3 × 35 mL). The organic phase was washed with brine (18 mL), dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (silica gel, pentane–EtOAc, 1:5) gave pure (*S*,*S*)-**10** as a colorless liquid in 98% ee.

Yield: 0.13 g (97%); $[\alpha]_D^{32}$ –8.3 (*c* 1.2, $CHCl_3$).

IR (film): 3409 (vs), 3064 (m), 3032 (m), 2976 (s), 2933 (s), 2875 (s), 1720 (s), 1497 (w), 1455 (m), 1374 (m), 1322 (w), 1274 (m), 1205 (w), 1051 (s), 918 (m), 801 (w), 743 (s), 701 (s), 614 (w), 465 (w) cm^{-1}.

^{1}H NMR (300 MHz, DMSO): δ = 1.03 (s, 3 H, $COHCH_3$), 3.23 (d, *J* = 10.6 Hz, 1 H, CH*H*OH), 3.37 (d, *J* = 10.4 Hz, 1 H, C*H*HOH), 3.40 (d, *J* = 9.6 Hz, 1 H, CHC*H*H), 3.59 (dd, *J* = 2.7, 7.2 Hz, 1 H, CH), 3.68 (dd, *J* = 2.8, 9.7 Hz, 1 H, CHCH*H*), 4.48 (s, 2 H, $CH_2C_6H_5$), 7.27–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (75 MHz, DMSO): δ = 22.13 ($COHCH_3$), 66.78 (CH_2OH), 72.16 ($CHCH_2$), 72.67 ($CH_2C_6H_5$), 73.66 (COH), 74.28 (CH), 127.75 (pCH^{Ph}), 127.92 (oCH^{Ph}), 128.65 (mCH^{Ph}), 139.22 (C^{Ph}).

MS (EI, 70 eV): *m*/*z* (%) = 226 (1) $[M]^+$, 107 (13), 92 (13), 91 (100), 75 (14).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.36; H, 8.31.

(2*R*,3*R*)-4-(Benzyloxy)-2-methylbutane-1,2,3-triol [(*R*,*R*)-10]

(a) From (*R*,*R*)-**4**: By the procedure described for its *S*,*S*-enantiomer, the acetal of the alcohol (*R*,*R*)-**4** (1.4 g, 5.3 mmol) was cleaved with ion-exchange resin (DOWEX™ 50X2-200) to give the corresponding triol (*R*,*R*)-**10** as a colorless liquid in 98% ee after purification.

Yield: 1.19 g (100%).

(b) From (*R*,*R*)-**9**: By the procedure described for the *S*,*S*-enantiomer, a 1 M soln of TBAF in THF (5.1 mL, 5.1 mmol) was used to cleave (*R*,*R*)-**9** (0.6 g, 1.7 mmol) to give the corresponding triol (*R*,*R*)-**10** as a colorless liquid after purification.

Yield: 0.37 g (97%); $[\alpha]_D^{33}$ +8.6 (*c* 1.0, $CHCl_3$).

All spectroscopic data were consistent with those of the *S*,*S*-enantiomer.

(2*S*,3*S*)-2-Methylbutane-1,2,3,4-tetrol [(*S*,*S*)-1]

Pd/C (0.20 g) was added to a soln of (*S*,*S*)-**10** (0.84 g, 3.5 mmol) in MeOH (35 mL). The mixture was stirred under H_2 for 2 h, and then filtered over Celite, which was washed with MeOH; the filtrate was then concentrated in vacuo. Purification by flash chromatography (silica gel, MeOH–EtOAc, 1:5) gave pure (*S*,*S*)-**1** as a colorless oil in 98% de and ee.

Yield: 0.47 g (100%); $[\alpha]_D^{24}$ –10.8 (*c* 0.7, MeOH).

IR ($CHCl_3$): 3747 (w), 3408 (s), 2943 (m), 2889 (m), 2510 (vs), 1699 (w), 1652 (w), 1460 (m), 1385 (m), 1215 (w), 1096 (m), 1042 (s), 791 (w), 670 (w) cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 0.99 (s, 3 H, CH_3), 3.39 (d, *J* = 3.2 Hz, 2 H, CH_2OH), 3.43 (dd, *J* = 11.5, 8.5 Hz, 1 H, CHCH*H*), 3.53 (dd, *J* = 8.2, 2.7 Hz, 1 H, CH), 3.64 (dd, *J* = 11.4, 2.7 Hz, 1 H, CHC*H*H).

^{13}C NMR (75 MHz, D_2O): δ = 19.05 (CH_3), 61.79 ($CHCH_2$), 66.06 (CH_2OH), 74.01 (COH), 75.01 (CH).

MS (EI, 70 eV): *m*/*z* (%) = 105 (36), 87 (15), 75 (100), 61 (18), 59 (12), 58 (14), 57 (44).

MS (CI, 100 eV, methane): *m*/*z* (%) = 137 (5) $[M^+ + 1]$, 119 (13), 115 (10), 101 (100), 83 (25), 79 (50), 75 (16), 71 (52), 61 (22).

HRMS (EI): *m*/*z* calcd for $C_4H_9O_3$ $[M^+ - CH_3O]$: 105.05517; found: 105.05516.

Anal. Calcd for $C_5H_{12}O_4$+2H_2O: C, 34.88; H, 9.37. Found: C, 34.71; H, 9.71.

(2*R*,3*R*)-2-Methylbutane-1,2,3,4-tetrol [(*R*,*R*)-1]

By the procedure described for its *S*,*S*-enantiomer, (*R*,*R*)-**10** (0.37 g, 1.6 mmol) was debenzylated to give the corresponding tetrol (*R*,*R*)-**1** after purification as a colorless oil in 98% de and ee.

Yield: 0.22 g (100%); $[\alpha]_D^{24}$ +11.7 (*c* 1.0, MeOH) {Lit.[3] $[\alpha]_D^{22}$ +7.3 (*c* 0.8, MeOH)}.

All spectroscopic data were consistent with those of the *S*,*S*-enantiomer.

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