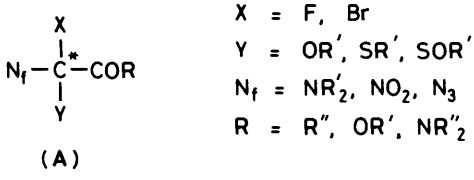
# Chemistry of Novel Compounds with Multifunctional Carbon Structure. Part 2.[1] The First Example of Optically Active Multifunctional Carbon Compounds

**Yoshio Takeuchi,* Masahiro Asahina, Kazuhiro Nagata, and Toru Koizumi**
*Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan*

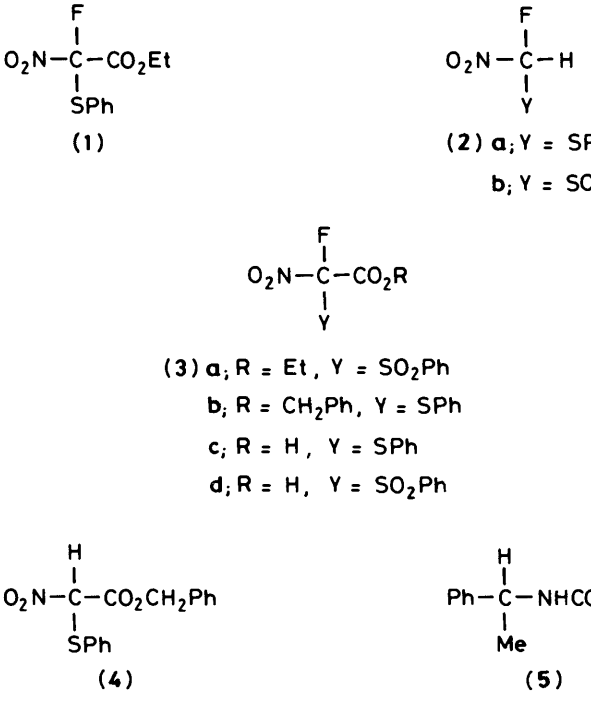
Synthesis of optically active tetrafunctional carbon compounds, (+)- and (−)-fluoronitro(phenylthio)acetates (**1**), has been achieved for the first time by a repeated transesterification method using titanium alkoxides. The fluorine-containing trifunctional carbon compounds, (±)-fluoro(phthalimido)acetate (**6**) and (±)-α-fluoro-α-nitro-β-phenylpropionate (**9**), could also be resolved successfully in the same manner.

In a previous communication,[2] we reported the synthesis and resolution of some multifunctional carbon compounds [structure (**A**)].† This novel class of compounds introduces new ideas in the field of theoretical and synthetic organic chemistry. For example, the optically active multifunctional carbon compounds are of special interest since they have the potential to serve as new types of chiral auxiliaries and versatile synthon molecules for the syntheses of optically active natural products. Furthermore, they can be convenient models for spectroscopic study and research on the steric aspects of reaction mechanisms. However, resolution of these compounds presents potential problems‡ since all of the ligands surrounding the central carbon atom are electronegative labile groups. Having succeeded in preliminary work in the analytical chromatographic resolution[3] of some multifunctional carbon compounds, we next attempted to resolve them chemically, on a preparative scale, as a prelude to the development of the applications mentioned above. Special attention was paid to the fluorine atom, considering its contribution toward possible stabilisation of the unusual multifunctionalised structure and also the utilisation of $^{19}F$ n.m.r. This paper presents a full account of the results to date for our continuing study on the resolution of multifunctional carbon compounds and the possible applications derived therefrom.



(A)

We first attempted to convert the multifunctional esters into the corresponding acids in order to form the amide or ester diastereoisomers using chiral amines or alcohols. Both saponificative and non-saponificative[4] hydrolyses of the sulphide (**1**) and the sulphone (**3a**), however, produced the decarboxylated products (**2a**) and (**2b**) instead of the corresponding carboxylic acids (**3c**) and (**3d**). This result can be ascribed to the tendency of the tetrafunctional esters to undergo decarboxylation[5] or, alternatively, the tendency of the tetrafunctional esters to undergo direct decarbalkoxylation with the aid of nucleophiles.[6] Reductive cleavage by catalytic hydrogenolysis[7] of the benzyl ester (**3b**) was also unsuccessful since the reduction of the nitro group to the amino group proceeded faster than the hydrogenolysis of the benzyl group,§ giving several products. Since geminally functionalised nitroacetic acids appeared to be quite unstable under ambient conditions, we employed the method of direct conversion of esters into acyl chlorides.[8] Although the acid chloride prepared by reaction of the trifunctional carbon compound (**4**) with chlorosulphonic acid and phthaloyl chloride was treated *in situ* with α-phenylethyl alcohol, the diastereoisomeric phenylethyl



