Enantioselective Construction of Quaternary Stereogenic Centres Possessing a Fluorine Atom

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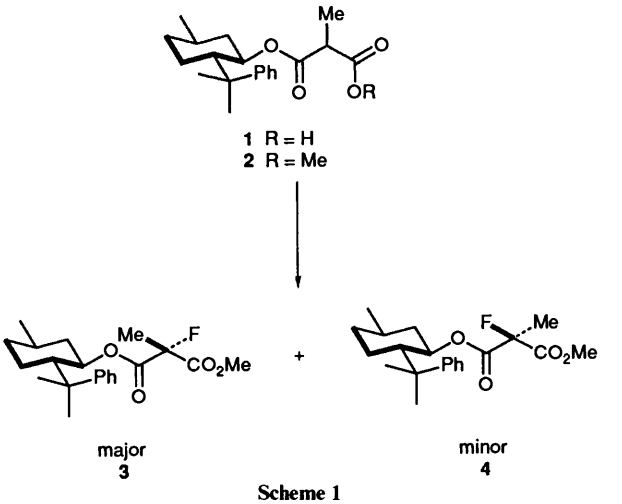
Fluorination of methyl (1*R*,3*R*,4*S*)-8-phenylmenthyl methylmalonates **2** using lithium hexamethyldisilazide and 1-fluoro-2,4,6-trimethylpyridinium triflate (trifluoromethanesulfonate), gave the (*R*)-**3** and (*S*)-**4** isomers in a 3.8:1 ratio, while fluorination of ethyl-, propyl- and benzyl-malonates **10**, **11** and **12** provided the (*R*)-**13**, **15** and **17** and (*S*)-**14**, **16** and **18** isomers in a 1:1.6–2.0 ratio. On the other hand, alkylation of (1*R*,3*R*,4*S*)-8-phenylmenthyl hydrogen fluoromalonates **26** in the presence of lithium hexamethyldisilazide, followed by esterification with diazomethane, produced the (*R*)-**3**, **13**, **15**, **17**-and **27** and (*S*)-**4**, **14**, **16**, **18** and **28** isomers in a 1:5.7–35 ratio.

Since significant physical and biological properties are shown by compounds possessing a fluorine atom, the regio- and stereoselective introduction of a fluorine atom into molecules is an interesting problem.[1] In this respect, the development of a general synthetic method towards monofluorinated chiral building blocks is one of the current topics for research. Kitazume and his co-workers reported the enantioselective production of optically active fluoro compounds by biological means.[2] The method was very efficient for the preparation of particular types of compounds. Enantioselective fluorination of carbonyl compounds has been tried without success using chiral *N*-fluorosultams.[3]

Recently we developed a versatile method for the creation of quaternary stereogenic centres through the diastereoselective alkylation of chiral half-esters of monosubstituted malonic acids.[4] As an extension of this methodology, the enantioselective synthesis of monofluorinated chiral building blocks was investigated *via* both fluorination to chiral esters of monoalkylmalonic acids[5] and alkylation to chiral esters of monofluoromalonate. We now wish to report the highly diastereoselective construction of quaternary stereogenic centres by the latter approach. Our results further support the putative mechanism, previously proposed for the diastereoselective alkylation of chiral half-esters.[4]

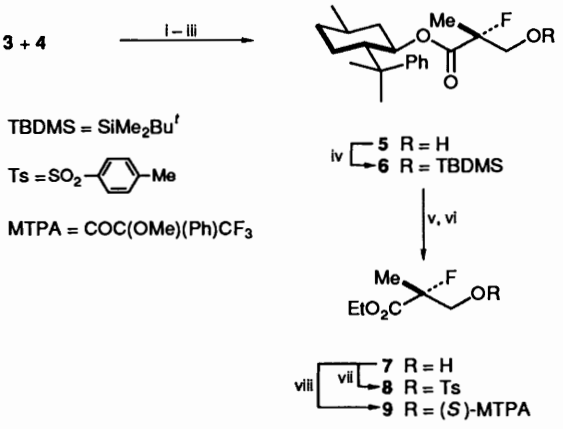
Firstly, a diastereoselective fluorination to phenylmenthyl half esters[4,6] was examined. Among the known fluorinating reagents,[7,8] 1-fluoro-2,4,6-trimethylpyridinium triflate (trifluoromethanesulfonate) (FTT)[8] was tested for the fluorination of the 8-phenylmenthyl half-esters **1**[4] of methylmalonic acid in the presence of an excess of lithium hexamethyldisilazide (LHMDS). Due to the high polarity of the products, the crude product was esterified with diazomethane before purification. The fluorinated compounds **3** and **4** were obtained in 38% yield in a 1.5:1 ratio. On the other hand, the reaction of methyl 8-phenylmenthyl methylmalonates **2**, derived from **1**, with FTT[8] under basic conditions gave an epimeric mixture of fluorides **3** and **4** in better yield. The 2.5:1 mixture of **3** and **4** was produced in 77% yield on treatment of **2** with FTT[8] in the presence of sodium hydride in tetrahydrofuran (THF) at 0 °C. Yield, as well as selectivity, was improved by the use of LHMDS instead of sodium hydride. Thus, reaction of **2** with LHMDS in THF, followed by treatment of the resulting enolate anion with FTT[8] at −78 °C to room temperature for 15 h provided a 3.8:1 mixture of **3** and **4** in 87% yield (Scheme 1). When the lithium enolate was allowed to react with *N*-fluoro-*N*-propylsulfonamide[7f] in THF at −78 °C to room temperature, a 5.7:1 mixture of **3** and **4** was obtained in 21% yield. It was difficult in this case to separate the desired products from compounds derived from the reagents. All the above reactions produced the same stereoisomer **3** as the major product, the structure of which was determined by its correlation with a known compound[3c] as follows.



