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Enantiocontrolled Synthesis of Chiral Propane-1,3-diol Derivatives Possessing Fluorinated Quaternary Stereogenic Centers

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Abstract: A general method for the preparation of chiral propane-1,3-diol derivatives possessing fluorinated quaternary stereogenic centers was established as follows. The diastereoselective alkylation of (1*R*,3*R*,4*S*)-8-phenylmenthyl hydrogen fluoromalonate **9**, followed by the reduction of the resulting carboxylic acids **10** - **13** in two steps, provided the alcohols **14** - **17**. After protection of the hydroxyl group with *p*-methoxybenzyl group, the phenylmenthyl esters **21** - **24** were converted into chiral propane-1,3-diols **25** and **30** - **32** *via* the acids **29**.

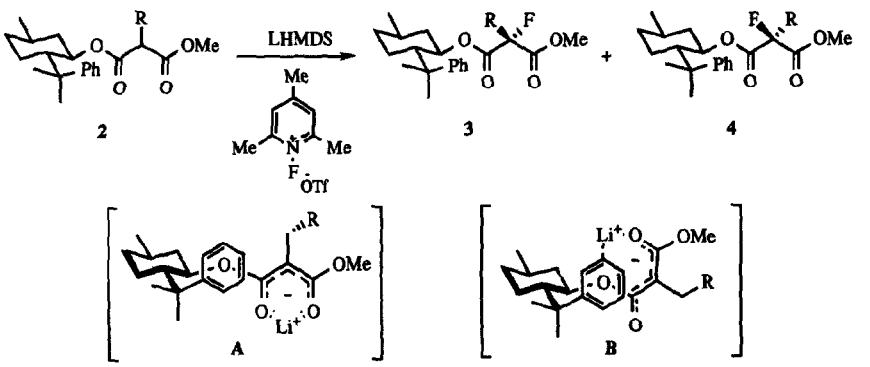
Introduction

The enhancement of biological activities in a number of natural products by selective introduction of fluorine atom(s) has been encountered.[1] Therefore, there is a considerable current interest in the development of efficient methodology for the asymmetric synthesis of organofluorine compounds where at least one of the stereogenic centers bears a fluorine atom. [2-10] In the course of our study for the synthesis of chiral propane-1,3-diols as versatile building blocks from malonic acids,[11,12] we have developed an enantiocontrolled construction of the quaternary stereogenic center bearing a fluorine atom.[13] Here we would like to describe the further investigation aimed at the general preparation of chiral propane-1,3-diol derivatives **1** possessing a fluorine atom at the stereogenic center.

1

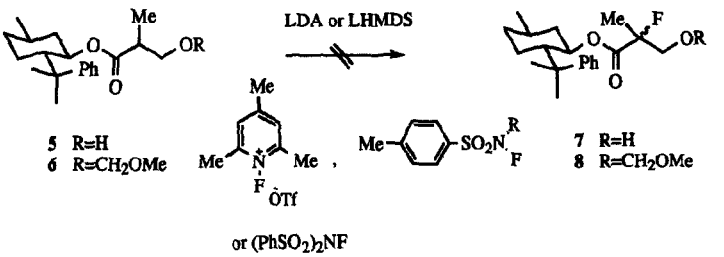
Results and Discussion

Previously, fluorination of (1*R*,3*R*,4*S*)-8-phenylmenthyl methyl alkylmalonates **2** using lithium hexamethyldisilazide (LHMDS) and 1-fluoro-2,4,6-trimethylpyridinium triflate[14] was studied (Scheme 1).[13] It was interesting that the absolute configuration introduced to the methylmalonate was opposite to those of the other alkylmalonates. It was thus considered that two different transition states (**A** and **B**) were operated during the fluorination; the conformation **A** would be the preferred one to the methylmalonate, while **B** would be favoured for other alkylmalonates. Although the yields of fluorination forming two diastereoisomers **3** and **4** were high, the diastereoselectivities were low. Therefore, the fluorination was further tested using *N*-fluorobenzenesulfonimide[15] and *N*-fluoro-*N*-alkylsulfonamides[16] in the presence of various bases. However, no improvement was observed.



