Asymmetric Syntheses of Chiral Propane-1,3-diols Starting from Malonic Acid

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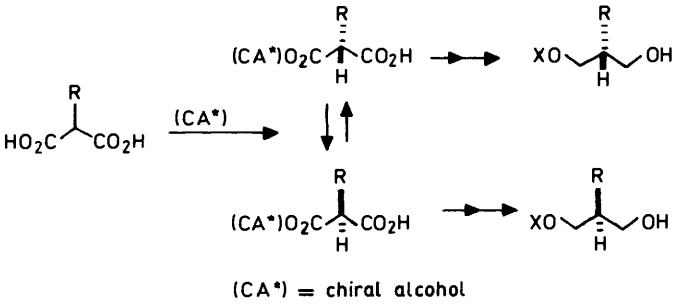
Syntheses of chiral intermediates having one tertiary asymmetric centre were carried out *via* chiral half-esters of monoalkylmalonic acids. The menthyl half-ester of ethylmalonic acid afforded a single diastereoisomer through crystallisation-induced asymmetric transformation (second-order asymmetric transformation). Furthermore enantioselective preparation of unsymmetrical propane-1,3-diol derivatives was achieved by the use of 8-phenylmenthyl half-esters.

Unsymmetrical propane-1,3-diol derivatives are fundamental chiral building blocks. Recently several approaches to the preparation of chiral propane-1,3-diols using biological techniques have been reported,[1] but only a few chemical methodologies for this purpose have been developed.[2] We envisaged that if an equilibrium existed between the two epimers of monoalkylmalonic half-esters, derived from chiral alcohols, the ratio of the two isomers should depend on their difference in enthalpy of formation (Scheme 1). Work based on the above assumption led us to find a versatile and selective synthesis of optically pure compounds.[3]



Scheme 1.

Results and Discussion

Preparation of chiral malonic half-esters was easily achieved by the condensation of a monoalkylmalonic acid and one mole equivalent of a chiral alcohol such as menthol or 8-phenylmenthol[4] using dicyclohexylcarbodi-imide (DCC) in the presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP).[5] In the case of 8-phenylmenthol, DCC must be added to the reaction mixture below −30 °C, otherwise decarboxylation occurred as a side reaction. Menthyl half-esters (**1**)—(**3**) of methyl-, propyl-, and isopropyl-malonic acids were obtained in 62, 63, and 76% yield, while 8-phenylmenthyl half-esters (**29**)—(**31**) were synthesized in 60, 69, and 66% yield, respectively. The ratios of two diastereoisomers of some resulting half-esters were determined by 500 MHz ^{1}H n.m.r. spectroscopy. The menthyl half-esters were composed of two isomers in the ratio ~11:9. On the other hand the ratio of the 8-phenylmenthyl esters varied between 3:2 and 7:3.

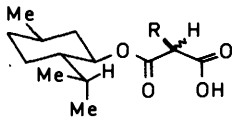
Direct and chemoselective reduction of the carboxylic acid group using diborane failed. Therefore the functional group was reduced after activation. Menthyl half-esters (**1**)—(**3**) were first converted into the corresponding acid chlorides with oxalyl chloride and then reduced with tetrabutylammonium borohydride[6] in dichloromethane to give the epimeric mixture of hydroxy esters in good yield. The ratios of the two isomers were determined as ~3:2 by h.p.l.c. analysis, and the major isomers (**4**), (**6**), and (**8**) were isolated as pure forms by h.p.l.c. separation. The primary alcohol group of compounds (**4**), (**6**), and (**8**) was protected with the t-butyldimethylsilyl (TBDMS) (systematically: dimethyl-t-butylsilyl) group and the ester group of the resulting ethers (**5**), (**7**), and (**9**) was reduced with di-isobutylaluminium hydride (DIBAL) to give the unsymmetrical propane-1,3-diols (**13**), (**15**), and (**17**), respectively. The optical purities (>99 e.e.) of the products were determined by their conversion into the Mosher's esters (**14**), (**16**), and (**18**) using (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA)[7,†] and DCC in the presence of DMAP. All properties of 3-(dimethyl-t-butylsiloxy)-2-methylpropan-1-ol (**13**), $[\alpha]_D^{25}$ −13.15° (*c* 0.28 in $CHCl_3$),[8] and its MTPA ester (**14**), thus obtained, were identical with those of the authentic compound (**13**), $[\alpha]_D^{29}$ −13.22° (*c* 0.61 in $CHCl_3$), and its MTPA ester (**14**) prepared from (*R*)-methyl 3-hydroxy-2-methylpropionate (**19**) *via* the corresponding TBDMS ether (**20**).

The absolute stereochemistries of the propyl and isopropyl derivatives were assigned on the basis of the following transformation combined with spectral measurement. The primary alcohols (**6**) and (**8**) were converted with triphenylphosphine and tetrachloromethane[9] into the chlorides (**21**) and (**23**), which were then dechlorinated with tributyltin hydride in the presence of azoisobutyronitrile (AIBN). The 'methyl' compounds (**22**) and (**24**) thus formed were reduced with DIBAL to the alcohols (**25**) and (**27**), which were converted as above into the (*S*)-MTPA esters (**26**) and (**28**). The n.m.r. spectra of the esters (**26**) and (**28**) showed the primary alcohol hydrogens as a pair of double doublets, indicative of an (*S*,*S*) configuration for both compounds (**26**) and (**28**).[10]

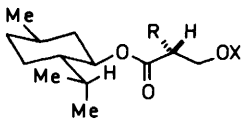
In the case of 8-phenylmenthyl half-esters (**29**)—(**31**), the more preferred formation of one diastereoisomer [(**32**), (**33**), and (**35**) respectively] was observed on reduction of the corresponding 1-succinimido ester.[11] Particularly, when the isopropylmalonic half-ester (**31**) was converted, by treatment with *N*-hydroxysuccinimide and DCC in the presence of DMAP, into the 1-succinimido ester and the product reduced with sodium borohydride, the ratio of the two stereoisomers (**35**) and (**39**), obtained in 83% overall yield, was 5.2:1. The major alcohols (**33**) and (**35**) were transformed into the (*S*)-MTPA esters (**16**) and (**18**) of the corresponding propane-1,3-diol derivatives (**15**) and (**17**) and established the absolute configuration as shown. We considered from the above results that the thermodynamic equilibration occurred at the stage of the succinimido ester formation.

An unusual crystallisation-induced asymmetric transformation (second-order asymmetric transformation)[12] occurred

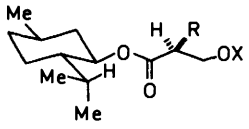
† 3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid.



