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An alternative approach to (*S*)- and (*R*)-2-methylglycidol *O*-benzyl ether derivatives

Alberto Avenoza,[a,*] Carlos Cativiela,[b] Jesús M. Peregrina,[a,*] David Sucunza[a] and María M. Zurbano[a]

[a]*Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, UA-CSIC, 26006 Logroño, Spain*
[b]*Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain*

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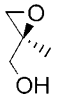
Abstract—This report describes the gram scale synthesis of (*S*)- and (*R*)-2,2,4-trimethyl-4-(hydroxymethyl)-1,3-dioxolanes using the Sharpless asymmetric dihydroxylation (AD) of the Weinreb amide of 2-methyl-2-propenoic acid. The 2-methylglycerol acetonides resultant from protection of the AD products were used as starting materials in the synthesis of *O*-benzyl ethers of the valuable C4-chiral building blocks (*S*)- and (*R*)-2-methylglycidol. © 2001 Elsevier Science Ltd. All rights reserved.

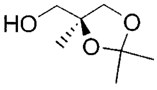
1. Introduction

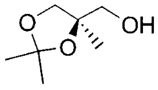
Optically active glycidols and their derivatives are a class of epoxides with great versatility and importance in organic synthesis, since the presence of a CH_2OR group allows the introduction of a third potentially electrophilic centre. As a result of their easy availability and the broad scope of their synthetically useful reactions, several publications have appeared in the literature.[1]

However, only minor attention has been paid to the enantiomers of 2-methylglycidol (*S*)- and (*R*)-**1**, although several uses are described. For example, selective protection or oxidation of (*S*)- and/or (*R*)-**1** and ring opening of the oxirane ring followed by functional group transformations led to the formation of aziridines,[2] oxazolines[3] or oxazolidines,[4] which were used in the asymmetric synthesis of a variety of α-methyl α-amino acids. Homochiral 2-methylglycidols were also used in the preparation of various natural products and their analogues.[5,6] Some examples of compounds synthesised using these chiral units are (22*E*,25*R*)-1α,25,26-trihydroxy-Δ^{22}-vitamin D_3,[7] (23*S*,25*R*)-calcitriol lactone,[8] dideoxyribosides,[9] analogue inhibitors of carnitine acetyltransferase,[10] a series of 1,25-dihydrocholecalciferol analogues,[11] several choline analogues,[12] some derivatives of cynchomalthoheptaosa,[13] and both enantiomers of frontalin.[14] Moreover, both enantiomers of **1** were used to prepare 2,2,4-trimethyl-4-(hydroxymethyl)-1,3-dioxolanes (*S*)- and (*R*)-**2**,[15] two important C4-building blocks, which together with their derivatives were extensively used in the asymmetric synthesis of numerous natural products.[16]


(*S*)-**1**


(*R*)-**1**


(*S*)-**2**


(*R*)-**2**

The first synthesis of enantiomerically pure **1** was achieved in 1983 using the Sharpless asymmetric epoxidation (AE)[17] of 2-methyl-2-propen-1-ol, which afforded the (*R*)-enantiomer[18] with 94% e.e. in 32% yield and the (*S*)-enantiomer[19] with 85% e.e. in 78% yield. It is widely recognised that while AE has great scope, allylic alcohol substrates such as 2-methyl-2-propen-1-ol[20] are not best suited to the methodology due to the water solubility of the product **1** and its sensitivity to nucleophilic opening.[21] These difficulties were reduced by using the modified AE procedure[22] combined with a non-aqueous work-up, which allowed the isolation of (*R*)-**1** in 47% yield and 95% e.e.[23] In spite of this, difficulties were still encountered in the isolation of **1**; therefore, Sharpless et al. developed an

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[*] Corresponding author. Fax: +34 941 299621; e-mail: alberto.avenoza@dq.unirioja.es

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alternative, which involves the in situ transformation of the crude AE product to obtain a *p*-nitrobenzoate ester (or two sulfonate derivatives).[24] More recently, (*R*)-**1** has been prepared by chemoenzymatic reactions with >99% e.e.[25] and by epoxidation of 2-methyl-2-propen-1-ol in supercritical carbon dioxide using a vanadyl salen oxo-transfer catalyst, which gave moderate 50% yield and 75% e.e.[26]