Scheme 1

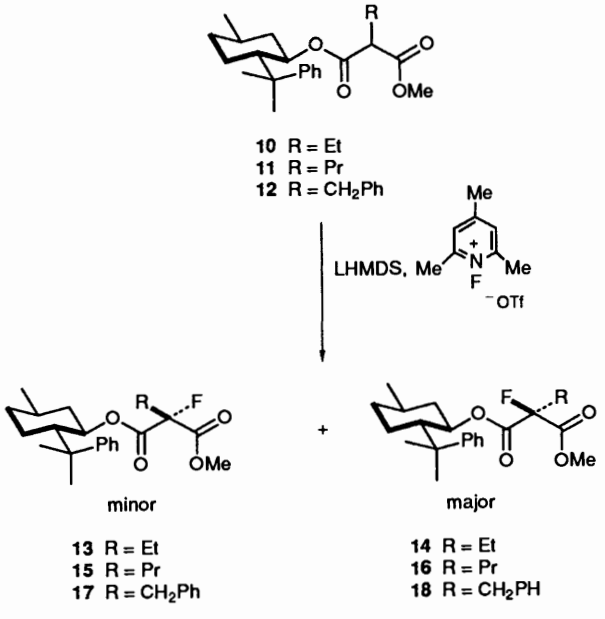
The 3.8:1 mixture of **3** and **4**, prepared from **2** with FTT[8] in the presence of LHMDS, was selectively hydrolysed with lithium hydroxide in aqueous methanol at room temperature. The resulting carboxylic acids, obtained in 89% yield, was reduced to the primary alcohols, in 67% yield, in two steps: formation of acid chlorides using oxalyl chloride followed by reduction with tetrabutylammonium borohydride. Protection of the hydroxy group using *tert*-butyldimethylsilyl chloride (TBDMSCl), 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and triethylamine afforded the corresponding TBDMS ethers in 98% yield. Separation of the major component **5** or **6** was carried out by high performance liquid chromatography (HPLC). The 8-phenylmenthyl group of **6** was removed by the action of potassium superoxide in the presence of 18-crown-6[9] to give the carboxylic acid having the TBDMS ether group. Treatment of the product with 10% hydrogen chloride in ethanol formed the hydroxy ester **7**, which was treated with toluene-*p*-sulfonyl chloride and DMAP in pyridine to give the tosylate **8** in 72% yield from **6**. A comparison of its specific rotation, $[\alpha]_D^{24}$ +1.9° (*c* 0.21 in MeOH), with the reported one of the 91% ee (*S*)-isomer, $[\alpha]_D$ −1.79° (*c* 1.34 in MeOH),[2c] determined the (*R*)-configuration for the product **8**. The optical purity (100% ee) of **7** was further confirmed by its

conversion into the (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) **9**[10] (Scheme 2).



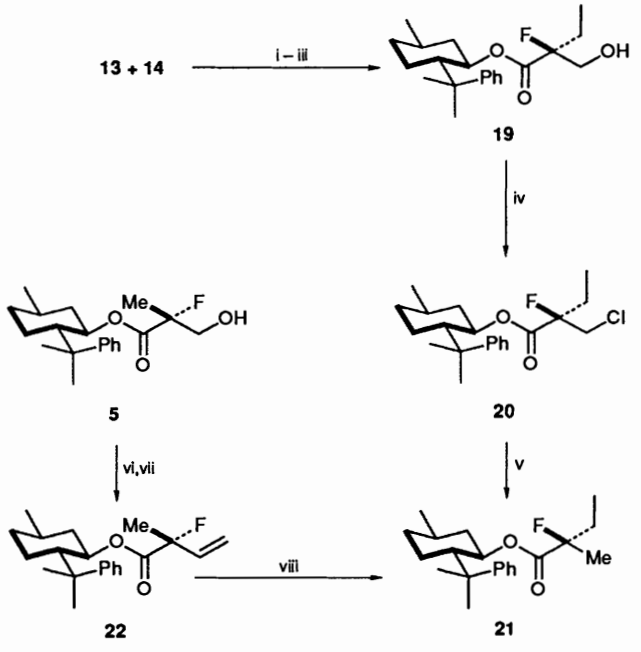
Scheme 2 *Reagents and conditions:* i, LiOH, room temp.; ii, $(COCl)_2$; iii, Bu_4NBH_4; iv, TBDMSCl, Et_3N, DMAP; v, KO_2, 18-crown-6, room temp.; vi, HCl, EtOH; vii, TsCl, DMAP, pyridine; viii, (*S*)-MTPAOH, DCC, DMAP

The methyl esters **10**, **11** and **12** of ethyl-, propyl- and benzylmalonates were prepared by reaction of the corresponding half esters[4,6] with diazomethane. The diesters **12** of benzylmalonates were obtained as a 97:3 diastereoisomeric crystalline compound by crystallisation induced asymmetric transformation.[6] Fluorination of **10**, **11** and **12** with FTT[8] in the presence of LHMDS in THF afforded mixtures of **13** and **14** (1:2), **15** and **16** (1:2), and **17** and **18** (1:1.6) in 96, 96 and 88% yields, respectively (Scheme 3).



Scheme 3

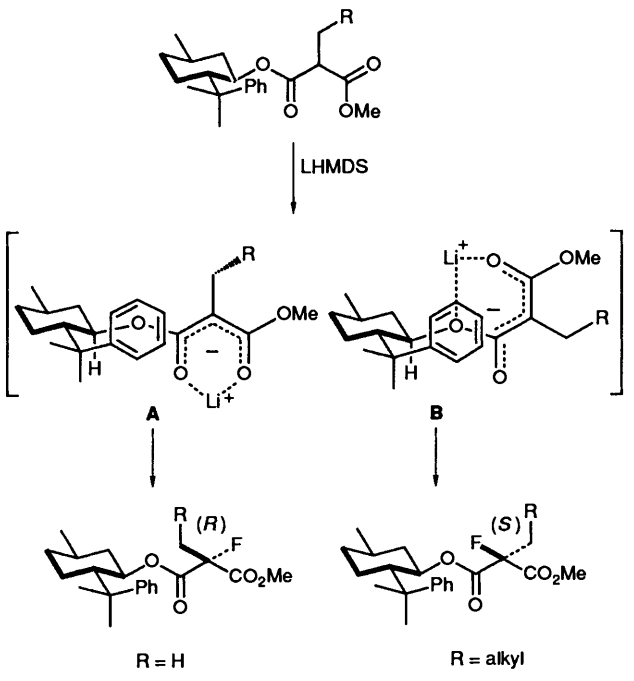
The stereochemistry of the major product **14** was decided on the basis of the following transformations. The 1:2 mixture of **13** and **14** was converted as above into an epimeric mixture of primary alcohols. After isolation of the major component **19** by HPLC, **19** was treated with triphenylphosphine in carbon tetrachloride to form the chloride **20** in 100% yield. Reduction of **20** using tributyltin hydride in the presence of azoisobutyronitrile (AIBN) provided the methyl compound **21**, $[\alpha]_D^{24}$ −6.81° (*c* 0.88 in $CHCl_3$), in 83% yield. The same compound **21** was prepared from the above alcohol **5**. Thus oxidation of **5** with Dess–Martin periodinane (DMP),[11] followed by Wittig reaction of the resulting aldehyde, obtained in 89% yield, produced the olefin **22** in 65% yield. Catalytic hydrogenation of **22** in the presence of 10% palladium on carbon furnished, in 99% yield, the fluoride **21**, which was identical with the above compound in all aspects. Therefore the stereogenic centre of the major malonate **14** was assigned to the (*S*)-configuration (Scheme 4).



