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TETRAHEDRON: *ASYMMETRY*

Asymmetrization of *meso*-1,3-diols utilising *Pseudomonas fluorescens* lipase

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Abstract

A convenient and enantioselective synthesis of monoacetates of *meso*-1,3-diols 2-substituted with an alkoxymethyl or a thiophenylmethyl group, by enzyme catalyzed acylation, is described. The absolute stereochemistries of two monoacetates were assigned by chemical correlation.

1. Introduction

Enzyme catalyzed acylation by asymmetrization of *meso*-diols is a useful method for the preparation of chiral building blocks.[1] Several good results were recently described for the preparation of 2-substituted 1,3-propanediols bearing one[2] or two[3] hydroxy or alkoxy groups β to the hydroxyl groups with lipases from *Pseudomonas fluorescens* (PFL) and from porcine pancreas (PPL) as catalysts (Scheme 1).

We have shown recently[4] that 2-alkoxymethylmalonates **1** and **2** and the sulfur derivative **3** are easily available by a short preparative method from diethyl methylenemalonate (Scheme 2) and we anticipated that compounds such as **1** and **2** should be valuable starting materials for preparation of asymmetrized tris(hydroxymethyl)methane[2b] through reduction followed by lipase-mediated acylation. We also planned to extend the investigation to the related compounds **3** and **4**.

2. Results and discussion

Reduction of compounds **1**, **2** and **4** in THF or diethylether gave the expected diols **5**, **6** and **8**. On the other hand, reduction of the sulfur compound **3** with $LiAlH_4$ in THF resulted in a mixture of the

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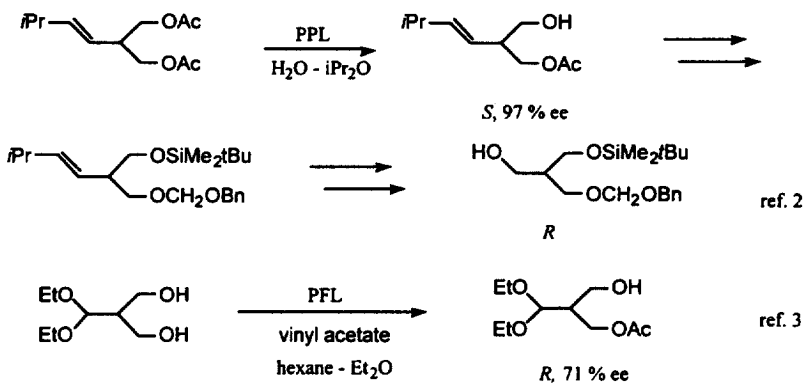
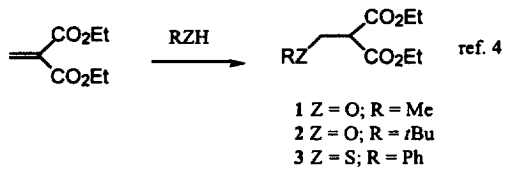
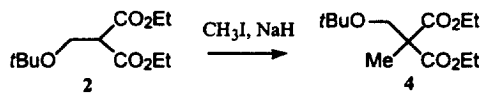


Scheme 1.



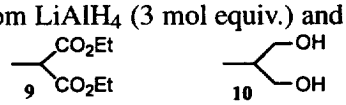


Scheme 2.

Table 1

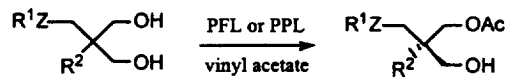
Malonate	Experimental Conditions	Diol	Isolated Yield (%)
1 : Z = O, R^1 = Me, R^2 = H	$LiAlH_4$, THF, reflux	**5**	72
2 : Z = O, R^1 = *t*Bu, R^2 = H	$LiAlH_4$, THF, reflux	**6**	71
3 : Z = S, R^1 = Ph, R^2 = H	AlH_3, Et_2O, r. t.	**7**	79
4 : Z = O, R^1 = *t*Bu, R^2 = Me	$LiAlH_4$, Et_2O , reflux	**8**	68

expected diol **7** in only 34% yield together with 40% of 2-methyl-diethylmalonate **9** probably formed by β-elimination of thiophenol in this basic medium, followed by conjugate reduction. Replacement of $LiAlH_4$ by $NaBH_4$ in methanol led to an increased yield of **9** (90%) along with a very small amount of **7**. Reduction with $Ca(BH_4)_2$ only yielded diol **10** from **9**, and finally a satisfactory result was obtained when using AlH_3[5] obtained in situ from $LiAlH_4$ (3 mol equiv.) and $AlCl_3$ (1 mol equiv.) (Table 1).



When diols **5–8** were submitted to asymmetric enzymatic acylation, mixtures of monoacetates and diacetates were obtained (Table 2). Enantiomeric excesses of monoacetates **11–14** were measured by ^1H NMR either in the presence of (+)-Eu(hfc)$_3$ (**11**, **12**, **14**) or by analysis of the (*S*)-O-acetyllactyl ester derivative[6] (**13**), or by chiral gas phase chromatography (**11**, **12**) that led to coherent results. NMR

Table 2



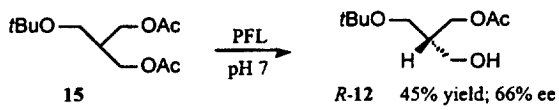
Entry	Diol	Experimental Conditions	Monoacetate[a]	Yield (%)[b]	A / B / C[c]	ee (%)
1	**5**	PFL, 4h, r.t.	**11**	33	41 : 38 : 21	9
2	**5**	PFL, 24h, r. t.	**11**	15	21 : 79 : 0	79
3	**6**	PPL, 28h, r. t.	**12**	52	56 : 0 : 44	38
4	**6**	PFL, 2h, r. t.	**12**	97	97 : 3 : 0	91
5	**7**	PFL, 2h30, r. t.	**13**	83	86 : 12 : 2	58
6	**7**	PFL, 3h, 7°C	**13**	76	80 : 5 : 15	88
7	**8**	PFL, 3-7J, r. t.	**14**	13	15 : 2 : 83	11

a Compounds **12** and **13** were assigned as *S* and *R*, respectively by chemical correlation. Configurations of Compounds **11** and **14** are probably *S* (see text); b Yield of isolated monoacetate; c Monoacetate (A) / diacetate (B) / diol (C) ratios by ^{1}H NMR of the crude product.

analyses from **11** and **13** needed deconvolution of signals, by the Bruker Win NMR program, instead of integration, as these signals were close to each other. All the NMR experiments were performed by comparing the results for racemic products, obtained by reaction of diols with acetic anhydride and pyridine, and the enantiomerically enriched monoacetates.