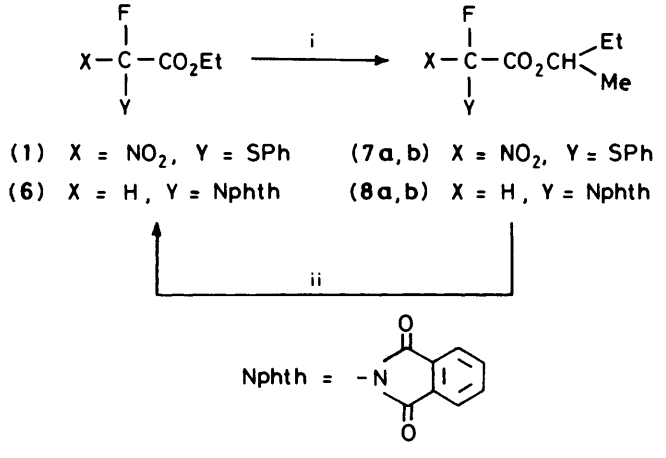

† The definition of 'multifunctional carbon' is a carbon atom bearing one or two different heteroatom-containing labile functional groups in addition to synthetically valuable carbonyl and halogen groups. Therefore, a compound containing such a functionalised carbon can be named[1] as a 'multifunctional carbon compound.' This should be strictly distinguished from the term 'multifunctional compound,' which is usually used rather ambiguously for compounds having many functional groups on different carbon atoms in the molecules.

‡ For example, bromonitroacetates produced dibromonitro- and nitroacetates in the presence of a catalytic amount of base. Some unfamiliar disproportionations seem to occur when azidobromonitroacetates were heated, of which the mechanism is now under investigation.

§ Even the corresponding *p*-nitrobenzyl ester was resistant to hydrogenolysis.

esters were not obtained. Instead unidentifiable products were produced, probably because of the unusually high reactivity of the multifunctionalised acid chloride structure.

To overcome these problems, we next turned our attention to the direct amidation or transesterification of the polyfunctional esters, a transformation which should be possible under much milder conditions. However, reaction of the ethyl ester (**1**) with α-phenylethylamine, with or without titanium tetra-alkoxide,[9] did not proceed at room temperature. Furthermore, the only isolable product of the reaction at elevated temperature was the carbamate (**5**), formed apparently as a result of direct C–C bond cleavage.[6] On the other hand, satisfactory results were obtained by transesterification of the ethyl esters with chiral alcohols. Among the possible methods of transesterification reported,[10] the use of titanium(IV) as a catalyst[9,11] seemed most suitable for our purpose because of the mild conditions used and also the chemoselectivity reported in reactions with several different functional groups. Indeed, the reaction of the ethyl ester (**1**) with an excess of (±)-s-butyl alcohol in the presence of $Ti(OPr^i)_4$ proceeded smoothly to afford a mixture of diastereoisomeric s-butyl esters (**7a** and **b**) in 73% yield. Determination of the diastereoisomeric ratio (*ca.* 1:1) of the mixture was difficult through its 200 MHz $^1H$ n.m.r. spectrum because of overlapping of the proton signals of both isomers. Fortunately, two distinctly separate fluorine signals, with Δδ 18.3 Hz, were observed in the $^{19}F$ n.m.r. spectrum of the diastereoisomeric mixture. The conversion of the mixture (**7a** and **b**) back into the ethyl ester (**1**) was carried out successfully, again in high yield, using ethanol with the aid of $Ti(OEt)_4$. In the same manner, α-fluoro-*N*-phthaloylglycine ester (**6**) gave the diastereoisomeric mixture (**8a** and **b**), which was again subjected to the transesterification to give the original ethyl ester (**6**) (Scheme 1).




**Scheme 1.** *Reagents and conditions:* i, $Bu^sOH$–$Ti(OPr^i)_4$, 100 °C, 2 h; ii, EtOH–$Ti(OEt)_4$, reflux, 2 h

We next attempted the ester-exchange reaction with an optically active alcohol in order to resolve the multifunctional carbon compounds. Reaction of the ethyl ester (**1**) with (+)-α-phenylethyl alcohol gave the isomeric phenylethyl esters (**10a** and **b**) in the ratio 1:1 as determined by the $^{19}F$ n.m.r. spectrum. Both diastereoisomers, (**10a**) and (**10b**), were easily separated by medium-pressure liquid chromatography (m.p.l.c.) and their physical data are shown in the Table. Each isomer was then converted into the ethyl ester in ethanol with the catalytic amount of $Ti(OEt)_4$, thereby providing the first optically active tetrafunctional carbon compounds, (+)-(**1**) and (−)-(**1**). Similarly, the trifunctional carbon compounds, (±)-(**6**) and (±)-(**9**), could be resolved after repeating the transesterification to afford (+)- and (−)-(**6**), and (+)- and (−)-(**9**), respectively (Scheme 2). No racemisation[11] at the multifunctionalised asymmetric centre was observed during those procedures as checked by cellulose tribenzoate (chiralcel OB)[12] chromatography. All the physical and spectral data for the optically active compounds are summarised in the Table.

Although the corresponding proton signals of the isomeric pairs (**10a** and **b**), (**11a** and **b**), and (**12a** and **b**) did not exhibit any significant chemical-shift difference (0—6 Hz) in the $^1H$ n.m.r. spectra, there were observed much bigger differences in the fluorine chemical shifts between each diastereoisomeric pair, *i.e.* 18.3 Hz for (**10a** and **b**) and 221.5 Hz for (**11a** and **b**), respectively. These values are comparable or even greater than those of the diastereoisomeric α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters reported by Mosher.[13] The large chemical-shift difference we observe presumably results from the fact that the fluorine atom is directly attached to the chiral carbon atom (*i.e.* a different situation from Mosher's case), and therefore receives more magnetic influence in each diastereoisomer.* The extremely small difference in the fluorine shifts for compounds (**12a** and **b**) is attributable to the presence of the benzyl group, which possibly creates magnetically equivalent environments for the diastereoisomeric fluorine atoms.