(*S*)- and (*R*)-2-Methylglycidol *O*-benzyl derivatives **11** were easily formed by the protection of (*S*)- or (*R*)-**1** as their benzyl ethers.[9] Recently, (*S*)- and (*R*)-**11** were prepared by chemoenzymatic synthesis from deracemisation of (±)-**11**,[15,27] which was obtained by epoxidation of methallyl alcohol using *m*-CPBA.[28] Other attempts using the AE or Sharpless asymmetric dihydroxylation (AD)[29] gave less satisfactory results with e.e. of <45%.[30]

Given the importance of both enantiomers of **1** and **2** (and their derivatives **7**, **8** and **11**), and the fact that (*S*)-**1** and (*R*)-**1** are not commercially available, we herein report a new straightforward synthetic procedure for the aforementioned C4-chiral building blocks.

2. Results and discussion

In order to obtain the required C4-building block, 2-methylglycerol acetonide (*R*)-**2** and its benzyl and methanesulfonyl derivatives, we decided to start our synthesis from the easily available olefin **3**,[31] which was subjected to AD in the presence of AD-mix β to give the diol (*S*)-**4** (81% yield, 93% e.e.), according to the previous method reported by Sharpless et al.[32] The amide group of diol (*S*)-**4** was hydrolysed using LiOH in MeOH at room temperature and the corresponding carboxylic acid group was esterified with AcCl in MeOH at reflux to introduce the methyl ester group, affording the dihydroxy ester (*S*)-**5**.[33] The diol function of (*S*)-**5** was protected using 2,2-dimethoxypropane (DMP) and *p*-toluenesulfonic acid (*p*-TsOH) to give the acetonide (*S*)-**6**. This compound has been previously prepared in racemic form by Lin et al.[34] and in enantiomerically pure form by enantioselective lipase-catalysed hydrolysis[35] of (±)-**5** (Scheme 1).

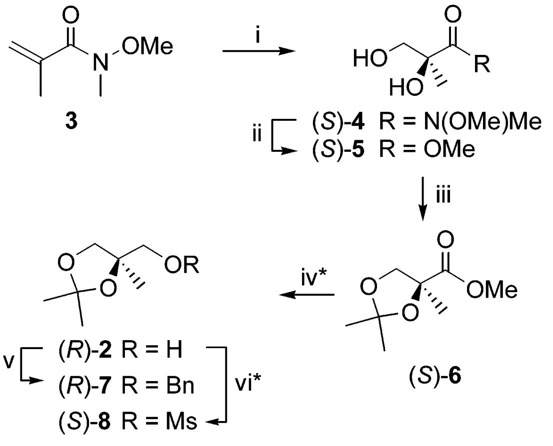
Treatment of (*S*)-**6** with $LiAlH_4$ gave the required alcohol (*R*)-**2** which was transformed into two derivatives, the *O*-benzyl ether (*R*)-**7** using benzyl bromide in the presence of NaH and Bu_4NI and the *O*-methanesulfonyl (*S*)-**8** by treatment with methanesulfonyl chloride in di-*iso*-propylethylamine (DIEA) (the apparent inversion [(*S*)-**6**→(*R*)-**2**→(*S*)-**8**] in the reactions is due to a switch in the CIP-priority and not a result of inversion at the stereogenic centre (see Scheme 1)).

(*S*)-2-Methylglycerol acetonide (*S*)-**2** and its derivatives (*S*)-**7** and (*R*)-**8** were obtained using the same strategy described above and also starting from olefin **3**, but using AD-mix α in the AD reaction.

The chiral building block (*R*)-**7** was used as the starting material for the preparation of 2-methylglycidyl benzyl ether (*R*)-**11**. To this end, the acetal protecting groups were cleaved by treatment of (*R*)-**7** with 2N aqueous HCl to give the diol (*S*)-**9**, which was selectively mesylated at the primary hydroxyl group, yielding alcohol (*R*)-**10**. Subsequent intramolecular Williamson etherification by the action of K_2CO_3 gave the required oxirane (*R*)-**11** (Scheme 2).