These analyses showed that enzymatic reactions with PFL led to poor results from **5** and **8**. An improvement was observed from **5** when the reaction time was increased (entry 2), however the yield of **11** was then lowered due to conversion of a part of **11** into diacetate. The low selectivity from **6**, in the presence of PPL, contrasted with the good yield and enantiomeric excess with PFL (entry 4). The predominant isomer had the *S* configuration in both cases, demonstrated below. The result was also satisfying from **7**, mainly when the reaction was run below room temperature (entry 6). In this case we obtained the *R* product.

We also prepared (*R*)-**12** in moderate yield and ee by hydrolysis of diacetate **15** (Scheme 3).



15 *R*-**12** 45% yield; 66% ee

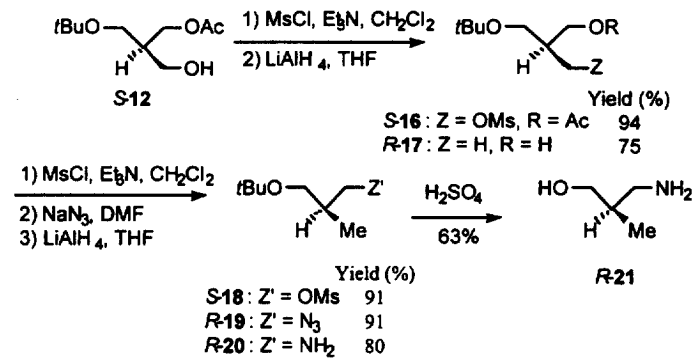
Scheme 3.

The *S* absolute configuration of monoacetate **12** (Table 2) was assessed by chemical correlation leading to the known aminoalcohol (*R*)-**21**.[7] The intermediate alcohol (*R*)-**17** is a known product[8] (Scheme 4).

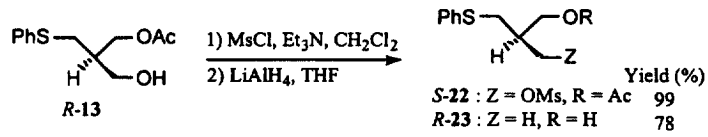
The predominant monoacetate **13** had the *R* configuration as shown by chemical correlation leading to the known (*R*)-**23**[9] (Scheme 5). As (*S*)-**12** and (*R*)-**13** correspond to the same selectivity, **11** and **14** are probably the *S* products.

The configuration of monoacetate **13** could also be checked by conversion to (*R*)-**21** through the intermediate (*S*)-**22** under conditions shown in Scheme 6.

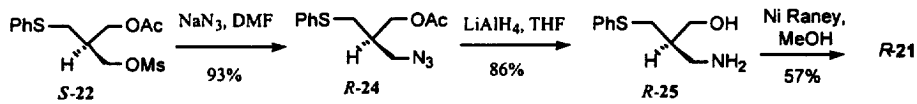
As mentioned above, enantiomerically enriched protected tris(hydroxymethyl)methanes are interesting synthetic intermediates that have been prepared efficiently, albeit in numerous steps, by several teams. We propose here a new method, in two steps, for obtaining **12**, for instance, starting from the easily available **2**. Thus our results constitute new examples of asymmetric acylation of *meso*-diols.



Scheme 4.



Scheme 5.



Scheme 6.

3. Experimental

Optical rotations were measured with a Perkin–Elmer 343 polarimeter. NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100.6 MHz for ^1H and ^{13}C, respectively, in $CDCl_3$ and using TMS as the internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. Chromatographic analyses were performed with a Hewlett Packard HP 6890 apparatus equipped with a 30 m Restek β-DEX-sm or a 25 m Chrompack Chirasil-DEX-CB column. IR spectra were recorded with a Genesis Matteson infrared spectrophotometer. Melting points were measured on a Reichert apparatus and are uncorrected. Elemental analyses were performed by the service de microanalyse, CNRS, ISCN, Gif sur Yvette. Mass spectra were obtained by GPC/MS (Varian 3300 DB5 sm/ITD 800 Finnigan MAT) or by HPLC/MS (Waters 510 Altech RP18 150 m×4.6 mm, Resil C_{18} 5 μ/Fisons LCD MD 800) or with a Varian mat 311 spectrometer (CRMPO, Rennes). The last instrument also led to high resolution mass measurements.

3.1. Preparation of the starting materials 1–4

Compounds **1–3** were prepared as previously described.[4] Crude compound **2** was not very stable and it was distilled without delay after preparation to avoid decomposition. Diethyl 2-(*tert*-butoxymethyl)-2-methylmalonate **4** was obtained in the following way. Diethyl 2-(*tert*-butoxymethyl)malonate **2** (4.78 g, 19.4 mmol) in dry THF (40 ml) was added dropwise, under argon, at 0°C and with stirring to sodium hydride (855 mg of 60% dispersion in mineral oil, prewashed with cyclohexane then THF, 21.4 mmol). The reaction mixture was stirred at room temperature for 1 h then a solution of methyl iodide (1.4 ml, 23.3 mmol) in dry THF (47 ml) was added dropwise. The reaction was allowed to proceed for 2 h at room temperature then the reaction mixture was hydrolysed with brine (60 ml). Evaporation, extraction by Et_2O (3×60 ml), drying ($MgSO_4$) then flash chromatography on silica gel (cyclohexane:AcOEt=7:3) led to **4** as a colorless oil (4.90 g, 97%). ^1H NMR δ 1.14 (s, 9H), 1.26 (t, 6H, J=7.1 Hz), 1.48 (s, 3H), 3.70 (s, 2H), 4.18 (q, 4H, J=7.1 Hz); ^{13}C NMR δ 14.0 (2C, CH_3), 18.4 (CH_3), 27.3 (3C, CH_3), 54.7 (quat. C),