The work described here represents the first synthesis of optically active compounds having chirality due to the presence of three or four distinctly different labile groups.[14] Electronic factors, in addition to the conventionally proposed steric factors, may participate in allowing us to resolve the racemates under diastereoisomeric environments since the multifunctionalised chiral carbon is surrounded by different heteroatom-containing ligands. Since the fluorine atom is comparable to hydrogen in steric bulkiness[15] compared with other groups, the smaller fluorine shift difference between compounds (**10a**) and (**10b**) than those between (**11a**) and (**11b**), or (**12a**) and (**12b**), cannot be explained simply by steric factors.[3] Also the relationship between the sign of c.d. curves and stereostructure of these compounds seems an attractive subject for investigation for theoretical and empirical spectroscopy.† Studies on the usefulness of the optically active multifunctional carbon compounds are now in progress in our laboratory.

## Experimental

M.p.s were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-181 spectrometer. E.i. mass spectra were taken with a JEOL JMS-D300 spectrometer. High-resolution mass spectrometry was used in place of microanalysis for those compounds which undergo decomposition, disproportionation, or explosion on distillation. I.r. spectra were recorded on a JASCO A-102 spectrophotometer. $^1H$ N.m.r.

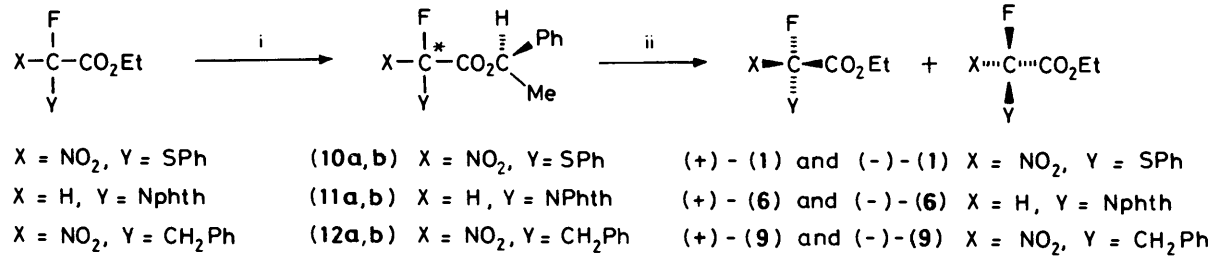
* Considering that the fluorine signals of MTPA esters are broadened because of long-range coupling with the methoxy protons,[13] the sharp fluorine signals of these multifunctional carbon compounds suggest that they are better reagents for determination of enantiomeric excess (work in progress).

† Very interesting results were obtained from the c.d. spectra of the resolved compounds. It is difficult to relate the chirality and the spectral curves before we get additional c.d. spectra of several kinds of multifunctional carbon compounds. These compounds are also important from the polarimetric point of view since they will serve as good models for investigation of atomic asymmetry, *i.e.* the relation between chirality and polarisability (J. H. Brewster, *J. Am. Chem. Soc.*, 1959, **81**, 5475; G. Bellucci, G. Berti, A. Borraccini, and F. Macchia, *Tetrahedron*, 1969, **25**, 2979; G. Bellucci, G. Berti, C. Bettoni, and F. Macchia, *J. Chem. Soc., Perkin Trans. 2*, 1973, 295) of the atoms attached to the asymmetric centre.

**Table.** Physical and spectral data for some optically active multifunctional carbon compounds

| Compound | Starting material | Yield (%)[a] | $[\alpha]_D$ (temp./°c; c/°)[b] | $^{19}$F n.m.r.[c] $\delta_F$(p.p.m.) | $\Delta\delta$ (Hz) | M.p. (°C) | Diastereoisomeric isomer |
|---|---|---|---|---|---|---|---|
| **(10a)** | **(1)** | 88 | +136.3 (24; 4.01) | −101.01 | 18.3 | | less polar |
| **(10b)** | **(1)** | | −93.4 (24; 4.67) | −100.94 | | | more polar |
| (+)-(1) | **(10a)** | 49 | +134.2 (25; 1.57) | −100.93 | | | |
| (−)-(1) | **(10b)** | 85 | −132.6 (25; 2.88) | −100.93 | | | |
| **(11a)** | **(6)** | 85 | +52.4 (25; 6.87) | −156.02 | 221.5 | 77—79 | less polar |
| **(11b)** | **(6)** | | +17.9 (25; 6.77) | −155.15 | | 68—69 | more polar |
| (−)-(6) | **(11a)** | 43 | −12.7 (25; 0.89) | −155.60 | | 87—89 | |
| (+)-(6) | **(11b)** | 32 | +13.3 (25; 0.57) | −155.60 | | 88—89 | |
| **(12a)** | **(9)** | 96 | +98.5 (26; 2.06) | −127.96 | 0.0 | | less polar |
| **(12b)** | **(9)** | | +1.2 (26; 2.11) | −127.96 | | | more polar |
| (+)-(9) | **(12a)** | 88 | +65.6 (26; 2.09) | −127.99 | | | |
| (−)-(9) | **(12b)** | 89 | −64.6 (26; 2.41) | −127.99 | | | |

[a] Isolated yields are based on single experiments and were not optimised. [b] Solvent $CHCl_3$. [c] Upfield shifts from internal standard ($CFCl_3$) are quoted as negative δ-values. The values refer to 254.2 MHz $^{19}$F n.m.r.




