Influence of a 2-fluoro substituent on diastereoselectivity in the 1,3-dipolar cycloadditions of nitrones

Masataka Ihara,* Yuko Tanaka, Nobuyuki Takahashi, Yuji Tokunaga and Keiichiro Fukumoto

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

It is clear that the role of 1,2-asymmetric induction on the 1,3-dipolar cycloaddition of nitrones is influenced by the presence of a fluorine atom at the C-2 position. 2-Fluoro nitrones, synthesized by three different methods, have been subjected to the intermolecular 1,3-dipolar cycloaddition with ethyl vinyl ether. The stereostructures of isoxazolidines formed were determined by their conversion into 2,7-dioxa-6-azabicyclo[3.2.1]octanes. The diastereoselectivity of 2-fluoro nitrones was the reverse of that of the corresponding 2-hydro nitrones. This fact supports that the conformation with relief from the dipole repulsion between the fluorine atom and the oxygen atom of the nitrone is a preferred one for 2-fluoro nitrones, while the corresponding 2-hydro nitrones adopt the conformation with the least 1,3-allylic strain.

Introduction

Because of their important physical and biological properties, the regio- and stereo-controlled synthesis of organofluorine compounds is of importance.[1] We observed earlier that the intramolecular 1,3-dipolar cycloaddition of the nitrone **1** produced, in a highly stereoselective manner, the bicyclic isoxazolidine **2**, convertible into 1β-methylcarbapenem **3**,[2] while the corresponding fluorinated nitrone **4** gave a 1 : 2.8 mixture of two stereoisomers **5** and **6**[3] (Scheme 1). The results could be explained as follows: the desired stereoisomer **2** was diastereoselectively formed *via* conformation **8**, this having the least 1,3-allylic strain. However, conformation **8** was not favourable for the fluorinated compound mainly because of the dipole repulsion between the fluorine atom and the oxygen atom of the nitrone; therefore, the alternative conformation **7** became the preferred one. In view of this, we were interested in studying the intermolecular 1,3-dipolar cycloaddition of nitrones possessing a fluorine atom at the C-2 position in order to confirm the above explanation. It was further considered that the cycloadducts would be useful as precursors of pharmacologically interesting compounds, such as fluoroamino acids.

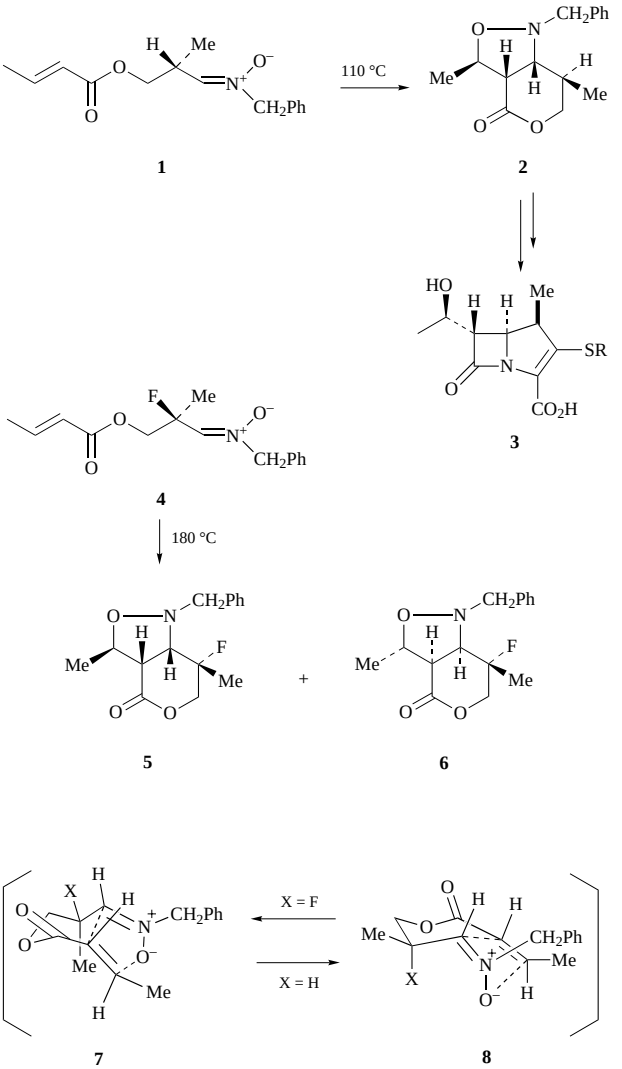
On the basis of the above considerations, the reaction of 3-oxygenated fluoro nitrones **9** with ethyl vinyl ether has been investigated, because the stereochemistry of the stereogenic centre, newly introduced by the cycloaddition, could be determined by the conversion of the cycloadduct **10** into 2,7-dioxa-6-azabicyclo[3.2.1]octanes **11** and **12** (Scheme 2). We herein describe our results which support our earlier assumption.

Results and discussion

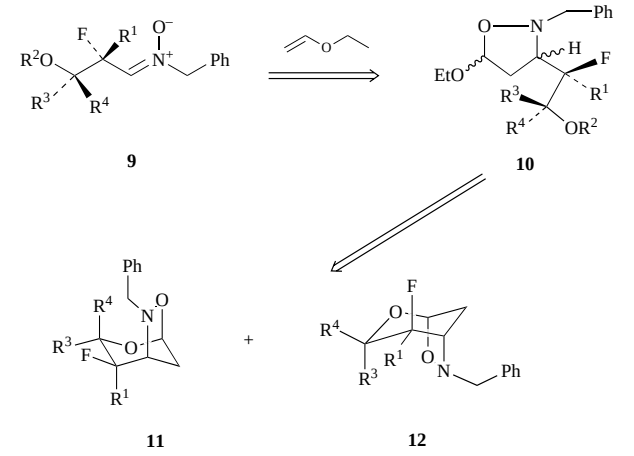
Preparation of nitrones

2-Fluoropropan-1-ol derivatives having a protected oxygen functionality at the C-3 position were synthesized by three different methods. The 2-methyl and 2-ethyl derivatives **17** and **19** were prepared as optically active compounds from the phenylmenthyl esters **13** and **15**, which were diastereoselectively synthesized starting with diethyl fluoromalonate.[4] The hydroxy group of **13** (an epimeric mixture in a *ca.* 5 : 1 ratio), was protected with a *tert*-butyldimethylsilyl (TBDMS) group. The reduction of the phenylmenthyl ester group of **14** was performed using lithium borohydride to give **17** (85%), $[a]_D^{24}$ +0.90 (MeOH). Other hydride reagents were ineffective for the reduction. The optical purity was established as 83% ee by conversion of **17** into **18** reaction with (*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA)[5] in the presence of DCC and DMAP[6] in $ClCH_2CH_2Cl$.[7] The corresponding ethyl compound **19**, $[a]_D^{24}$ + 1.39 ($CHCl_3$), was similarly prepared, and its optical purity was determined as 90% ee (Scheme 3).

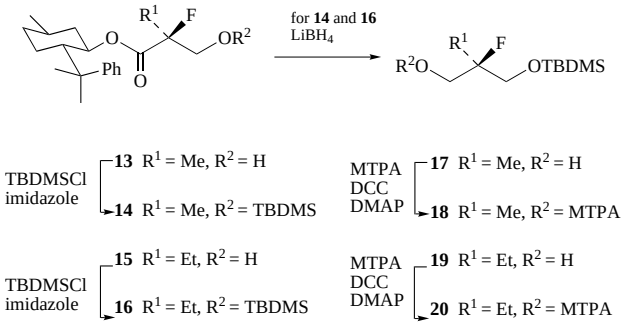
The 2-phenyl derivative **25** was synthesized through the



Scheme 1

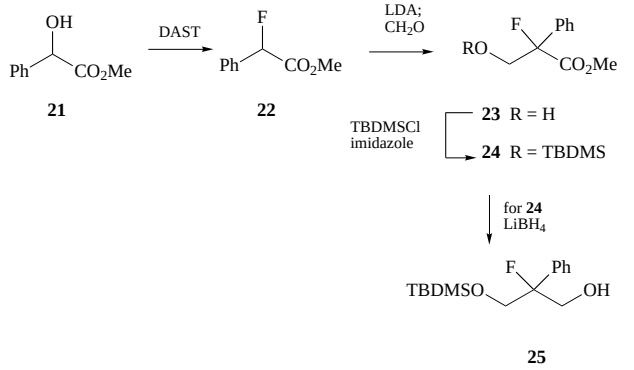


Scheme 2



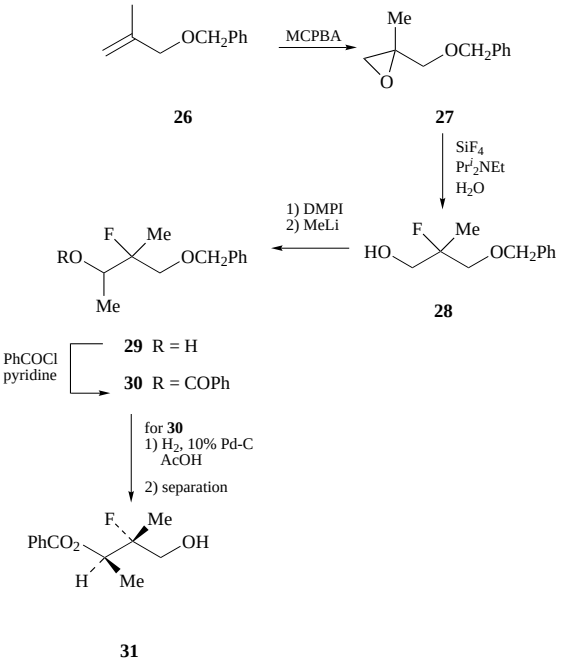
Scheme 3

fluorination of (±)-methyl mandelate **21**. Thus, the treatment of **21** with diethylaminosulfur trifluoride (DAST)[8] in CH_2Cl_2 provided **22** (92%). The aldol reaction of **22** with formaldehyde in the presence of LDA afforded **23** (58%) which was converted into **25** by the protection of the hydroxy group, followed by reduction with lithium borohydride (Scheme 4).



Scheme 4

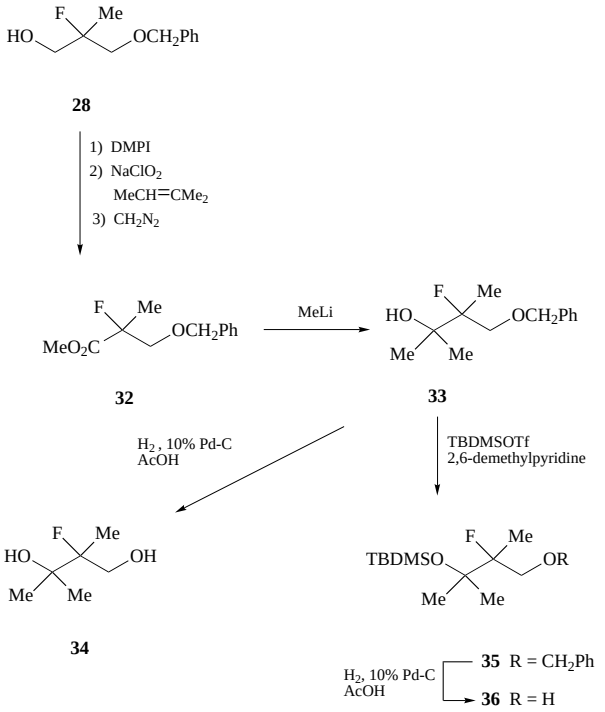
It was assumed that a large difference between the bulkiness of two groups neighbouring the fluorine atom would be required to obtain an interpretable result. For this purpose, the introduction of alkyl groups at the C-3 position was tried as shown in Scheme 5. Regioselective ring opening of the epoxide **27**, which was prepared from **26**, was carried out using tetrafluorosilane in the presence of diisopropylethylamine and water.[9] Oxidation of the resulting alcohol **28**, obtained in 69% yield, with the Dess–Martin periodinane (DMPI),[10] followed by reaction with methyllithium, provided the secondary alcohols **29** as a 1.7:1 mixture of two diastereoisomers in 75% overall yield. After benzoylation of **29**, the benzyl group of the resulting compound **30** was removed by hydrogenolysis utilizing 10% Pd–C in the presence of acetic acid. The relative configuration



Scheme 5

of the major isomer **31**, separated by the HPLC technique, was determined by further transformation (*vide infra*).