61.0 (2C, CH_2), 64.7 (CH_2), 72.9 (quat. C), 171.0 (2C, CO); IR (film): 2979, 2940, 1735, 1259, 1083, 1025 cm^{-1}; GPC/MS (chem. ionis. isobutane) m/z (rel. int.) 261 (MH^+, 17), 205 (100), 177 (84), 115 (20); GPC/MS (EI) m/z (rel. int.) 261 (MH^+, <2), 245 (4), 205 (100), 187 (30), 129 (67), 115 (36), 101 (27), 85 (20), 69 (21), 57 (77), 41 (85); anal. calcd for $C_{13}H_{24}O_5$: C, 59.98; H, 9.29, found: C, 59.75; H, 9.43.

*3.2. 2-(Methoxymethyl)propan-1,3-diol 5; 2-(*tert*-butoxymethyl)propan-1,3-diol 6; 2-(*tert*-butoxymethyl)-2-methyl-propan-1,3-diol 8*

Compound **6** was obtained by adding dropwise, under argon, at room temperature and with stirring diethyl 2-(*tert*-butoxymethyl)malonate (910 mg, 3.7 mmol) in dry THF (2 ml) to a suspension of $LiAlH_4$ (351 mg, 9.3 mmol) in THF (9 ml). The reaction mixture was stirred for 30 min at room temperature and then for 17 h at reflux. Hydrolysis with a small amount of water then Soxhlet extraction with THF for 24 h led to an oil after evaporation. Flash chromatography on silica gel (cyclohexane:AcOEt=1:1) yielded **6** as a colorless oil (426 mg, 71%). Compound **5**, a known product,[10] was obtained under the same experimental conditions. Compound **8** was prepared with Et_2O as solvent, and Soxhlet extraction was replaced by suction filtration on a sintered-glass funnel then the solid was washed several times with Et_2O. Flash chromatography on silica gel (cyclohexane:AcOEt=1:1) or recrystallization (cyclohexane:pentane) provided **8** as white crystals.

Data for **5**: ^1H NMR δ 2.00 (m, 1H), 3.09 (br s, 2H, OH), 3.35 (s, 3H), 3.53 (d, 2H, J=5.7 Hz), 3.77 (d, 4H, J=5.3 Hz); ^{13}C NMR δ 42.7 (CH), 59.1 (CH_3), 62.9 (2C, CH_2), 73.0 (CH_2); IR (film): 3367, 2881, 1095, 1037 cm^{-1}.

Data for **6**: ^1H NMR δ 1.20 (s, 9H), 1.95 (m, 1H), 2.86 (t, 2H, OH, J=5.3 Hz,), 3.56 (d, 2H, J=5.3 Hz), 3.78 (m, 4H); ^{13}C NMR δ 27.3 (3C, CH_3), 42.8 (CH), 63.0 (CH_2), 63.3 (2C, CH_2), 73.4 (quat. C); IR (film): 3367, 2973, 1363, 1197, 1078, 1035 cm^{-1}; MS (EI) m/z (rel. int.) 162 (M^+, 0.4), 147 (15), 105 (15), 89 (24), 59 (96), 57 (100), 43 (24), 41 (47), 28 (78); HRMS calcd for $C_8H_{18}O_3$ 162.1256, found 162.1249.

Data for **8**: mp 72.6–73°C; ^1H NMR δ 0.82 (s, 3H), 1.19 (s, 9H), 2.97 (br s, 2H, OH), 3.36 (s, 2H), 3.55 (br d, 2H, J_{AB}=11.1 Hz), 3.69 (d, 2H, J_{AB}=11.1 Hz); ^{13}C NMR δ 17.3 (CH_3), 27.2 (3C, CH_3), 40.1 (quat. C), 67.8 (2C, CH_2), 68.2 (CH_2), 73.4 (quat. C); IR (Nujol) 3324, 1463, 1363, 1058, 1037 cm^{-1}; anal. calcd for $C_9H_{20}O_3$: C, 61.33; H, 11.44, found: C, 61.37; H, 11.41.

3.3. 2-[(Phenylsulfanyl)methyl]propan-1,3-diol 7

$LiAlH_4$ (1.454 g, 38.3 mmol) and $AlCl_3$ (1.702 g, 12.8 mmol) in dry Et_2O (50 ml) were stirred for 30 min under argon, at room temperature. Diethyl 2-[(phenylsulfanyl)methyl)]malonate (1.637 g, 5.8 mmol) in Et_2O (29 ml) was then added dropwise at 0°C. The reaction was allowed to proceed for 1.5 h at room temperature. Hydrolysis with a small amount of water, addition of $MgSO_4$, filtration on a sintered-glass funnel then washing the solid several times with Et_2O led to an oil. Flash chromatography on silica gel (cyclohexane:AcOEt=1:1 then MeOH) yielded **7** as white crystals (908 mg, 79%), mp 45.0–45.5°C; ^1H NMR δ 1.94 (m, 1H), 2.63 (br s, 2H, OH), 2.99 (d, 2H, J=7.0 Hz), 3.82 (m, 4H), 7.18 (m, 1H), 7.28 (m, 2H), 7.34 (m, 2H); ^{13}C NMR δ 32.2 (CH_2), 41.6 (CH), 64.3 (2C, CH_2), 126.1 (CH), 129.0 (2C, CH), 129.2 (2C, CH), 136.1 (quat. C); IR (film): 3359, 2927, 2883, 1481, 1438, 1039, 740, 690 cm^{-1}; HPLC/MS (EI) m/z (rel. int.) 198 (M^+, 20), 123 (6), 110 (100); anal. calcd for $C_{10}H_{14}O_2S$: C, 60.58; H, 7.12; S, 16.17, found: C, 60.48; H, 7.19; S, 16.01.