**Scheme 2.** *Reagents and conditions:* i, (+)-α-phenylethyl alcohol–$Ti(OPr^i)_4$, 110 °C, 2 h; ii, EtOH–$Ti(OEt)_4$, reflux, 2—9 h

spectra were measured in $CDCl_3$ with $SiMe_4$ as internal standard and were recorded on JEOL PMX-60 (60MHz) or Varian XL-200 (200MHz) spectrometers, while $^{19}$F n.m.r. spectra were measured in $CDCl_3$ with $CFCl_3$ as internal standard and were taken with a JEOL GX-270 spectrometer. Upfield shifts are quoted as negative δ-values. Column chromatography and preparative t.l.c. (p.l.c.) were performed on Kieselgel 60 (Merck, Art. 9385 and Art. 7748 respectively).

*Ethyl Fluoronitro(phenylthio)acetate* (**1**).—To a solution of potassium fluoride[16] (0.697 g, 12 mmol) in EtOH (9 ml) was added in portions ethyl nitro(phenylthio)acetate (1.446 g, 6 mmol) and the mixture was stirred at room temperature for 1 h. The resultant precipitate was collected on a filter and dried. The potassium salt (1.455 g, 4.1 mmol) was suspended in tetrahydrofuran (THF) (25 ml) and perchloryl fluoride gas, generated by the method of Wehrenalp,[17] was passed through the mixture at 0 °C for 2 h. Evaporation of the solvent gave a yellow oil, which was purified by silica gel chromatography with n-hexane–ether (3:1) as eluant to give the *fluoroacetate* (**1**) (0.807 g, 76.0%); $\nu_{max.}$(neat) 1 760 (CO), 1 580 ($NO_2$), and 1 100 $cm^{-1}$ (C–F); $\delta_H$ 1.36 (3 H, t, *J* 6 Hz, Me), 4.42 (2 H, q, *J* 6 Hz, $CH_2$), and 7.50 (5 H, m, ArH); $\delta_F$ −100.925 p.p.m. (F, s) (Found: $M^+$, 259.0530. $C_{10}H_{10}FNO_4S$ requires *M*, 259.0315); *m/z* 213.0364 ($M^+ - NO_2$) ($C_{10}H_{10}FO_2S$ requires *m/z*, 213.0384).

*Ethyl Fluoronitro(phenylsulphonyl)acetate* (**3a**).—To a solution of compound (**1**) (20 mg, 0.08 mmol) in dichloromethane (2 ml) was added dropwise a solution of 80% *m*-chloroperbenzoic acid (37 mg, 0.17 mmol) in dichloromethane (2 ml) and the mixture was stirred at room temperature for 15 h. The organic layer was washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil, which was purified by silica gel p.l.c. (solvent ether) to afford the phenylsulphonyl derivative (**3a**) (18 mg, 77.0%); $\delta_H$ 1.40 (3 H, t, *J* 7 Hz, Me), 4.49 (2 H, q, *J* 7 Hz, $CH_2$), and 7.95 (5 H, m, ArH).

*Benzyl Fluoronitroacetate.*—Perchloryl fluoride gas was bubbled through a suspension of the potassium salt[16] of benzyl nitroacetate[18] (2.55 g, 8.2 mmol) in THF (60 ml) at 0 °C for 2 h. The crude product was purified by silica gel chromatography with n-hexane–ethyl acetate (4:1) as eluant to give *benzyl fluoronitroacetate* (0.734 g, 42.0%); $\nu_{max.}$(neat) 1 770 (CO), 1 590 ($NO_2$), and 995 $cm^{-1}$ (C–F); $\delta_H$ 5.33 (2 H, s, $CH_2$), 6.03 (1 H, d, $J_{H-F}$ 47 Hz, CH), and 7.43 (5 H, s, ArH); $\delta_F$ − 150.479 p.p.m. (F, d, *J* 47 Hz) (Found: $M^+$, 213.0392. $C_9H_8FNO_4$ requires *M*, 213.0437); *m/z* 167.0468 ($M^+ - NO_2$) ($C_9H_8FO_2$ requires *m/z*, 167.0506).