The preceeding alcohol **28** was further transformed into the ester **32** in 93% overall yield in three steps (Scheme 6). Treatment of **32** with methyllithium provided the tertiary alcohol **33** (87%). Deblocking of the benzyl group of **33** gave the diol **34**, whilst protection of the hydroxy group of **33** with a TBDMS group, followed by the removal of the benzyl group of the resulting compound **35**, produced the alcohol **36**.



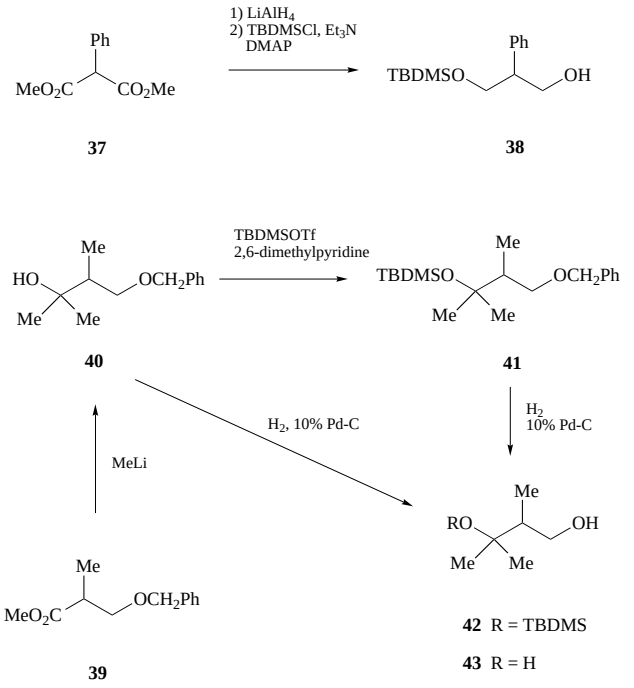
Scheme 6

In order to compare the degree of stereoselectivity, the corresponding alcohols **38**, **42** and **43** carrying a hydrogen atom instead of the fluorine atom were newly prepared starting with **37** and **39** as shown in Scheme 7.

Oxidation of the alcohol **17** with DMPI[10] in the presence of pyridine, followed by reaction with *N*-benzylhydroxylamine at

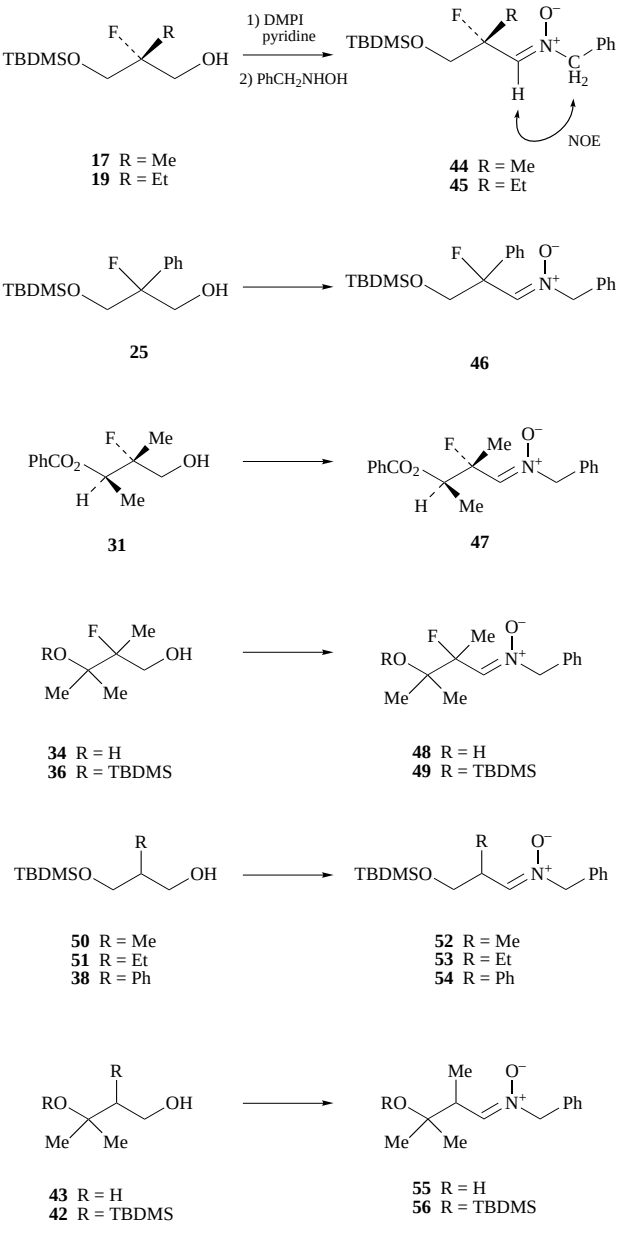
Table 1 1,3-Dipolar cycloaddition of nitrones having a fluorine atom at the C-2 position with ethyl vinyl ether

Entry	Nitrone	R^1	R^2	R^3	R^4	Isoxazolidines	Yield	Ratio of **A** to **B**
1	**44**	Me	TBDMS	H	H	**57**	86	1.1:1
2	**45**	Et	TBDMS	H	H	**58**	85	1.1:1
3	**46**	Ph	TBDMS	H	H	**59**	97	1:1.1
4	**47**	Me	PhCO	H	Me	**60**	100	2.5:1
5	**48**	Me	H	Me	Me	**61**	83	2.0:1
6	**49**	Me	TBDMS	Me	Me	**62**	84	4.1:1



37 **38** **40** **41** **42** R = TBDMS **43** R = H **39**

Scheme 7



17 R = Me **19** R = Et **44** R = Me **45** R = Et **25** **46** **31** **47** **34** R = H **36** R = TBDMS **48** R = H **49** R = TBDMS **50** R = Me **51** R = Et **38** R = Ph **52** R = Me **53** R = Et **54** R = Ph **43** R = H **42** R = TBDMS **55** R = H **56** R = TBDMS

Scheme 8

room temperature, gave the nitrone **44**, $[a]_{24}^{D}$ −41.4 ($CHCl_3$), in 53% overall yield. The ethyl compound **45**, $[a]_{24}^{D}$ −46.9 ($CHCl_3$), was similarly prepared in 63% overall yield from **19**. The geometry of the nitrones was assigned as *Z*-form on the basis of the observation of NOE (2.3%) between the olefinic hydrogen at 6.70 ppm and the benzylic hydrogens at 4.88 ppm of **45**. 2-Fluoro nitrones **46**–**49** and the 2-hydro nitrones **52**–**56** were synthesized by the same procedure as already described (Scheme 8). The olefinic hydrogens of all the nitrones resonate in the range 6.59–6.98 ppm.

1,3-Dipolar cycloaddition of nitrones

The cycloaddition of nitrones with ethyl vinyl ether was examined under various conditions. It has been found that the reaction rate of 2-fluoro nitrones is a little faster than that of the corresponding 2-hydro nitrones. In order to complete the reaction within a reasonable reaction time, a temperature above 80 °C was required. The cycloaddition of the hindered nitrones **48**, **49**, **55** and **56** was carried out for 16 h at 105 °C. Results of cycloaddition performed at 80 °C or 105 °C are shown in Tables 1 and 2 (Schemes 9 and 10). Four stereoisomers were obtained by each reaction, but no formation of regioisomers was observed.[11]

No appropriate catalyst for the cyclization was found. Although cycloadducts were produced by the treatment of nitrones with ethyl vinyl ether at 10 000 atm and room temperature, no improvement of yield and diastereoselectivity was observed.

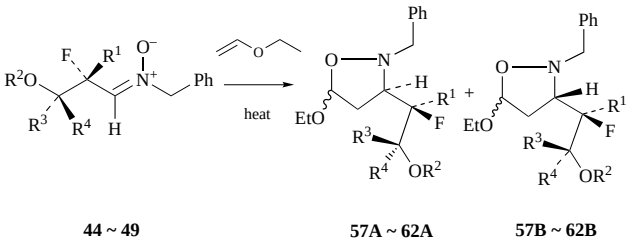
Isoxazolidines produced were converted into 2,7-dioxa-6-azabicyclo[3.2.1]octanes in order to establish their stereochemistry. Treatment of a mixture of **57A** and **57B** (Table 1, entry 1) with toluene-*p*-sulfonic acid in hot benzene provided **68A** (40%) and **68B** (37%). The structure of the major isomer **68A** was determined by the NOE (1.8%) between the methyl group (1.16 ppm, d, *J* 21.4 Hz) at the C-4 position and the axial hydrogen (2.62 ppm, dd, *J* 11.9, 2.8 Hz) at the C-8 position. On the other hand, the corresponding hydro-isoxazolidines **63A** and **63B** (Table 2, entry 1) gave a separable 1:1.6 mixture of **73A** and **73B** (81%). The NOE (3.4%) was observed between the methyl group (1.05 ppm, d, *J* 7.3 Hz) and the axial hydrogen (2.30 ppm, br d, *J* 11.6 Hz) of the minor product **73A**.

A 1.1:1 mixture of **69A** and **69B** was obtained from a mixture of the isoxazolidines **58A** and **58B** (Table 1, entry 2) carrying a fluorine atom and ethyl group, while a 1.2:1 mixture of **74A** and **74B** resulted from the corresponding non-fluorinated compounds **64A** and **64B** (Table 2, entry 2). Furthermore, a

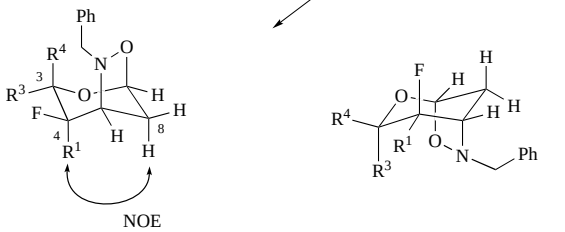
Table 2 1,3-Dipolar cycloaddition of nitrones having a hydrogen atom at the C-2 position with ethyl vinyl ether

Entry	Nitrone	R^1	R^2	R^3	R^4	Isoxazolidines	Yield	Ratio of **A** to **B**
1	**52**	Me	TBDMS	H	H	**63**	84	1:1.6
2	**53**	Et	TBDMS	H	H	**64**	88	1.2:1
3	**54**	Ph	TBDMS	H	H	**65**	95	1:4.6
4	**55**	Me	H	Me	Me	**66**	66	1:1.1
5	**56**	Me	TBDMS	Me	Me	**67**	11 (53)[a]	1:2.5

[a] Yield based on the recovered starting material.