3.4. (−)-3-Methoxy-2-(hydroxymethyl)propylacetate 11; (S)-3-(tert-butoxy)-2-(hydroxymethyl)propylacetate 12; (R)-3-hydroxy-2-[(phenylsulfanyl)methyl]propylacetate 13; 3-(tert-butoxy)-2-(hydroxymethyl)-2-ethylpropylacetate 14

Compound (−)-**11** was obtained by stirring 2-(methoxymethyl)propan-1,3-diol (149 mg, 1.24 mmol) and PFL (15 mg) in vinyl acetate (3 ml) for 24 h, at room temperature. Enzyme was then removed by filtration on a sintered-glass funnel. Washing (vinyl acetate), evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=1:1) provided (−)-**11** (30 mg, 15%, 79% ee, $[\alpha]_D^{20}$ − 1.47 ($CHCl_3$, c=1.7)) as a colorless oil. Diacetate could also be isolated. Compound (*S*)-**12** was obtained in the same way from diol **6** (517 mg, 3.2 mmol), PFL (83 mg), vinyl acetate (10 ml), in 2 h. It was obtained as a colorless oil (640 mg, 97%, 91% ee, $[\alpha]_D^{20}$+1.8 ($CHCl_3$, c=4.0)). In another experiment PFL was replaced by PPL. Compound (*S*)-**12** was thus obtained in 52% yield and 38% ee. Compound (*R*)-**13** was obtained by a similar procedure to (−)-**11**, in 3 h at 7°C, starting from diol **7** (105 mg, 0.53 mmol) and PFL (10 mg) in vinyl acetate (5 ml). Flash chromatography (cyclohexane:AcOEt=6:4) provided (*R*)-**13** as a colorless oil (97 mg, 76%, 88% ee, $[\alpha]_D^{20}$ +14.7 ($CHCl_3$, c=7.4)). Compound **14** was obtained by a similar procedure as for (−)-**11**, in 3–7 days, starting from diol **8** (80 mg, 0.45 mmol) and PFL (15 mg) in vinyl acetate (2 ml). Flash chromatography (cyclohexane:AcOEt=8:2) provided **14** as a colorless oil (13 mg, 13%, 11% ee, $[\alpha]_D^{20}$ was very low and could not be measured).

Data for **11**: ^{1}H NMR δ 2.07 (s, 3H), 2.14 (m, 1H), 2.58 (br s, 1H, OH), 3.35 (s, 3H), 3.48 (dd, 1H, *J*=9.3, 6.0 Hz), 3.53 (dd, 1H, *J*=9.3, 5.4 Hz), 3.71 (d, 2H, *J*=5.1 Hz), 4.18 (d, 2H, *J*=6.0 Hz); ^{13}C NMR δ 20.8 (*C*H$_3$), 40.7 (*C*H), 59.1 (*C*H$_3$), 62.2 (*C*H$_2$), 62.5 (*C*H$_2$), 72.4 (*C*H$_2$), 171.3 (*C*O); IR (film): 3448, 2898, 1741, 1247, 1108, 1039 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 163 (MH^+, <0.5), 145 (2), 131 (1), 84 (6), 71 (29), 61 (20), 57 (18), 45 (56), 43 (100); anal. calcd for $C_7H_{14}O_4$+0.05H_2O: C, 51.58; H, 8.65, found: C, 51.39; H, 8.69.

Data for **12**: ^{1}H NMR δ 1.20 (s, 9H), 2.07 (s, 3H), 2.07 (m, 1H), 2.95 (m, 1H, OH), 3.49 (dd, 1H, *J*=8.8, 5.9 Hz), 3.57 (dd, 1H, *J*=8.8, 4.7 Hz), 3.74 (m, 2H), 4.17 (d, 2H, *J*=6.5 Hz); ^{13}C NMR δ 20.9 (*C*H$_3$), 27.3 (3C, *C*H$_3$), 40.5 (*C*H), 62.3 (*C*H$_2$), 62.8 (*C*H$_2$), 63.4 (*C*H$_2$), 73.5 (quat. C), 171.2 (*C*O); IR (film): 3453, 2973, 1741, 1243, 1039 cm^{-1}; GPC/MS m/z (rel. int.) 205 (MH^+, <0.5), 149 (39), 131 (100), 87 (16), 59 (27), 57 (27), 43 (90); anal. calcd for $C_{10}H_{20}O_4$+0.2H_2O: C, 57.73; H, 9.81, found: C, 57.79; H, 9.97.

Data for **13**: ^{1}H NMR δ 2.06 (s, 3H), 2.09 (m, 2H, OH and H-2), 2.96 (dd, 1H, *J*=13.5, 6.9 Hz), 3.02 (dd, 1H, *J*=13.5, 7.0 Hz), 3.69 (m, 2H), 4.24 (d, 2H, *J*=5.6 Hz), 7.18 (m, 1H), 7.28 (m, 2H), 7.36 (m, 2H); ^{13}C NMR δ 20.8 (*C*H$_3$), 32.3 (*C*H$_2$), 40.3 (*C*H), 61.7 (*C*H$_2$), 63.5 (*C*H$_2$), 126.3 (*C*H), 129.0 (2C, *C*H), 129.4 (2C, *C*H), 135.9 (quat. C), 171.4 (*C*O); IR (film): 3442, 3056, 2952, 2892, 1733, 1481, 1438, 1243, 1039, 740, 692 cm^{-1}; HPLC/MS (EI) m/z (rel. int.) 240 (M^+, 39), 149 (63), 131 (17), 123 (45), 110 (100), 109 (43); anal. calcd for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34, found: C, 59.62; H, 6.83; S, 12.98.