Scheme 1

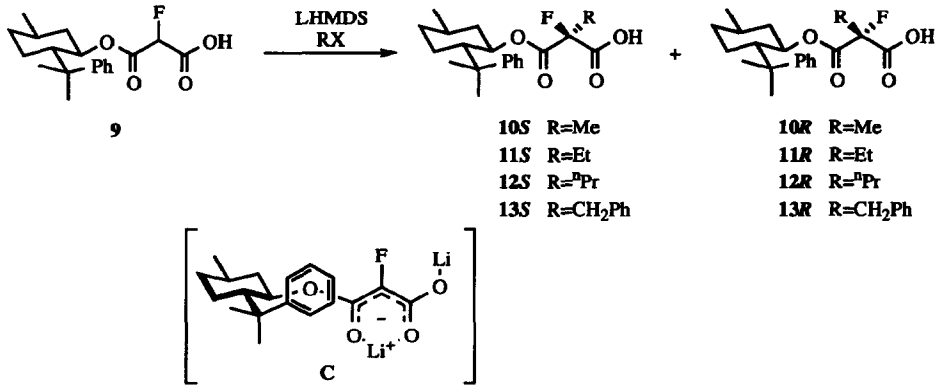
Next, the reaction of (1*R*,3*R*,4*S*)-8-phenylmenthyl 3-hydroxy-2-methylpropionate **5** with the above fluorinating agents in the presence of lithium bases was investigated, but no formation of the desired compound **7** was observed (Scheme 2). Treatment of the corresponding methoxymethyl ether **6** with fluorinating agents and lithium bases resulted in only the elimination of methoxymethyl alcohol.



Scheme 2

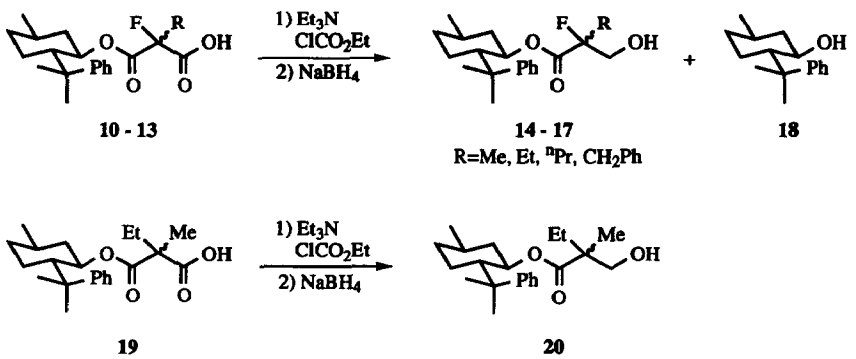
Better diastereoselectivity was obtained by the alkylation of (1*R*,3*R*,4*S*)-8-phenylmenthyl hydrogen fluoromalonate **9** as we had previously found.[13b] Namely, the dianion formed by the reaction of **9** with excess LHMDS was exposed with methyl iodide in tetrahydrofuran (THF) at -78 °C to ambient temperature to provide the 5 : 1 mixture of **10*S*** and **10*R*** in 92% yield. Similar reactions using ethyl iodide, *n*-propyl iodide and benzyl bromide produced the 10 : 1 mixture of **11*S*** and **11*R*** in 82% yield, the 5.7 : 1 mixture of **12*S*** and in **12*R*** in 70% yield, and the 15 : 1 mixture of **13*S*** and **13*R*** in 59% yield, respectively. Since all the absolute configurations of the major products were *S*, it was deduced that the alkylation would proceed mainly *via* the transition state depicted as **C**.[13b]

Next, we focused our attention on the transformation of the half esters **10** - **13** prepared by the above diastereoselective alkylation of **9** into the chiral propane-1,3-diol derivatives possessing a fluorinated quaternary center. Mixed anhydride formation from acids **10** - **13** using ethyl chloroformate in the presence of



Scheme 3

triethylamine, followed by reduction with sodium borohydride,[17] provided the diastereoisomeric mixtures of alcohols **14** - **17** in 33, 33, 47 and 45% yields, respectively. It was noteworthy that the phenylmenthyl ester moiety was reduced by the reaction to afford a considerable amount of 8-phenylmenthol **18**. When the half ester **19** carrying methyl and ethyl groups in the absence of a fluorine atom was treated by the above two steps procedure, the alcohol **20** was obtained in 87% yield without formation of **18**.