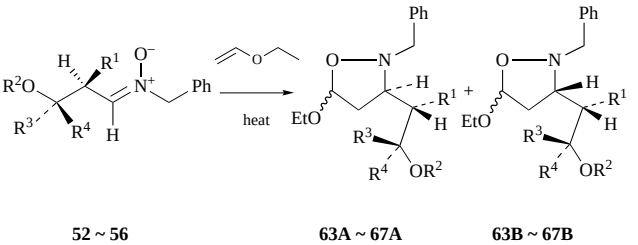
44 ~ 49 **57A ~ 62A** **57B ~ 62B**



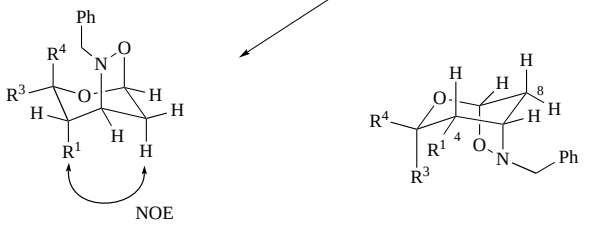
68A R^1 = Me, R^3 = R^4 = H
69A R^1 = Et, R^3 = R^4 = H
70A R^1 = Ph, R^3 = R^4 = H
71A R^1 = R^4 = Me, R^3 = H
72A R^1 = R^3 = R^4 = Me

68B R^1 = Me, R^3 = R^4 = H
69B R^1 = Et, R^3 = R^4 = H
70B R^1 = Ph, R^3 = R^4 = H
71B R^1 = R^4 = Me, R^3 = H
72B R^1 = R^3 = R^4 = Me

Scheme 9



52 ~ 56 **63A ~ 67A** **63B ~ 67B**



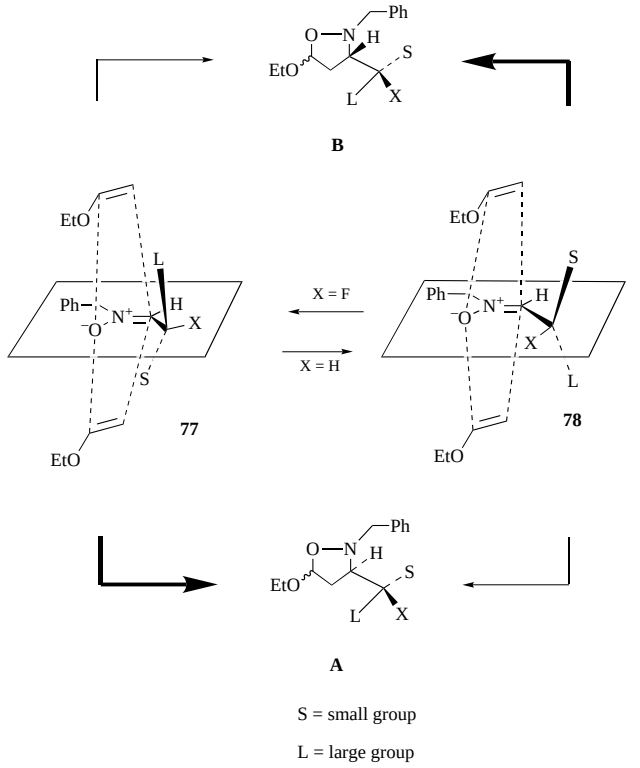
73A R^1 = Me, R^3 = R^4 = H
74A R^1 = Et, R^3 = R^4 = H
75A R^1 = Ph, R^3 = R^4 = H
76A R^1 = R^3 = R^4 = Me

73B R^1 = Me, R^3 = R^4 = H
74B R^1 = Et, R^3 = R^4 = H
75B R^1 = Ph, R^3 = R^4 = H
76B R^1 = R^3 = R^4 = Me

Scheme 10

1:1.1 mixture of **70A** and **70B** and a 1:4.6 mixture of **75A** and **75B** were produced in the case of the phenyl compounds (Table 1, entry 3 and Table 2, entry 3). Structures of the bridged products were determined by NOE experiments and comparison with spectral data.

The compounds which belong to a series of **A** are produced by the approach of the ethyl vinyl ether from the less hindered side of the conformation **77** of nitrones or from the hindered side of conformation **78** (Scheme 11). On the other hand, the



Scheme 11

attacks of the dipolarophile from the other sides of the two conformations lead to a series of **B**. Although the observed results support that conformation **77** with the relief from the dipole repulsion is the preferred form for the fluoro nitrones, while the non-fluorinated ones take the conformation **78** with the least 1,3-allylic strain, the differences of the ratios of the two stereoisomers are rather small.

The isoxazolidines **60** (Table 1, entry 4), obtained in 100% yield from **47** possessing a tertiary carbon at the C-3 position, was transformed, in two steps, into **71A** and **71B** in the ratio of 2.5:1. The stereostructure of the major product **71A** was established by the NOE experiments; 2.3% NOE between the equatorial hydrogen (4.29 ppm, dq, *J* 19.8, 6.8 Hz) at the C-3 and the methyl group (1.29 ppm, d, *J* 22.3 Hz) at the C-4 position and 2.1% NOE between the axial hydrogen (2.04 ppm, dd, *J* 12.3, 1.7 Hz) at the C-8 and the methyl group at the C-4 position.

The 1,3-dipolar cycloaddition of the tertiary alcohol **48** gave a 2.0:1 mixture of isoxazolidines **61A** and **61B**, both of which were separated by column chromatography (Table 1, entry 5). The structure of **72A**, derived from **61A**, was determined by the NOE (1.4%) between the hydrogen (2.02 ppm, dd, *J* 11.9, 2.1

Hz) at the C-8 and the methyl group (1.37 ppm, d, *J* 23.1 Hz) at the C-4 position. The corresponding hydro compounds **66A** and **66B** were obtained in the ratio of 1:1.1 (Table 2, entry 4). The stereostructure of **76B**, derived from the major product **66B**, was established by the NOE (1.2%) between the axial hydrogen (1.89 ppm, d, *J* 11.3 Hz) at the C-8 and the axial hydrogen (1.75 ppm, dq, *J* 7.1, 1.9 Hz) at the C-4 position.

A comparably good degree of diastereoselectivity was observed on the cycloaddition of the TBDMS ether **49** (Table 1, entry 6), a 4.1:1 mixture of **62A** and **62B** being obtained in 84% yield. The corresponding hydroisoxazolidines **67A** and **67B** were produced in a ratio of 1:2.5 (Table 2, entry 5). The stereostructures of the products were determined by correlation with the previously described compounds. These findings support the above assumption. Conformations **77** and **78** were favourable ones for fluoro- and hydro-nitrones, respectively, although the fluorine and the hydrogen atoms would not be entirely on the plane of the nitrones.

Experimental

All reactions were carried out under a positive atmosphere of dry N_2, unless otherwise indicated. Solvents were distilled prior to use: THF, Et_2O, hexane and benzene were freshly distilled from Na and benzophenone; CH_2Cl_2, $ClCH_2CH_2Cl$ and DMF were distilled from CaH_2 and stored over 4 Å molecular sieves; pyridine and triethylamine were distilled from KOH and stored over KOH. All extracts were dried over $MgSO_4$, and the solvent was removed by rotary evaporation under reduced pressure. All new compounds are homogenous on HPLC and TLC, and their purities were further verified by 300 or 500 MHz ^{1}H NMR spectra. *J* Values are recorded in Hz.

(−)-(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl (2′*S*)-3′-(*tert*-butyldimethylsiloxy)-2′-fluoro-2′-methylpropionate 14

A mixture of **13**[4] (134 mg, 0.397 mmol), TBDMSCl (89.9 mg, 0.596 mmol) and imidazole (54.1 mg, 0.795 mmol) in dry DMF (2.7 cm^3) was stirred for 12 h at room temperature. After addition of water, the mixture was extracted with AcOEt. The extract was washed with water and brine, dried and evaporated. The residue was subjected to column chromatography on silica gel with AcOEt–hexane (1:20, v/v) as the eluent to give **14** (165 mg, 92%) as an oil, $[\alpha]_D^{23}$ −15.3 (*c* 2.93, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 and 1250; δ_H(300 MHz, $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.85 (3H, d, *J* 6.2, 1-Me), 0.88 (9H, s, Bu^t), 0.94–1.08 (3H, m), 1.25 (3H, s, 8-Me), 1.26 (3H, d, *J* 21.2, CFMe), 1.36 (3H, s, 8-Me), 1.40–1.60 (3H, m), 1.94–2.10 (2H, m), 3.60–3.93 (2H, m), 4.83–5.20 (1H, m, 3-H) and 7.10–7.36 (5H, m, Ph); *m*/*z* (EI) 331.2070 (M$^+$ − CMe_2Ph. $C_{17}H_{32}FO_3Si$ requires 331.2105).

(−)-(1*R*,3*R*,4*S*)-8-Phenyl-*p*-menthan-3-yl (2′*S*)-2′-(*tert*-butyldimethylsiloxymethyl)-2′-fluorobutyrate 16

An oil (95%), $[\alpha]_D^{23}$ −15.3 (*c* 11.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1760, 1730 and 1260; δ_H(300 MHz, $CDCl_3$) −0.05–0.13 (6H, m, $SiMe_2$), 0.65–1.12 (15H, m), 1.16–1.80 (12H, m), 1.95–2.12 (4H, m), 3.28–3.96 (2H, m, $CFCH_2$), 4.79–5.00 (1H, m, 3-H) and 7.06–7.34 (5H, m, Ph); *m*/*z* (EI) 325.2240 (M$^+$ − CMe_2Ph. $C_{18}H_{34}FO_4Si$ requires 345.2261).

Methyl 3-(*tert*-butyldimethlysiloxy)-2-fluoro-2-phenylpropionate 24

An oil (99%), ν_{max}(neat)/cm^{-1} 1745 and 1260; δ_H(300 MHz, $CDCl_3$) 0.065 (3H, s, SiMe), 0.073 (3H, s, SiMe), 0.88 (9H, s, Bu^t), 3.81 (3H, s, OMe), 3.94 (1H, dd, *J* 16.1 and 11.4, 3-H), 4.34 (1H, dd, *J* 31.5 and 11.4, 3H) and 7.31–7.61 (5H, m, Ph); *m*/*z* (EI) 313.1587 (M$^+$ + H. $C_{16}H_{26}FO_3Si$ requires 313.1635).

(+)-(2*R*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methylpropan-1-ol 17

To a suspension of $LiBH_4$ (191 mg, 8.77 mmol) in dry THF (1.0 cm^3) at 0 °C was added a solution of **14** (197.3 mg, 0.437 mol) in dry THF (3.0 cm^3), and the mixture was stirred for 18 h at 45 °C. After the addition of saturated aq. $NaHCO_3$, the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with AcOEt–hexane (1:20, v/v) yielded **17** (83.2 mg, 85%) as an oil, $[\alpha]_D^{24}$ +0.90 (*c* 10.1, MeOH); ν_{max}(neat)/cm^{-1} 3400 and 1260; δ_H(300 MHz, $CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, Bu^t), 1.31 (3H, d, *J* 21.9, CFMe), 2.07 (1H, br t, *J* 6.6, OH) and 3.60–3.83 (4H, m); *m*/*z* (EI) 1625.0720 (M$^+$ − Bu^t. $C_6H_{14}FO_2Si$ requires 165.0747).

(+)-(2*R*)-2-(*tert*-Butyldimethylsiloxymethyl)-2-fluorobutan-1-ol 19

An oil (66%), $[\alpha]_D^{24}$ +1.39 (*c* 0.59, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3420 and 1260; δ_H(300 MHz, $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.85–0.96 (12H, m), 1.56–1.78 (2H, m), 2.09 (1H, br t, *J* 6.4, OH) and 3.61–3.82 (4H, m); *m*/*z* (EI) 237.1687 (M$^+$ + H. $C_{11}H_{26}FO_2Si$ requires 237.1686).

3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-phenylpropan-1-ol 25

An oil (90%), ν_{max}(neat)/cm^{-1} 3420 and 1260; δ_H(300 MHz, $CDCl_3$) 0.02 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.88 (9H, s, Bu^t), 2.28 (1H, br t, *J* 7.0, OH), 3.88–4.25 (4H, m) and 7.28–7.46 (5H, m, Ph); *m*/*z* (EI) 207.0872 (M$^+$ − H − F − Bu^t. $C_{11}H_{15}O_2Si$ requires 207.0841).

(2*R*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methylpropyl (*S*)-(3,3,3-trifluoro-2-methoxy-2-phenyl)propionate 18

To a stirred solution of **17** (6.9 mg, 31 μmol), (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (8.7 mg, 37 μmol) and DMAP (3.8 mg, 31 μmol) in dry $ClCH_2CH_2Cl$ (0.5 cm^3) at 0 °C was added DCC (9.6 mg, 46 μmol). After being stirred for 14 h at room temperature, the reaction mixture was diluted with Et_2O and then filtered through Celite. Evaporation of the solvent gave **18** as an oil, ν_{max}(neat)/cm^{-1} 1760 and 1250; δ_H(300 MHz, $CDCl_3$) 0.04 (6H, s, $SiMe_2$), 0.88 (9H, s, Bu^t), 1.32 (3H, d, *J* 21.6, CFMe), 3.42–3.76 (5H, m), 4.30–4.54 (2H, m, CH_2OCO) and 7.35–7.60 (5H, m, Ph); *m*/*z* (EI) 381.1170 (M$^+$ − Bu^t. $C_{16}H_{21}F_4O_4Si$ requires 381.1145).