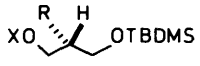
(1) R = Me
(2) R = Pr
(3) R = Pr^i



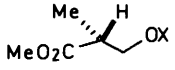
(4) R = Me, X = H
(5) R = Me, X = TBDMS
(6) R = Pr, X = H
(7) R = Pr, X = TBDMS
(8) R = Pr^i, X = H
(9) R = Pr^i, X = TBDMS



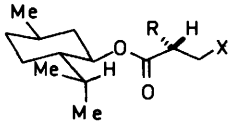
(10) R = Me
(11) R = Pr
(12) R = Pr^i



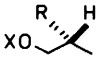
(13) R = Me, X = H
(14) R = Me, X = (*S*)-MTPA
(15) R = Pr, X = H
(16) R = Pr, X = (*S*)-MTPA
(17) R = Pr^i, X = H
(18) R = Pr^i, X = (*S*)-MTPA



(19) X = H
(20) X = TBDMS

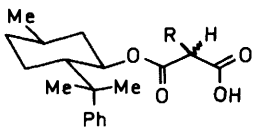


(21) R = Pr, X = Cl
(22) R = Pr, X = H
(23) R = Pr^i, X = Cl
(24) R = Pr^i, X = H

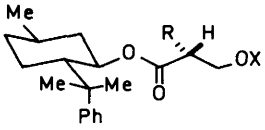


(25) R = Pr, X = H
(26) R = Pr, X = (*S*)-MTPA
(27) R = Pr^i, X = H
(28) R = Pr^i, X = (*S*)-MTPA

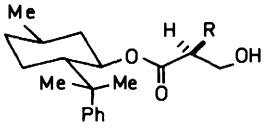
TBDMS = $SiMe_2Bu^t$
MTPA = $COC(OMe)(Ph)CF_3$



(29) R = Me
(30) R = Pr
(31) R = Pr^i



(32) R = Me, X = H
(33) R = Pr, X = H
(34) R = Pr, X = TBDMS
(35) R = Pr^i, X = H
(36) R = Pr^i, X = TBDMS

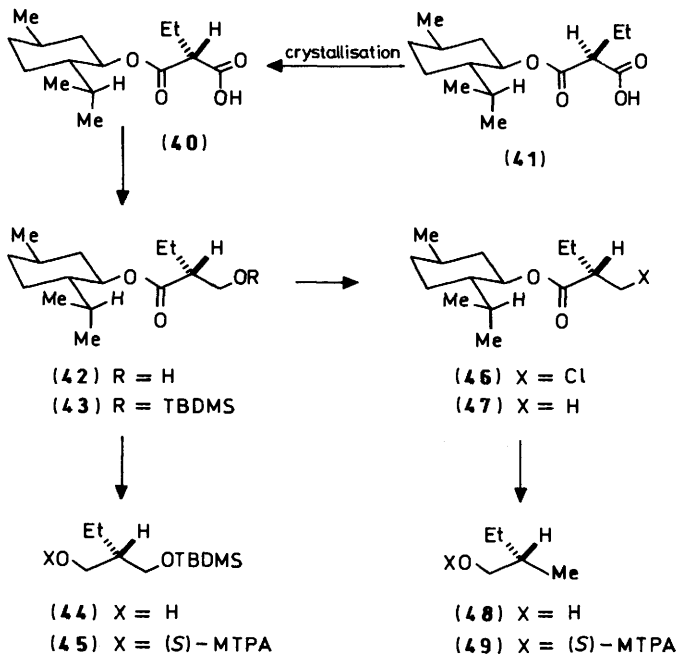


(37) R = Me
(38) R = Pr
(39) R = Pr^i

with the menthyl half-ester of ethylmalonic acid. The 500 MHz ^{1}H n.m.r. ($CDCl_3$) and 25 MHz ^{13}C n.m.r. ($CDCl_3$) spectra of the oily product prepared from ethylmalonic acid and (−)-menthol as above indicated the ratio of the two epimers (**40**) and (**41**) as 11:9 (see Experimental section). When the product was set aside for several days at room temperature, the oily compound became crystalline, m.p. 71—73 °C; $[\alpha]_D^{25}$ −56.4° (*c* 1.64 in $CHCl_3$). The ^{1}H and ^{13}C n.m.r. spectra showed that the crystalline compound (**40**), obtained in 82% yield from ethylmalonic acid, was nearly a single stereoisomer (>99% diastereoisomeric excess; see Experimental section).

The crystalline menthyl ester (**40**) was converted into the alcohol (**42**), m.p. 64—65 °C; $[\alpha]_D^{30}$ −59.69° (*c* 2.55 in $CHCl_3$) in 71% yield in two steps; (i) chlorination with oxalyl chloride and (ii) reduction with tetrabutylammonium borohydride[6] at −78 °C. If the reaction was carried out on a small scale, no significant epimerisation was observed. The optical purity (>99% e.e.) of the propane-1,3-diol derivative (**44**), $[\alpha]_D^{26}$ −11.41° (*c* 1.42 in $CHCl_3$), synthesised from (**42**) in 81% overall yield as above, was verified from the ^{1}H n.m.r. spectrum of its (*S*)-MTPA ester (**45**).

Furthermore the alcohol (**42**) was converted, in 96% overall yield in two steps as above, into the 'methyl' compound (**47**). After reduction of compound (**47**) with DIBAL, the resulting alcohol (**48**) was condensed with (*S*)-MTPA as above (Scheme 2). The (*S*)-MTPA ester (**49**) thus formed showed the primary alcohol hydrogens as a pair of double doublets in the ^{1}H n.m.r.



Scheme 2.

spectrum, indicating the (*S*,*S*)-configuration.[10] The ^{1}H n.m.r. spectrum of compound (**49**) was identical with that of an authentic sample prepared from (−)-(*S*)-2-methylbutan-1-ol.

Examples of second-order asymmetric transformations are few, and the phenomenon had not previously been utilised for the synthesis of chiral precursors.[12] The present method should be applicable to syntheses of a variety of chiral building blocks, since numerous monoalkylmalonic acids can be prepared readily, the chiral auxiliaries are recyclable. Applications of the above methodology for the synthesis of biologically important compounds are in progress.