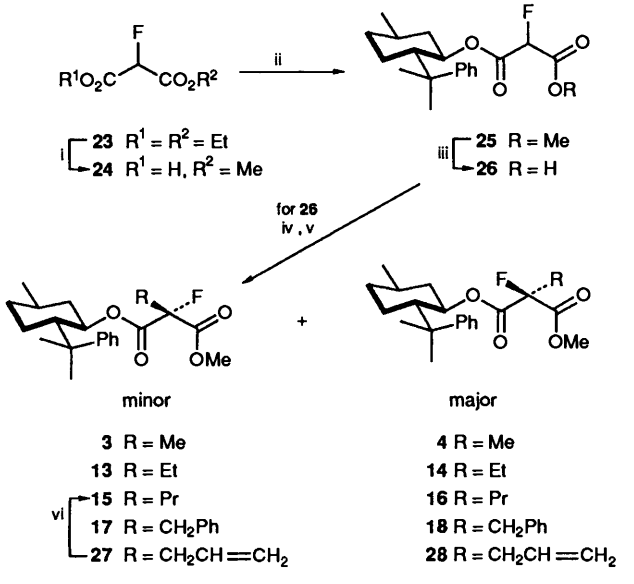
Scheme 4 *Reagents and conditions:* i, LiOH, room temp.; ii, $(COCl)_2$; iii, Bu_4NBH_4; iv, Ph_3P, CCl_4, heat; v, Bu_3SnH, AIBN; vi, DMP; vii, $Ph_3P = CH_2$; viii, H_2, Pd–C

The result, the preferred formation of the opposite stereoisomers **3** and **14** from **2** and **10**, respectively, is consistent with the previous observation on the diastereoselective alkylation to chiral half-esters.[4] It is thus assumed that the major pathway of the fluorination of the diester **2** of methylmalonic acid would be access of FTT[8] to the less hindered α-side of the conformation **A**, leading to the (*R*)-isomer **3**, while the other conformation **B** would be preferred for the reaction of anions derived from monoalkylmalonates **10**, **11** and **12**. In conformation **A**, the alkyl group (R) directed to the α-side would prevent the approach of FTT[8] from the α-side, while in the conformation **B**, rotation of the R group is not restricted (Scheme 5). From consideration of the above reaction mechanism, the stereochemistries at the quaternary stereogenic centre of the major products **16** and **18** were deduced to be (*S*).

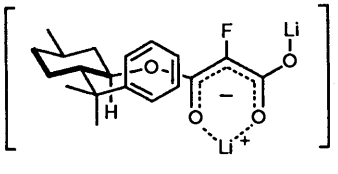
For the purpose of improving the diastereoselectivity as well as solving the reaction mechanism, alkylation to the chiral esters of fluoromalonic acid was next examined. Esterification of the half-ester **24**, derived from diethyl fluoromalonate **23**, with 8-phenylmenthol, using dicyclohexylcarbodiimide (DCC) in the presence of DMAP failed. After several trials, the barrier was overcome by the action of a sulfonyl chloride or an acid chloride in pyridine. Namely, reaction of **24** with 8-phenylmenthol in the presence of methanesulfonyl chloride or pivaloyl chloride in pyridine at 0 °C to room temperature for 5 h produced the diesters **25** in 52 or 87% yield. Alkylation of **25** using LHMDS resulted in poor yield and selectivity. In order to enhance the nucleophilicity, the diester **25** was hydrolysed with lithium hydroxide to the chiral half-esters **26**, which were converted, by reaction with excess LHMDS, into dianions. Treatment with methyl iodide in THF at −78 °C to room temperature, followed by reaction with diazomethane, afforded a 1:6.5 mixture of **3** and **4** in 88.5% yield. A remarkable



Scheme 5



Scheme 6 *Reagents and conditions:* i, KOH, MeOH; ii, (−)-8-phenylmenthol, pivaloyl chloride, pyridine; iii, LiOH; iv, LHMDS, alkyl halide, −78 °C–room temp.; v, CH_2N_2; vi, H_2, Pd–C



C

Fig. 1

diastereoselectivity (94% de) was observed on the ethylation and the 1:35 mixture of **13** and **14** was obtained in 73% yield after esterification. Reactions with propyl iodide and benzyl bromide, followed by esterifications, provided a 1:5.7 mixture of **15** and **16** and a 1:11 mixture of **17** and **18** in 70 and 12% yield, respectively. A 1:30 mixture of **27** and **28** was gained in 93% yield by reaction with allyl bromide, followed by the diazomethane treatment, and was quantitatively converted into a 1:30 mixture of **15** and **16** by catalytic hydrogenation (Scheme 6). It is noteworthy that all the major products, produced from **26** by the above reactions, possess the (*S*)-configuration at the newly introduced stereogenic centre. The above result indicates that the alkylation of the fluoromalonates **26** proceeds *via* the transition stage **C** (Fig. 1), which corresponds to the preferred conformation **A** of the methylmalonates **2**; this fact further supports the above consideration of the reaction mechanism. Thus, we succeeded in the diastereoselective construction of quaternary stereogenic centres possessing a fluorine atom by the alkylation of the fluoromalonates **26**.

Experimental

General Methods.—M.p.s were determined on a Yanako micromelting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR-Report-100 spectrophotometer. NMR spectra were taken for $CDCl_3$ solutions on JEOL JNM-PMX-60, JEOL-FX-90A and JEOL JNM-GX-500 spectrometers. Chemical shifts are reported relative to internal $SiMe_4$, and *J* values are given in Hz. Mass spectra were measured on a JEOL-DX-300 and a JEOL-DX-303 spectrometer. Optical rotations were determined on a JASCO-DIP-340 polarimeter. $[\alpha]$ Values are given in 10^{-1} deg cm^3 g^{-1}. Solvents were freshly distilled prior to use: tetrahydrofuran (THF) and Et_2O were distilled from sodium-benzophenone; CH_2Cl_2 was distilled from P_2O_5. All extracts were dried over $MgSO_4$. Flash chromatography was performed on Merck Kieselgel 60 (230–400 mesh). HPLC was carried out with a Gilson HPLC system Model 302/303 and monitored by UV absorption and refractive-index measurements.

Methyl(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*ylMethylmalonates* **2**.—To a solution of (1*R*,3*R*,4*S*))-8-phenyl-*p*-menthan-3-yl hydrogen methylmalonates **1**[6] (100 mg, 0.03 mmol) in MeOH (5 cm^3) was added an excess of CH_2N_2 in Et_2O and the mixture was set aside for 30 min at room temperature. After evaporation, the residue was taken up into Et_2O. The solution was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography with hexane–AcOEt (95:5 v/v) as eluent to give the *methyl esters* **2** (104 mg, 95%) as an oil (Found: M^+, 346.2123. $C_{21}H_{30}O_4$ requires *M*, 346.2142); $[\alpha]_D^{21}$ +18.76 (*c* 1.13 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 and 1730 (C=O); δ_H(500 MHz) 0.86 and 0.87 [3 H, (1.5:1), each d, *J* 5.6, 1-Me], 1.18 (1.2 H, d, *J* 7.5, CH*Me*), 1.21 (3 H, s, 8-Me), 1.23 and 1.24 [3 H (1.5:1), each s, 8-Me], 1.31 (1.8 H, d, *J* 5.4, CH*Me*), 2.58 (0.6 H, q, *J* 5.4, C*H*Me), 2.99 (0.4 H, q, *J* 7.5, C*H*Me), 3.64 and 3.73 [3 H, (1.5:1), each s, OMe], 4.82 and 4.86 [1 H (1:1.5), each dt, *J* 4.2 and 10.7, 3-H], 7.16–7.19 (1 H, m, ArH) and 7.21–7.32 (4 H, m, 4 × ArH); *m/z* 346 (M^+).