(2*R*)-2-(*tert*-Butyldimethylsiloxymethyl)-2-fluorobutyl (*S*)-(3,3,3-trifluoro-2-methoxy-2-phenyl)propionate 20

An oil, ν_{max}(neat)/cm^{-1} 1760 and 1250; δ_H(300 MHz, $CDCl_3$) 0.00 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.86 (9H, s, Bu^t), 0.94 (3H, t, *J* 7.7, CH_2*Me*), 1.45–1.84 (2H, m, $CFCH_2$Me), 3.50–3.75 (5H, m), 4.26–4.59 (2H, m, CH_2OCO) and 7.34–7.61 (5H, m, Ph); *m*/*z* (EI) 395.1265 (M$^+$ − Bu^t. $C_{17}H_{23}F_4O_4Si$ requires 395.1302).

Methyl 2-fluorophenylacetate 22

To a stirred solution of methyl mandelate (810 mg, 4.87 mmol) in dry CH_2Cl_2 (15 cm^3) at −78 °C was slowly added DAST (1.57 g, 9.74 mmol), and the mixture was stirred for 19 h at room temperature. After dilution with AcOEt, the mixture was washed with saturated aq. $NaHCO_3$, water and brine, dried and evaporated to give a residue. This was chromatographed on silica gel with Et_2O–hexane (1:5, v/v) as the eluent to afford **22** (752 mg, 92%) as an oil (Found: C, 64.15; H, 5.4. $C_9H_9FO_2$ requires C, 64.3; H, 5.4%); ν_{max}(neat)/cm^{-1} 1760 and 1220; δ_H(300 MHz, $CDCl_3$) 3.77 (3H, s, OMe), 5.79 (1H, d, *J* 47.6, CFH) and 7.34–7.51 (5H, m, Ph); *m*/*z* (EI) 168 (M$^+$).

Methyl 2-fluoro-3-hydroxy-2-phenylpropionate 23

To a stirred LDA solution, prepared from diisopropylamine (309 mg, 3.05 mmol) and 1.56 M BuLi in hexane (1.82 cm^3, 2.84 mmol) in dry THF (15 cm^3) at −78 °C, was added **22** (352 mg, 2.03 mmol) in dry THF (15 cm^3). After thr mixture had been stirred for 30 min at −78 °C, an excess of gaseous formaldehyde was introduced at −78 °C. The mixture was then further stirred

for 70 min at the same temperature after which it was partitioned between 10% aq. HCl and Et_2O. The organic layer was separated, washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated. The residue was subjected to column chromatography on silica gel with AcOEt–hexane (3:7, v/v) as the eluent to give **23** (239 mg, 58%) as a solid. Recrystallization of this from Et_2O–hexane afforded needles, mp 66.0–66.5 °C (Found: C, 60.35; H, 5.3. $C_{10}H_{11}FO_3$ requires C, 60.6; H, 5.6%); ν_{max}(neat)/cm^{-1} 3620, 3500, 1750 and 1265; δ_H(300 MHz, $CDCl_3$) 2.32 (1H, br s, OH), 3.83 (3H, s, OMe), 3.94–4.12 (1H, m, 3-H), 4.22–4.46 (1H, m, 3-H) and 7.36–7.59 (5H, m, Ph); *m*/*z* (EI) 198 (M^+).

3-Benzyloxy-1,2-epoxy-2-methylpropane 27

A mixture of **26**[12] (13.3 g, 88.5 mmol), $NaHCO_3$ (22.3 g, 266 mmol) and *m*-CPBA (22.9 g, 106 mmol) in CH_2Cl_2 (200 cm^3) was stirred for 2 h at room temperature. The reaction mixture was partitioned between 10% aq. $Na_2S_2O_3$ and Et_2O. The organic layer was separated, washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated. The product was purified by column chromatography on silica gel with AcOEt–hexane (1:39 v/v) as the eluent to give **27** (10.7 g, 73%) as an oil; ν_{max}(neat)/cm^{-1} 1110; δ_H(300 MHz, $CDCl_3$) 1.40 (3H, s, 2-Me), 2.63 (1H, d, *J* 4.8, 1-H), 2.75 (1H, d, *J* 4.8, 1-H), 3.46 (1H, d, *J* 11.0, 3-H), 3.58 (1H, d, *J* 11.0, 3-H), 4.54 (1H, d, *J* 12.1, OC*H*HPh), 4.60 (1H, d, *J* 12.1, OCH*H*Ph) and 7.34 (5H, s, Ph); *m*/*z* (EI) 177.0916 ($M^+ - H$. $C_{11}H_{13}O_2$ requires 177.0899).

3-Benzyloxy-2-fluoro-2-methylpropanol 28

To a stirred solution of diisopropylethylamine (9.73 cm^3, 55.8 mmol) and water (4.02 cm^3, 223 mmol) in Et_2O (100 cm^3) with ice cooling was slowly added a solution of **27** (9.28 g, 55.8 mmol) in dry Et_2O (50 cm^3). During the addition, an excess of tetrafluorosilane was simultaneously introduced to the reaction mixture. After being stirred for 2 h at 0 °C followed by treatment with potassium fluoride (30 g), the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–hexane (1:17, v/v) gave **28** (7.10 g, 69%) as an oil (Found: C, 66.75; H, 7.7. $C_{11}H_{15}FO_2$ requires C, 66.65; H, 7.65%); ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 1.36 (3H, d, *J* 22.3, 2-Me), 1.95–2.00 (1H, br s, OH), 3.38–3.79 (4H, m, 1- and 3-H_2), 4.59 (2H, d, *J* 3.3, OCH_2Ph) and 7.22–7.38 (5H, m, Ph); *m*/*z* (EI) 198 (M^+).

4-Benzyloxy-3-fluoro-3-methylbutan-2-ol 29

To a stirred mixture of Dess–Martin periodinane (2.51 g, 5.92 mmol) in dry CH_2Cl_2 (3.5 cm^3) at room temperature was added a solution of **28** (3.63 mg, 1.83 mmol) in dry CH_2Cl_2 (4.5 cm^3). After being stirred for 2 h, the mixture was partitioned between saturated aq. $NaHCO_3$–2% aq. $Na_2S_2O_3$ (1:7, v/v) and Et_2O. The organic layer was separated, washed with water and brine, dried and evaporated to afford the crude aldehyde, which was used in the following reaction without purification.

To a stirred solution of the above product in dry THF (15 cm^3) at 0 °C was added 1.04 M MeLi in Et_2O (2.28 cm^3, 2.37 mmol). The mixture was stirred for 12 h at the same temperature and then poured into saturated aq. NH_4Cl with ice cooling. The mixture was extracted with Et_2O and the extract was washed with brine, dried and evaporated. Column chromatography of the product on silica gel with AcOEt–hexane (1:9, v/v) as the eluent provided **29** (293 mg, 75%) as an oil (Found: C, 67.8; H, 8.0. $C_{12}H_{17}FO_2$ requires C, 67.9; H, 8.05%); ν_{max}(neat)/cm^{-1} 3450; δ_H(300 MHz, $CDCl_3$) 1.15–1.23 (3H, m, 1-H_3), 1.31 and 1.33 [3H, (1:1.7), each d, each *J* 22.3, 3-Me], 2.23–2.34 (1H, m, OH), 2.47–2.73 (2H, m, 4-H_2), 3.94–4.08 (1H, br s, 2-H), 4.55–4.62 (2H, m, OCH_2Ph) and 7.24–7.44 (5H, m, Ph); *m*/*z* (EI) 212 (M^+).

3-Benzyloxy-2-fluoro-1,2-dimethylpropyl benzoate 30

A mixture of **29** (185 mg, 0.872 mmol) and benzoyl chloride (0.163 cm^3, 1.40 mmol) in dry pyridine (0.377 cm^3, 4.67 mmol) was stirred for 2.5 h at room temperature. After dilution with Et_2O, the mixture was washed with water, 10% aq. $KHSO_4$ and brine, dried and evaporated. The residue was chromatographed on silica gel with AcOEt–hexane (1:9, v/v) as the eluent to give **30** (277 mg, 98%) as a pale yellowish oil (Found: C, 71.8; H, 6.55. $C_{19}H_{21}FO_3$ requires C, 72.15; H, 6.7%); ν_{max}(neat)/cm^{-1} 1720; δ_H(300 MHz, $CDCl_3$) 1.34–1.40 (3H, m, 1-Me), 1.42–1.52 (3H, m, 2-Me), 3.56–3.66 (2H, m, 3-H_2), 4.54–4.58 (2H, m, OCH_2Ph), 5.34–5.48 (1H, m, 1-H), 7.22–7.72 (8H, m, 8 × ArH) and 7.98–8.18 (2H, m, 2 × ArH); *m*/*z* (EI) 316 (M^+).

2-Fluoro-3-hydroxy-1,2-dimethylpropyl benzoate 31

A mixture of **30** (975 mg, 3.08 mmol), 10% Pd–C (25 mg) and AcOH (6 × 10^{-3} cm^3) in MeOH (12 cm^3) was stirred for 12 h at room temperature under a H_2 atmosphere. The mixture was filtered through Celite after which it was evaporated to afford a residue. This was purified by column chromatography on silica gel. Elution with AcOEt–hexane (1:4, v/v) afforded a 1.7:1 mixture of alcohols (565 mg, 81%). The major isomer **31** was separated by HPLC using Dynamax Microsorb silica (5 μm, 4 × 250 mm) with CH_2Cl_2–hexane–AcOEt (2:8:1, v/v/v, 1.0 cm^3 min^{-1}) as the eluent (Found: C, 63.9; H, 6.75. $C_{12}H_{15}FO_3$ requires C, 63.7; H, 6.7%); ν_{max}(neat)/cm^{-1} 3500 and 1720; δ_H(300 MHz, $CDCl_3$) 1.42 (3H, d, *J* 22.0, 2-Me), 1.44 (3H, dd, *J* 6.6 and 1.5, 1-Me), 2.26–2.32 (1H, br s, OH), 3.66–3.80 (2H, m, 3-H_2), 5.45 (1H, dq, *J* 14.7 and 6.6, 1-H), 7.62–7.43 (3H, m, 3 × ArH) and 8.01–8.04 (2H, m, 2 × ArH); *m*/*z* (EI) 209 ($M^+ - OH$).

Methyl 3-benzyloxy-2-fluoro-2-methylpropionate 32

After the oxidation of **28** (1.66 g, 8.38 mmol) using Dess–Martin periodinane (11.5 g, 27.1 mmol), to a stirred mixture of the resulting aldehyde, *tert*-butyl alcohol (45 cm^3), pH 3.5 phosphate buffer (30 cm^3) and 2-methylbut-2-ene (2.88 cm^3, 27.1 mmol) at room temperature was added $NaClO_2$ (2.03 g, 18.0 mmol). The mixture was stirred for 2 h at room temperature and then diluted with Et_2O. After acidification by addition of 10% aq. $KHSO_4$ with ice cooling, the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to give the corresponding acid, which was used in the following reaction without purification.

A mixture of the crude acid and an excess of diazomethane in THF (35 cm^3) was kept for 3 h at room temperature. Concentration of the mixture under reduced pressure afforded a residue, which was chromatographed on silica gel. Elution with Et_2O–hexane (2:9, v/v) provided **32** (1.76 g, 93%) as an oil, ν_{max}(neat)/cm^{-1} 1760; δ_H(300 MHz, $CDCl_3$) 1.54 (3H, d, *J* 21.2, 2-Me), 3.59–3.86 (2H, m, 3-H_2), 3.81 (3H, s, OMe), 4.51–4.68 (2H, m, OCH_2Ph) and 7.21–7.36 (5H, m, Ph); *m*/*z* (EI) 226.1043 (M^+. $C_{12}H_{15}FO_3$ requires 226.1005).