Experimental

General Methods.—M.p.s were measured on a Yanako micro-melting-point apparatus and are uncorrected. I.r. spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured for $CDCl_3$ solutions on JEOL JNM-PMX-60, JEOL-FX-90A, JEOL-PS-100, and JNM-GX-500 spectrometers. Chemical shifts are reported as δ_H- and δ_C-values relative to internal $SiMe_4$. Ordinary mass spectra were taken on a Hitachi M-52G instrument, and accurate mass spectra with JEOL-JMS-01SG-2 and JEOL-DX-300 spectrometers. High-pressure liquid chromatography (h.p.l.c.) was carried out using a Gilson h.p.l.c. system with Dynamax columns (Microsorb Si, 4.6 × 250 mm or 10 × 250 mm, 5 μm) monitored by u.v. absorptions and refractive-index measurements. Optical rotations were determined on a JASCO-DIP-340 polarimeter. All new compounds described in the Experimental section were homogeneous on t.l.c. and h.p.l.c.

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen Methylmalonate* (**1**).—To a stirred solution of methylmalonic acid (1.18 g, 10 mmol), (−)-menthol (1.56 g, 10 mmol), and DMAP (50 mg, 0.40 mmol) in a mixture of MeCN (30 ml) and CH_2Cl_2 (30 ml) at −40 °C was added a solution of DCC (2.22 g, 10.7 mmol) in CH_2Cl_2 (30 ml) during 40 min. The mixture was stirred for 6 h at −40 °C and then for 10 h at room temperature. After filtration, the filtrate was evaporated to give a residue, which was taken up into a mixture of a small excess of dilute aqueous $NaHCO_3$ and Et_2O. The aqueous layer was further washed with Et_2O and then acidified with conc. HCl. After extraction with Et_2O several times, the combined extract was dried (Na_2SO_4) and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with benzene–AcOEt (9:1) afforded the epimeric mixture of the *half-esters* (**1**) (1.598 g, 62%) as an oil (Found: C, 65.5; H, 9.7. $C_{14}H_{24}O_4$ requires C, 65.6; H, 9.45%); $[\alpha]_D^{24}$ −63.96° (*c* 1.34 in $CHCl_3$); $\nu_{max.}$ 2 850—2 300 (OH) and 1 720 cm^{-1} (C=O); δ_H (500 MHz) 0.74 and 0.76 [3 H (11:9), each d, each *J* 7.2 Hz, CH*Me*], 0.88 and 0.89 [3 H (9:11), each d, *J* 7.5 Hz, CH*Me*], 0.91 (3 H, d, *J* 7.4 Hz, CH*Me*), 1.46 (3 H, d, *J* 7.5 Hz, COCH*Me*), 3.40—3.47 (1 H, m, OCOCH), and 4.71—4.77 (1 H, m, 3-H); *m*/*z* 257 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen Propylmalonate* (**2**).—According to the same procedure as above, propylmalonic acid (1.46 g, 10 mmol) was converted into the *half-esters* (**2**) (1.79 g, 63%) as an oil (Found: M^+ + H, 285.2098. $C_{16}H_{29}O_4$ requires *m*/*z* 285.2066); $\nu_{max.}$ 2 850—2 300 (OH) and 1 720 cm^{-1} (C=O); δ_H (100 MHz) 0.73 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.83—1.01 (6 H, m, 2 × CH*Me*), 3.37 (1 H, br t, *J* 7.4 Hz, OCOCH), and 4.58—4.82 (1 H, m, 3-H); δ_C(25 MHz) 13.68 (Me), 16.03 and 16.15 (Me), 20.55 and 20.72 (Me), 22.02 (Me), 23.37 (CH_2), 26.01 and 26.18 (CH), 30.76 (CH_2), 31.49 (CH), 34.23 (CH_2), 40.39 and 40.56 (CH_2), 46.97 (CH), 51.84 (CH) 75.73 (CH), 168.79 (C=O), and 175.60 (C=O); *m*/*z* 285 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen Isopropylmalonate* (**3**).—Isopropylmalonic acid (1.46 g, 10 mmol) was converted as above into the *half-esters* (**3**) (2.16 g, 76%) as an oil (Found: M^+ + H, 285.2102. $C_{16}H_{29}O_4$ requires *m*/*z* 285.2066); $\nu_{max.}$ 2 850—2 300 (OH) and 1 720 cm^{-1} (C=O); δ_H(90 MHz) 0.75 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.84—1.08 (6 H, m, 2 × CH*Me*), 3.16 (1 H, d, *J* 8.6 Hz, OCOCH), and 4.58—4.87 (1 H, m, 3-H); *m*/*z* 285 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl Hydrogen* (R)-*Ethylmalonate* (**40**).—Ethylmalonic acid (1.32 g, 10 mmol) was esterified as above and the ester was purified by silica gel column chromatography to give the epimeric half-esters (**40**) and (**41**) as an oil; δ_H(500 MHz) 0.75 and 0.76 [3 H (11:9), each d, each *J* 7.4 Hz, CH*Me*], 0.88 and 0.89 [3 H (9:11), each d, each *J* 7.4 Hz, CH*Me*], 0.91 (3 H, d, *J* 7.4 Hz, CH*Me*), 0.99 and 1.00 [3 H (9:11), each t, each *J* 7.4 Hz, CH_2*Me*), 3.29 and 3.31 [1 H (9:11), each t, each *J* 7.4 Hz, OCOCH], and 4.75 (1 H, dt, *J* 4.3 and 11.3 Hz, 3-H); δ_C(25 MHz) 11.74 (Me), 16.01 (Me), 20.71 (Me), 21.98 (Me), 22.32 (CH_2), 23.22 (CH_2), 26.00 and 26.11 (CH), 31.36 (CH), 34.16 (CH_2), 40.55 and 40.71 (CH_2), 46.88 (CH), 53.46 (CH), 75.83 (CH), 168.96 (C=O), and 175.45 (C=O).