*Benzyl Fluoronitro(phenylthio)acetate* (**3b**).—Benzyl fluoronitroacetate (0.40 g, 1.9 mmol) was added dropwise to a solution of potassium fluoride (0.224 g, 3.8 mmol) in MeOH (5 ml) at room temperature. The resultant precipitate was collected and dissolved in THF (60 ml). To the solution was added in portions benzenesulphenyl chloride (0.549 g, 3.8 mmol) and the mixture was stirred at room temperature for 5 h. Ether (5 ml) was added to the mixture and the resultant precipitate was removed by filtration. Concentration of the filtrate gave a yellow oil, which was chromatographed on silica gel with n-hexane–ether (3:1) as eluant to afford the *phenylthio derivative* (**3b**) as an oil (0.483 g, 79.1%); $\nu_{max.}$(neat) 1 770 (CO), 1 585 ($NO_2$), and 1 195 $cm^{-1}$ (C–F); $\delta_F$ 5.33 (2 H, s, $CH_2$), 7.33 (5 H, s, $CH_2$*Ph*), and 7.40 (5 H, s, SPh); $\delta_F$ − 100.795 p.p.m. (F, s) (Found: $M^+$, 321.0423. $C_{15}H_{12}FNO_4S$ requires *M*, 321.0469); *m/z* 275.0505 ($M^+ - NO_2$) ($C_{15}H_{12}FO_2S$ requires *m/z*, 275.0541).

*Benzyl Nitro(phenylthio)acetate* (**4**).—To a solution of the

potassium salt[16] of benzyl nitroacetate (1.244 g, 4 mmol) in THF (110 ml) was added dropwise benzenesulphenyl chloride (1.156 g, 8 mmol) at room temperature and the solution was stirred for 2 h. Evaporation of the solvent gave a brown oil, which was chromatographed on silica gel with n-hexane–ethyl acetate (4:1) as eluant to yield the *(phenylthio)acetate* (**4**) as a yellow oil (1.018 g, 84.0%); $\nu_{max.}$(neat) 1 755 (CO) and 1 570 $cm^{-1}$ ($NO_2$); $\delta_H$ 5.17 (2 H, s, $CH_2$), 6.10 (1 H, s, CH), and 7.33 (10 H, m, ArH) (Found: $M^+$, 303.0551. $C_{15}H_{13}NO_4S$ requires *M*, 303.0563); *m/z* 257.0690 ($M^+ - NO_2$) ($C_{15}H_{13}O_2S$ requires *m/z*, 257.0637).

*Ethyl Fluoro(phthalimido)acetate* (**6**).—A mixture of ethyl bromofluoroacetate (0.925 g, 5 mmol) and potassium phthalimide (1.110 g, 6 mmol) in *N,N*-dimethylformamide (10 ml) was heated at 90 °C for 2 h. Evaporation of the solvent at reduced pressure gave a crude product, which was purified by silica gel column chromatography with benzene–ethyl acetate (3:1) as eluant to afford the *phthalimido derivative* (**6**) as a solid (0.861 g, 68.6%). Recrystallisation from ethyl acetate gave an analytical sample; m.p. 103—104 °C (Found: C, 57.2; H, 4.0; N, 5.9. $C_{12}H_{10}FNO_4$ requires C, 57.37; H, 4.01; N, 5.58%); $\nu_{max.}$(KBr) 1 760 (CO), 1 720 (CON), and 1 065 $cm^{-1}$ (C–F); $\delta_H$ 1.27 (3 H, t, *J* 7 Hz, Me), 4.33 (2 H, q, *J* 7 Hz, $CH_2$), 6.44 (1 H, d, $J_{H-F}$ 48 Hz, CH), and 7.99 (4 H, m, ArH); $\delta_F$ − 155.605 p.p.m. (F, d, $J_{F-H}$ 48 Hz); *m/z* 252 ($M^+ + 1$) and 232 ($M^+ - F$).

*s-Butyl Fluoronitro(phenylthio)acetate* (**7a** *and* **b**).—A solution of the ethyl ester (**1**) (0.130 g, 0.5 mmol) and titanium tetraisopropoxide (0.074 ml, 0.25 mmol) in s-butyl alcohol (4.6 ml, 50 mmol) was heated at 100 °C under argon for 2 h. The solvent was evaporated off under reduced pressure and the residue was dissolved in ether (15 ml). The organic layer was washed successively with 1M-HCl, water, sat. aq. $NaHCO_3$, and water, and was dried over $MgSO_4$. Evaporation of the solvent gave a crude ester, which was purified by silica gel column chromatography with n-hexane–ether (2:1) as eluant to afford a 1:1 mixture of the diastereoisomeric s-butyl esters (**7a** and **b**) (0.105 g, 73.2%); $\nu_{max.}$(neat) 1 770 (CO) and 1 590 $cm^{-1}$ ($NO_2$); $\delta_H$ 0.93 (3 H, t, *J* 7 Hz, $CH_2$*Me*), 1.33 (3 H, d, *J* 6 Hz, CH*Me*), 1.63 (2 H, q, *J* 7 Hz, $CH_2$), 5.05 (1 H, q, *J* 6 Hz, CH), and 7.53 (5 H, s, Ph); $\delta_F$ − 100.769 (s) and −100.841 p.p.m. (s); *m/z* 241 ($M^+ - NO_2$) and 185 ($M^+ - NO_2$ − s-butyl).

*Conversion of the s-Butyl Esters* (**7a** *and* **b**) *into the Ethyl Ester* (**1**).—To a solution of the diastereoisomeric s-butyl esters (**7a** and **b**) (26.2 mg, 0.0913 mmol) in EtOH (1 ml) was added a drop of titanium tetraethoxide and the mixture was heated at reflux for 2 h. A crude product, obtained after evaporation of the solvent, was purified by p.l.c. with n-hexane–ether (2:1) as solvent to give the ethyl ester (**1**) (15.7 mg, 66.4%).