4-Benzyloxy-3-fluoro-2,3-dimethylbutan-2-ol 33

To a solution of 1.04 M MeLi in Et_2O (0.605 cm^3, 0.629 mmol) in dry THF (1.5 cm^3) at 0 °C was added a solution of **32** (65 mg, 0.29 mmol) in dry THF (2.0 cm^3), and the mixture was stirred for 15 min at 0 °C. After being poured onto saturated aq. NH_4Cl, the mixture was extracted with Et_2O. The extract was washed with brine, dried and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with AcOEt–hexane (1:17, v/v) afforded **33** (56 mg, 87%) as an oil (Found: C, 69.0; H, 8.45. $C_{13}H_{19}FO_2$ requires C, 68.85; H, 8.27%); ν_{max}(neat)/cm^{-1} 3450; δ_H(300 MHz, $CDCl_3$) 1.23 (3H, s, Me), 1.26 (3H, s, Me), 1.40 (3H, d, *J* 22.7, 2-Me), 2.82 (1H, d, *J* 1.8, OH), 3.69 (2H, d, *J* 18.3, 4-H_2), 4.59 (2H, s, OCH_2Ph) and 7.28–7.39 (5H, m, Ph); *m*/*z* (EI) 226 (M^+).

2-Fluoro-2,3-dimethylbutane-1,3-diol 34
A mixture of **33** (980 mg, 4.33 mmol), 10% Pd–C (20 mg) and AcOH (6×10^{-3} cm^3) in MeOH (20 cm^3) was stirred for 12 h at room temperature under an H_2 atmosphere. The mixture was filtered through Celite, after which evaporation of the filtrate gave a residue, which was chromatographed on silica gel. Elution with AcOEt–hexane (2:3, v/v) provided **34** (464 mg, 79%) as an oil, ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 1.27 (3H, s, Me), 1.30 (3H, s, Me), 1.34 (3H, d, *J* 22.0, 2-Me), 2.56–2.62 (1H, br s, OH), 2.63–2.78 (1H, br s, OH), 3.65–3.76 (1H, m, 1-H) and 3.92–4.03 (1H, m, 1-H); *m*/*z* (EI) 121.0665 ($M^+ - Me$. $C_5H_{10}FO_2$ requires 121.0677).

3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2,3-dimethylbutan-1-ol 36
An oil (85%), ν_{max}(neat)/cm^{-1} 3350; δ_H(300 MHz, $CDCl_3$) 0.10 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.84 (9H, s, Bu^t), 1.27 (3H, s, Me), 1.28 (3H, s, Me), 1.36 (3H, d, *J* 22.3, 2-Me), 2.40–2.79 (1H, br s, OH), 3.58–3.76 (1H, m, 1-H) and 3.80–3.92 (1H, m, 1-H); *m*/*z* (EI) 235.1509 ($M^+ - Me$. $C_{11}H_{24}FO_2Si$ requires 235.1530).

1-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-2-fluoro-2,3-dimethylbutane 35
To a stirred mixture of **33** (12.0 mg, 53 μmol) and 2,6-dimethylpyridine (0.015 cm^3, 0.133 mmol) in dry CH_2Cl_2 (0.5 cm^3) at 0 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.016 cm^3, 69 μmol), and the mixture was stirred for 2 h at the same temperature. After dilution with Et_2O, the mixture was washed with water, 10% aq. $KHSO_4$ and brine, dried and evaporated to give a residue. This was purified by silica gel column chromatography. Elution with AcOEt–hexane (1:19 v/v) afforded **35** (16.0 mg, 90%) as a pale yellowish oil (Found: C, 67.05; H, 9.75; $C_{19}H_{33}FO_2Si$ requires C, 67.0; H, 9.75%); ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) 0.05 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.80 (9H, s, Bu^t), 1.24 (6H, s, 2 × Me), 1.39 (3H, d, *J* 22.3, 2-Me), 3.54–3.76 (2H, s, 1-H_2), 4.49 (1H, d, *J* 12.1, OC*H*HPh), 4.66 (1H, d, *J* 12.1, OCH*H*Ph) and 7.26–7.35 (5H, m, Ph); *m*/*z* (EI) 283 ($M^+ - Bu^t$).

1-Benzyloxy-3-(*tert*-butyldimethylsiloxy)-2,3-dimethylbutane 41
An oil (91%) (Found: C, 70.55; H, 10.6. $C_{19}H_{34}O_2Si$ requires C, 70.75; H, 10.65%); ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) 0.03 (6H, s, $SiMe_2$), 0.81 (9H, s, Bu^t), 0.97 (3H, d, *J* 6.9, 2-Me), 1.18 (3H, s, Me), 1.24 (3H, s, Me), 1.69–1.81 (1H, m, 3-H), 3.21 (1H, t, *J* 9.1, 1-H), 3.69 (1H, dd, *J* 9.1 and 3.8, 1-H), 4.44 (1H, d, *J* 11.9, OC*H*HPh), 4.49 (1H, d, *J* 11.9, OCH*H*Ph) and 7.22–7.34 (5H, m, Ph); *m*/*z* (EI) 265 ($M^+ - Bu^t$)

3-(*tert*-Butyldimethylsiloxy)-2-phenylpropan-1-ol 38
To a suspension of $LiAlH_4$ (2.85 g, 75.1 mmol) in dry Et_2O (200 cm^3) at 0 °C was added a solution of dimethyl phenylmalonate (12.1 g, 51.0 mmol) in dry Et_2O (50 cm^3), and the mixture was stirred for 22 h at room temperature. After addition of Et_2O and water (10.0 cm^3), the mixture was further stirred and then filtered through Celite. Evaporation of the filtrate gave the crude diol (8.85 g) as a colourless oil.

To a mixture of the above product, *tert*-butyldimethylsilyl chloride (4.12 g, 26.5 mmol) and DMAP (162 mg, 1.33 mmol) in dry CH_2Cl_2 (26 cm^3) at 0 °C was added triethylamine (4.06 cm^3, 29.2 mmol), and the mixture was stirred for 12 h at room temperature. The mixture was partitioned between water and Et_2O. The organic layer was separated, washed with 10% aq. $KHSO_4$ and brine, dried and evaporated. Column chromatography of the residue on silica gel with AcOEt–hexane (1:19, v/v) afforded **38** (2.99 g, 44%) as an oil (Found: C, 67.7; H, 9.8. $C_{15}H_{26}O_2Si$ requires C, 67.6; H, 9.85%); ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 0.00 (6H, s, $SiMe_2$), 0.85 (9H, s, Bu^t), 2.30–3.30 (2H, m), 3.50–4.30 (4H, m) and 7.00–7.50 (5H, m, Ph); *m*/*z* (EI) 209 ($M^+ - Bu^t$).

4-Benzyloxy-2,3-dimethylbutan-2-ol 40
To a stirred solution of 1.04 M MeLi in Et_2O (14.4 cm^3, 15.3 mmol) in dry hexane (15 cm^3) at 0 °C was added a solution of **39**[13] (1.26 g, 6.11 mmol) in dry THF (25 cm^3). After being stirred for 10 min at 0 °C, the mixture was poured into saturated aq. NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with AcOEt–hexane (1:5 v/v) provided **40** (1.40 g, 90%) as a pale yellowish oil; ν_{max}(neat)/cm^{-1} 3450; δ_H(300 MHz, $CDCl_3$) 0.89 (3H, d, *J* 7.0, 3-Me), 1.13 (3H, s, Me), 1.20 (3H, s, Me), 1.86–1.96 (1H, m, 3-H), 3.48–3.60 (2H, m, 4-H_2), 4.52 (2H, s, OCH_2Ph) and 7.27–7.38 (5H, m, Ph); *m*/*z* (EI) 193.1227 ($M^+ - Me$. $C_{12}H_{17}O_2$ requires 193.1228).

3-(*tert*-Butyldimethylsiloxy)-2,3-dimethylbutan-1-ol 42
A mixture of **41** (1.09 g, 3.40 mmol) and 10% Pd–C (20 mg) in MeOH (15 cm^3) was stirred for 12 h at room temperature under an H_2 atmosphere. Filtration through Celite, followed by evaporation of the filtrate, gave a residue, which was chromatographed on silica gel. Elution with AcOEt–hexane (3:17, v/v) provided **42** (729 mg, 93%) as an oil (Found: C, 61.8; H, 12.25. $C_{12}H_{28}O_2Si$ requires C, 62.0; H, 12.1%); ν_{max}(neat)/cm^{-1} 3375; δ_H(300 MHz, $CDCl_3$) 0.11 (6H, s, $SiMe_2$), 0.85 (9H, s, Bu^t), 0.91 (3H, d, *J* 7.1, 2-Me), 1.20 (3H, s, Me), 1.30 (3H, s, Me), 1.57–1.71 (1H, m, 2-H), 3.34 (1H, br t, *J* 4.7, OH) and 3.66 (2H, m, 1-H_2); *m*/*z* (EI) 175 ($M^+ - Bu^t$).

2,3-Dimethylbutane-2,4-diol 43
A pale yellowish oil (96%), ν_{max}(neat)/cm^{-1} 3550; δ_H(300 MHz, $CDCl_3$) 0.86 (3H, d, *J* 7.3, 2-Me), 1.19 (3H, s, Me), 1.27 (3H, s, Me), 1.75–1.87 (1H, m, 2-H), 3.14–3.48 (2H, br s, 2 × OH) and 3.64–3.74 (2H, m, 1-H_2); *m*/*z* (EI) 103.0776 ($M^+ - Me$. $C_5H_{11}O_2$ requires 103.0758).

(−)-*N*-[(2*R*)-3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-methylpropylidene]benzylamine *N*-oxide 44
To a stirred mixture of Dess–Martin periodinane (151 mg, 0.357 mmol) and pyridine (55.0 mg, 0.357 mmol) in dry CH_2Cl_2 (0.8 cm^3) at room temperature was added a solution of **17** (26.5 mg, 0.119 mmol) in dry CH_2Cl_2 (0.2 cm^3), and the mixture was stirred for 1 h at the same temperature. After addition of Et_2O, saturated aq. $NaHCO_3$ and 10% aq. $Na_2S_2O_3$, the resulting mixture was further stirred for 30 min at the same temperature. The aqueous layer was separated and extracted with Et_2O and the combined organic layer and extracts were washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give the aldehyde as an oil; ν_{max}(neat)/cm^{-1} 1745 and 1260; δ_H(300 MHz, $CDCl_3$) 0.05 (6H, s, $SiMe_2$), 0.07 (9H, s, Bu^t), 0.89 (3H, d, *J* 10.3, 2-Me), 3.71–3.99 (2H, m, 3-H_2) and 9.78 (d, *J* 5.1, CHO), which was used in the next reaction without purification.

A mixture of the above product and *N*-benzylhydroxylamine (22.0 mg, 0.179 mmol) in dry CH_2Cl_2 (0.65 cm^3) was stirred for 12 h at room temperature. After dilution with CH_2Cl_2, the mixture was washed with 10% $KHSO_4$ and brine, dried and evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with AcOEt–hexane (3:7, v/v) provided **44** (20.6 mg, 53%) as an oil, $[\alpha]_D^{24}$ −41.4 (*c* 1.44, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1600 and 1250; δ_H(300 MHz, $CDCl_3$) 0.01 (6H, s, $SiMe_2$), 0.85 (9H, s, Bu^t), 1.60 (3H, d, *J* 22.7, 2-Me), 3.78 (1H, dd, *J* 18.9 and 11.2, 3-H), 4.24 (1H, dd, *J* 30.9 and 11.2, 3-H), 4.85 (1H, d, *J* 13.7, NC*H*HPh), 4.90 (1H, d, *J* 13.7, NCH*H*Ph), 6.74 (1H, d, *J* 12.1, 1-H) and 7.38 (5H, br s, Ph); δ_C(125 MHz, $CDCl_3$) −5.5, −5.4, 17.5, 18.3, 25.9, 65.2, 70.5, 96.7, 129.1, 129.2, 129.4, 132.5 and 138.3; *m*/*z* (EI) 325.1899 (M^+. $C_{17}H_{28}FNO_2Si$ requires 325.1873).