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Ethylmalonates* **10**.—(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl hydrogen ethylmalonates[4] (212 mg, 0.61 mmol) was converted as above into *methyl esters* **10** (219 mg, 99%) as an oil (Found: C, 72.95; H, 9.05. $C_{22}H_{32}O_4$ requires C, 73.3; H, 8.95%); $[\alpha]_D^{23}$ −5.49 (*c* 1.20 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1748 and 1726 (C=O); δ_H(500 MHz) 0.85 and 0.87 [3 H (1.5:1), each d, *J* 2.4, 1-Me], 0.90 (3 H, t, *J* 7.3, CH_2*Me*), 1.22 and 1.31 (each 3 H, each s, 8-Me_2), 1.74–1.78 (2 H, m, C*H*$_2$Me), 2.55 (0.6 H, t, *J* 7.9, C*H*CH_2), 2.80 (0.4 H, dd, *J* 6.7 and 8.8, C*H*CH_2), 3.65 and 3.72 [3 H (1.5:1), each s, OMe), 4.81 and 4.85 [1 H (1:1.5), each dt, *J* 4.9 and 12.1, 3-H], 7.12–7.18 (1 H, m, ArH) and 7.20–7.32 (4 H, m, 4 × ArH); *m/z* 360 (M^+).

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Propylmalonates* **11**.—(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl hydrogen propylmalonates[6] (216 mg, 10.6 mmol) were converted as above into *methyl esters* **11** (215 mg, 96%) as an oil (Found: C, 73.7; H, 9.15. $C_{23}H_{34}O_4$ requires C, 73.75; H, 9.15%); ν_{max}(neat)/cm^{-1} 1755 and 1720 (C=O); δ_H(500 MHz) 2.65 (0.6 H, t, *J* 7.0, C*H*CH$_2$), 2.88 (0.4 H, dd, *J* 6.2 and 8.0, C*H*CH$_2$), 3.65 and 3.71 [3 H (1.2:1), each s, OMe], 4.81 and 4.85 [1 H, (1:1.2), each dt, *J* 4.4 and 10.3, 3-H], 7.17–7.19 (1 H, m, ArH) and 7.22–7.35 (4 H, m, 4 × ArH); *m*/*z* 374 (M$^+$).

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Benzylmalonate* **12**.—(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl hydrogen benzylmalonates[4] (230 mg, 0.56 mmol) were converted as above into *methyl esters* **12** (219 mg, 93%) as an oil, which after being set aside for several days, became prisms, m.p. 62–63 °C (Found: C, 76.8; H, 8.05. $C_{27}H_{34}O_4$ requires C, 76.75; H, 8.1%); $[\alpha]_D^{25}$ −6.29 (*c* 0.26 in CHCl$_3$); ν_{max}(neat)/cm^{-1} 1748 and 1730 (C=O); δ_H(500 MHz) 0.85 (3 H, d, *J* 6.5, 1-Me), 1.12 and 1.17 (each 3 H, each s, 8-Me$_2$), 3.00–3.07 (3 H, m, C*H*C*H*$_2$Ph), 3.61 and 3.67 [3 H (97:3), each s, OMe], 4.81 (1 H, dt, *J* 4.6 and 11.0, 3-H) and 7.10–7.31 (10 H, m, 10 × ArH); *m*/*z* 422 (M$^+$).

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Fluoromalonates* **25**.—To a solution of diethyl fluoromalonate **23** (400 mg, 2.25 mmol) in MeOH (8 cm^3) was added a solution of KOH (85%; 148 mg, 2.25 mmol) in MeOH (8 cm^3) and the mixture was stirred for 2 h at room temperature. After concentration under reduced pressure, the residue was taken up into water. The aq. solution was washed with a mixture of hexane–Et$_2$O (1:1 v/v) and then acidified with 10% aq. HCl under ice cooling. The mixture was thoroughly extracted with AcOEt. The extract was washed with brine, dried and evaporated under reduced pressure to give the half-esters **24** (307 mg, 100%) as an oil; δ_H(60 MHz) 3.93 (3 H, s, OMe), 5.39 (1 H, d, *J* 49.0, CHF) and 8.15 (1 H, s, CO$_2$H), which were used in the following reaction without purification.

To a stirred solution of (−)-8-phenylmenthol (50 mg, 0.22 mmol) and the above half-esters **24** (44 mg, 0.32 mmol) in dry pyridine (1 cm^3) at 0 °C was slowly added pivaloyl chloride (0.05 cm^3, 0.37 mmol) under Ar. The mixture was stirred for 5 h at 0 °C to room temperature and then diluted with benzene. The resulting mixture was washed with 10% aq. KHSO$_4$ and brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with hexane–AcOEt (93:7 v/v) to give *methyl esters* **25** (69 mg, 87%) as an oil (Found: M$^+$, 350.1894. $C_{20}H_{27}FO_4$ requires *M*, 350.1892); $[\alpha]_D^{27}$ +12.05 (*c* 1.17 in CHCl$_3$); ν_{max}(neat)/cm^{-1} 1799, 1757 and 1739 (C=O); δ_H(500 MHz) 0.87 and 0.89 [3 H (5:2), each d, each *J* 6.1, 1-Me], 1.22 and 1.26 [3 H (5:2), each s, 8-Me], 1.31 and 1.32 [3 H (2:5) each s, 8-Me], 3.74 and 3.84 [3 H (5:2), each s, OMe], 4.06 and 4.78 [1 H (5:2), each d, *J* 48.0, CHF], 4.91–5.02 (1 H, m, 3-H), 7.17–7.26 (1 H, m, ArH) and 7.27–7.44 (4 H, m, 4 × ArH).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Hydrogen Fluoromalonates* **26**.—To a solution of the above methyl esters **25** (244 mg, 0.67 mmol) in EtOH (6 cm^3) was added a solution of LiOH·H$_2$O (28 mg, 0.66 mmol) in water (3 cm^3) at room temperature, and the mixture was stirred for 30 min at the same temperature under N$_2$. After evaporation under reduced pressure, the residue was partitioned between Et$_2$O (20 cm^3) and water (7 cm^3). The ethereal layer was extracted three times with saturated aq. NaHCO$_3$ (3 cm^3 each). The combined aqueous layers were acidified with 10% aq. HCl and then thoroughly extracted with AcOEt. The extract was washed with brine, dried and evaporated under reduced pressure to give the *half-esters* **26** (251 mg, 99%) as an oil (Found: M$^+$, 336.1759. $C_{19}H_{25}FO_4$ requires *M*, 336.1735); $[\alpha]_D^{27}$ +6.85 (*c* 1.01 in CHCl$_3$); ν_{max}(neat)/cm^{-1} 3255 (OH) and 1755 (C=O); δ_H(500 MHz) 0.88 and 0.89 [3 H, (1:2.5), each d, *J* 7.0, 1-Me], 1.22 and 1.32 (each 3 H, each s, 8-Me$_2$), 4.03 and 4.69 [1 H (2.5:1), each d, *J* 48.0, CHF], 4.95 and 4.97 [1 H, (1:2.5), each dt, *J* 5.5 and 12.0, 3-H], 5.42 (1 H, br s, OH), 7.12–7.16 (1 H, m, ArH) and 7.23–7.30 (4 H, m, 4 × ArH).