After the product was set aside for 5 days at room temperature, the oily compound became crystalline to afford the (2R)-*half-ester* (**40**) (2.21 g, 82%), m.p. 71—73 °C (Found: C, 66.35; H, 9.95. $C_{15}H_{26}O_4$ requires C, 66.65; H, 9.7%); $[\alpha]_D^{25}$ −56.4° (*c* 1.64 in $CHCl_3$); $\nu_{max.}$ 2 850—2 300 (OH) and 1 721 cm^{-1} (C=O); δ_H(500 MHz) 0.75 (3 H, d, *J* 7.4 Hz, CH*Me*), 0.89 (3 H, d, *J* 7.4 Hz, CH*Me*), 0.91 (3 H, d, *J* 7.4 Hz, CH*Me*), 1.00 (3 H, t, *J* 7.4 Hz, CH_2*Me*), 3.31 (1 H, t, *J* 7.4 Hz, OCOCH), and 4.75 (1 H, dt, *J* 4.3 and 11.3 Hz, 3-H); δ_C(25 MHz) 11.74 (Me), 16.01 (Me), 20.71 (Me), 21.98 (Me), 22.32 (CH_2), 23.22 (CH_2), 26.00 (CH), 31.36 (CH), 34.16 (CH_2), 40.55 (CH_2), 46.88 (CH), 53.46 (CH), 75.83 (CH), 168.96 (C=O), and 175.45 (C=O); *m*/*z* 271 (M^+ + 1).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Methylmalonate* (**29**).—To a stirred solution of methylmalonic acid (270 mg, 1.85 mmol), (−)-8-phenylmenthol (389 mg, 1.68 mmol), and DMAP (10 mg, 0.08 mmol) in a mixture of MeCN (7 ml) and CH_2Cl_2 (14 ml) at −78 °C was slowly added a solution of DCC (381 mg, 1.85 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred for 16 h at −30 °C and then for 8 h at 18 °C. After filtration, the filtrate was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with acetone–benzene (1:5) gave the *half-esters* (**29**) (362 mg, 60%) as an oil (Found: M^+, 332.1941. $C_{20}H_{28}O_4$ requires *M*, 332.1986); $[\alpha]_D^{25}$ +16.83° (*c* 6.07 in $CHCl_3$); $\nu_{max.}$ 2 850—2 300 (OH) and 1 730 cm^{-1} (C=O); δ_H(90 MHz) 2.57 (0.7 H, q, *J* 7.4 Hz, OCOCH), 2.60 (0.3 H, q, *J* 7.3 Hz, OCOCH), and 4.86 (1 H, dt, *J* 4.6 and 10.8 Hz, 3-H); *m*/*z* 332 (M^+).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Propylmalonate* (**30**).—Propylmalonic acid (137 mg, 0.938 mmol) was converted as above into the *half-esters* (**30**) (202 mg, 69%) as an oil (Found: C, 73.6; H, 9.1. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95%); $\nu_{max.}$ 2 850—2 300 (OH) and 1 736 cm^{-1} (C=O); δ_H(90 MHz) 2.50 (0.6 H, t, *J* 7.0 Hz, OCOCH), 2.60 (0.4 H, t, *J* 7.3 Hz, OCOCH), and 4.92 (1 H, dt, *J* 4.6 and 10.4 Hz, 3-H); *m*/*z* 316 ($M^+ - CO_2$).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Isopropylmalonate* (**31**).—Isopropylmalonic acid (161 mg, 1.11 mmol) was converted as above into the *half-esters* (**31**) (262 mg, 66%) as an oil (Found: C, 73.1; H, 8.9. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95%); $[\alpha]_D^{24}$ +8.77° (*c* 2.94 in $CHCl_3$); $\nu_{max.}$ 2 850—2 300 (OH) and 1 730 cm^{-1} (C=O); δ_H(90 MHz) 2.46 (0.6 H, d, *J* 8.0

Hz, OCOCH), 3.20 (0.4 H, d, *J* 5.7 Hz, OCOCH), and 4.55—5.00 (1 H, m, 3-H).

(1R,3R,4S)-*Menthan*-3-*yl* (2R)-3-*Hydroxy*-2-*methylpropionate* (**4**).—A mixture of the half-ester (**1**) (100 mg, 0.39 mmol) and oxalyl chloride (0.2 ml) in dry CH_2Cl_2 (4 ml) was refluxed for 2 h and then evaporated under protection from moisture. A solution of the residue in dry CH_2Cl_2 (4 ml) was added dropwise to a stirred solution of tetrabutylammonium borohydride (100 mg) in dry CH_2Cl_2 (4 ml) at −78 °C and the mixture was stirred for 30 min at the same temperature. After dilution with CH_2Cl_2, the mixture was washed successively with 5% aqueous NaOH, 5% aqueous citric acid, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–Et_2O (4:1) afforded the epimeric mixture of alcohols (**4**) and (**10**) (70 mg, 75%) as an oil. H.p.l.c. using Microsorb Si (4.6 × 250 mm or 10 × 250 mm, 5 μm) with hexane–Et_2O (4:1; 1 or 4 ml min^{-1}) as eluant determined the ratio (~3:2) of the two isomers (**4**) and (**10**) and gave the major, and faster running, (2R)-*isomer* (**4**) as a solid, m.p. 53—55 °C (Found: M^+ + H, 243.1920. $C_{14}H_{27}O_3$ requires *m/z* 243.1959); $[\alpha]_D^{26}$ −60.48° (*c* 1.01 in $CHCl_3$); $\nu_{max.}$ 3 600—3 400 (OH) and 1 705 cm^{-1} (C=O); δ_H(100 MHz) 0.75 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.88 (6 H, br d, *J* 7.2 Hz, 2 × CH*Me*), 1.17 (3 H, d, *J* 7.3 Hz, CH*Me*), 2.48—2.79 (1 H, m, OCOCH), 3.64—3.81 (2 H, m, CH_2O), and 4.70 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 243 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-*Hydroxymethylvalerate* (**6**).—The half-ester (**2**) (45 mg, 0.158 mmol) was transformed as above into the epimeric alcohols (**6**) and (**11**) (32 mg, 76%) in the ratio ~3:2. H.p.l.c. purification as above gave the major, (2R)-*isomer* (**6**) as an oil (Found: M^+ + H, 271.2293. $C_{16}H_{31}O_3$ requires *m/z* 271.2273); $[\alpha]_D^{24}$ −57.84° (*c* 2.1 in $CHCl_3$); δ_H(100 MHz) 0.72 (6 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.92 (3 H, t, *J* 7.2 Hz, CH_2Me), 0.91 (3 H, d, *J* 7.1 Hz, CH*Me*), 2.40—2.65 (1 H, m, OCOCH), 3.58—3.79 (2 H, m, CH_2O), and 4.70 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 271 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-*Hydroxymethyl*-3-*methylbutyrate* (**8**).—The half-ester (**3**) (330 mg, 1.16 mmol) was similarly transformed into the epimeric alcohols (**8**) and (**12**) (222 mg, 71%) in the ratio ~3:2. H.p.l.c. separation as above afforded the major, (2R)-*isomer* (**8**) as an oil (Found: M^+ + H, 271.2295. $C_{16}H_{31}O_3$ requires *m/z* 271.2273); $[\alpha]_D^{24}$ −55.78° (*c* 4.2 in $CHCl_3$); δ_H(90 MHz) 0.77 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.85—0.98 (12 H, m, 4 × CH*Me*), 2.20—2.45 (1 H, m, OCOCH), 3.60—3.95 (2 H, m, CH_2O), and 4.75 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 271 (M^+ + 1).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-*Hydroxymethylbutyrate* (**42**).—The crystalline half-ester (**40**) (50 mg, 0.185 mmol) was similarly reduced into the (2R)-*alcohol* (**42**) (46 mg, 71%) as needles, m.p. 64—65 °C (Found: C, 70.0; H, 11.2. $C_{15}H_{28}O_3$ requires C, 70.25; H, 11.0%); $[\alpha]_D^{30}$ −59.69° (*c* 2.55 in $CHCl_3$); δ_H(100 MHz) 0.73 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.90 (6 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.94 (3 H, t, *J* 7.3 Hz, CH_2Me), 2.35—2.60 (1 H, m, OCOCH), 3.59—3.90 (2 H, m, CH_2O), and 4.73 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H), whose purity was further verified by h.p.l.c.