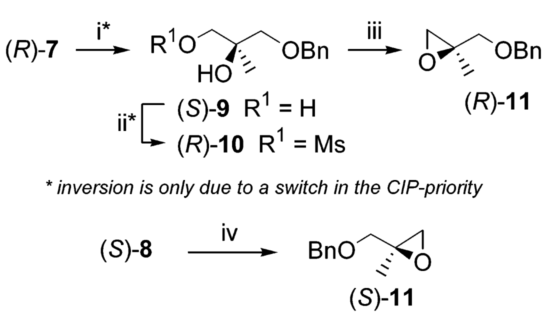
(*S*)-2-Methylglycidyl benzyl ether (*S*)-**11** was synthesised using the same methodology but instead of starting from (*S*)-**7**, we applied a divergent route from (*S*)-**8**; therefore its hydrolysis was carried out with 2N HCl to give the corresponding diol, which was treated in situ with benzyl bromide in the presence of NaH and Bu_4NI giving directly (*S*)-**11** (Scheme 2).

The enantiomeric purity of the 2-methylglycidyl benzyl ethers, the two 2-methylglycerol acetonides and their derivatives was established by preparation of the Mosher esters of alcohols (*S*)- and (*R*)-**1**, which were



* inversion is only due to a switch in the CIP-priority

Scheme 1. (i) AD-mix β [for (*S*)-**4**] or AD-mix α [for (*R*)-**4**], $MeSO_2NH_2$, $^tBuOH/H_2O$ (1:1), 0°C, 12 h, 81%; (ii) (a) $LiOH·H_2O$, $H_2O/MeOH$ (1:3), rt, 2 h; (b) AcCl, MeOH, reflux, 12 h, 85%; (iii) DMP, *p*-TsOH, toluene, reflux, 4 h, 93%; (iv) $LiAlH_4$, THF, rt, 4 h, 90%; (v) BnBr, NaH, Bu_4NI, THF, rt, 92%; (vi) MsCl, DIEA, CH_2Cl_2, rt, 87%.



* inversion is only due to a switch in the CIP-priority

Scheme 2. (i) 2N HCl, THF, rt, 2 h, 95%; (ii) MsCl, DIEA, CH_2Cl_2, rt, 93%; (iii) K_2CO_3, THF, reflux, 79%; (iv) (a) 2N HCl, rt, 2 h, 87%; (b) BnBr, NaH, Bu_4NI, THF, rt, 63%.

obtained from the acid hydrolysis of (*S*)-**8** and (*R*)-**8** and subsequent epoxide formation by treatment with NaH in THF (Scheme 3). Alcohol (*S*)-**1** was coupled with (*R*)-(−)-methoxytrifluorophenylacetic acid ((*R*)-MTPA) in the presence of DCC and DMAP to give the Mosher ester **12** according to the literature protocol.[36] In the same way, a mixture of the alcohols (*S*)-**1** and (*R*)-**1** (in a ratio of 1:3) was transformed into Mosher esters **12** and **13**, respectively. Analysis of the NMR spectra of ester **12** showed that the enantiomeric purity of compound (*S*)-**12** was at least 96% (only one isomer was observed in the ^1H and ^{19}F NMR spectra) (Scheme 3).

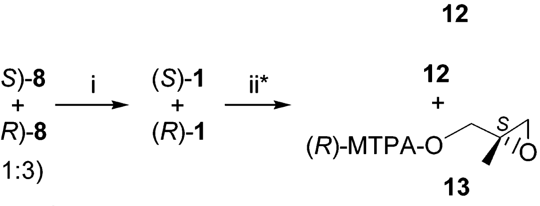
3. Conclusions

In summary, starting from commercially available 2-methyl-2-propenoic acid, we have developed a straightforward gram scale synthetic route to prepare the valuable 2-methylglycerol acetonide building blocks, (*S*)-**2** and (*R*)-**2**, over five steps in enantiomerically pure form and with an overall yield of 58%. (*R*)-**2** was used as the starting material in stereodivergent syntheses of the 2-methylglycidol *O*-benzyl derivatives (*S*)-**11** (three steps, 48% yield) and (*R*)-**11** (four steps, 64% yield).

4. Experimental

4.1. General

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer, using $CDCl_3$ with TMS as the internal standard (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Optical rotations were measured on a Perkin–Elmer 341 polarimeter in a 1 cm cell of 1 mL capacity. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 1000 spectrometer. Mass spectra were obtained by electrospray ionisation (ESI) on a Hewlett–Packard 5989B mass spectrometer.