*s-Butyl Fluoro(phthalimido)acetate* (**8a** *and* **b**).—A solution of the ethyl ester (**6**) (109.5 mg, 0.44 mmol) and titanium tetraisopropoxide (0.06 ml, 0.20 mmol) in s-butyl alcohol (5 ml) was heated at 110 °C under argon for 2 h. The solvent was evaporated off under reduced pressure and the residue was dissolved in ether (15 ml). The organic layer was washed successively with 1M-HCl, water, sat. aq. $NaHCO_3$, and water, and was dried over $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by silica gel column chromatography with benzene–ether (2:1) as eluant to afford a 1:1 mixture of the diastereoisomeric s-butyl esters (**8a** and **b**) (88.3 mg, 72.5%); $\delta_H$ 0.88 (3 H, t, *J* 8 Hz, $CH_2$*Me*), 0.96 (3 H, t, *J* 8 Hz, $CH_2$*Me*), 1.28 (3 H, d, *J* 8 Hz, CH*Me*), 1.34 (3 H, d, *J* 8 Hz, CH*Me*), 1.66 (4 H, m, $CH_2$ × 2), 5.80 (2 H, m, MeC*H* × 2), 6.33 (2 H, d, $J_{H-F}$ 49 Hz, CHF × 2), and 7.8—8.0 (8 H, m, ArH); $\delta_F$ − 155.595 p.p.m. (d, $J_{H-F}$ 49 Hz).

*Conversion of the s-Butyl Esters* (**8a** *and* **b**) *into the Ethyl Ester* (**6**).—To a solution of the diastereoisomeric s-butyl esters (**8a** and **b**) (69.8 mg, 0.25 mol) in EtOH (3 ml) was added titanium tetraethoxide (0.025 ml, 0.08 mol) and the mixture was heated at reflux for 2.5 h. The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography with n-hexane–ether (3:1) as eluant to give the ethyl ester (**6**) (55.2 mg, 88.0%).

(R)-α-*Phenylethyl Fluoronitro(phenylthio)acetates* (**10a**) *and* (**10b**).—A solution of the ethyl ester (**1**) (168.4 mg, 0.65 mmol) and titanium tetraisopropoxide (76.7 mg, 0.27 mmol) in (*R*)-(+)-α-phenylethyl alcohol (1.26 g) was heated at 110 °C for 1.5 h. Excess of phenylethyl alcohol was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography with n-hexane–ether (2:1) as eluant to give a 1:1 mixture of diastereoisomeric (*R*)-phenylethyl esters (**10a** and **b**) (191.2 mg, 87.8%). The two isomers were separated by m.p.l.c. (Kusano ID-22; eluant n-hexane–ethyl acetate 199:1; flow rate 2.0 ml $min^{-1}$) to give isomer (**10a**) (less polar isomer) and isomer (**10b**) (more polar one).

For (**10a**): $[\alpha]_D^{24}$ +136.3° (*c* 4.01 in $CHCl_3$); $\nu_{max.}$(neat) 1 765 (CO), 1 580 ($NO_2$), and 1 055 $cm^{-1}$ (C–F); $\delta_H$ 1.63 (3 H, d, *J* 6 Hz, Me), 6.03 (1 H, q, *J* 6 Hz, CH), 7.37 (5 H, s, CPh), and 7.54 (5 H, m, SPh); $\delta_F$ − 101.009 p.p.m. (F, s); *m/z* 289 ($M^+ - NO_2$) and 185 [$M^+ - CO_2CH(Me)Ph$]. For (**10b**): $[\alpha]_D^{24}$ −93.4° (*c* 4.67 in $CHCl_3$); $\nu_{max.}$(neat) 1 765 (CO), 1 580 ($NO_2$), and 1 055 $cm^{-1}$ (C–F); $\delta_H$ 1.64 (3 H, d, *J* 6 Hz, Me), 6.02 (1 H, q, *J* 6 Hz, CH), 7.38 (5 H, s, CPh), and 7.50 (5 H, m, SPh); $\delta_F$ −100.937 p.p.m. (F, s); *m/z* 289 ($M^+ - NO_2$) and 185 [$M^+ - CO_2CH(Me)Ph$].

*Optically Active Ethyl Fluoronitro(phenylthio)acetates* (+)-(**1**) *and* (−)-(**1**).—Compounds (**10a**) and (**10b**) were transformed into the corresponding optically active ethyl esters, (+)-(**1**) and (−)-(**1**), in 49.3 and 85.2% yield, respectively, by the transesterification method mentioned above. For (+)-(**1**): $[\alpha]_D^{25}$ +134.2° (*c* 1.57 in $CHCl_3$). For (−)-(**1**): $[\alpha]_D^{25}$ −132.6° (*c* 2.88 in $CHCl_3$).