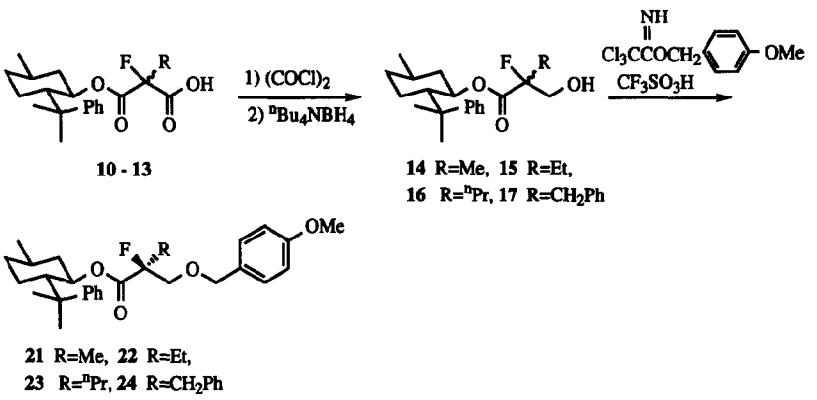


Scheme 4

The transformation of the acids **10** - **13** into the alcohols **14** - **17** was carried out effectively by Raber's method,[18] formation of acid chloride, followed by reduction with tetrabutylammonium borohydride ($^{n}Bu_4NBH_4$) in dichloromethane at -78 °C (Scheme 5). The epimeric mixture of alcohols **14** - **17** were gained in 76, 71, 61 and 72% overall yields, respectively.

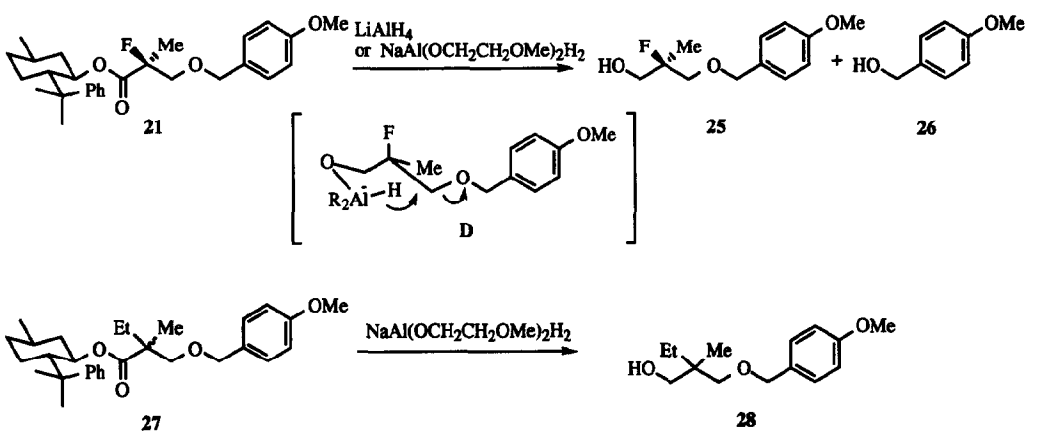
When the hydroxyl group was protected with *tert*-butyldiphenylsilyl group, several difficulties have been found during the further conversion. Therefore, the *p*-methoxybenzyl group was introduced to the alcohols **14** - **17** by the reaciton with *p*-methoxybenzyl-2,2,2-trichloroacetimidate in the presence of trifluoromethanesulfonic acid.[19] After the protection, the products were purified by HPLC on silica gel. The methyl and benzyl compounds **21** and **24** were obtained easily as the pure states, but the isolations of the ethyl and *n*-propyl

derivatives **22** and **23** were carried out incompletely by the above method. The ether **22** and **23** were obtained as 82 and 75% d.e., respectively.



Scheme 5

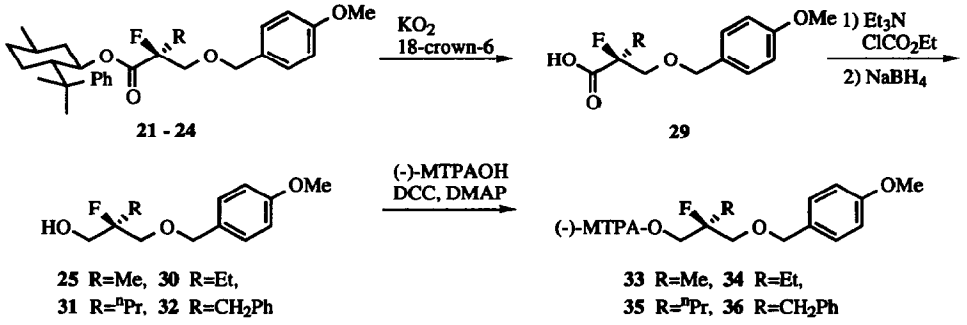
When methyl compound **21** was reduced with lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, the chiral alcohol **25** was produced in 56 or 77% yield (Scheme 6). It is interesting that these reductions gave *p*-methoxybenzyl alcohol (**26**) which would be formed by over reduction through the intermediate **D**. For the purpose of comparison of the reactivity, the phenylmenthyl ester **27** bearing no fluorine atom was reduced with the hydride reagents. Reaction of **27** with sodium bis(2-methoxyethoxy)aluminum hydride for 28 h under the same conditions afforded the alcohol **28** in only 8% yield along with the starting material **27** in 78% and no formation of **26** was found. The enhanced reactivity towards the nucleophiles by the presence of fluorine atom on the neighboring carbon is remarkable.