*inversion is only due to a switch in the CIP-priority

Scheme 3. (i) (a) 2N HCl, THF, rt, 2 h; (b) NaH, THF, rt, 2 h, 90%; (ii) (*R*)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 6 h, 48%.

4.2. Methyl 2,3-dihydroxy-2-methylpropenoates (*R*)-5 and (*S*)-5

To a solution of (*S*)-**4** (8.60 g, 52.7 mmol) in H_2O/MeOH (1:3, 120 mL), at rt, was added $LiOH{\cdot}H_2O$ (11.1 g, 264 mmol) and the mixture stirred for 2 h. The *N*,*O*-dimethylhydroxylamine formed in the reaction and MeOH were removed and the mixture was acidified with conc. HCl to pH 1–2. After removing the solvent, the white solid was dissolved in MeOH/HCl, previously prepared by dropwise addition of AcCl (30 mL) to pre-cooled MeOH (120 mL) at 0°C, and the mixture was heated under reflux for 12 h. The mixture was concentrated and the residue partitioned between H_2O (50 mL) and $CHCl_3$/*iso*-propanol (3:1, 100 mL). The aqueous layer was successively washed with $CHCl_3$/*iso*-propanol (4×100 mL), dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography (hexane/ethyl acetate, 3:7) to give (*S*)-**5** as a colourless oil (5.98 g, 44.6 mmol, 85%). $[\alpha]_D^{25}=-1.0$ (*c* 2.66, MeOH). ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 3.57 (d, 1H, $J=11.2$ Hz, CH_2), 3.80 (d, 1H, $J=11.2$ Hz, CH_2), 3.81 (s, 3H, CO_2CH_3). Anal. calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.61; H, 7.45%. Spectral data were identical to those reported in the literature (Ref. 37).

Compound (*R*)-**5** (5.95 g, 85%) was obtained using the method described for its enantiomer (*S*)-**5**, but starting with (*R*)-**4** (8.62 g, 52.7 mmol). $[\alpha]_D^{25}=+0.8$ (*c* 2.66, MeOH). Anal. calcd for $C_5H_{10}O_4$: C, 44.77; H, 7.51. Found: C, 44.58; H, 7.48%.

4.3. Methyl 2,2,4-trimethyl-1,3-dioxolane-4-carboxylates (*R*)-6 and (*S*)-6

A solution of compound (*S*)-**5** (1.57 g, 11.7 mmol), 2,2-DMP (6.22 g, 58.5 mmol) and TsOH (45 mg, 0.23 mmol) in toluene (25 mL) was heated under reflux for 2 h and then distilled over 15 min to remove the MeOH formed. 2,2-DMP (6.22 g, 58.5 mmol) was added, and the procedure was repeated until TLC analysis showed no remaining starting material and clean formation of a single product. The solvent was removed to give a yellow oil, which was purified by column chromatography (hexane/ethyl acetate, 9:1) to give (*S*)-**6** as an oil (1.90 g, 10.9 mmol, 93%). $[\alpha]_D^{25}=+4.7$ (*c* 1.22, MeOH). ^1H NMR ($CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.72 (s, 3H, CO_2CH_3), 3.74 (d, 1H, $J=8.7$ Hz, CH_2), 4.33 (d, 1H, $J=8.7$ Hz, CH_2). Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.61; H, 8.45%. Spectral data were identical to those reported in the literature (Ref. 34).

Using the method described for its enantiomer (*S*)-**6**, compound (*R*)-**6** (1.81 g, 93%) was obtained from compound (*R*)-**5** (1.50 g, 11.2 mmol). $[\alpha]_D^{25}=-4.4$ (*c* 1.14, MeOH). Anal. calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.90; H, 8.61%.