(R)-α-*Phenylethyl Fluoronitro(phthalimido)acetates* (**11a**) *and* (**11b**).—A solution of the ethyl ester (**6**) (125.7 mg, 0.5 mmol) and titanium tetraisopropoxide (69.4 mg, 0.24 mmol) in (*R*)-(+)-α-phenylethyl alcohol (1.00 g) was heated at 110 °C for 2 h. Excess of phenylethyl alcohol was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography with benzene–ether (2:1) as eluant to give a 1:1 mixture of diastereoisomeric phenylethyl esters (**11a** and **b**) (139.2 mg, 85.1%). The two isomers were separated by m.p.l.c. in a similar manner as for (**10a** and **b**) (eluant n-hexane–ethyl acetate 5:1). Compound (**11a**) (less polar isomer) had m.p. 77—79 °C; $[\alpha]_D^{25}$ +52.4° (*c* 6.87 in $CHCl_3$); $\nu_{max.}$(KBr) 1 785 ($CO_2$), 1 735 (CON), and 1 040 $cm^{-1}$ (C–F); $\delta_H$ 1.71 (3 H, d, *J* 6 Hz, Me), 6.13 (1 H, q, *J* 6 Hz, OCH), 6.34 (1 H, d, $J_{H-F}$ 51 Hz, FCH), 7.36 (5 H, s, Ph), and 7.84—7.95 (4 H, m, phthalyl); $\delta_F$ −156.018 p.p.m. (d, $J_{F-H}$ 51 Hz); *m/z* 327 ($M^+$) and 309 ($M^+ - F$). Compound (**11b**) (more polar isomer) had m.p. 68—69 °C; $[\alpha]_D^{25}$ +17.9° (*c* 6.77 in $CHCl_3$); $\nu_{max.}$(KBr) 1 785 ($CO_2$), 1 735 (CON), and 1 050 $cm^{-1}$ (C–F); $\delta_H$ 1.59 (3 H, d, *J* 6 Hz, Me), 6.13 (1 H, q, *J* 6 Hz, OCH), 6.34 (1 H, d, $J_{H-F}$ 51 Hz, FCH), 7.37 (5 H, m, Ph), and 7.86—7.98 (4 H, m, phthalyl); $\delta_F$ −155.149 p.p.m. (d, $J_{F-H}$ 51 Hz); *m/z* 327 ($M^+$) and 309 ($M^+ - F$).

*Optically Active Ethyl Fluoro(phthalimido)acetates* (+)-(**6**) *and* (−)-(**6**).—Compounds (**11a**) and (**11b**) were transformed into the corresponding optically active ethyl esters, (−)-(**6**) and (+)-(**6**), in 43.1 and 31.6% yield, respectively, by the

transesterification method mentioned above. For (−)-(**6**): m.p. 87—89 °C; $[\alpha]_D^{25}$ −12.7 (*c* 0.89 in $CHCl_3$). For (+)-(**6**): m.p. 88—89 °C; $[\alpha]_D^{25}$ +13.3 (*c* 0.57 in $CHCl_3$).

*Ethyl α-Fluoro-α-nitro-β-phenylpropionate* (**9**).—To a solution of potassium fluoride[16] (0.183 g, 3.16 mmol) in EtOH (10 ml) was added in portions a solution of ethyl α-nitro-β-phenylpropionate[19] (0.298 g, 1.34 mmol) in EtOH (5 ml) and the mixture was stirred at room temperature for 0.5 h. Evaporation of the solvent gave a pale yellow solid, which was collected on a filter and dried. This potassium salt (1.395 g, 4.11 mmol) was dissolved in THF (80 ml), and freshly generated perchloryl fluoride gas[17] was passed through the solution at room temperature for 1 h. The precipitate was removed by filtration, and concentration of the filtrate gave *ethyl α-fluoro-α-nitro-β-phenylpropionate* (**9**) (0.979 g, 98.8%) as a pale yellow oil; $\nu_{max.}$(neat) 1 765 (CO), 1 580 ($NO_2$), and 1 080 $cm^{-1}$ (C–F); $\delta_H$ 1.38 (3 H, t, *J* 6 Hz, Me), 3.75 (2 H, d, $J_{H-F}$ 23 Hz, PhC$H_2$), 4.37 (2 H, q, *J* 6 Hz, C$H_2$Me), and 7.35 (5 H, m, Ar); $\delta_F$ −127.991 p.p.m. (F, t, $J_{F-H}$ 23.2 Hz) (Found: $M^+$, 241.0729. $C_{11}H_{12}FNO_4$ requires *M*, 241.0749); *m/z* 195.0839 ($M^+ - NO_2$) ($C_{11}H_{12}FO_2$ requires *m/z*, 195.0822).