Scheme 6

In order to accomplish the transformation of the esters **21** - **24** into the alcohols **25** and **30** - **32** without formation of *p*-mehtoxybenzyl alcohol, whose separation from the desired product was not readily, the phenylmenthyl esters were first hydrolyzed to acids **29** (Scheme 7). The hydrolysis was achieved by using

potassium superoxide in the presence of 18-crown-6 at room temperature in benzene.[20] Mixed anhydride formation from the resulting acids **29**, followed by reduction with sodium borohydride,[17] furnished the chiral alcohols **25** and **30** - **32** in 71 - 77% overall yield for three steps. The optical purities of the chiral propane-1,3-diols **25** and **30** - **32** were determined as 100, 82, 75 and 100% e.e., respectively, by their conversion into (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetates **33** - **36**.



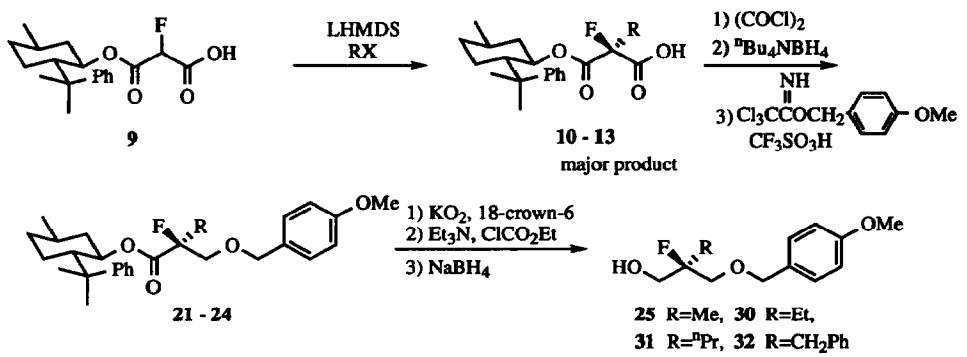
21 - 24 **29**

25 R=Me, **30** R=Et,
31 R=^{n}Pr, **32** R=CH_2Ph

33 R=Me, **34** R=Et,
35 R=^{n}Pr, **36** R=CH_2Ph

Scheme 7

Thus, a general method for the preparation of propane-1,3-diols possessing a fluorinated quaternary stereogenic center has been established. The route is summarized in Scheme 8. Namely, diastereoselective alkylation gave mainly (*S*)-acids **10** - **13**, which were converted into *p*-methoxybenzyl ethers **21** - **24**. The phenylmenthyl ester group of **21** - **24** was removed *via* the corresponding carboxylic acid to provide the target chiral propane-1,3-diols. Homochiral building blocks could be obtained by the separation of diastereoisomers of the intermediates. Syntheses of biologically active compounds utilizing these chiral precursors are in progress.



9

10 - 13
major product

21 - 24

25 R=Me, **30** R=Et,
31 R=^{n}Pr, **32** R=CH_2Ph

Scheme 8

Experimental Section

General Procedure: Infrared spectra were recorded on a JASCO-IR-Report-100 spectrophotometer. ^{1}H-NMR spectra were taken on Hitachi R-1200, Hitachi R-3000 and JEOL GX-500 spectrometers using TMS as an internal standard. Optical rotations were measured by JASCO-DIP-370 polarimeter. Mass spectra were recorded on JEOL-DX-300 and JEOL-JMS-DX-303 instruments. HPLC was carried out using a Gilson HPLC

system (Model 302/303) equipped with a 10 × 250 mm column of Dynamax Microsorb silica (5 μm) and monitored by using UV and refractive index detectors.