4.4. (2,2,4-Trimethyl-1,3-dioxolane-4-yl)methanols (*R*)-2 and (*S*)-2

To a vigorously stirred suspension of $LiAlH_4$ (0.85 g, 22.4 mmol) in THF (10 mL), at 0°C, was added dropwise a solution of (*S*)-**6** (1.56 g, 8.96 mmol) in THF (15 mL). After stirring the mixture for 4 h, at rt, the mixture was cooled and carefully quenched by the addition of H_2O (1 mL), 1N NaOH solution (5.1 mL) and further H_2O (5.1 mL). After stirring at rt for 3 h, the white precipitate was filtered off and washed thoroughly with ethyl acetate. The filtrate was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 7:3) to give (*R*)-**2** as an oil (1.18 g, 8.06 mmol, 90%). $[\alpha]_D^{25}=+5.5$ (*c* 0.78, dichloromethane). ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.41 (d, 1H, $J=9.9$ Hz, CH_2), 3.47 (d, 1H, $J=9.9$ Hz, CH_2), 3.68 (d, 1H, $J=9.0$ Hz, CH_2), 3.93 (d, 1H, $J=9.0$ Hz, CH_2). Anal. calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.84; H, 9.21%. Spectral data were identical to those reported in the literature (Ref. 19).

Using the method described for its enantiomer (*R*)-**2**, compound (*S*)-**2** (1.12 g, 90%) was obtained from compound (*R*)-**6** (1.48 g, 8.50 mmol). $[\alpha]_D^{25}=-5.9$ (*c* 1.29, dichloromethane). Anal. calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.12; H, 9.09%.

4.5. 4-Benzyloxymethyl-2,2,4-trimethyl-1,3-dioxolanes (*R*)-7 and (*S*)-7

Alcohol (*R*)-**2** (1.29 g, 8.82 mmol) was dissolved in THF (25 mL) and the resultant solution was added to NaH (0.39 g, 9.71 mmol) at 0°C, under an inert atmosphere. The reaction was warmed to rt and BnBr (1.85 g, 10.6 mmol) and Bu_4NI (1.00 g, 2.62 mmol) were added to the mixture. After stirring for 18 h, the reaction was quenched by the addition of H_2O (15 mL) and extracted with ethyl acetate (25 mL). The organic extract was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 9.5:0.5) to give (*R*)-**7** as an oil (1.80 g, 8.12 mmol, 92%). $[\alpha]_D^{25}=-3.0$ (*c* 0.8, dichloromethane). ^1H NMR ($CDCl_3$): δ 1.36 (s, 3H, CH_3), 1.41 (s, 6H, $2CH_3$), 3.34 (d, 1H, $J=9.0$ Hz, CH_2), 3.42 (d, 1H, $J=9.0$ Hz, CH_2), 3.70 (d, 1H, $J=8.7$ Hz, CH_2), 4.03 (d, 1H, $J=8.7$ Hz, CH_2), 4.57 (m, 2H, CH_2), 7.34 (m, 5H, Ph). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.61; H, 8.45%. Spectral data were identical to those reported in the literature (Ref. 23).

Using the method described for its enantiomer (*R*)-**7**, compound (*S*)-**7** (1.82 g, 92%) was obtained from compound (*S*)-**2** (1.30 g, 8.89 mmol). $[\alpha]_D^{25}=+2.7$ (*c* 1.05, dichloromethane). Anal. calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.92; H, 8.21%.

4.6. (2,2,4-Trimethyl-1,3-dioxolane-4-yl)methyl methanesulfonates (*R*)-8 and (*S*)-8

To a stirred solution of alcohol (*R*)-**2** (0.30 g, 2.05 mmol) and di-*iso*-propylethylamine (0.32 g, 2.46 mmol) in dry dichloromethane (15 mL), at 0°C, methanesulfonyl chloride (0.29 g, 2.46 mmol) was added dropwise, under an inert atmosphere. The reaction mixture was stirred at rt for 3 h and then a saturated aqueous $NaHCO_3$ solution (10 mL) was added. The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 7:3) to give (*S*)-**8** as an oil (0.40 g, 1.79 mmol, 87%). $[\alpha]_D^{25}=+1.0$ (*c* 1.22, MeOH). ^1H NMR ($CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.04 (s, 3H, SO_2CH_3), 3.72 (d, 1H, $J=9.0$ Hz, CH_2), 3.99 (d, 1H, $J=9.0$ Hz, CH_2), 4.05 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): δ 22.0, 26.4, 27.1 (CH_3), 37.4 (SO_2CH_3), 71.1, 72.2 (CH_2), 78.8 ($C(CH_3)O$), 110.3 ($CO_2(CH_3)_2$). ESI$^+$ (m/z) = 225. Anal. calcd for $C_8H_{16}O_5S$: C, 42.84; H, 7.19; S, 14.30. Found: C, 42.32; H, 7.31; S, 14.12%.