(−)-*N*-[(2*R*)-2-(*tert*-Butyldimethylsiloxymethyl)-2-fluorobutylidene]benzylamine *N*-oxide 45
An oil (63%): $[\alpha]_D^{24}$ −46.9 (*c* 1.29, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1600

and 1255; δ_H(300 MHz, $CDCl_3$) 0.01 (6H, s, $SiMe_2$), 0.82–0.92 (12H, m), 1.66–1.87 (1H, m, 3-H), 2.21–2.48 (1H, m, 3-H), 3.78 (1H, dd, *J* 18.3 and 11.3, OC*H*HCF), 4.29 (1H, dd, *J* 31.7 and 11.3, OCH*H*CF), 4.88 (2H, s, NCH_2Ph), 6.70 (1H, d, *J* 12.1, 1-H) and 7.39 (5H, br s, Ph); δ_C(125 MHz, $CDCl_3$) −5.4, 7.6, 18.3, 24.1, 25.9, 64.5, 70.4, 99.7, 129.0, 129.1, 129.3, 132.5 and 137.8; *m*/*z* (EI) 339.2017 (M^+. $C_{18}H_{30}FNO_2Si$ requires 339.2030).

_N_-[3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2-phenylpropylidene]-benzylamine _N_-oxide 46

Needles (82%), mp 79.0–79.5 °C; ν_{max}(neat)/cm^{-1} 1610, 1590 and 1260; δ_H(300 MHz, $CDCl_3$) −0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.84 (9H, s, Bu^t), 4.02 (1H, dd, *J* 17.6 and 11.4, 3-H), 4.59 (1H, dd, *J* 31.5 and 11.4, 3-H), 4.89 (2H, s, NCH_2Ph), 6.95 (1H, d, *J* 11.7, 1-H) and 7.20–7.52 (10H, m, 2 × Ph); δ_C(75 MHz, $CDCl_3$) −5.5, 18.3, 25.8, 66.5, 70.8, 125.2, 128.2, 128.6, 128.95, 129.04, 129.3, 132.5 and 137.3; *m*/*z* (EI) 387.2030 (M^+. $C_{22}H_{30}FNO_2Si$ requires 387.2030).

_N_-(3-Benzoyloxy-2-fluoro-2-methylbutylidene)benzylamine _N_-oxide 47

Needles (75%), mp 103–104 °C; ν_{max}(neat)/cm^{-1} 1720 and 1600; δ_H(300 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.6, 3-Me), 1.76 (3H, d, *J* 23.4, 2-Me), 4.92 (2H, s, NCH_2Ph), 5.87 (1H, dq, *J* 19.8 and 6.6, 3-H), 6.77 (1H, d, *J* 12.8, 1-H), 7.35–7.58 (8H, m, 8 × ArH) and 8.01–8.04 (2H, m, 2 × ArH); *m*/*z* (EI) 329.1440 (M^+. $C_{19}H_{20}FNO_3$ requires 329.1427).

_N_-(2-Fluoro-3-hydroxy-2,3-dimethylbutylidene)benzylamine _N_-oxide 48

A pale yellowish oil (44%) (Found: C, 65.25; H, 7.6; N, 5.85. $C_{13}H_{18}FNO_2$ requires C, 65.15; H, 7.45; N, 5.9%); ν_{max}(neat)/cm^{-1} 3200 and 1260; δ_H(300 MHz, $CDCl_3$) 1.18 (3H, s, Me), 1.22 (3H, d, *J* 3.3, Me), 1.67 (3H, d, *J* 23.1, 2-Me), 4.94 (1H, s, NCH_2Ph), 6.42 (1H, br s, OH), 6.91 (1H, d, *J* 14.6, 1-H) and 7.40–7.46 (5H, m, Ph); *m*/*z* (EI) 224 (M^+ − Me).

_N_-[3-(*tert*-Butyldimethylsiloxy)-2-fluoro-2,3-dimethylbutylidene]benzylamine _N_-oxide 49

An oil (86%) (Found: C, 64.25; H, 9.15; N, 4.2. $C_{19}H_{32}FNO_2Si$ requires C, 64.35; H, 9.4; N, 3.95%); ν_{max}(neat)/cm^{-1} 1580; δ_H(300 MHz, $CDCl_3$) −0.04 (3H, s, SiMe), 0.03 (3H, s, SiMe), 0.75 (9H, s, Bu^t), 1.19 (3H, d, *J* 1.6, Me), 1.20 (3H, s, Me), 1.70 (3H, d, *J* 22.5, 2-Me), 4.83–4.95 (2H, m, NCH_2Ph), 6.69 (1H, d, *J* 12.1, 1-H) and 7.37 (5H, s); *m*/*z* (EI) 296 (M^+ − Bu^t).

_N_-[3-(*tert*-Butyldimethylsiloxy)-2-methylpropylidene]benzylamine _N_-oxide 52

An oil (81%), ν_{max}(neat)/cm^{-1} 1595 and 1250; δ_H(300 MHz, $CDCl_3$) −0.02 (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.84 (9H, s, Bu^t), 1.10 (3H, d, *J* 7.0, 2-Me), 3.13–3.27 (1H, m, 2-H), 3.55 (1H, dd, *J* 9.8 and 5.1, 3-H), 3.69 (1H, dd, *J* 9.8 and 4.6, 3-H), 4.87 (2H, s, NCH_2Ph), 6.60 (1H, d, *J* 7.0, 1-H) and 7.37 (5H, s, Ph); δ_C(75 MHz, $CDCl_3$) −5.7, 13.0, 18.0, 25.7, 34.1, 64.2, 69.1, 128.6, 128.7, 129.0, 132.7 and 142.2; *m*/*z* (EI) 307.1985 (M^+. $C_{17}H_{29}NO_2Si$ requires 307.1968).

_N_-[2-(*tert*-Butyldimethylsiloxymethyl)butylidene]benzylamine _N_-oxide 53

An oil (47%), ν_{max}(neat)/cm^{-1} 1597, 1590 and 1260; δ_H(300 MHz, $CDCl_3$) −0.03, (3H, s, SiMe), 0.00 (3H, s, SiMe), 0.84 (9H, s, Bu^t), 0.90 (3H, t, *J* 7.5, 3-Me), 1.44–1.65 (2H, m, 3-H_2), 2.99–3.11 (1H, m, 2-H), 3.65 (1H, dd, *J* 9.9 and 4.6, C*H*HO), 3.74 (1H, dd, *J* 9.9 and 4.2, CH*H*O), 4.88 (2H, s, NCH_2Ph), 6.59 (1H, d, *J* 7.3, 1-H) and 7.38 (5H, br s, Ph); δ_C(75 MHz, $CDCl_3$) −5.9, 11.2, 17.7, 21.0, 25.4, 61.6, 69.0, 128.3, 128.6, 132.7, 140.90 and 140.94; *m*/*z* (EI) 321.2130 (M^+. $C_{18}H_{31}NO_2Si$ requires 321.2124).

_N_-[3-(*tert*-Butyldimethylsiloxy)-2-phenylpropylidene]benzylamine _N_-oxide 54

Needles (58%), mp 113.7–114.2 °C (Found: C, 71.6; H, 8.5; N, 3.8. $C_{22}H_{31}NO_2Si$ requires C, 71.5; H, 8.45; N, 3.8%); ν_{max}(neat)/cm^{-1} 1590 and 1260; δ_H(300 MHz, $CDCl_3$) −0.08 (6H, s, $SiMe_2$), 0.81 (9H, s, Bu^t), 3.85 (1H, dd, *J* 9.8 and 5.9, 3-H), 3.98 (1H, dd, *J* 9.8 and 4.9, 3-H), 4.31–4.40 (1H, m, 2-H), 4.91 (2H, s, NCH_2Ph), 6.98 (1H, d, *J* 7.3, 1-H), 7.22–7.32 (5H, m, Ph) and 7.37–7.41 (5H, m, Ph); δ_C(75 MHz, $CDCl_3$) −5.6, 18.1, 25.8, 45.5, 64.4, 69.5, 127.0, 128.3, 128.4, 128.8, 129.0, 129.2, 132.8, 138.6 and 139.2; *m*/*z* (EI) 369 (M^+).

_N_-(3-Hydroxy-2,3-dimethylbutylidene)benzylamine _N_-oxide 55

An oil (27%), ν_{max}(neat)/cm^{-1} 3450 and 1600; δ_H(300 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.1, 2-Me), 1.14 (3H, s, Me), 1.24 (3H, s, Me), 3.16–3.27 (1H, m, 2-H), 4.93 (2H, s, NCH_2Ph), 6.70 (1H, d, *J* 7.4, 1-H) and 7.31–7.43 (5H, m, Ph); *m*/*z* (EI) 221.1407 (M^+. $C_{13}H_{19}NO_2$ requires 221.1415).

_N_-[3-(*tert*-Butyldimethylsiloxy)-2,3-dimethylbutylidene]benzylamine _N_-oxide 56

An oil (90%), ν_{max}(neat)/cm^{-1} 1595; δ_H(300 MHz, $CDCl_3$) −0.05 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.73 (9H, s, Bu^t), 1.03 (3H, d, *J* 6.9, 2-Me), 1.11 (3H, s, Me), 1.18 (3H, s, Me), 2.98–3.07 (1H, m, 2-H), 4.86 (2H, s, NCH_2Ph), 6.59 (1H, d, *J* 8.0, 1-H) and 7.36 (5H, s, Ph); *m*/*z* (EI) 278.1575 (M^+ − Bu^t. $C_{15}H_{24}NO_2Si$ requires 278.1575).

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′-fluoro-1′-methylethyl]-5-ethoxyisoxazolidines 57

An oil (86%), ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) −0.02–0.10 (6H, m, $SiMe_2$), 0.82–0.95 (9H, m, Bu^t), 1.10–1.60 (6H, m), 1.87–2.67 (2H, m), 3.23–4.45 (7H, m), 5.02–5.25 (1H, m, 5-H) and 7.17–7.45 (5H, m, Ph); *m*/*z* (EI) 397.2321 (M^+. $C_{21}H_{36}FNO_3Si$ requires 397.2341).

2-Benzyl-3-[1′-(*tert*-butyldimethylsiloxymethyl)-1′-fluoropropyl]-5-ethoxyisoxazolidines 58

An oil (85%), ν_{max}(neat)/cm^{-1} 1260 and 1255; δ_H(300 MHz, $CDCl_3$) 0.01–0.11 (6H, m, $SiMe_2$), 0.63–1.03 (9H, m, Bu^t), 1.10–1.28 (6H, m), 1.52–2.68 (6H, m), 3.22–4.44 (7H, m), 5.01–5.22 (1H, m, 5-H) and 7.19–7.47 (5H, m, Ph); *m*/*z* (EI) 411.2581 (M^+. $C_{22}H_{38}FNO_3Si$ requires 411.2605).

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′-fluoro-1′-phenylethyl]-5-ethoxyisoxazolidines 59

An oil (97%), ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) −0.25–0.20 (6H, m, $SiMe_2$), 0.60–1.30 (12H, m), 2.10–2.59 (2H, m), 3.13–4.50 (7H, m), 4.67–5.30 (1H, m, 5-H), 7.11–7.63 (10H, m, 2 × Ph); *m*/*z* (EI) 459.2642 (M^+. $C_{26}H_{38}FNO_3Si$ requires 459.2605).

2-Benzyl-3-(2′-benzoyloxy-1′-fluoro-1′-methylpropyl)-5-ethoxyisoxazolidines 60

A pale yellowish oil (100%), ν_{max}(neat)/cm^{-1} 1720 and 1180; δ_H(300 MHz, $CDCl_3$) 0.98–1.58 (9H, m), 2.33–2.77 (2H, m), 3.25–4.44 (6H, m), 5.12–5.66 (2H, m), 7.23–7.59 (8H, m) and 7.94–8.04 (2H, m); *m*/*z* (EI) 401.2011 (M^+. $C_{23}H_{28}FNO_4$ requires 401.2003).

2-Benzyl-3-(1′-fluoro-2′-hydroxy-1′,2′-dimethylpropyl)-5-ethoxyisoxazolidines 61

Compound **61A**: a pale yellowish oil (55%), ν_{max}(neat)/cm^{-1} 3350; δ_H(300 MHz, $CDCl_3$) 1.12–1.51 (12H, m), 2.38–2.86 (2H, m), 3.36–4.69 (6H, m), 5.26–5.32 (1H, m) and 7.26–7.36 (5H, m, Ph); *m*/*z* (EI) 311.1897 (M^+. $C_{17}H_{26}FNO_3$ requires 311.1874).