All reactions were carried out under a positive atmosphere of dry Ar unless otherwise indicated. Solvents were distilled prior to use: THF, Et_2O, and benzene were freshly distilled from Na benzophenone; CH_2Cl_2 was distilled from CaH_2 and kept over 4-Å molecular sieves; hexane was distilled from CaH_2 and kept over Na wire. Unless otherwise noted, all extracts were dried over $MgSO_4$ and the solvent was removed by rotary evaporation under reduced pressure. Silica gel column chromatography was carried out with Merck Kieselgel 60 Art. 7734, while Merck Kieselgel 60 Art. 9835 was used for flash chromatography.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Fluoro-3'-hydroxy-2'-methylpropionates (14). To a solution of carboxylic acids **10**[12] (714 mg, 2.04 mmol) in dry CH_2Cl_2 (20 ml) was added $(COCl)_2$ (1.30 ml, 14.9 mmol) and the mixture was stirred for 2 h at room temperature and then heated for 2 h under reflux. Evaporation of the solvent and the excess reagent under reduced pressure gave the corresponding acid chlorides as an oil, which were taken up into dry CH_2Cl_2 (12 ml). To the stirred mixture at -78 °C was added dropwise a solution of $^nBu_4NBH_4$ (735 mg, 2.86 mmol) in dry CH_2Cl_2 (3 ml). After having been stirred for 1 h at -78 °C, the resulting mixture was diluted with CH_2Cl_2 and then washed with 5% aqueous NaOH, 5% aqueous citric acid and brine. The organic layer was dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt-hexane (1 : 4 v/v) provided the 5 : 1 diastereoisomeric mixture of alcohols **14** (537 mg, 76%) as an oil: IR (neat, cm^{-1}) 3485, 1750, 1733; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.6 Hz), 1.25 and 1.35 (each 3H, each s), 1.31 (2.5 H, d, J = 21.6 Hz), 1.41 (0.5H, d, J = 21.3 Hz), 2.07 (1H, dt, J = 10.8 and 3.0 Hz), 3.51 - 3.82 (2H, m), 4.92 and 4.93 (1H, each ddd, J = 10.0, 10.0 and 5.1 Hz), 7.12 - 7.19 (1H, m), 7.25 - 7.31 (4H, m); exact mass found M^+ 336.2107, $C_{20}H_{29}FO_3$ requires 336.2099.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Fluoro-2'-hydroxymethylbutyrates (15). The carboxylic acids **11**[12] (196 mg, 0.538 mmol) were converted as above into the alcohols **15** (135 mg, 71%) as an oil: IR (neat, cm^{-1}) 3470, 1748, 1729; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.6 Hz), 0.92 (3H, t, J = 7.3 Hz), 1.27 and 1.38 (each 3H, each s), 1.55 - 1.76 (2H, m), 3.69 - 3.84 (2H, m), 4.90 and 4.91 (each 1H, each ddd, J = 12.0, 12.0 and 4.5 Hz), 7.15 - 7.19 (1H, m), 7.23 - 7.30 (4H, m); exact mass found M^+ 350.2261, $C_{21}H_{31}FO_3$ requires 350.2256.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Fluoro-2'-hydroxymethylpentanoates (16). The carboxylic acids **12**[12] (146 mg, 0.386 mmol) were similarly converted into the alcohols **16** (83 mg, 61%) as an oil: IR (neat, cm^{-1}) 3480, 1748, 1728; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, J = 6.6 Hz), 0.92 and 0.93 (3H, each t, J = 7.3 Hz), 1.26 and 1.37 (each 3H, each s), 1.20 - 1.76 (4H, m), 1.92 (1H, dt, J = 5.8 and 3.0 Hz), 3.47 - 3.88 (2H, m), 4.90 and 4.91 (1H, each ddd, J = 10.6, 10.6 and 4.0 Hz), 7.10 - 7.17 (1H, m), 7.18 - 7.37 (4H, m); exact mass found M^+ 364.2387, $C_{22}H_{33}FO_3$ requires 364.2412.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Benzyl-2'-fluoro-3'-hydroxypropionates (17). According to the above procedure, the acids **13**[12] (163 mg, 0.383 mmol) were converted into the alcohols **17** (114 mg, 72%) as an oil: IR (neat, cm^{-1}) 3480, 1748, 1728; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, d, J =