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Fluoro*(*methyl*)*malonates* **3** *and* **4**.—*Method A*. To a stirred solution of the methyl esters **2** (25 mg, 0.072 mmol) in dry THF (2 cm^3) at −78 °C was slowly added LHMDS in THF (1 mol dm^{-3}; 0.11 cm^3, 0.11 mmol) under Ar. After being stirred for 30 min at the same temperature, to the resulting mixture was added FTT[8] (31 mg, 0.11 mmol) at −78 °C and the mixture was stirred for 15 h at −78 °C to room temperature under Ar. After dilution with benzene, the mixture was washed with 5% aq. KHSO$_4$ and brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane–AcOEt (95:5 v/v) as eluent to give a 3.8:1 mixture of *esters* **3** and **4** (22.5 mg, 87%) as an oil (Found: M$^+$, 364.2068. $C_{21}H_{29}FO_4$ requires *M*, 364.2048); ν_{max}(neat)/cm^{-1} 1753 (C=O); δ_H(500 MHz) 0.84 and 0.85 [3 H (3.8:1), each d, *J* 6.6, 1-Me], 1.24 and 1.26 [3 H, (1:3.8), each s, 8-Me], 1.30 and 1.31 [3 H (3.8:1), each s, 8-Me], 1.56 and 1.69 [3 H (1:3.8), each d, *J* 23.0, CFMe], 3.80 and 3.81 [3 H, (1:3.8), each s, OMe], 4.89 and 4.95 [1 H, (3.8:1), each dt, *J* 4.0 and 11.1, 3-H], 7.18–7.20 (1 H, m, ArH) and 7.23–7.26 (4 H, m, 4 × ArH); *m*/*z* 364 (M$^+$).

Method B. To a stirred solution of the half-esters **26** (55 mg, 0.16 mmol) in dry THF (2 cm^3) at −78 °C was slowly added LHMDS in THF (1 mol dm^{-3}; 0.49 cm^3, 0.49 mmol) under Ar and the mixture was stirred for 30 min at the same temperature. After addition of MeI (0.051 cm^3, 0.82 mmol) at −78 °C, the mixture was stirred for 16 h at −78 °C to room temperature. After dilution with AcOEt, the resulting mixture was washed with 10% aq. HCl and brine, dried and evaporated under reduced pressure to give a residue, which was treated with an excess of CH_2N_2 in Et$_2$O. After being set aside for 30 min, evaporation of the solvent and excess of reagent afforded a residue, which was taken up into Et$_2$O. The ethereal solution was washed with saturated aq. NaHCO$_3$ and brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography eluting with hexane–AcOEt (93:7 v/v) to provide a 1:6.5 mixture of esters **3** and **4** (65.8 mg, 88.5%) as an oil; δ_H(500 MHz) 0.84 and 0.85 [3 H (1:6.5), each d, *J* 6.6, 1-Me], 1.24 and 1.26 [3 H, (6.5:1), each s, 8-Me], 1.30 and 1.31 [3 H (1:6.5), each s, 8-Me], 1.56 and 1.69 [3 H (6.5:1), each d, *J* 23.0, CFMe], 3.80 and 3.81 [3 H (6.5:1), each s, OMe], 4.89 and 4.95 [1 H (1:6.5), each dt, *J* 4.0 and 11.1, 3-H], other spectral data of which were identical with those of the above product, prepared by method A.

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Ethyl*(*fluoro*)*malonates* **13** *and* **14**.—*Method A*. According to the above method A, the methyl esters **10** (400 mg, 1.11 mmol) were converted, using LHMDS in THF (1 mol dm^{-3}; 2.22 cm^3, 2.22 mmol) and FTT[8] (802 mg, 2.76 mmol), into a 1:2 mixture of *esters* **13** and **14** (403 mg, 96%) as an oil (Found: M$^+$, 378.2235. $C_{22}H_{31}FO_4$ requires *M*, 378.2207); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H(500 MHz) 0.85 and 0.86 [3 H (1:2), each d, *J* 6.1, 1-Me], 0.95 and 1.00 [3 H, (2:1), each t, *J* 7.3, CH$_2$*Me*], 1.26 and 1.28 [3 H (2:1), each s, 8-Me], 3.82 (3 H, s, OMe), 4.92 and 4.94 [1 H (1:2), each dt, *J* 4.3 and 8.0, 3-H], 7.18–7.19 (1 H, m, ArH) and 7.26–7.31 (4 H, m, 4 × ArH); *m*/*z* 378 (M$^+$).

Method B. According to the above method B, ethylation using LHMDS in THF (1 mol dm^{-3}; 0.45 cm^3, 0.45 mmol) and ethyl iodide (0.06 cm^3, 0.74 mmol), followed by esterification with an excess of CH_2N_2, half-esters **26** (50 mg, 0.15 mmol) were converted into a 1:35 mixture of esters **13** and **14** (41 mg, 73%) as an oil; δ_H(500 MHz) 0.85 and 0.86 [3 H (1:35), each d, *J* 6.1,

1-Me], 0.95 and 1.00 [3 H (35:1), each t, *J* 7.3, CH_2Me], 1.26 and 1.28 [3 H (35:1), each s, 8-Me] and 4.92 and 4.94 [1 H (1:35), each dt, *J* 4.3 and 8.0, 3-H], other spectral data of which were identical with those of the above product, prepared by the method A.

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Fluoro*(*propyl*)-*malonates* **15** *and* **16**.—*Method A*. According to the above method A, the methyl esters **11** (173 mg, 0.46 mmol) were converted, using LHMDS in THF (1 mol dm^{-3}; 0.92 cm^3, 0.92 mmol) and FTT[8] (334 mg, 1.15 mmol), into a 1:2 mixture of *esters* **15** and **16** (173 mg, 96%) as an oil (Found: M^+, 392.2384. $C_{23}H_{33}FO_4$ requires *M*, 392.2361); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H(500 MHz) 0.85 and 0.86 [3 H (2:1), each d, *J* 6.7, 1-Me], 0.94 and 0.97 [3 H (2:1), each t, *J* 7.9, CH_2Me], 1.26 and 1.27 [3 H (2:1), each s, 8-Me], 1.30 and 1.32 [3 H (1:2), each s, 8-Me], 3.81 (3 H, s, OMe), 4.92 and 4.94 [1 H (1:2), each dt, *J* 4.9 and 10.2, 3-H], 7.14–7.19 (1 H, m, ArH) and 7.25–7.31 (4 H, m, 4 × ArH).