Using the method described for its enantiomer (*S*)-**8**, compound (*R*)-**8** (0.46 g, 87%) was obtained from compound (*S*)-**2** (0.35 g, 2.39 mmol). $[\alpha]_D^{25}=-1.1$ (*c* 1.19, MeOH). Anal. calcd for $C_8H_{16}O_5S$: C, 42.84; H, 7.19; S, 14.30. Found: C, 42.41; H, 7.53; S, 14.61%.

4.7. 3-Benzyloxy-2-methylpropane-1,2-diol (*S*)-9

To a solution of (*R*)-**7** (1.60 g, 7.20 mmol) in THF (10 mL), at rt, 2N HCl (10 mL) was added. After stirring for 2 h, the mixture was extracted with ethyl acetate (20 mL). The organic phase was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 6:4) to give (*S*)-**9** as an oil (1.25 g, 6.86 mmol, 95%). $[\alpha]_D^{25}=+6.8$ (*c* 1.05, dichloromethane). ^1H NMR ($CDCl_3$): δ 1.14 (s, 3H, CH_3), 3.52 (m, 4H, $2CH_2$), 4.54 (m, 2H, CH_2Ph), 7.32 (m, 5H, Ph). Anal. calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.61; H, 8.45%. Spectral data were identical to those reported in the literature (Ref. 23).

4.8. (3-Benzyloxy-2-hydroxy-2-methyl)propyl methanesulfonate (*R*)-10

To a stirred solution of diol (*S*)-**9** (1.25 g, 6.86 mmol) and di-*iso*-propylethylamine (1.07 g, 8.23 mmol) in dry dichloromethane (30 mL), at 0°C under an inert atmosphere, was added dropwise methanesulfonyl chloride (0.96 g, 8.23 mmol). The reaction mixture was stirred at rt for 3 h and saturated aqueous $NaHCO_3$ solution (15 mL) was added. The organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 6:4) to give (*R*)-**10** as an oil (1.58 g, 5.76 mmol, 84%). $[\alpha]_D^{25}=-2.4$ (*c* 1.07, MeOH). ^1H NMR ($CDCl_3$): δ 1.24 (s, 3H, CH_3), 3.01 (s, 3H, SO_2CH_3), 3.38 (d, 1H, $J=9.3$ Hz, CH_2), 3.45 (d, 1H, $J=9.3$ Hz, CH_2), 4.12 (d, 1H, $J=9.9$ Hz, CH_2), 4.17 (d, 1H, $J=9.9$ Hz, CH_2), 4.56 (m, 2H, CH_2), 7.34 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.1 (CH_3), 37.2 (SO_2CH_3), 71.0, 73.0, 73.3, 73.4 ($3CH_2$, $C(CH_3)OH$), 127.7, 127.9, 128.4, 137.4 (Ph). ESI$^+$ (m/z) = 275. Anal. calcd for $C_{12}H_{18}O_5S$: C, 52.54; H, 6.61; S, 11.69. Found: C, 52.23; H, 6.94; S, 11.12%.

4.9. 2-Benzyloxymethyl-2-methyloxirane (*R*)-11

The mesylate (*R*)-**10** (1.58 g, 5.76 mmol) was dissolved in dry MeOH (50 mL), which was treated with anhydrous K_2CO_3 (4.02 g, 29.1 mmol). The reaction mixture was stirred at rt for 4 h. Concentration of the mixture was followed by dilution with H_2O (10 mL) and extraction with ethyl acetate (30 mL). The separated organic phase was dried (Na_2SO_4), concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate, 9.5:0.5) to give (*R*)-**11** as an oil (0.81 g, 4.55 mmol, 79%). $[\alpha]^{25}_{D}=-10.4$ (*c* 1.26, MeOH). ^1H NMR ($CDCl_3$): δ 1.41 (s, 3H, CH_3), 2.64 (d, 1H, *J*=4.8 Hz, CH_2 oxirane), 2.76 (d, 1H, *J*=4.8 Hz, CH_2 oxirane), 3.45 (d, 1H, *J*=10.8 Hz, CH_2OCH_2Ph), 3.59 (d, 1H, *J*=10.8 Hz, CH_2OCH_2Ph), 4.55 (d, 1H, *J*=12.0 Hz, CH_2Ph), 4.60 (d, 1H, CH_2Ph), 7.32 (m, 5H, Ph). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.61; H, 7.45%. Spectral data were identical to those reported in the literature (Ref. 9a).