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2R)-3-*Hydroxy*-2-*methylpropionate* (**32**).—To a stirred solution of the half-ester (**29**) (233 mg, 0.647 mmol) and *N*-hydroxysuccinimide (89 mg, 0.776 mmol) in dry tetrahydrofuran (THF) (4 ml) at 0 °C was added dropwise a solution of DCC (160 mg, 0.777 mmol) in dry THF (1 ml) at 0 °C. After having been stirred for 1 h at room temperature, the reaction mixture was filtered and then evaporated. The residue was purified by silica gel column chromatography. Elution with hexane–AcOEt (17:3) yielded the corresponding 1-succinimido ester (274 mg, 99%). To a stirred mixture of $NaBH_4$ (73 mg, 1.94 mmol) in dry THF (3 ml) at 0 °C was added a solution of the above product (274 mg) in dry THF (1 ml) and the mixture was stirred for 1 h at room temperature and then poured into 1% hydrochloric acid. The resulting mixture was extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (4:1) afforded the epimeric mixture of alcohols (**32**) and (**37**) (136 mg, 66%). H.p.l.c. using Microsorb Si with hexane–AcOEt (23:2) as eluant determined the ratio (~2:1) and gave the major, (2R)-*isomer* (**32**) as an oil (Found: C, 75.2; H, 9.6. $C_{20}H_{30}O_3$ requires C, 75.45; H, 9.49%); $[\alpha]_D^{27}$ −7.4° (*c* 0.81 in $CHCl_3$); $\nu_{max.}$ 1 718 cm^{-1} (C=O); δ_H(90 MHz) 2.29—2.54 (1 H, m, OCOCH), 3.50 (2 H, d, *J* 5.8 Hz, CH_2OH), 4.75 (1 H, dt, *J* 4.6 and 10.6 Hz, 3-H), and 7.00—7.41 (5 H, m, Ph).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2R)-2-*Hydroxymethylvalerate* (**33**).—The half-ester (**30**) (53 mg, 0.146 mmol) was converted as above into the epimeric mixture of the alcohols (**33**) and (**38**) (28 mg, 56%). H.p.l.c. using Microsorp Si with hexane–AcOEt (9:1) determined the ratio (~2:1) and gave the major, (2R)-*isomer* (**33**) as an oil (Found: C, 76.1; H, 10.1. $C_{22}H_{34}O_3$ requires C, 76.25; H, 9.9%); $[\alpha]_D^{26}$ −0.36° (*c* 1.11 in $CHCl_3$); $\nu_{max.}$ 1 715 cm^{-1} (C=O); δ_H(90 MHz) 3.54 (2 H, d, *J* 4.9 Hz, CH_2OH), 4.83 (1 H, dt, *J* 4.6 and 10.9 Hz, 3-H), and 7.05—7.40 (5 H, m, Ph).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2R)-2-*Hydroxymethyl*-3-*methylbutyrate* (**35**).—To a stirred solution of the half-ester (**31**) (60 mg, 0.166 mmol), *N*-hydroxysuccinimide (21 mg, 0.183 mmol), and DMAP (5 mg) in dry CH_2Cl_2 (2 ml) at 0 °C was added dropwise a solution of DCC (38 mg, 0.183 mmol) in dry CH_2Cl_2 (2 ml) and the mixture was stirred for 15 h at room temperature. After filtration, the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography. Elution with benzene–AcOEt (9:1) yielded the corresponding 1-succinimido ester (76 mg, 100%) as an oil. To a stirred solution of the product (76 mg) in THF (5 ml) at 0 °C was added $NaBH_4$ (30 mg) and the mixture was stirred for 1 h at room temperature. After dilution with AcOEt, the mixture was poured into 5% aqueous citric acid. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Silica gel column chromatography of the crude product with hexane–AcOEt (9:1) as eluant gave the epimeric mixture of alcohols (**35**) and (**39**) (48 mg, 83%). H.p.l.c. using Microsorb Si with hexane–Et_2O (4:1) as eluant determined the ratio (~5.2:1) and afforded the major, (2R)-*isomer* (**35**) (Found: $M^+ - C_6H_5$, 269.2120. $C_{16}H_{29}O_3$ requires *m/z* 269.2115); $\nu_{max.}$ 1 718 cm^{-1} (C=O); δ_H(90 MHz) 0.71—0.89 (9 H, m, 3 × CH*Me*), 1.16 (3 H, s, Me), 1.29 (3 H, s, Me), 3.45—3.82 (2 H, m, CH_2O), 4.80 (1 H, dt, *J* 4.6 and 10.6 Hz, 3-H), and 7.10—7.25 (5 H, m, Ph).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-3-(*Dimethyl*-*t*-*butylsiloxy*-2-*methyl*)*propionate* (**5**).—To a solution of the alcohol (**4**) (48 mg, 0.198 mmol), TBDMSCI (38 mg, 0.257 mmol), and DMAP (5 mg) in a mixture of dry CH_2Cl_2 (1 ml) and dry DMF (1 ml) at 0 °C was added Et_3N (0.1 ml) and the mixture was stirred for 10 h at room temperature. After dilution with benzene, the mixture was washed successively with 10% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. Silica gel column chromatography of the residue with hexane–Et_2O (19:1) as eluant gave the *ether* (**5**) (58 mg, 82%) as an oil (Found: M^+ + H, 357.2831. $C_{20}H_{41}O_3Si$ requires *m/z* 357.2825); δ_H(100 MHz) 0.03 (6 H, s, $SiMe_2$), 0.75