(R)-α-*Phenylethyl α-Fluoro-α-nitro-β-phenylpropionates* (**12a**) *and* (**12b**).—A solution of the ethyl ester (**9**) (186.1 mg, 0.772 mmol) and titanium tetraisopropoxide (99.8 mg, 0.35 mmol) in (*R*)-(+)-α-phenylethyl alcohol (1.76 g) was heated at 110 °C for 1.2 h. Excess of phenylethyl alcohol was removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography with n-hexane–ether (3:2) as eluant to give a 1:1 mixture of diastereoisomeric phenylethyl esters (**12a** and **b**) (235.4 mg, 96.2%). The two isomers were separated by m.p.l.c. in a similar manner to that described above (eluant n-hexane–ether 100:1). For isomer (**12a**) (less polar isomer): $[\alpha]_D^{26}$ +98.5° (*c* 2.06 in $CHCl_3$); $\delta_H$ 1.59 (3 H, d, *J* 6.5 Hz, Me), 3.73 (2 H, d, $J_{H-F}$ 23.1 Hz, $CH_2$), 5.97 (1 H, q, *J* 6.5 Hz, CH), and 7.2—7.4 (10 H, m, ArH); $\delta_F$ − 127.960 p.p.m. (F, t, $J_{F-H}$ 23 Hz). For isomer (**12b**) (more polar isomer): $[\alpha]_D^{26}$ +1.20° (*c* 2.11 in $CHCl_3$); $\delta_H$ 1.58 (3 H, d, *J* 6.5 Hz, Me), 3.70 (2 H, d, $J_{H-F}$ 23.0 Hz, $CH_2$), 5.96 (1 H, q, *J* 6.5 Hz, CH), and 7.2—7.4 (10 H, m, ArH); $\delta_F$ − 127.960 p.p.m. (F, t, $J_{F-H}$ 23 Hz).

*Optically Active Ethyl α-Fluoro-α-nitro-β-phenylpropionates* (+)-(**9**) *and* (−)-(**9**).—Compounds (**12a**) and (**12b**) were transformed into the corresponding optically active ethyl esters, (+)-(**9**) and (−)-(**9**), in 88.1 and 88.7% yield, respectively, by the transesterification method mentioned above. For (+)-(**9**): $[\alpha]_D^{26}$ +65.6° (*c* 2.09 in $CHCl_3$). For (−)-(**9**): $[\alpha]_D^{26}$ −64.6° (*c* 2.41 in $CHCl_3$).

## References


1 Part 1, Y. Takeuchi, A. Murayama, T. Hagi, and T. Koizumi, *Nippon Kagaku Kaishi*, 1985, 2029.
2 Y. Takeuchi, M. Asahina, A. Murayama, K. Hori, and T. Koizumi, *J. Org. Chem.*, 1986, **51**, 955.
3 Y. Takeuchi, T. Hagi, A. Murayama, T. Koizumi, and A. Ichida, submitted for publication in *J. Liq. Chromatogr.*
4 S. G. Cohen and A. Schneider, *J. Am. Chem. Soc.*, 1941, **63**, 3382; T.-L. Ho and G. A. Olah, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 774.
5 M. T. Shipchandler, *Synthesis*, 1979, 666 and references cited therein.
6 Y. Takeuchi, T. Hagi, K. Nagata, and T. Koizumi, unpublished work.
7 B. ElAmin, G. M. Anantharamaiah, G. P. Royer, and G. E. Means, *J. Org. Chem.*, 1979, **44**, 3442; W. H. Hartung and R. Simonoff, *Org. React.*, 1953, **7**, 263 and references cited therein.
8 W. J. Middleton, *J. Org. Chem.*, 1979, **44**, 2291.
9 P. Schnurrenberger, M. F. Züger, and D. Seebach, *Helv. Chim. Acta*, 1982, **65**, 1197; B. Weidmann and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 31.
10 Y. Otsuji, N. Matsumura, and E. Imoto, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 852; R. T. Coutts and K. K. Midha, *J. Pharm. Sci.*, 1969, **58**, 949; D. P. Roelofsen, J. A. Hagendoorn, and H. Bekkum, *Chem. Ind. (London)*, 1966, 1622; M. Pereyre, G. Colin, and J. Delvigne, *Bull. Soc. Chim. Fr.*, 1969, 263.
11 D. Seebach, E. Hungerbühler, and R. Naef, *Synthesis*, 1982, 138; H. Rehwinkel and W. Steglich, *ibid.*, p. 826.
12 A. Ichida, T. Shibata, I. Okamoto, Y. Yuki, H. Namikoshi, and Y. Toga, *Chromatographia*, 1984, **19**, 280; Y. Okamoto, M. Kawashima, K. Yamamoto, and K. Hatada, *Chem. Lett.*, 1984, 739; T. Shibata, I. Okamoto, and K. Ishii, *J. Liq. Chromatogr.*, 1986, **9**, 313.
13 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
14 H. Hirschmann and K. R. Hanson, *Top. Stereochem.*, 1983, **14**, 183.
15 J. C. Tatlow, *Chem. Ind. (London)*, 1978, 522; (b) M. Shlosser, *Tetrahedron*, 1978, **34**, 3; P. Goldman, *Science*, 1969, **164**, 1123; N. Ishikawa, *Kagaku*, 1976, **31**, 656; T. Kitazume, T. Sato, T. Kobayashi, and J. T. Lin, *J. Org. Chem.*, 1986, **51**, 1003.
16 A. Ostazyński, J. Wielgat, and T. Urbański, *Tetrahedron*, 1969, **25**, 1929.
17 G. B. Wehrenalp, *J. Inorg. Nucl. Chem.*, 1956, **2**, 266.
18 H. Hellman, G. Hallman, and F. Lingens, *Chem. Ber.*, 1953, **86**, 1346.
19 E. Kaji and S. Zen, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 337.


*Received* 11*th September* 1986; *Paper* 6/1816