6.6 Hz), 1.23 and 1.33 (each 3H, each s), 1.47 (1H, t, J = 2.3 Hz), 2.96 (1H, dd, J = 24.2 and 14.3 Hz), 3.04 (1H, dd, J = 27.5 and 14.3 Hz), 3.57 - 3.90 (2 H, m), 4.81 and 4.82 (each 1H, each ddd, J = 11.6, 11.0 and 4.8 Hz), 7.08 - 7.16 (1H, m), 7.18 - 7.36 (9H, m); exact mass found M^+ 412.2462, $C_{26}H_{33}FO_3$ requires 412.2412.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl (2'*S*)-2'-Fluoro-3'-(*p*-methoxybenzyloxy)-2'-methylpropionate (21). To a stirred solution of the alcohols **14** (255 mg, 0.759 mmol) in CH_2Cl_2-hexane (1 : 2 v/v, 27 ml) at 0 °C were added *p*-methoxybenzyl-2,2,2-trichloroacetimidate (643 mg, 2.28 mmol) and CF_3SO_3H (10 µl), and the mixture was stirred for 1 h at 0 °C. After addition of cold H_2O, the mixture was thoroughly extracted with CH_2Cl_2. The extract was washed with H_2O and brine, dried and evaporated. Chromatography of the residue on silica gel with Et_2O-hexane (1 : 9 v/v) as eluent gave the diastereoisomeric mixture of **21** and its epimer (224 mg, 65%). HPLC separation using a 10 × 250 mm column of Dynamax microsorb silica (5 µm) with Et_2O-hexane (4 : 96 v/v, 4 ml min^{-1}) as eluent provided the major ether **21** as an oil: $[\alpha]_D^{23}$ -14.9 (c 1.80, $CHCl_3$); IR (neat, cm^{-1}) 1742, 1725; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 6.1 Hz), 1.23 and 1.35 (each 3H, each s), 1.31 (3H, d, J = 20.8 Hz), 3.53 (1H, dd, J = 17.7 and 11.0 Hz), 3.65 (1H, dd, J = 21.5 and 11.0 Hz), 3.80 (3H, s), 4.49 and 4.52 (each 1H, each d, J = 11.6 Hz), 4.91 (1H, ddd, J = 10.6, 10.6 and 4.8 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.12 - 7.18 (1H, m), 7.27 (2H, d, J = 8.6 Hz), 7.25 - 7.31 (4H, m); exact mass found M^+ 456.2678, $C_{28}H_{37}FO_4$ requires 456.2674. *Anal.* Calcd for $C_{28}H_{37}FO_4$: C, 73.66; H, 8.17. Found: C, 73.22; H, 8.09.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Fluoro-2'-(*p*-methoxybenzyloxymethyl)butyrates (22). According to the above method, the alcohols **15** (106 mg, 0.303 mmol) were transformed into the ethers (105 mg, 74%). HPLC purification as above provided the 10 : 1 diastereoisomeric mixture of **22** and its epimer as an oil: $[\alpha]_D^{26}$ -22.3 (82% d.e., c 0.78, $CHCl_3$); IR (neat, cm^{-1}) 1748, 1722; ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 and 0.83 [3H (1 : 10), each d, J = 6.2 Hz], 0.91 (3H, t, J = 7.3 Hz), 1.22 and 1.37 (each 3H, each s), 1.54 - 1.67 (2H, m), 3.56 and 3.58 [1H (1 : 10), each dd, each J = 16.5 and 11.0 Hz], 3.69 (1H, dd, J = 29.3 and 11.0 Hz), 3.79 (3H, s), 4.49 and 4.53 (each 1H, each d, J = 11.7 Hz), 4.89 and 4.92 [1H (10 : 1), each ddd, J = 10.6, 10.6 and 4.8 Hz), 6.86 (2H, d, J = 8.8 Hz), 7.10 - 7.18 (1H, m), 7.24 (2H, d, J = 8.8 Hz), 7.25 - 7.31 (4H, m); exact mass found M^+ 470.2812, $C_{29}H_{39}FO_4$ requires 470.2833.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl 2'-Fluoro-2'-(*p*-methoxybenzyloxymethyl)pentanoate (23). The alcohols **16** (68 mg, 0.19 mmol) were converted as above into the diastereoisomeric mixture of the ethers (58 mg, 64%), whose HPLC purification gave the 7 : 1 mixture of **23** and its epimer as an oil: $[\alpha]_D^{29}$ -18.7 (75% d.e., c 1.63, $CHCl_3$); IR (neat, cm^{-1}) 1743, 1722; ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 and 0.83 [3H (1 : 7), each d, J = 6.2 Hz], 0.90 (3H, t, J = 7.3 Hz), 1.23 and 1.37 (each 3H, each s), 1.24 - 1.71 (4H, m), 3.56 and 3.58 [1H (1 : 7), each dd, each J = 16.5 and 11.0 Hz], 3.70 (1H, dd, J = 29.3 and 11.0 Hz), 3.79 (3H, s), 4.47 and 4.53 (each 1H, each d, J = 11.7 Hz), 4.89 and 4.92 [1H (7 : 1), each ddd, J = 10.6, 10.6 and 4.8 Hz], 6.86 (2H, d, J = 8.8 Hz), 7.13 - 7.18 (1H, m), 7.24 (2H, d, J = 8.8 Hz), 7.25 - 7.38 (4H, m); exact mass found M^+ 484.2978, $C_{30}H_{41}FO_4$ requires 484.2989.