Data for **14**: ^{1}H NMR δ 0.85 (s, 3H), 1.18 (s, 9H), 2.08 (s, 3H), 3.24 (m, 1H, OH), 3.31 (d, 1H, *J*=8.7 Hz), 3.38 (d, 1H, *J*=8.7 Hz), 3.54 (m, 2H), 4.09 (d, 1H, *J*=11.0 Hz), 4.14 (d, 1H, *J*=11.0 Hz); ^{13}C NMR ($CDCl_3$) δ 17.3 (*C*H$_3$), 20.8 (*C*H$_3$), 27.2 (3C, *C*H$_3$), 39.1 (quat. C), 66.6 (*C*H$_2$), 67.5 (*C*H$_2$), 68.5(*C*H$_2$), 73.4 (quat. C), 171.2 (*C*O); IR (film): 3455, 2973, 1733, 1365, 1243, 1199, 1085, 1039 cm^{-1}.

3.5. 3-(Acetyloxy)-2-(tert-butoxymethyl)propylacetate 15

This compound was obtained together with (±)-**12** which was prepared to measure the ee of (*S*)-**12**. Preparation of **15** was not optimised. Diol **6** (4.219 g, 26 mmol), Ac_2O (2.5 ml, 26 mmol) and pyridine

(2.1 ml, 26 mmol) were stirred under argon, at room temperature for 3 h. Aqueous saturated $NaHCO_3$ (90 ml) was then added. Extraction by CH_2Cl_2 (3×100 ml), washing of the combined organic phases successively with 10% aqueous HCl (100 ml), H_2O (100 ml), then brine (100 ml), drying ($MgSO_4$), evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=7:3) led to (±)-**12** (2.611 g, 49%) and to **15** (1.911 g, 30%) as colorless oils. Data for **15**: ^{1}H NMR δ 1.16 (s, 9H), 2.05 (s, 6H), 2.21 (m, 1H), 3.38 (d, 2H, *J*=5.8 Hz), 4.11 (dd, 1H, *J*=11.1, 6.2 Hz), 4.15 (dd, 1H, *J*=11.1, 5.9 Hz); ^{13}C NMR δ 20.8 (2C, CH_3), 27.3 (3C, CH_3), 38.6 (CH) 59.0 (CH_2), 62.6 (2C, CH_2) 72.8 (quat. C), 170.9 (2C, CO); IR (film): 2973, 1747, 1365, 1234, 1039 cm^{-1}; anal. calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00, found: C, 58.27; H, 9.19.

3.6. (R)-3-(tert-*Butoxy*)-2-(*hydroxymethyl*)*propylacetate* **12**

Diacetate **15** (416 mg, 1.7 mmol) was stirred for 24 h with a mixture of pH 7 buffer solution (15 ml), and of PFL (25 mg). Throughout this reaction, the pH was maintained at 7 by adding 1 M NaOH under pH stat monitoring. Extraction by CH_2Cl_2 (3×15 ml), saturation of the aqueous phase with NaCl, other extractions by CH_2Cl_2 (2×20 ml), drying of the combined organic phases ($MgSO_4$), evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=1:1) provided (*R*)-**12** (156 mg, 45%, 66% ee, $[\alpha]_D^{20}$ −1.2 ($CHCl_3$, c=2.75)).

3.7. (S)-3-(tert-*Butoxy*)-2-{[(*methylsulfonyl*)*oxy*]*methyl*}*propylacetate* **16**

Compound (*S*)-**12** (1.00 g, 4.9 mmol), Et_3N (1.02 ml, 7.35 mmol) and CH_2Cl_2 (14 ml) were mixed under argon at 0°C. Mesyl chloride (455 μl, 5.88 mmol) was then added dropwise. The reaction was allowed to proceed for 2.3 h at the same temperature with TLC monitoring. CH_2Cl_2 was then added. Washing of the organic phase (10% HCl), drying $(MgSO)_4$, evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=1:1) led to (*S*)-**16** as a colorless oil (1.292 g, 94%, 91% ee, $[\alpha]_D^{20}$ +1.5 ($CHCl_3$, c=4.0)). ^{1}H NMR δ 1.17 (s, 9H), 2.07 (s, 3H), 2.30 (m, 1H), 3.02 (s, 3H), 3.39 (dd, 1H, *J*=6.0, 9.1 Hz), 3.43 (dd, 1H, *J*=5.4, 9.1 Hz), 4.12 (dd, 1H, *J*=6.6, 11.3 Hz), 4.18 (dd, 1H, *J*=5.8, 11.3 Hz), 4.29 (dd, 1H, *J*=5.6, 9.6 Hz), 4.32 (dd, 1H, *J*=5.7, 9.6 Hz); ^{13}C NMR δ 20.8 (CH_3), 27.3 (3C, CH_3), 37.1, 39.0, 58.3 (CH_2), 61.9 (CH_2), 67.7 (CH_2), 73.1 (quat. C), 170.8 (CO); IR (film): 2975, 1733, 1359, 1243, 1178, 1083, 1043, 964, 835 cm^{-1}; GPC/MS (chem. ionis. isobutane) m/z (rel. int.) 283 (MH^+, 0.4), 227 (4), 209 (51), 131 (100); anal. calcd for $C_{11}H_{22}O_6S$: C, 46.79; H, 7.85; S, 11.35, found: C, 46.78; H, 7.94; S, 11.21.

3.8. (R)-3-(tert-*Butoxy*)-2-*methylpropan*-1-*ol* **17**

Compound (*S*)-**16** (1.254 g, 4.45 mmol) in dry THF (5 ml) was added dropwise, under argon and with stirring to a refluxing suspension of $LiAlH_4$ (1.012 g, 26.7 mmol) in dry THF (5 ml). Reflux was pursued for 5 min. Cooling, hydrolysis with a small amount of water, dilution with Et_2O, filtration, washing of the solid phase with Et_2O, drying of the organic phase ($MgSO_4$) and evaporation provided the crude (*R*)-**17**, a known product,[8] as a colorless oil that was used without further purification in the next step (458 mg, 70%, 91% ee, $[\alpha]_D^{20}$ +13.2 ($CHCl_3$, c=2.6) (lit.[8] $[\alpha]_D^{20}$ +0.49 (MeOH, c=4.0) for 100% ee)). ^{1}H NMR δ 0.84 (d, 3H, *J*=6.9 Hz), 1.20 (s, 9H), 1.99 (m, 1H), 3.30 (m, 2H), 3.57 (m, 3H, OH and next CH_2); ^{13}C NMR δ 13.4 (CH_3), 27.3 (3C, CH_3), 35.5 (CH), 68.0 (CH_2), 69.1 (CH_2), 73.3 (quat. C); IR (film): 3413, 2977, 2873, 1361, 1197, 1079, 1039 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 147 (MH^+, 5), 131 (13), 91 (100), 73 (12), 59 (85), 57 (68), 41 (48).