(3 H, d, *J* 7.2 Hz, CH*Me*), 0.86 (9 H, s, Bu^t), 0.89 (6 H, d, *J* 7.0 Hz, 2 × CH*Me*), 1.13 (3 H, d, *J* 7.2 Hz, CH*Me*), 2.40—2.74 (1 H, m, OCOCH), 3.50—3.85 (2 H, m, CH_2O), and 4.63 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 357 ($M^+ + 1$).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-(*Dimethyl-t-butylsiloxymethyl*)*valerate* (**7**).—The alcohol (**6**) (35 mg, 0.13 mmol) was converted as above into the *ether* (**7**) (43 mg, 87%) as an oil (Found: $M^+ + H$, 385.3135. $C_{22}H_{45}O_3Si$ requires *m/z* 385.3135); $[\alpha]_D^{24}$ −44.88° (*c* 4.3 in $CHCl_3$); δ_H(90 MHz) 0.01 (6 H, s, $SiMe_2$), 0.70 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.81 (9 H, s, Bu^t), 0.85 (6 H, d, *J* 7.1 Hz, 2 × CH*Me*), 2.30—2.65 (1 H, m, OCOCH), 3.45—3.87 (2 H, m, CH_2O), and 4.65 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 357 ($M^+ + 1$).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-(*Dimethyl-t-butylsiloxymethyl*)-3-*methylbutyrate* (**9**).—The alcohol (**8**) (63 mg, 0.23 mmol) was converted as above into the *ether* (**9**) (87 mg, 97%) as an oil (Found: $M^+ + H$, 385.3120. $C_{22}H_{45}O_3Si$ requires *m/z* 385.3135); $[\alpha]_D^{24}$ −44.32° (*c* 7.8 in $CHCl_3$); δ_H(90 MHz) 0.01 (6 H, s, $SiMe_2$), 0.83 (9 H, s, Bu^t), 2.14—2.42 (1 H, m, OCOCH), 3.55—3.91 (2 H, m, CH_2O), and 4.69 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 357 ($M^+ + 1$).

(1R,3R,4S)-p-*Menthan*-3-*yl* (2R)-2-(*Dimethyl-t-butylsiloxymethyl*)*butyrate* (**43**).—The alcohol (**42**) (47 mg, 0.184 mmol) was converted as above into the *ether* (**43**) (61 mg, 91%) as an oil (Found: $M^+ + H$, 371.2985. $C_{21}H_{43}O_3Si$ requires *m/z* 371.2979); $[\alpha]_D^{28}$ −36.71° (*c* 5.9 in $CHCl_3$); δ_H(100 MHz) 0.02 (6 H, s, $SiMe_2$), 0.77 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.85 (9 H, s, Bu^t), 0.87 (6 H, d, *J* 7.1 Hz, 2 × CH*Me*), 0.90 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.30—2.57 (1 H, m, OCOCH), 3.50—3.89 (2 H, m, CH_2O), and 4.68 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 371 ($M^+ + 1$).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2R)-2-(*Dimethyl-t-butylsiloxymethyl*)*valerate* (**34**).—The alcohol (**33**) (20 mg, 0.057 mmol) was converted as above into the *ether* (**34**) (15 mg, 54%) as an oil (Found: C, 73.45; H, 10.2. $C_{28}H_{48}O_3Si$ requires C, 73.0; H, 10.5%); $[\alpha]_D^{27}$ −7.4° (*c* 0.81 in $CHCl_3$); $\nu_{max.}$ 1 720 cm^{-1} (C=O); δ_H(60 MHz) 0.01 (6 H, s, $SiMe_2$), 0.84 (9 H, s, Bu^t), 3.46—3.87 (2 H, m, CH_2O), 4.77 (1 H, dt, *J* 4.0 and 10.2 Hz, 3-H), and 6.94—7.38 (5 H, m, Ph); *m/z* 403 (M^+ − Bu^t).

(2S)-3-(*Dimethyl-t-butylsiloxy*)-2-*methylpropyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**14**).—(*A*) To a stirred solution of the ester (**5**) (50 mg, 0.14 mmol) in dry THF (1 ml) at −20 °C was added dropwise 1M-DIBAL in hexane (0.351 ml, 0.351 mmol) and the mixture was stirred for 1 h at −20 °C. After addition of water (0.35 ml), the resulting mixture was further stirred for 30 min and then filtered through Celite. The filtrate, including the washings with Et_2O, was dried ($MgSO_4$) and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with hexane–Et_2O (4:1) afforded the alcohol (**13**) (24 mg, 85%); $[\alpha]_D^{25}$ −13.15° (*c* 0.28 in $CHCl_3$); δ_H(100 MHz) 0.05 (6 H, s, $SiMe_2$), 0.86 (3 H, d, *J* 7.2 Hz, CH*Me*), 1.74—2.06 (1 H, m, OCOCH), 2.85 (1 H, br s, OH), and 3.45—3.80 (4 H, m, 2 × CH_2O).

To a stirred solution of the above alcohol (**13**) (8 mg, 0.039 mmol), (−)-(*S*)-MTPA (15 mg, 0.064 mmol), and DMAP (1 mg) in dry CH_2Cl_2 (1 ml) at 0 °C was added dropwise a solution of DCC (13.6 mg, 0.066 mmol) in dry CH_2Cl_2 (1 ml) and the mixture was stirred for 15 h at room temperature. After filtration, the filtrate was washed successively with 10% aqueous $KHSO_4$ and water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel column chromatography with hexane–Et_2O (19:1) to give the *MTPA ester* (**14**) (15.6 mg, 95%) (Found: $M^+ - C_4H_9$, 363.1212. $C_{16}H_{22}F_3O_4Si$ requires *m/z* 363.1238); δ_H(100 MHz) 0.01 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 0.92 (3 H, d, *J* 7.1 Hz, CH*Me*), 1.90—2.17 (1 H, m, OCOCH), 3.45—3.55 (5 H, m, CH_2OSi and OMe), 4.26 (2 H, d, *J* 7.0 Hz, CO_2CH_2), and 7.30—7.55 (5 H, m, Ph).

(*B*) Protection of (*R*)-methyl 3-hydroxy-2-methylpropionate (**19**) (500 mg, 4.24 mmol) as the case of compound (**4**) gave the TBDMS ether (**20**) (930 mg, 89%), $[\alpha]_D^{30}$ −19.58° (*c* 1.94 in $CHCl_3$); δ_H(60 MHz) 0.01 (6 H, s, $SiMe_2$), 0.85 (9 H, s, Bu^t), 1.07 (3 H, d, *J* 7.0 Hz, CH*Me*), 2.45—2.75 (1 H, m, 2-H), and 3.62 (3 H, s, OMe).