4.10. 2-Benzyloxymethyl-2-methyloxirane (*S*)-11

To a solution of (*S*)-**8** (0.30 g, 1.34 mmol) in THF (5 mL), at rt, aqueous HCl (2N, 5 mL) was added. After stirring for 2 h, the mixture was extracted with ethyl acetate (20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give (*S*)-(2,3-dihydroxy-2-methyl)propyl methanesulfonate, which was dissolved in THF (15 mL) and the mixture was added to NaH (0.11 g, 2.81 mmol) at 0°C, under an inert atmosphere. Then, the reaction was warmed to rt and BnBr (0.28 g, 1.60 mmol) and Bu_4NI (0.15 g, 0.40 mmol) were added to the mixture. After stirring for 36 h, the reaction was quenched by the addition of H_2O (10 mL) and extracted with ethyl acetate (20 mL). The organic phase was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane/ethyl acetate, 9.5:0.5) to give (*S*)-**11** as an oil (0.15 g, 0.84 mmol, 63%). $[\alpha]^{25}_{D}=+10.9$ (*c* 1.20, MeOH). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.61; H, 7.45%.

4.11. (2*R*,2′*R*)-2-((2′-Methoxy-2′-(trifluoromethyl)-phenylacetyloxy)methyl)-2-methyloxirane 12

To a solution of (*S*)-**8** (0.14 g, 0.63 mmol) in THF (5 mL), at rt, aqueous HCl (2N, 5 mL) was added. After stirring for 2 h, the mixture was extracted with ethyl acetate (20 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give (*S*)-(2,3-dihydroxy-2-methyl)propyl methanesulfonate, which was used without further purification. This diol was dissolved in THF (8 mL) and the mixture was added to NaH (25 mg, 0.63 mmol) at 0°C, under an inert atmosphere. After stirring for 3 h, the mixture was concentrated in vacuo to give (*S*)-2-methylglycidol **1** with a purity greater than 95% (^1H NMR) and it was used without further purification. To a solution of (*S*)-**1**, DCC (0.13 g, 0.63 mmol) and DMAP (7.7 mg, 0.06 mmol) in dry dichloromethane (6 mL), at rt, a solution of (*R*)-(+)-MTPA (0.16 g, 0.69 mmol) in dry dichloromethane (4 mL) was added. After stirring the mixture for 6 h, the resultant white suspension was filtered to remove *N*,*N*′-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry, to which ethyl ether (20 mL) was added. The resultant suspension was filtered to remove the acylurea and the solvent was evaporated. The residue was purified by column chromatography (hexane/ethyl acetate, 9.5:0.5) to give **12** as an oil (99 mg, 0.32 mmol, 52%). $[\alpha]^{25}_{D}=+29.2$ (*c* 0.33, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 2.66, 2.75 (2d, 2H, *J*=4.5 Hz, CH_2O), 3.56 (s, 3H, CH_3O), 4.16, 4.50 (2d, 2H, *J*=12.0 Hz, CH_2OCO), 7.36–7.45 (m, 3H, Ph), 7.48–7.60 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 18.2 (CH_3), 51.9 (CH_2O), 54.4 ($C(CH_3)CH_2O$), 55.5 (CH_3O), 68.8 (CH_2OCO), 121.3 ($C(CF_3)$), 125.1 ($C(CF_3)$), 127.3, 128.4, 129.7, 131.9 (Ph), 166.2 (CH_2OCO). ^{19}F NMR ($CDCl_3$): δ −71.9. ESI^+ (*m*/*z*)=305. Anal. calcd for $C_{14}H_{15}F_3O_4$: C, 55.26; H, 4.97. Found: C, 55.07; H, 4.63%.

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