3.9. (S)-3-(tert-Butoxy)-2-methylpropylmethanesulfonate 18

A mixture of compound (*R*)-**17** (113 mg, 0.77 mmol), dry CH_2Cl_2 (2.5 ml) and Et_3N (161 µl, 1.16 mmol) were stirred under argon and at 0°C. Mesyl chloride (72 µl, 0.93 mmol) was then added dropwise. The reaction was allowed to proceed for 2.3 h at the same temperature with TLC monitoring then CH_2Cl_2 was added. Washing of the organic phase (10% HCl), drying ($MgSO_4$), evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=1:1) led to (*S*)-**18** as a colorless oil (158 mg, 91%, 91% ee, $[\alpha]_D^{20}$ +8.5 ($CHCl_3$, c=2.1)). ^{1}H NMR δ 1.00 (d, 3H, *J*=6.9 Hz), 1.17 (s, 9H), 2.07 (m, 1H), 3.00 (s, 3H), 3.24 (dd, 1H, *J*=8.9, 7.1 Hz), 3.32 (dd, 1H, *J*=8.9, 5.0 Hz), 4.16 (dd, 1H, *J*=9.3, 5.8 Hz), 4.23 (dd, 1H, *J*=9.3, 5.3 Hz); ^{13}C NMR δ 13.7 (*C*H$_3$), 27.4 (3C, *C*H$_3$), 34.1 (*C*H), 37.0 (*C*H$_3$), 62.3 (*C*H$_2$), 72.3 (*C*H$_2$), 72.7 (quat. C); IR (film): 2973, 2879, 1353, 1176, 1081, 962, 829 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 225 (MH$^+$, <2), 209 (5), 170 (95), 151 (32), 97 (9), 79 (13), 73 (31), 57 (100), 41 (45); anal. calcd for $C_9H_{20}O_4S$: C, 48.19; H, 8.99; S, 14.29, found: C, 47.89; H, 9.01; S, 14.11.

3.10. (R)-1-Azido-3-(tert-butoxy)-2-methylpropane 19

Sodium azide (250 mg, 3.85 mmol) was added portionwise, with stirring, under argon and at room temperature to a solution of compound (*S*)-**18** (460 mg, 2.14 mmol) in DMF (4.5 ml). The reaction mixture was stirred for 7.25 h at 75°C. Cooling, addition of water (10 ml), extraction (Et_2O, 3×20 ml), drying of the combined organic phases ($MgSO_4$), evaporation then flash chromatography on silica gel (light petroleum:Et_2O=7:3) led to (*R*)-**19** as a colorless oil (324 mg, 93%, 91% ee (estimated from (*S*)-**18**), $[\alpha]_D^{20}$ +5.2 ($CHCl_3$, c=1)). ^{1}H NMR δ 0.95 (d, 3H, *J*=6.8 Hz), 1.17 (s, 9H), 1.90 (m, 1H), 3.23 (m, 3H), 3.36 (dd, 1H, *J*=12.0, 5.5 Hz); ^{13}C NMR δ 14.9 (*C*H$_3$), 27.4 (3C, *C*H$_3$), 34.6 (*C*H), 54.8 (*C*H$_2$), 63.6 (*C*H$_2$), 72.4 (quat. C); IR (film): 2975, 2100, 1363, 1197, 1081 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 172 (MH$^+$, <1), 144 (18) 128 (12), 116 (13), 86 (31), 70 (27), 57 (100), 41 (55).

3.11. (R)-3-(tert-Butoxy)-2-methyl-1-propanamine 20

A solution of compound (*R*)-**19** (400 mg, 2.34 mmol) in dry THF (3.5 ml) was added dropwise under argon, at 0°C and with stirring to a suspension of $LiAlH_4$ (115 mg, 3.0 mmol), in dry THF (3 ml). The reaction mixture was stirred for 6 h at room temperature. Hydrolysis with a small amount of water, addition of Et_2O, suction filtration on a sintered-glass funnel then washing the solid several times with Et_2O, drying the organic phase ($MgSO_4$) and evaporation provided (*R*)-**20** as a colorless oil that was used without further purification in the next step (286 mg, 84%, 91% ee (estimated from (*S*)-**18**), $[\alpha]_D^{20}$ +4.3 ($CHCl_3$, c=1,8)). ^{1}H NMR δ 0.89 (d, 3H, *J*=6.8 Hz), 1.18 (s, 9H), 1.46 (br s, 2H, NH_2), 1.69 (m, 1H), 2.56 (dd, 1H, *J*=12.6, 6.0 Hz), 2.74 (dd, 1H, *J*=12.6, 6.1 Hz), 3.22 (dd, 1H, *J*=8.8, 6.9 Hz), 3.25 (dd, 1H, *J*=8.8, 5.9 Hz); ^{13}C NMR δ 15.0 (*C*H$_3$), 27.4 (3C, *C*H$_3$), 37.1 (*C*H), 46.3 (*C*H$_2$), 65.5 (*C*H$_2$), 72.3 (quat. C); IR (film): 3376, 2971, 2873, 1361, 1199, 1081 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 146 (MH$^+$, 22), 130 (2), 90 (19), 88 (70), 72 (26), 57 (76), 41 (100).