Reduction of ester (**20**) (400 mg, 1.62 mmol) with DIBAL as above yielded the alcohol (**13**) (300 mg, 91%) as an oil; $[\alpha]_D^{29}$ −13.22° (*c* 0.61 in $CHCl_3$), whose n.m.r. data were identical with those of the sample prepared by method (A). The alcohol (**13**) (10 mg, 0.049 mmol) was converted as above into the corresponding (*S*)-MTPA ester (**14**) (19 mg, 93%), the n.m.r. spectrum of which was superposable on that of the specimen prepared by method (A).

(2S)-2-(*Dimethyl-t-butylsiloxymethyl*)*pentyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**16**).—(*A*) The ester (**7**) (25 mg, 0.065 mmol) was reduced as above to the alcohol (**15**) (12.8 mg, 85%) as an oil, $[\alpha]_D^{24}$ −6.20° (*c* 0.49 in $CHCl_3$); δ_H(60 MHz) 0.01 (6 H, s, $SiMe_2$), 0.80 (9 H, s, Bu^t), and 3.45—3.61 (4 H, m, 2 × CH_2O).

The alcohol (**15**) (5 mg, 0.021 mmol) was converted as above into the (S)-*MTPA ester* (**16**) (8.9 mg, 92%) as an oil (Found: $M^+ + H$, 449.2369. $C_{22}H_{36}F_3O_4Si$ requires *m/z* 449.2335); δ_H(90 MHz) 0.01 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 3.45—3.60 (5 H, m, CH_2O and OMe), 4.25 (1 H, dd, *J* 6.3 and 10.5 Hz, 1-H), 4.37 (1 H, dd, *J* 5.8 and 10.5 Hz, 1-H), and 7.35—7.60 (5 H, m, Ph); *m/z* 449 ($M^+ + 1$).

(*B*) The phenylmenthyl ester (**34**) (14 mg, 0.03 mmol) was reduced with DIBAL and then converted as above into the (*S*)-MTPA ester (**16**) (10 mg, 70% for two steps) as an oil, whose n.m.r. spectrum was identical with that of the specimen (**16**) prepared by method (A).

(2S)-2-(*Dimethyl-t-butylsiloxymethyl*)-3-*methylbutyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**18**).—(*A*) The menthyl ester (**9**) (78 mg, 0.203 mmol) was reduced as above to the alcohol (**17**) (41 mg, 87%) as an oil, $[\alpha]_D^{28}$ −8.51° (*c* 2.5 in $CHCl_3$); δ_H(90 MHz) 0.12 (6 H, s, $SiMe_2$), 0.90 (9 H, s, Bu^t), 0.92 (6 H, d, *J* 7.1 Hz, 2 × CH*Me*), 1.35—1.95 (2 H, m, 2- and 3-H), 3.00 (1 H, br s, OH), and 3.65—3.95 (4 H, m, 2 × CH_2O); *m/z* 232 (M^+).

The alcohol (**17**) (20 mg, 0.086 mmol) was transformed as above into the (S)-*MTPA ester* (**18**) (37 mg, 95%) as an oil (Found: $M^+ + H$, 449.2378. $C_{22}H_{36}F_3O_4Si$ requires *m/z* 449.2335); δ_H(100 MHz) 0.01 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 0.91 (6 H, d, *J* 7.1 Hz, 2 × CH*Me*), 3.40—3.60 (5 H, m, CH_2OSi and OMe), 4.26 (1 H, dd, *J* 6.7 and 10.5 Hz, 1-H), 4.49 (1 H, dd, *J* 6.2 and 10.5 Hz, 1-H), and 7.30—7.54 (5 H, m, Ph); *m/z* 449 ($M^+ + 1$).

(*B*) The phenylmenthyl ester (**35**) (25 mg, 0.072 mmol) was protected with the TBDMS group as above to give the ether (**36**) (33 mg, 99%) as an oil, δ_H(90 MHz) 0.05 (6 H, s, $SiMe_2$), 0.85 (9 H, d, *J* 7.1 Hz, 3 × CH*Me*), 0.89 (9 H, s, Bu^t), 1.23 (3 H, s, Me), 1.35 (3 H, s, Me), 3.50—3.92 (2 H, m, CH_2O), 4.80 (1 H, dt, *J* 4.6 and 10.6 Hz, 3-H), and 7.12—7.32 (5 H, m, Ph).

Reduction of the ester (**36**) (14 mg, 0.0304 mmol) with DIBAL, followed by esterification as above, afforded the (*S*)-MTPA ester (**18**) (10 mg, 72% for two steps), whose n.m.r. spectrum was identical with that of the sample (**18**), prepared by method (A).

(2S)-2-(*Dimethyl-t-butylsiloxymethyl*)*butyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**45**).—The menthyl ester

(**43**) (59 mg, 0.159 mmol) was reduced as above to give the alcohol (**44**) (31 mg, 89%) as an oil, $[\alpha]_D^{26}$ −11.41° (*c* 1.42 in $CHCl_3$); δ_H(100 MHz) 0.08 (6 H, s, $SiMe_2$), 0.89 (9 H, s, Bu^t), 0.92 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.25 (2 H, quintet, *J* 7.1 Hz, 3-H_2), 1.42—1.90 (1 H, m, 2-H), 2.89 (1 H, br s, OH), and 4.55—4.89 (4 H, m, 2 × CH_2O).

The *alcohol* (**44**) (12 mg, 0.055 mmol) was converted as above into the (S)-*MTPA ester* (**45**) (22 mg, 93%) as an oil (Found: $M^+ - C_4H_9 + H$, 378.1445. $C_{17}H_{25}F_3O_4Si$ requires *m/z* 378.1472); δ_H(100 MHz) 0.01 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 0.91 (3 H, t, *J* 7.1 Hz, CH_2Me), 3.45—3.65 (5 H, m, CH_2O and OMe), 4.25 (1 H, dd, *J* 7.0 and 10.2 Hz, 1-H), 4.39 (1 H, dd, *J* 6.1 and 10.2 Hz, 1-H), and 7.25—7.52 (5 H, m, Ph).

(2S)-2-*Methylbutyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**49**).—A mixture of the alcohol (**42**) (36 mg, 0.14 mmol) and Ph_3P (74 mg, 0.281 mmol) in dry CCl_4 (3 ml) was refluxed for 15 h and then diluted with hexane. After filtration, the filtrate was washed with water, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (24:1) afforded the chloride (**46**) (38 mg, 98%) as an oil, δ_H(100 MHz) 0.75 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.90 (6 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.92 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.50—2.79 (1 H, m, OCOCH), 3.48—3.82 (2 H, m, CH_2Cl), and 4.71 (1 H, dt, *J* 4.5 and 10.5 Hz, CH–O).