Compound **61B**: a pale yellowish oil (28%), ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 0.89 (3H, s), 1.12–1.28 (9H, m), 3.30–4.44 (5H, m), 5.07–5.38 (1H, m), 6.00–6.20 (1H, m) and

7.27–7.43 (5H, m, Ph); *m/z* (EI) 311.1914 (M^+. $C_{17}H_{26}FNO_3$ requires 311.1874).

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′-fluoro-1′,2′-dimethylpropyl]-5-ethoxyisoxazolidines 62

Compound **62A**: an oil (80%), ν_{max}(neat)/cm^{-1} 1170; δ_H(300 MHz, $CDCl_3$) 0.08–0.15 (6H, m), 0.84–0.90 (9H, m), 1.13–1.56 (12H, m), 2.42–2.86 (2H, m), 3.28–4.46 (5H, m), 5.16–5.34 (1H, m, 5-H) and 7.22–7.42 (5H, m, Ph); *m/z* (EI) 425.2768 (M^+. $C_{23}H_{40}FNO_3Si$ requires 425.2759).

Compound **62B**: a pale yellowish oil (84%), ν_{max}(neat)/cm^{-1} 1180; δ_H(300 MHz, $CDCl_3$) 0.90–0.16 (6H, m, $SiMe_2$), 0.86–0.90 (9H, m, Bu^t), 1.09–1.58 (12H, m), 2.11–2.48 (2H, m), 3.24–4.52 (5H, m), 4.98–5.08 (1H, m, 5-H) and 7.21–7.44 (5H, m, Ph); *m/z* (EI) 425.2769 (M^+. $C_{23}H_{40}FNO_3Si$ requires 425.2759).

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′-methylethyl]-5-ethoxyisoxazolidines 63

An oil (84%), ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) −0.01–0.30 (6H, m, $SiMe_2$), 0.91–1.27 (15H, m), 1.30–2.55 (3H, m), 2.87–3.03 (1H, m), 3.31–4.28 (6H, m), 5.09–5.18 (1H, m, 5-H) and 7.23–7.43 (5H, m, Ph); *m/z* (EI) 379.2546 (M^+. $C_{21}H_{37}NO_3Si$ requires 379.2543).

2-Benzyl-3-[1′-(*tert*-butyldimethylsiloxymethyl)propyl]-5-ethoxyisoxazolidines 64

An oil (88%), ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) −0.10–0.04 (6H, m, $SiMe_2$), 0.93–1.72 (17H, m), 2.20–2.26 (1H, m), 2.32–2.49 (1H, m), 2.95–3.14 (1H, m), 3.30–3.89 (6H, m), 4.05–4.28 (1H, m), 5.05–5.19 (1H, m, 5-H) and 7.20–7.46 (5H, m); *m/z* (EI) 393.2694 (M^+. $C_{22}H_{39}NO_3Si$ requires 393.2699).

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′-phenylethyl]-5-ethoxyisoxazolidines 65

An oil (95%), ν_{max}(neat)/cm^{-1} 1260 and 1255; δ_H(300 MHz, $CDCl_3$) −0.10–0.06 (6H, m, $SiMe_2$), 1.16–1.40 (9H, m, Bu^t), 1.52 –1.55 (3H, m), 2.15–2.40 (1H, m), 3.17–4.46 (9H, m), 5.19–5.30 (1H, m, 5-H) and 7.19–7.60 (10H, m); *m/z* (EI) 441.2686 (M^+. $C_{26}H_{39}NO_3Si$ requires 441.2699).

2-Benzyl-3-(2′-hydroxy-1′,2′-dimethylpropyl)-5-ethoxyisoxazolidines 66

Compound **66A**: an oil (32%), ν_{max}(neat)/cm^{-1} 1260; δ_H(300 MHz, $CDCl_3$) 0.84–1.74 (12H, m), 1.89–2.72 (2H, m), 3.12–4.23 (5H, m), 5.08–5.17 (1H, m) and 7.22–7.43 (5H, m, Ph); *m/z* (EI) 247.1594 (M^+ − HOEt. $C_{15}H_{21}NO_2$ requires 247.1571).

Compound **66B**: an oil (34%), ν_{max}(neat)/cm^{-1} 3350 and 1280; δ_H(300 MHz, $CDCl_3$) 0.78–1.32 (12H, m), 2.06–2.67 (2H, m), 3.14–4.39 (5H, m), 5.31–5.34 (1H, m, 5-H) and 7.25–7.40 (5H, m); *m/z* (EI) 247.1553.

2-Benzyl-3-[2′-(*tert*-butyldimethylsiloxy)-1′,2′-dimethylpropyl]-5-ethoxyisoxazolidines 67B

An oil (60%) (Found: C, 68.1; H, 10.0; N, 3.55. $C_{23}H_{41}NO_3Si$ requires C, 67.95; H, 9.9; N, 3.45%); ν_{max}(neat)/cm^{-1} 1160; δ_H(300 MHz, $CDCl_3$) 0.04–0.09 (6H, m, $SiMe_2$), 0.82–1.24 (9H, m, Bu^t), 1.62–1.71 (1H, m), 2.04–2.39 (2H, m), 3.02–4.22 (5H, m), 5.02–5.05 (1H, m, 5-H) and 7.18–7.43 (5H, m, Ph); *m/z* (EI) 407 (M^+ + H).

6-Benzyl-4-fluoro-4-methyl-2,7-dioxa-6-azabicyclo[3.2.1]-octanes 68A, B

A mixture of **57A**, **B** (51.9 mg, 0.136 mmol) and toluene-*p*-sulfonic acid (13.0 mg, 0.068 mmol) in benzene (2.0 cm^3) was heated under reflux for 7 h. After dilution with AcOEt, the mixture was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with AcOEt–hexane (1:10, v/v) provided **68A** (12.0 mg, 40%) as an oil, ν_{max}(neat)/cm^{-1} 1460 and 1450; δ_H(300 MHz, $CDCl_3$) 1.16 (3H, d, *J* 21.4, 4-Me), 2.02–2.11 (1H, m, 8-H), 2.62 (1H, dd, *J* 11.9 and 2.8, 8-H), 3.41 (1H, br d, *J* 4.9, 5-H), 3.65 (1H, br dd, *J* 15.6, 12.2, 3-H), 3.76 (1H, br d, *J* 12.8, NC*H*HPh), 3.82 (1H, br dd, *J* 39.1, 12.2, 3-H), 4.21 (1H, d, *J* 12.8, NCH*H*Ph), 5.62 (1H, br d, *J* 3.7, 1-H) and 7.16–7.57 (5H, m, Ph); *m/z* (EI) 237.1141 (M^+. $C_{13}H_{16}FNO_2$ requires 237.1165).

Further elution with AcOEt–hexane afforded **68B** (11.2 mg, 37%) as an oil, ν_{max}(neat)/cm^{-1} 1440 and 1420; δ_H(300 MHz, $CDCl_3$) 1.47 (3H, d, *J* 22.6, 4-Me), 2.08 (1H, br dd, *J* 12.5 and 1.5, 8-H), 2.13–2.21 (1H, m, 8-H), 3.50 (1H, br dd, *J* 8.5, 6.1, 5-H), 3.56 (1H, br d, *J* 10.4, 3-H), 3.88 (1H, d, *J* 13.4, NC*H*HPh), 4.08 (1H, dd, *J* 11.0 and 10.4, 3-H), 4.23 (1H, d, *J* 13.4, NH*H*Ph), 5.56 (1H, br dd, *J* 5.5 and 3.1, 1-H) and 7.22–7.46 (5H, m, Ph); *m/z* (EI) 237.1141.

6-Benzyl-4-ethyl-4-fluoro-2,7-dioxa-6-azabicyclo[3.2.1]octanes 69A, B

Compound **69A**: an oil (41%), $[\alpha]_D^{24}$ +54.5 (*c* 0.47, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1440, 1455 and 1450; δ_H(300 MHz, $CDCl_3$) 0.56 (3H, t, *J* 7.3, 4-CH_2CH_3), 1.48 (1H, dq, *J* 29.9 and 7.3, 4-C*H*H), 1.55 (1H, dq, *J* 30.5 and 7.3, 4-CH*H*), 2.06–2.14 (1H, m, 8-H), 2.58 (1H, dd, 1H, *J* 11.9 and 2.7, 8-H), 3.51 (1H, br d, *J* 5.5, 5-H), 3.64 (1H, dd, *J* 15.9 and 12.8, 3-H), 3.72 (1H, d, *J* 12.2, NC*H*HPh), 3.81 (1H, dd, *J* 39.1 and 12.8, 3-H), 4.23 (1H, d, *J* 12.2, NCH*H*Ph), 5.63 (1H, br d, *J* 3.1, 1-H) and 7.28–7.38 (5H, m, Ph); δ_C(125 MHz, $CDCl_3$) 5.4, 26.3, 32.0, 60.7, 62.0, 67.5, 98.6, 128.0, 128.7, 129.4 and 136.5; *m/z* (EI) 251.1304 (M^+. $C_{14}H_{18}FNO_2$ requires 251.1322).

Compound **69B**: an oil (36%), $[\alpha]_D^{24}$ −51.2 (*c* 0.55, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1460 and 1455; δ_H(300 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.3, 4-CH_2CH_3), 1.83 (2H, br dq, *J* 25.0, 7.3, 4-CH_2), 2.05 (1H, br dd, *J* 12.2 and 1.8, 8-H), 2.16 (1H, br ddd, *J* 12.2, 6.1 and 3.1, 8-H), 3.56 (1H, br dd, *J* 8.5 and 6.1, 1-H), 3.60 (1H, br d, *J* 11.0, 3-H), 3.90 (1H, d, *J* 13.4, NC*H*HPh), 4.02 (1H, br t, *J* 11.0, 3-H), 4.22 (1H, d, *J* 13.4, NCH*H*Ph), 5.55 (1H, dd, *J* 5.5 and 3.1, 1-H) and 7.28–7.44 (5H, m, Ph); δ_C(125 MHz, $CDCl_3$) 7.0, 28.0, 34.5, 61.8, 63.4, 66.2, 97.4, 127.6, 128.5, 128.8 and 136.9; *m/z* (EI) 251.1300 (M^+).

6-Benzyl-4-fluoro-4-phenyl-2,7-dioxa-6-azabicyclo[3.2.1]octanes 70A, B

Compound **70A**: an oil (34%), ν_{max}(neat)/cm^{-1} 1490 and 1450; δ_H(300 MHz, $CDCl_3$) 2.10–2.24 (1H, m, 8-H), 2.84 (1H, br dd, *J* 12.1 and 3.3, 8-H), 3.73–3.91 (3H, m), 4.13 (1H, d, *J* 13.2, NC*H*HPh), 4.35 (1H, dd, *J* 40.1 and 13.0, 3-H), 5.72 (1H, br d, *J* 3.3, 1-H) and 7.18–7.63 (10H, m, Ph); *m/z* (EI) 299.1342 (M^+. $C_{18}H_{18}FNO_2$ requires 299.1322).

Compound **70B**: an oil (38%), ν_{max}(neat)/cm^{-1} 1490 and 1450; δ_H(300 MHz, $CDCl_3$) 1.94 (1H, br d, *J* 12.8, 8-H), 1.98–2.11 (1H, m, 8-H), 3.70 (1H, br dd, *J* 9.3 and 6.0, 5-H), 3.95 (1H, d, *J* 13.2, NC*H*HPh), 4.17–4.43 (3H, m), 5.65 (1H, br dd, *J* 5.5 and 2.6, 1-H) and 7.23–7.55 (10H, m, 2 × Ph); *m/z* (EI) 299.1333 (M^+).

6-Benzyl-4-fluoro-3,4-dimethyl-2,7-dioxa-6-azabicyclo[3.2.1]-octanes 71A, B

A mixture of **60A**, **B** (61.0 mg, 0.151 mmol) and KOH (13 mg, 0.28 mmol) in MeOH (4.5 cm^3) was stirred for 19 h at room temperature. After concentration under reduced pressure, the residue was taken up into Et_2O. The organic layer was washed with brine, dried and evaporated. Column chromatography of the residue on silica gel with AcOEt–hexane (1:17, v/v) as eluent gave the corresponding alcohols (40.0 mg, 98%) as a pale yellowish oil, ν_{max}(neat)/cm^{-1} 3500; δ_H(300 MHz, $CDCl_3$) 1.25–1.52 (9H, m), 2.37–2.81 (2H, m), 3.15–4.52 (8H, m), 5.02–5.32 (2H, m) and 7.23–7.41 (5H, m, Ph); *m/z* (EI) 297.1717 (M^+. $C_{16}H_{24}FNO_3$ requires 297.1740).