(1*R*,3*R*,4*S*)-8-Phenyl-*p*-methan-3-yl (2'S)-2'-Benzyl-2'-fluoro-3'-(*p*-methoxybenzyloxy)-propionate (24). The alcohols **17** (101 mg, 0.245 mmol) were similarly transformed into ethers (91 mg,

70%). HPLC separation as above provided the ether **24** as an oil: $[\alpha]_D^{29}$ -7.1 (c 1.06, $CHCl_3$); IR (neat, cm^{-1}) 1743, 7122; ^1H NMR (500 MHz, $CDCl_3$) δ 0.74 (3H, d, *J* = 6.1 Hz), 1.19 and 1.33 (each 3H, each s), 2.98 (2H, d, *J* = 24.4 Hz), 3.58 (1H, dd, *J* = 15.9 and 11.0 Hz), 3.77 (1H, dd, *J* = 26.3 and 11.0 Hz), 3.79 (3H, s), 4.45 and 4.51 (each 1H, each d, *J* = 11.6 Hz), 4.80 (1H, ddd, *J* = 10.4, 10.4 and 4.3 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 7.11 - 7.14 (1H, m), 7.24 (2H, d, *J* = 8.6 Hz), 7.20 - 7.28 (9H, m) ; exact mass found M^+ 532.3016, $C_{34}H_{41}FO_4$ requires 532.2989.

(2*R*)-2-Fluoro-3-(*p*-methoxybenzyloxy)-2-methyl-1-propanol (25). The mixture of the ester **21** (77 mg, 0.17 mmol), KO_2 (36 mg, 0.51 mmol) and 18-crown-6 (45 mg, 0.17 mmol) in benzene (5 ml) was stirred for 4 h at room temperature. The resulting mixture was partitioned between saturated aqueous K_2CO_3 and Et_2O. The aqueous layer was acidified with 10% aqueous $KHSO_4$ under ice cooling and then thoroughly extracted with CH_2Cl_2. The extract was dried and evaporated to give the crude acid **29** (R = Me) (30 mg, 0.12 mmol), which was dissolved in dry THF (2 ml). To the mixture at 0 °C were added Et_3N (35 μl, 0.25 mmol) and $ClCO_2Et$ (24 μl, 0.25 mmol), and the mixture was stirred for 2 h at 0 °C. After filtration through Celite, $NaBH_4$ (24 mg, 0.62 mmol) was added slowly to the filtrate at room temperature. The mixture was stirred for 1 h at the same temperature and then partitioned between 10% aqueous $KHSO_4$ and Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried and evaporated. The residue was chromatographed on silica gel with Et_2O-hexane (1 : 2 v/v) as eluent to afford the alcohol **25** (29 mg, 71% for 3 steps) as an oil: $[\alpha]_D^{25}$ -6.1 (c 0.62, $CHCl_3$); IR (neat, cm^{-1}) 3415; ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, d, *J* = 22.3 Hz), 2.00 (1H, t, *J* = 5.8 Hz), 3.45 - 3.62 (2H, m), 3.68 (2H, dd, *J* = 17.9 and 5.8 Hz), 3.81 (3H, s), 4.47 and 4.53 (each 1H, each d, *J* = 11.7 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 7.26 (2H, d, *J* = 8.8 Hz); exact mass found M^+ 228.1149, $C_{12}H_{17}FO_3$ requires 228. 1161.

(2*R*)-2-Fluoro-2-(*p*-methoxybenzyloxymethyl)-1-butanol (30). According to the same procedure as above, the esters **22** (16.9 mg, 0.036 mmol) were converted into the alcohol **30** (6.6 mg, 76%) as an oil: $[\alpha]_D^{25}$ - 8.3 (82% e.e., c 0.65, $CHCl_3$), IR (neat, cm^{-1}) 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.5 Hz), 1.62 - 1.79 (2H, m), 2.02 (1H, t, *J* = 5.5 Hz), 3.51 - 3.66 (2H, m), 3.73 (2H, dd, *J* = 17.9 and 5.5 Hz), 3.81 (3H, s), 4.47 and 4.53 (each 1H, each d, *J* = 11.7 Hz), 6.88 (2H d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz); exact mass found M^+ 242.1327, $C_{13}H_{19}FO_3$ requires 242.1318.

(2*R*)-2-Fluoro-2-(*p*-methoxybenzyloxymethyl)-1-pentanol (31). The esters **23** (31.6 mg, 0.065 mmol) were transformed as above into the alcohol **31** (13.5 mg, 77%) as an oil: $[\alpha]_D^{29}$ -5.1 (75% e.e., c 1.31, $CHCl_3$); IR (neat , cm^{-1}) 3420; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.33 - 1.43 (2H, m), 1.60 - 1.71 (2H, m). 2.03 (1H, t, *J* = 6.2 Hz), 3.50 - 3.63 (2H, m), 3.72 (2H, dd, *J* = 18.3 and 6.2 Hz), 3.81 (3H, s), 4.47 and 4.53 (each 1H, each d, *J* = 11.7 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz); exact mass found M^+ 256.1488, $C_{14}H_{21}FO_3$ requires 256.1475.