To a stirred solution of the chloride (**46**) (35 mg, 0.127 mmol) and AIBN (3 mg) in dry benzene (1 ml) under reflux was slowly added a solution of Bu_3SnH (0.1 ml) in dry benzene (1 ml) and the mixture was stirred for 10 h under reflux and Ar. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with hexane–AcOEt (19:1) gave the non-halogenated compound (**47**) (30 mg, 98%), δ_H(60 MHz) 0.76 (3 H, d, *J* 7.1 Hz, CH*Me*), 2.25 (1 H, sextet, *J* 7.1 Hz, OCOCH), and 4.65 (1 H, dt, *J* 4.5 and 10.5 Hz, CH–O).

To a stirred solution of compound (**47**) (30 mg, 0.125 mmol) in dry THF (1.5 ml) at −20 °C was added 1M-DIBAL in hexane (0.35 ml, 0.35 mmol) and the mixture was stirred for 1 h at −20 °C. After addition of water (0.35 ml), the resulting mixture was further stirred for 30 min at room temperature and then filtered through Celite. The combined filtrate and washings were dried ($MgSO_4$) and evaporated to give the crude alcohol (**48**).

To a stirred solution of the product, (*S*)-MTPA (30 mg, 0.128 mmol), and DMAP (3 mg) in dry CH_2Cl_2 (1 ml) at 0 °C was added dropwise a solution of DCC (30 mg, 0.145 mmol) in dry CH_2Cl_2 (2 ml) and the mixture was stirred for 15 h at room temperature. After dilution with hexane followed by filtration, the filtrate was washed successively with 10% aqueous $KHSO_4$ and water, dried ($MgSO_4$), and evaporated. Silica gel column chromatography of the residue with hexane–Et_2O (97:3) as eluant afforded the (S)-*MTPA ester* (**49**) (27 mg, 72% for two steps) as an oil (Found: M^+, 304.1282. $C_{15}H_{19}F_3O_3$ requires *M*, 304.1285); δ_H(100 MHz) 0.90 (3 H, t, *J* 7.0 Hz, CH_2Me), 0.92 (3 H, d, *J* 7.0 Hz, CH*Me*), 3.52—3.56 (3 H, br s, OMe), 4.04 (1 H, dd, *J* 6.0 and 11.0 Hz, 1-H), 4.25 (1 H, dd, *J* 5.5 and 11.0 Hz, 1-H), and 7.30—7.56 (5 H, m, Ph); *m/z* 304 (M^+), whose n.m.r. spectrum was identical with that of an authentic sample prepared from (*S*)-2-methylbutan-1-ol and (*S*)-MTPA.

(2S)-2-*Methylpentyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**26**).—The alcohol (**6**) (80 mg, 0.296 mmol) was converted as above into the chloride (**21**) (65 mg, 76.5%) as an oil, $[\alpha]_D^{24}$ −54.11° (*c* 6.4 in $CHCl_3$); δ_H(90 MHz) 0.78 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.88 (6 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.89 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.58—2.89 (1 H, m, OCOCH), 3.44—3.85 (2 H, m, CH_2Cl), and 4.74 (1 H, dt, *J* 4.5 and 10.5 Hz, CH–O).

The chloride (**21**) (65 mg, 0.225 mmol) was reduced as above to give the non-halogenated compound (**22**) (54 mg, 95%) as an oil, $[\alpha]_D^{24}$ −55.18° (*c* 5.1 in $CHCl_3$); δ_H(90 MHz) 0.79 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.91 (6 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.92 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.20—2.51 (1 H, m, OCOCH), and 4.68 (1 H, dt, *J* 4.5 Hz and 10.6 Hz, CH–O).

Reduction of the ester (**22**) (3.0 mg, 0.118 mmol) with DIBAL, followed by esterification of the resulting crude alcohol (**25**) with (*S*)-MTPA as above, afforded the (S)-*MTPA ester* (**26**) (26 mg, 69% for two steps) as an oil (Found: M^+, 318.1403. $C_{16}H_{21}F_3O_3$ requires *M*, 318.1442); δ_H(100 MHz) 0.92 (3 H, d, *J* 7.0 Hz, CH*Me*), 3.53—3.56 (3 H, br s, OMe), 4.03 (1 H, dd, *J* 7.0 and 10.5 Hz, 1-H), 4.22 (1 H, dd, *J* 6.5 and 10.5 Hz, 1-H), and 7.32—7.54 (5 H, m, Ph).

(2S)-2,3-*Dimethylbutyl* (S)-3,3,3-*Trifluoro*-2-*methoxy*-2-*phenylpropionate* (**28**).—The alcohol (**8**) (62 mg, 0.229 mmol) was converted as above into the chloride (**23**) (55 mg, 83%) as an oil, $[\alpha]_D^{25}$ −57.5° (*c* 5.5 in $CHCl_3$); δ_H(90 MHz) 0.76 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.86—1.05 (12 H, m, 4 × CH*Me*), 2.38—2.64 (1 H, m, OCOCH), 3.50—3.88 (2 H, m, CH_2Cl), and 4.74 (1 H, dt, *J* 4.5 and 10.5 Hz, CH–O).

The chloride (**23**) (55 mg, 0.19 mmol) was reduced as above to the non-halogenated compound (**24**) (43 mg, 90%) as an oil, $[\alpha]_D^{24}$ −49.34° (*c* 4.32 in $CHCl_3$); δ_H(90 MHz) 0.78 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.85—1.02 (12 H, m, 4 × CH*Me*), and 4.67 (1 H, dt, *J* 4.5 and 10.5 Hz, CH–O).

Reduction of the ester (**24**) (50 mg, 0.196 mmol) with DIBAL, followed by esterification of the resulting crude alcohol (**27**) with (*S*)-MTPA as above, gave the (S)-*MTPA ester* (**28**) (38 mg, 61%) as an oil (Found: M^+, 318.1451. $C_{16}H_{21}F_3O_3$ requires *M*, 318.1442); δ_H(100 MHz) 0.80—0.92 (9 H, m, 3 × CH*Me*), 3.52—3.56 (1 H, br s, OMe), 4.07 (1 H, dd, *J* 7.0 and 10.5 Hz, 1-H), 4.30 (1 H, dd, *J* 6.0 and 10.5 Hz, 1-H), and 7.30—7.55 (5 H, m, Ph).

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