3.12. (R)-3-Amino-2-methylpropan-1-ol 21

Sulfuric acid (160 µl of the 18 M reagent) was added dropwise, at room temperature and with stirring to a solution of compound (*R*)-**20** (157 mg, 1.08 mmol) in dry ethanol (3 ml). The reaction mixture was heated to reflux and this temperature was maintained for 7 h. Cooling, evaporation, addition of water (0.5 ml), saturation with NaOH, extraction (CH_2Cl_2, 3×5 ml), drying the combined organic phases ($MgSO_4$),

evaporation and flash chromatography on silica gel (CH_2Cl_2:MeOH:*i*PrNH$_2$=85:10:5) led to the known[7] (*R*)-**21** as a colorless oil (59 mg, 63%, 91% ee (estimated from (*S*)-**18**), $[\alpha]_D^{20}$ +5.4 (MeOH, c=3.4) (lit.[7] $[\alpha]_D^{20}$ +8.9 (MeOH c=22.6) for 100% ee)). ^{1}H NMR δ 0.84 (d, 3H, *J*=6.9 Hz), 1.81 (m, 1H), 2.70 (dd, 1H, *J*=12.2, 8.6 Hz), 2.86 (br s, 3H, OH and NH_2), 2.93 (dd, 1H, *J*=12.2, 3.8 Hz), 3.55 (dd, 1H, *J*=10.6, 8.2 Hz), 3.68 (dd, 1H, *J*=10.6, 4.0 Hz); ^{13}C NMR δ 14.6 (*C*H$_3$), 36.6 (*C*H), 47.9 (*C*H$_2$), 69.0 (*C*H$_2$); IR (film): 3500–3000, 2906, 1602, 1463, 1037 cm^{-1}.

3.13. (S)-3-[(Methylsulfonyl)oxy]-2-[(phenylsulfanyl)methyl]propylacetate **22**

Triethylamine (305 μl, 2.18 mmol) was added with stirring, at room temperature and under argon to a solution of compound (*R*)-**13** (349 mg, 1.45 mmol) in dry CH_2Cl_2 (4.5 ml). The mixture was cooled to 0°C then mesyl chloride (135 μl, 1.74 mmol) was added dropwise. The reaction was allowed to proceed for 1.5 h at room temperature, with TLC monitoring. CH_2Cl_2 was then added, the organic phase was washed with 10% HCl then dried ($MgSO_4$). Evaporation then flash chromatography on silica gel (cyclohexane:AcOEt=6:4) led to (*S*)-**22** as a colorless oil (462 mg, 99%, 88% ee (estimated from (*R*)-**13**), $[\alpha]_D^{20}$ − 4.5 ($CHCl_3$, c=1.9)). ^{1}H NMR δ 2.05 (s, 6H), 2.30 (m, 1H), 2.99 (s, 3H), 2.99 (dd, 1H, *J*=13.8, 7.3 Hz), 3.03 (dd, 1H, *J*=13.8, 6.8 Hz), 4.17 (dd, 1H, *J*=11.5, 6.4 Hz), 4.22 (dd, 1H, *J*=11.5, 5.4 Hz), 4.32 (dd, 1H, *J*=10.1, 5.0 Hz), 4.37 (dd, 1H, *J*=10.1, 5.3 Hz), 7.22 (m, 1H), 7.30 (m, 2H), 7.36 (m, 2H); ^{13}C NMR δ 20.7 (*C*H$_3$), 32.1 (*C*H$_2$), 37.2, 37.8, 60.3 (*C*H$_2$), 67.9 (*C*H$_2$), 126.8 (*C*H), 129.2 (2C, *C*H), 130.0 (2C, *C*H), 134.9 (quat. C), 170.5 (*C*O); IR (film): 3021, 2935, 1733, 1361, 1234, 1172, 1045, 962, 829, 744, 692 cm^{-1}; HPLC/MS (EI) m/z (rel. int.) 318 (M$^+$, 23), 222 (14), 209 (7), 162 (52), 161 (62), 149 (25), 147 (34), 135 (33), 129 (67), 123 (90), 110 (100), 109 (79); anal. calcd for $C_{13}H_{18}O_5S_2$: C, 49.04; H 5.70; S, 20.14, found: C, 48.86; H, 5.61; S, 19.91.

3.14. (R)-2-Methyl-3-(phenylsulfanyl)propan-1-ol **23**

A solution of compound (*S*)-**22** (90 mg, 0.28 mmol) in dry THF (0.5 ml) was added dropwise, with stirring and under argon to a refluxing suspension of $LiAlH_4$ (64 mg, 1.70 mmol) in dry THF (3 ml). After 5 min stirring, the reaction mixture was cooled. Hydrolysis with a small amount of water, addition of Et_2O, suction filtration on a sintered-glass funnel then washing the solid several times with Et_2O, drying of the organic phase ($MgSO_4$), evaporation then flash chromatography on silica gel (cyclohexane:AcOEt=6:4) provided (*R*)-**23**, a known product,[9] as a colorless oil (40 mg, 78%, 88% ee (estimated from (*R*)-**13**), $[\alpha]_D^{20}$ −13.8 (CH_2Cl_2, c=3.0) (lit.[9] $[\alpha]_D^{20}$ −17.0 (CH_2Cl_2, c=1) for 100% ee)). ^{1}H NMR δ 1.04 (d, 3H, *J*=6.8 Hz), 1.71 (br s, 1H, OH), 1.94 (m, 1H), 2.83 (dd, 1H, *J*=12.9, 6.5 Hz), 3.07 (dd, 1H, *J*=12.9, 6.5 Hz), 3.61 (m, 2H), 7.17 (m, 1H), 7.27 (m, 2H), 7.34 (m, 2H); ^{13}C NMR δ 16.4 (*C*H$_3$), 35.5 (*C*H), 37.4 (*C*H$_2$), 66.8 (*C*H$_2$), 125.8 (*C*H), 128.9 (2C, *C*H), 129.0 (2C, *C*H), 136.7 (quat. C); IR (film): 3353, 3058, 2956, 2878, 1583, 1481, 1438, 1033, 983, 738, 690 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 182 (M$^+$, 43), 165 (2), 149 (4), 123 (26), 110 (100), 77 (12), 65 (18), 57 (20), 51 (18), 45 (38), 39 (30).