(2*R*)-2-Benzyl-2-fluoro-3-(*p*-methoxybenzyloxy)-1-propanol (32). The ester **24** (21.1 mg, 0.04 mmol) was similarly converted into the alcohol **32** (9.7 mg, 77%) as an oil: $[\alpha]_D^{24}$ -5.3 (c 0.93, $CHCl_3$); IR (neat, cm^{-1}) 3435; ^1H NMR (300 MHz, $CDCl_3$); δ 1.96 (1H, t, *J* = 5.7 Hz), 2.98 - 3.07 (2H, m), 3.40 - 3.56 (2H, m), 3.69 (2H, dd, *J* = 17.9 and 5.7 Hz), 3.81 (3H, s), 4.44 (1H, d, *J* = 11.7 Hz), 4.50 (1H, d, *J* = 11.7

Hz), 6.89 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 7.20 - 7.28 (5H, m); exact mass found M^+ 304.1475, $C_{18}H_{21}FO_3$ requires 304.1475.

(2*S*)-2-Fluoro-3-(*p*-methoxybenzyloxy)-2-methylpropyl (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropinonate (33). To a stirred solution of the alcohol **25** (6.2 mg, 0.027 mmol), (-)-(S)-MTPAOH (9.6 mg, 0.041 mmol) and DMAP (1 mg, 0.008 mmol) in dry CH_2Cl_2 (0.7 ml) at 0 °C was slowly added a solution of DCC (11.2 mg, 0.054 mmol) in dry CH_2Cl_2 (0.3 ml), and the mixture was stirred for 3 h at room temperature. After dilution with hexane, followed by filtration through Celite, the filtrate was washed with 10% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and brine, and dried. Evaporation of the solvents gave a residue, which was subjected to chromatography on silica gel. Elution with Et_2O-hexane (1 : 4 v/v) provided the (*S*)-MTPA ester **33** (14.4 mg, 96%) as an oil: ^1H NMR (300 MHz, C_6D_6) δ 1.14 (3H, d, J = 21.2 Hz), 3.18 (2H, dd, J = 16.5 and 10.3 Hz), 4.34 (1H, dd, J = 36.6 and 12.1 Hz), 4.40 (1H, dd, J = 34.0 and 12.1 Hz); exact mass found M^+ 444.1576, $C_{22}H_{24}F_4O_5$ requires 444.1558.

(2*S*)-2-Fluoro-2-(*p*-methoxybenzyloxymethyl)butyl (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate (34). According to the above method carried out under the same conditions, the alcohol **30** (6.1 mg, 0.025 mmol) was converted into the (*S*)-MTPA ester **34** (11.5 mg, 99%) as an oil: ^1H NMR (300 MHz, C_6D_6) δ 4.38 (0.09 H, dd, J = 20.8 and 11.7 Hz), 4.43 (0.91 H, dd, J = 17.9 and 11.7 Hz), 4.47 (0.09 H, dd, J = 21.8 and 11.7 Hz), 4.50 (0.91 H, dd, J = 17.2 and 11.7 Hz); exact mass found M^+ 458.1705, $C_{23}H_{26}F_4O_5$ requires 458.1715.

(2*S*)-2-Fluoro-2-(*p*-methoxybenzyloxymethyl)pentyl (S)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate (35). The alcohol **31** (8.6 mg, 0.034 mmol) was converted as above into the (*S*)-MTPA ester **35** (15.6 mg, 98%) as an oil: ^1H NMR (300 MHz, C_6D_6) δ 4.40 (0.12H, dd, J = 22.4 and 12.4 Hz), 4.45 (0.88H, dd, J = 24.2 and 12.4 Hz), 4.50 (0.12H, dd, J = 25.4 and 11.7 Hz), 4.52 (0.88 Hz, dd, J = 22.7 and 11.7 Hz); exact mass found M^+ 472.1839, $C_{24}H_{28}F_4O_5$ requires 472.1871.

(2*S*)-2-Benzyl-2-fluoro-3-(*p*-methoxybenzyloxy)propyl (S)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionate (36). The alcohol **32** (8.8 mg, 0.029 mmol) was similarly transformed into the (*S*)-MTPA ester **36** (14.4 mg, 96%) as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 2.98 (1H, dd, J = 26.2 and 14.6 Hz), 3.02 (1H, dd, J = 22.3 and 14.6 Hz), 3.35 (1H, dd, J = 14.7 and 10.4 Hz), 3.43 (1H, dd, J = 1.34 and 10.4 Hz), 4.41 (2H, d, J = 18.9 Hz); exact mass found M^+ 520.1844, $C_{28}H_{28}F_4O_5$ requires 520.1871.

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