Method B. According to the above method B, propylation using LHMDS in THF (1 mol dm^{-3}; 0.56 cm^3, 0.56 mmol) and propyl iodide (0.09 cm^3, 0.93 mmol), followed by esterification with an excess of CH_2N_2, the half-esters **26** (63 mg, 0.19 mmol) was converted into a 1:5.7 mixture of esters **15** and **16** (51.5 mg, 70%) as an oil; δ_H(500 MHz) 0.85 and 0.86 [3 H (5.7:1), each d, *J* 6.7, 1-Me], 0.94 and 0.97 [3 H (5.7:1), each t, *J* 7.9, CH_2Me], 1.26 and 1.27 [3 H (5.7:1), each s, 8-Me], 1.30 and 1.32 [3 H (1:5.7), each s, 8-Me] and 4.92 and 4.94 [1 H (1:5.7), each dt, *J* 4.9 and 10.2, 3-H], other spectral data of which were identical with those of the above product, prepared by the method A.

Method C. A mixture of the allyl compounds **27** and **28** (20 mg, 0.05 mmol) and 5% Pd–C (50 mg) in MeOH (5 cm^3) was stirred for 10 h under H_2 (1 atm) at room temperature. Filtration through Celite, followed by evaporation of the filtrate under reduced pressure, gave a residue, which was taken up into Et_2O. The organic solution was washed with 5% aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. Flash chromatography of the residue with hexane–AcOEt (95:5 v/v) as eluent afforded a 1:30 mixture of esters **15** and **16** (20 mg, 99%) as an oil; δ_H(500 MHz) 0.85 and 0.86 [3 H (30:1), each d, *J* 6.7, 1-Me], 0.94 and 0.97 [3 H (30:1), each t, *J* 7.9, CH_2Me], 1.26 and 1.27 [3 H (30:1), each s, 8-Me], 1.30 and 1.32 [3 H (1:30), each s, 8-Me] and 4.92 and 4.94 [1 H (1:30), each dt, *J* 4.9 and 10.2, 3-H], other spectral data of which were identical with those of the above product, prepared by the method A.

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Benzyl*(*fluoro*)-*malonates* **17** *and* **18**.—*Method A*. According to the above method A, the methyl esters **12** (101 mg, 0.24 mmol) were converted, using LHMDS in THF (1 mol dm^{-3}; 0.48 cm^3, 0.48 mmol) and FTT[8] (152 mg, 0.52 mmol), into a 1:1.6 mixture of esters **17** and **18** (94 mg, 88%) as an oil (Found: C, 70.8; H, 7.5. $C_{27}H_{33}FO_4 \cdot H_2O$ requires C, 70.7; H, 7.7%); ν_{max}(neat)/cm^{-1} 1752 (C=O); δ_H(500 MHz) 0.81 (3 H, d, *J* 8.0, 1-Me), 3.21 (0.62 H, dd, *J* 19.0 and 23.0, C*H*HPh), 3.33 (0.62 H, dd, *J* 19.0 and 27.5, CH*H*Ph), 3.37 (0.38 H, dd, *J* 15.6 and 25.4, C*H*HPh), 3.40 (0.38 H, dd, *J* 15.6 and 25.4, CH*H*Ph), 3.74 and 3.77 [3 H (1.6:1), each s, OMe], 4.85 and 4.89 [1 H (1:1.6), each dt, *J* 4.7 and 10.9, 3-H] and 7.13–7.32 (10 H, m, 10 × ArH); *m*/*z* 440 (M^+).

Method B. According to the above method B, benzylation using LHMDS in THF (1 mol dm^{-3}; 0.36 cm^3, 0.36 mmol) and benzyl bromide (0.07 cm^3, 0.59 mmol), followed by esterification with an excess of CH_2N_2, the half-esters **26** (40 mg, 0.12 mmol) were converted into a 1:11 mixture of esters **17** and **18** (7 mg, 12%) as an oil; δ_H(500 MHz) 3.21 (0.92 H, dd, *J* 19.0 and 23.0, C*H*HPh), 3.33 (0.92 H, dd, *J* 19.0 and 27.5, CH*H*Ph), 3.37 (0.08 H, dd, *J* 15.6 and 25.4, C*H*HPh), 3.40 (0.08 H, dd, *J* 15.6 and 25.4, CH*H*Ph), 3.74 and 3.77 [3 H (11:1), each s, OMe] and 4.85 and 4.89 [1 H (1:11), each dt, *J* 4.7 and 10.9, 3-H], other spectral data were identical with those of the product prepared by the method A.

Methyl (1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl Allyl*(*fluoro*)-*malonates* **27** *and* **28**.—According to the method B, allylation using LHMDS in THF (1 mol dm^{-3}; 0.45 cm^3, 0.45 mmol) and allyl bromide (0.1 cm^3, 1.16 mmol), followed by esterification with an excess of CH_2N_2, half-esters **26** (50 mg, 0.15 mmol) were converted into the 1:30 mixture of *esters* **27** and **28** (54 mg, 93%) as an oil (Found: M^+, 390.2184. $C_{23}H_{31}FO_4$ requires *M*, 390.2204); δ_H(500 MHz) 0.86 (3 H, d, *J* 7.2, 1-Me), 1.25 and 1.27 [3 H (30:1), each s, 8-Me], 1.31 and 1.32 [3 H (1:30), each s, 8-Me], 2.60–2.82 (2 H, m, $CFCH_2CH$=), 3.80 and 3.81 [3 H (30:1), each s, OMe], 4.91 and 4.94 [1 H (1:30), each dt, *J* 4.8 and 10.9, 3-H], 5.18–5.21 (2 H, m, CH=CH_2), 5.68–5.77 (1 H, m, CH=CH_2), 7.15–7.19 (1 H, m, ArH) and 7.25–7.32 (4 H, m, 4 × ArH); *m*/*z* 390 (M^+).

Ethyl (2R)-2-*Fluoro*-2-*methyl*-3-p-*tolylsulfonyloxypropionate* **8**.—To a solution of the 3.8:1 mixture of esters **3** and **4** (59 mg, 0.16 mmol), prepared by the method A, in MeOH (6 cm^3) was added a solution of $LiOH \cdot H_2O$ (13.6 mg, 0.32 mmol) in water (2 cm^3) and the mixture was stirred for 15 h at room temperature under N_2. After addition of 2 drops of AcOH, evaporation of MeOH under reduced pressure gave a residue, which was partitioned between 5% $KHSO_4$ and CH_2Cl_2. The aqueous layer was thoroughly extracted with CH_2Cl_2. The combined extracts were washed with brine, dried and evaporated under reduced pressure to give the corresponding acids (50 mg, 89%) as a syrup, which were used in the following reaction without purification.