3.15. (R)-3-Azido-2-[(phenylsulfanyl)methyl]propylacetate **24**

Sodium azide (149 mg, 2.29 mmol) was added portionwise at room temperature, under argon and with stirring to a solution of compound (*S*)-**22** (404 mg, 1.27 mmol) in DMF (5 ml). The reaction was allowed to proceed for 4 h at 75°C. Cooling, addition of water (10 ml), extraction (Et_2O, 3×15 ml), drying, evaporation and flash chromatography on silica gel (cyclohexane:AcOEt=7:3) provided (*R*)-**24**

as a colorless oil (291 mg, 86%, 88% ee, $[\alpha]_D^{20}$ −10.6 ($CHCl_3$, c=2)). ^1H NMR δ 2.05 (s, 6H), 2.12 (m, 1H), 2.97 (d, 2H, *J*=6.8 Hz), 3.49 (dd, 1H, *J*=12.4, 5.6 Hz), 3.53 (dd, 1H, *J*=12.4, 6.0 Hz), 4.13 (dd, 1H, *J*=11.4, 6.0 Hz), 4.16 (dd, 1H, *J*=11.4, 5.5 Hz), 7.20 (m, 1H), 7.30 (m, 2H), 7.36 (m, 2H); ^{13}C NMR δ 20.8 (CH_3), 33.0 (CH_2), 38.0 (*C*H), 51.3 (CH_2), 63.7 (CH_2), 126.6 (*C*H), 129.1 (2C, *C*H), 129.7 (2C, *C*H), 135.4 (quat. C), 170.7 (*C*O); IR (film): 3073, 2933, 2103, 1741, 1234, 1039, 740, 692 cm^{-1}; GPC/MS (EI) m/z (rel. int.) 237 (M^+-N_2, 3), 137 (51), 110 (34), 109 (45), 91 (27), 65 (21), 43 (100).

3.16. (R)-3-Amino-2-[(phenylsulfanyl)methyl]propan-1-ol **25**

A solution of compound (*R*)-**24** (159 mg, 0.6 mmol) in dry THF (0.8 ml) was added dropwise, under argon, at 0°C and with stirring to a suspension of $LiAlH_4$ (50 mg, 1.32 mmol), in dry THF (1.5 ml). The reaction mixture was stirred for 2 h at room temperature. Hydrolysis with a small amount of water, addition of Et_2O, suction filtration on a sintered-glass funnel then washing of the solid several times with Et_2O, drying of the organic phase ($MgSO_4$) and evaporation provided (*R*)-**25** as a colorless oil that was used without further purification in the next step (73 mg, 62%, 88% ee, $[\alpha]_D^{20}$ −10.4 ($CHCl_3$, c=4,7)). It could also be chromatographed (CH_2Cl_2:MeOH:*i*$PrNH_2$=80:15:5). ^1H NMR δ 1.85 (m, 1H), 2.60 (br s, 3H, OH and NH_2), 2.89 (dd, 1H, *J*=13.1, 7.3 Hz), 2.92 (m, 1H); 2.95 (dd, 1H, *J*=13.1, 6.7 Hz), 3.07 (m, 1H), 3.81 (m, 2H), 7.17 (m, 1H), 7.27 (m, 2H), 7.34 (m, 2H); ^{13}C NMR δ 33.4 (CH_2), 41.0 (*C*H), 44.7 (CH_2), 66.0 (CH_2), 125.9 (*C*H), 128.9 (2C, *C*H), 129.0 (2C, *C*H), 136.4 (quat. C); IR (film): 3359, 3292, 3075, 1583, 1481, 1438, 1025, 740, 690 cm^{-1}.

3.17. Reduction of compound **25** *by Raney nickel*

A suspension of Raney nickel (3 g) in MeOH (10 ml) was obtained by washing with water several times and decantations followed by replacement of water by MeOH. A solution of compound (*R*)-**25** (105 mg, 0.53 mmol) in MeOH (1 ml) was then added to this suspension. The reaction mixture was stirred for 1 h with TLC monitoring. Filtration on Celite, washing with MeOH and evaporation provided (*R*)-**21** (27 mg, 57%, 88% ee, $[\alpha]_D^{20}$ −1.7 (MeOH, c=1) (for the crude product)).

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References

1. For reviews see: (a) Wong, C.-H.; Whitesides, G. M. Enzymes in Synthetic Organic Chemistry, *Tetrahedron Organic Chemistry Series*, Volume 12; Pergamon, 1994. (b) Xie, Z.-F. *Tetrahedron: Asymmetry* **1991**, *2*, 733–750. (c) Boland, W.; Frößl, C.; Lorenz, M. *Synthesis* **1991**, 1049–1072. (d) Faber, K.; Riva, S. *Synthesis* **1992**, 895–910. (e) Theil, F. *Chem. Rev.* **1995**, *95*, 2203–2227. (f) Schoffers, E.; Golebiowski, A.; Johnson C. R. *Tetrahedron* **1996**, *52*, 3769–3826.
2. (a) Ehrler, L.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 379–388. (b) Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *57*, 1540–1554.
3. Egri, G.; Fogassy, E.; Novák, L.; Poppe, L. *Tetrahedron: Asymmetry* **1997**, *8*, 547–557.
4. Delépine, J.-L.; Pecquet, P.; Betton M.-C.; Huet, F. *Synth. Commun.* **1996**, *26*, 2816–2829.
5. Gawronski, J. K.; Walborsky, H. M. *J. Org. Chem.* **1986**, *51*, 2863–2870.
6. Mosandi, A.; Gessner, M.; Günther, C.; Deger, W.; Singer, G. J. *High Resolution Chromatography & Chromatography Comm.* **1987**, *10*, 67–70.
7. Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479–2490.
8. Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505–3511.
9. Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans.* **1987**, 1623–1633.
10. Musso, H.; Naumann, K.; Grychtol, K. *Chem. Ber.* **1967**, *100*, 3614–3626.