To a solution of the above carboxylic acids (50 mg, 0.14 mmol) in dry CH_2Cl_2 (2 cm^3) was added $(COCl)_2$ (0.1 cm^3, 1.15 mmol) and the mixture was stirred for 12 h at room temperature under N_2 and then heated for 1 h under reflux. Evaporation of the solvent and the excess of reagent under reduced pressure provided the corresponding acid chlorides, which were dissolved in dry CH_2Cl_2 (3 cm^3). To the resulting mixture at −78 °C was added slowly a solution of Bu_4NBH_4 (60 mg, 0.233 mmol) in dry CH_2Cl_2 (2 cm^3) under Ar. After being stirred for 30 min at the same temperature, the reaction mixture was diluted with CH_2Cl_2. The mixture was washed with 5% aq. NaOH, 5% aq. citric acid and brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography with hexane–AcOEt (4:1 v/v) as eluent to give a 3.8:1 mixture of alcohols (33 mg, 67%) as an oil, a part of which was further purified by HPLC using Dynamax microsorb silica 5 μm (10 × 25 mm). Elution with hexane–AcOEt (85:15 v/v; 4 cm^3 min^{-1}) afforded the alcohol **5** as a major product; $[\alpha]_D^{22}$ −0.35 (*c* 0.45 in $CHCl_3$); δ_H(500 MHz) 1.26 and 1.36 (each 3 H, each s, 8-Me_2), 1.40 (3 H, d, *J* 22.0, CFMe), 1.88 (1 H, ddd, *J* 2.0, 6.0 and 8.2, OH), 3.59 (1 H, ddd, *J* 6.0, 11.9 and 16.2, C*H*HOH), 3.65 (1 H, ddd, *J* 8.2, 11.9 and 23.8, CH*H*OH), 4.93 (1 H, dt, *J* 5.1 and 10.0, 3-H), 7.16–7.20 (1 H, m, ArH) and 7.28–7.35 (4 H, m, 4 × ArH).

The above mixture (35 mg, 0.104 mmol) of alcohol **5** and its epimer was dissolved in dry CH_2Cl_2 (2 cm^3) together with TBDMSCl (31 mg, 0.208 mmol), DMAP (5 mg, 0.041 mmol) and Et_3N (0.1 cm^3, 0.718 mmol). The mixture was stirred for 6 h at room temperature under N_2 before dilution with benzene. The resulting mixture was washed with 6% aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography with hexane–Et_2O (97:3 v/v) as eluent to afford a 3.8:1 mixture of ethers (46 mg, 98%) as an oil. HPLC

separation of a 4 × 25 mm column of Dynamax microsorb silica 5 μm with hexane–Et_2O (98:2 v/v) as eluent (1 cm^3 min^{-1}) gave the major isomer **6** (retention time: 8.0 min) as an oil, $[\alpha]_D^{24}$ −3.45 (*c* 1.10 in $CHCl_3$); δ_H(500 MHz) 1.42 (3 H, d, *J* 20.0, CFMe), 3.68 (1 H, dd, *J* 12.0 and 18.0, CFC*H*HOTBDMS), 3.82 (1 H, dd, *J* 12.0 and 26.0, CFCH*H*OTBDMS) and 4.90 (1 H, dt, *J* 5.0 and 10.0, 3-H), which was identical with the compound derived from the above pure alcohol **5**.

The later eluate gave the minor isomer (retention time: 9.6 min) as an oil; $[\alpha]_D^{25}$ −17.82 (*c* 0.46 in $CHCl_3$); δ_H(500 MHz) 1.27 (3 H, d, *J* 21.0, CFMe), 3.69 (1 H, dd, *J* 11.0 and 17.0, CFC*H*HOTBDMS), 3.83 (1 H, dd, *J* 11.0 and 25.0, CFCH*H*OTBDMS) and 4.94 (1 H, dt, *J* 5.0 and 10.0, 3-H).

A mixture of the above ether **6** (11 mg, 0.026 mmol), KO_2 (7 mg, 0.099 mmol) and 18-crown-6 (9 mg, 0.033 mmol) in benzene (1 cm^3) was stirred for 6 h at room temperature under N_2. The mixture was concentrated under a stream of N_2 and the residue was dissolved in water (5 cm^3). The mixture was washed with Et_2O and then acidified with saturated aq. $KHSO_4$. The resulting mixture was thoroughly extracted with CH_2Cl_2. The combined extracts were dried and evaporated under reduced pressure to give the crude carboxylic acid, which was dissolved in HCl–EtOH (10% w/v; 1 cm^3). The mixture was stirred for 15 h at room temperature under N_2 and then heated for 1 h under reflux. After concentration of the mixture under a stream of N_2, the residue was taken up into CH_2Cl_2. The organic solution was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure to give the crude hydroxy ester **7**, which was treated for 6 h at room temperature with toluene-*p*-sulfonyl chloride (50 mg, 0.26 mmol) in the presence of DMAP (5 mg, 0.04 mmol) in dry pyridine (0.5 cm^3) under N_2. After removal of pyridine by a stream of N_2, the residue was taken up into benzene. The organic solution was washed with 5% aq. $KHSO_4$ and saturated aq. $NaHCO_3$, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography with hexane–AcOEt (85:15 v/v) as eluent to give the *tosylate* **8** (5.7 mg, 72% from **6**) as an oil (Found: M^+, 304.0781. $C_{13}H_{17}FO_5S$ requires *M*, 304.0780); $[\alpha]_D^{24}$ +1.90 (*c* 0.21 in MeOH) {lit.,[3c] (*S*)-isomer (91% ee); $[\alpha]_D$ −1.79 (*c* 1.34 in MeOH)}; δ_H(500 MHz) 1.29 (3 H, t, *J* 7.0, CH_2Me), 4.22 (1 H, dd, *J* 11.0 and 17.0, CFC*H*HOTs), 4.32 (1 H, dd, *J* 11.0 and 23.0, CFH*H*OTs) and 7.37 and 7.82 (each 2 H, each d, each *J* 6.0, 4 × ArH); *m/z* 304 (M^+).

Ethyl (2R)-2-*Fluoro*-2-*methyl*-3-[(2S)-(3,3,3-*trifluoro*-2-*methoxy*-2-*phenylpropionyloxy*)*propionate* **9**.—To a stirred mixture of the above hydroxy ester **7** (5.0 mg, 0.064 mmol), (−)-(*S*)-MTPA (15 mg, 0.064 mmol) and DMAP (1 mg, 0.008 mmol) in dry CH_2Cl_2 (1 cm^3) at 0 °C was added slowly a solution of DCC (13.6 mg, 0.066 mmol) in dry CH_2Cl_2 (1 cm^3). The mixture was stirred for 15 h at room temperature under N_2 and then diluted with hexane. After filtration through Celite, the filtrate was washed with 5% aq. $KHSO_4$, saturated aq. $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was subjected to chromatography on silica gel with hexane–AcOEt (95:5 v/v) as eluent to provide the (S)-*MTPA ester* **9** (5.1 mg, 85%) as an oil (Found: M^+, 366.1091. $C_{16}H_{18}F_4O_5$ requires *M*, 366.1089); δ_H(500 MHz) 1.27 (3 H, t, *J* 7.0, CH_2Me), 1.60 (3 H, d, *J* 21.0, CFMe), 4.22 (2 H, q, *J* 7.0, CH_2Me), 4.57 (1 H, dd, *J* 12.0 and 18.0, CFC*H*HOMTPA) and 4.64 (1 H, dd, *J* 12.0 and 24.0, CFCH*H*OMTPA); *m/z* 366 (M^+).

(1R,3R,4S)-8-*Phenyl*-p-*menthan*-3-*yl* (2R)-2-*Fluoro*-2-*methylbutyrate* **21**.—*Method A*. The 1:2 mixture of ethyl compounds **13** and **14** (403 mg, 1.07 mmol), prepared by method A, was hydrolysed using $LiOH{\cdot}H_2O$ (135 mg, 3.21 mmol) as above to give the corresponding acids (227 mg, 65%), which were transformed, according to the above processes; formation of acid chlorides using $(COCl)_2$ (0.63 cm^3, 6.96 mmol), followed by reduction with Bu_4NBH_4 (358 mg, 1.39 mmol), into the alcohols (179 mg, 74%). The major alcohol **19**; δ_H(500 MHz) 0.87 (3 H, d, *J* 7.1, 1-Me), 0.92 (3 H, t, *J* 7.5, CH_2Me), 1.27 and 1.38 (each 3 H, each s, 8-Me_2), 3.69–3.84 (2 H, m, CH_2OH), 4.90 (1 H, dt, 4.5 and 12.0, 3-H), 7.15–7.19 (1 H, m, ArH) and 7.23–7.30 (4 H, m, 4 × ArH) was separated by HPLC utilizing Dynamax microsorb silica 5 μm (10 × 25 mm) with hexane–AcOEt (85:15 v/v, 4 cm^3 min^{-1}).

A mixture of the above alcohol **19** (13 mg, 0.037 mmol) and PPh_3 (50 mg, 0.192 mmol) in dry CCl_4 (2 cm^3) was heated for 10 h under reflux and Ar and then diluted with hexane. After filtration, the filtrate was washed with water, dried and evaporated under reduced pressure to afford a residue, which was subjected to flash chromatography. Elution with hexane–Et_2O (95:5 v/v) provided the chloride **20** (13.7 mg, 100%) as an oil (Found: M^+, 370.1862 and 368.1930. $C_{21}H_{30}ClFO_2$ requires *M*, 370.1889 and 368.1929); ν_{max}(neat)/cm^{-1} 1754 and 1723 (C=O); δ_H(90 MHz) 0.88 (3 H, d, *J* 6.5, 1-Me), 1.27 and 1.39 (each 3 H, each s, 8-Me_2), 3.74 (1 H, dd, *J* 12.3 and 22.3, CFC*H*HCl), 3.54 (1 H, dd, *J* 12.3 and 16.3, CFCH*H*Cl) and 4.78 (1 H, dt, *J* 4.5 and 11.0, 3-H).

A mixture of the chloride **20** (13.7 mg, 0.037 mmol), AIBN (3 mg, 0.018 mmol) and Bu_3SnH (0.1 cm^3, 0.37 mmol) in dry benzene (2 cm^3) was heated for 6 h under reflux and Ar. After addition of CCl_4 (1 cm^3), the mixture was heated for 1 h under reflux and then stirred for 1 h at room temperature with 10% NH_4OH. The organic layer was washed with water, dried and evaporated under reduced pressure to give a residue, which was subjected to flash chromatography. Elution with hexane–Et_2O (95:5 v/v) afforded the *fluoride* **21** (10.3 mg, 83%) as an oil (Found: M^+, 334.2308. $C_{21}H_{31}FO_2$ requires *M*, 334.2306); $[\alpha]_D^{24}$ −6.81 (*c* 0.88 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 and 1722 (C=O); δ_H(500 MHz) 0.86 (3 H, d, *J* 6.8, 1-Me), 0.92 (3 H, t, *J* 7.5, CH_2Me), 1.27 and 1.36 (each 3 H, each s, 8-Me_2), 1.44 (3 H, d, *J* 21.5, CFMe) and 4.89 (1 H, dt, *J* 4.5 and 11.0, 3-H); *m/z* 334.

Method B. A mixture of the alcohol **5** (25 mg, 0.074 mmol) and DMP[11] (41 mg, 0.097 mmol) in dry CH_2Cl (2 cm^3) was stirred for 10 h at room temperature under Ar. After addition of saturated aq. $NaHCO_3$ (10 cm^3) containing $Na_2S_2O_3$ (10 mg), the mixture was stirred for 10 min. The aqueous solution was thoroughly extracted with pentane–hexane (1:1 v/v). The combined extracts were washed with brine, dried and evaporated under reduced pressure. The residue was subjected to flash chromatography with hexane–AcOEt (85:15 v/v) to give the corresponding aldehyde (22 mg, 89%) as an oil (Found: M^+, 334.1951. $C_{20}H_{27}FO_3$ requires *M*, 334.1943); δ_H(90 MHz) 9.15 (1 H, d, *J* 7.2, CFCHO); *m/z* 334 (M^+).

To a stirred suspension of $MePPh_3Br$ (64 mg, 0.179 mmol) in dry THF (2 cm^3) at 0 °C was added slowly LHMDS (1 mol dm^{-3}; 0.15 cm^3, 0.15 mmol) and the mixture was stirred for 30 min at room temperature under Ar. To a stirred solution of the aldehyde (20 mg, 0.059 mmol) in dry THF (2 cm^3) at room temperature was added the above mixture. The resulting mixture was stirred for 30 min at the same temperature under Ar and then poured onto 5% aq. $KHSO_4$. The mixture was thoroughly extracted with hexane–Et_2O (1:1 v/v) and the combined extracts were washed with brine and dried. Evaporation under reduced pressure afforded a residue, which was subjected to flash chromatography. Elution with hexane–Et_2O (95:5 v/v) provided the olefin **22** (12.9 mg, 65%) as an oil (Found: M^+, 332.2143. $C_{21}H_{29}FO_2$ requires *M*, 332.2150); *m/z* 332 (M^+).

A mixture of the olefin (12 mg, 0.036 mmol) and 10% Pd–C (30 mg) in AcOEt (2 cm^3) was stirred for 10 h at room temperature under H_2 (1 atm). After filtration through Celite, evaporation of the filtrate under reduced pressure gave a residue, which was taken up into hexane–Et_2O (1:1 v/v). The

organic solution was washed with saturated $NaHCO_3$ and brine, dried and evaporated under reduced pressure. The residue was purified by flash chromatography with hexane–Et_2O (96:4 v/v) to provide the fluoride **21** (12 mg, 99%) as an oil, ^1H NMR spectrum (500 MHz) of which was identical with that of the compound **21** prepared by method A.

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