A mixture of the above alcohols (26.0 mg, 87 μmol) and toluene-*p*-sulfonic acid (9.2 mg, 48 μmol) in benzene (3 cm^3) was heated for 6 h at 50 °C. After dilution with Et_2O, the mixture was washed with saturated aq. $NaHCO_3$ and brine, dried and evaporated to afford a residue, which was subjected to column

chromatography on silica gel. Elution with Et_2O–hexane (1:7, v/v) provided **71A** (13.6 mg, 56%) as a solid, mp 88–90 °C (Found: C, 66.75; H, 7.25; N, 5.75. $C_{14}H_{18}FNO_2$ requires C, 66.9; H, 7.2; N, 5.55%); ν_{max}(neat)/cm^{-1} 1180; δ_H(300 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.8, 3-Me), 1.29 (3H, d, *J* 22.3, 4-Me), 2.04 (1H, dd, *J* 12.3 and 1.7, 8-H), 2.12–2.20 (1H, m, 8-H), 3.51 (1H, dd, *J* 9.3 and 5.7, 5-H), 3.87 (1H, d, *J* 13.6, NC*H*HPh), 4.20 (1H, d, *J* 13.6, NCH*H*Ph), 4.29 (1H, dq, *J* 19.8 and 6.8, 3-H), 5.51 (1H, dd, *J* 5.1 and 2.9, 1-H) and 7.23–7.44 (5H, m, Ph); *m*/*z* (EI) 251 (M$^+$).

Further elution gave **71B** (5.6 mg, 22%) as an oil (Found: C, 66.65; H, 7.35; N, 5.25); ν_{max}(neat)/cm^{-1} 1200; δ_H(300 MHz, $CDCl_3$) 1.24 (3H, d, *J* 23.1, 4-Me), 1.39 (3H, d, *J* 7.3, 3-Me), 2.00–2.11 (1H, m, 8-H), 2.58 (1H, dd, *J* 11.9 and 2.4, 8-H), 3.37 (1H, t, *J* 4.4, 5-H), 3.74 (1H, d, *J* 12.5, NC*H*HPh), 3.98 (1H, dq, *J* 24.2 and 7.3, 3-H), 4.16 (1H, d, *J* 12.5, NCH*H*Ph), 5.63 (1H, d, *J* 3.3, 1-H) and 7.26–7.39 (5H, m, Ph); *m*/*z* (EI) 251 (M$^+$).

6-Benzyl-4-fluoro-3,3,4-trimethyl-2,7-dioxa-6-azabicyclo[3.2.1]-octanes 72A, B

Compound **72A**: a pale yellowish oil (64%) (Found: C, 67.75; H, 7.6; N, 5.3. $C_{15}H_{20}FNO_2$ requires C, 67.9; H, 7.6; N, 5.3%); ν_{max}(neat)/cm^{-1} 1150; δ_H(300 MHz, $CDCl_3$) 1.18 (3H, s, 3-Me), 1.37 (3H, d, *J* 23.1, 4-Me), 1.85 (3H, d, *J* 6.6, 3-Me), 2.02 (1H, dd, *J* 11.9 and 2.1, 8-H), 2.15–2.23 (1H, m, 8-H), 3.48 (1H, dd, *J* 7.8 and 6.2, 5-H), 3.85 (1H, d, *J* 13.5, NC*H*HPh), 4.15 (1H, d, *J* 13.5, NCH*H*Ph), 5.52–5.54 (1H, m, 1-H) and 7.26–7.45 (5H, m, Ph); *m*/*z* (EI) 265 (M$^+$).

Compound **72B**: a pale yellowish oil (53%) (Found: C, 68.0; H, 7.6; N, 5.45); ν_{max}(neat)/cm^{-1} 1150; δ_H(300 MHz, $CDCl_3$) 1.19 (3H, s, 3-Me), 1.22 (3H, d, *J* 23.4, 4-Me), 1.50 (3H, s, 3-Me), 2.00–2.08 (1H, m, 8-H), 2.51 (1H, dd, *J* 11.7 and 3.4, 8-H), 3.40 (1H, dd, *J* 5.2 and 1.1, 5-H), 3.74 (1H, d, *J* 12.6, NC*H*HPh), 4.16 (1H, d, *J* 12.6, NCH*H*Ph), 5.61 (1H, d, *J* 3.3, 1-H) and 7.26–7.40 (5H, m, Ph); *m*/*z* (EI) 265 (M$^+$).

6-Benzyl-4-methyl-2,7-dioxa-6-azabicyclo[3.2.1]octanes 73A, B

Compound **73A**: an oil (31%), ν_{max}(neat)/cm^{-1} 1460 and 1450; δ_H(500 MHz, $CDCl_3$) 1.05 (3H, d, *J* 7.3, 4-Me), 1.84–1.93 (1H, m, 4-H), 1.94–1.98 (1H, m, 8-H), 2.30 (1H, br d, *J* 11.6, 8-H), 3.31 (1H, br d, *J* 11.0, 5-H), 3.36 (1H, dd, *J* 11.0 and 4.9, 3-H), 3.79 (1H, br d, *J* 12.8, NC*H*HPh), 4.18 (1H, br d, *J* 12.8, NCH*H*Ph), 4.20 (1H, br dd, *J* 11.0 and 5.5, 3-H), 5.56 (1H, br d, *J* 3.1, 1-H) and 7.27–7.42 (5H, m, Ph); *m*/*z* (EI) 219.1259 (M$^+$).

Compound **73B**: an oil (50%), ν_{max}(neat)/cm^{-1} 1470 and 1460; δ_H(500 MHz, $CDCl_3$) 0.71 (3H, d, *J* 6.7, 4-Me), 1.78–1.86 (1H, m, 4-H), 1.98 (1H, br d, *J* 11.6, 8-H), 2.18–2.25 (1H, m, 8-H), 3.21 (1H, br d, *J* 5.5, 5-H), 3.59 (1H, br t, *J* 11.0, 3-H), 3.65 (1H, dd, *J* 11.0 and 6.7, 3-H), 3.73 (1H, d, *J* 12.8, NC*H*HPh), 4.21 (1H, d, *J* 12.8, NCH*H*Ph), 5.59 (1H, br d, *J* 3.7, 1-H) and 7.25–7.42 (5H, m, Ph); *m*/*z* (EI) 219.1246 (M$^+$. $C_{13}H_{17}NO_2$ requires 219.1259).

6-Benzyl-4-ethyl-2,7-dioxa-6-azabicyclo[3.2.1]octanes 74A, B

Compound **74A**: an oil (40%), ν_{max}(neat)/cm^{-1} 1465 and 1455; δ_H(500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.3, 4-CH_2CH_3), 1.34–1.44 (1H, m, 4-C*H*H), 1.45–1.55 (1H, m, 4-CH*H*), 1.55–1.63 (1H, m, 4-H), 1.93–2.02 (1H, m, 8-H), 2.23 (1H, br d, *J* 11.6, 8-H), 3.39–3.42 (m, 2H), 3.80 (1H, br d, *J* 12.8, NC*H*HPh), 4.14 (1H, dd, *J* 11.0 and 4.6, 3-H), 4.17 (1H, br d, *J* 12.8, NCH*H*Ph), 5.55 (1H, br d, *J* 3.1, 1-H) and 7.25–7.42 (5H, m, Ph); *m*/*z* (EI) 233.1398 (M$^+$).

Compound **74B**: an oil (33%), ν_{max}(neat)/cm^{-1} 1470 and 1460; δ_H(500 MHz, $CDCl_3$) 0.53 (3H, t, *J* 7.3, 4-CH_2CH_3), 1.07–1.19 (2H, m), 1.49–1.53 (1H, m, 4-H), 1.95 (1H, br d, *J* 11.6, 8-H), 2.20–2.28 (1H, m, 8-H), 3.37 (1H, br d, *J* 5.5, 5-H), 3.59 (1H, br t, *J* 10.9, 3-H), 3.66 (1H, t, *J* 10.9, 3-H), 3.71 (1H, br d, *J* 12.8, NC*H*HPh), 4.23 (1H, br d, *J* 12.8, NCH*H*Ph), 5.60 (1H, br d, *J* 3.1, 1-H) and 7.25–7.41 (5H, m, Ph); *m*/*z* (EI) 233.1432 (M$^+$. $C_{14}H_{19}NO_2$ requires 233.1416).

6-Benzyl-4-phenyl-2,7-dioxa-6-azabicyclo[3.2.1]octanes 75A, B

Compound **75A**: an oil (11%), ν_{max}(neat)/cm^{-1} 1500 and 1460; δ_H(500 MHz, $CDCl_3$) 1.84–1.91 (1H, m, 8-H), 2.24 (1H, br d, *J* 12.2, 8-H), 3.03–3.09 (1H, m, 4-H), 3.56–3.64 (1H, m, 5-H), 3.86 (1H, br d, *J* 11.6, 3-H), 4.02 (1H, d, *J* 13.4, NC*H*HPh), 4.20 (1H, d, *J* 13.4, NCH*H*Ph), 4.47 (1H, dd, *J* 11.6 and 4.9, 3-H), 5.66 (1H, br d, *J* 3.1, 1-H) and 7.28–7.46 (10H, m, Ph); *m*/*z* (EI) 281.1409 (M$^+$. $C_{18}H_{19}NO_2$ requires 281.1416).

Compound **75B**: an oil (50%), ν_{max}(neat)/cm^{-1} 1500 and 1455; δ_H(500 MHz, $CDCl_3$) 2.16 (1H, br d, *J* 11.6, 8-H), 2.31 (1H, br ddd, *J* 11.6, 5.9 and 3.5, 8-H), 2.96 (1H, br dd, *J* 11.6 and 6.1, 4-H), 3.68 (1H, br d, *J* 5.9, 5-H), 3.83 (1H, br d, *J* 12.8, NC*H*HPh), 3.86 (1H, br dd, *J* 11.0 and 6.1, 3-H), 4.13 (1H, d, *J* 12.8, NCH*H*Ph), 4.20 (1H, br dd, *J* 11.6 and 11.0, 3-H), 5.68 (1H, br d, *J* 3.5, 1-H) and 7.18–7.40 (10H, m, 2 × Ph); *m*/*z* (EI) 281.1402.

6-Benzyl-3,3,4-trimethyl-2,7-dioxa-6-azabicyclo[3.2.1]octane 76B

A pale yellowish oil (74%), ν_{max}(neat)/cm^{-1} 1180; δ_H(300 MHz, $CDCl_3$) 0.84 (3H, d, *J* 7.1, 4-Me), 1.15 (3H, s, Me), 1.39 (3H, s, Me), 1.75 (1H, dq, *J* 7.1 and 1.9, 4-H), 1.89 (1H, d, *J* 11.3, 8-H), 2.15–2.22 (1H, m, 8-H), 3.15 (1H, dd, *J* 5.8 and 1.9, 5-H), 3.68 (1H, d, *J* 12.9, NC*H*HPh), 4.12 (1H, d, *J* 12.9, NCH*H*Ph), 5.59 (1H, d, *J* 3.6, 1-H) and 7.21–7.40 (5H, m, Ph); *m*/*z* (EI) 247.1557 (M$^+$. $C_{15}H_{21}NO_2$ requires 247.1571).

Acknowledgements

We thank Mr K. Kawamura, Ms K. Mushiake, Ms M. Suzuki, Ms A. Satoh and Ms Y. Maehashi of this Institute for microanalyses, spectral measurements and the preparation of the paper.

References

1 (*a*) J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; (*b*) R. Feller and Y. Kobayashi, in *Biomedical Aspects of Fluorine Chemistry*, Kodansha and Elsevier Ltd., Tokyo, 1982; (*c*) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
2 M. Ihara, M. Takahashi, K. Fukumoto and T. Kametani, *J. Chem. Soc., Chem. Commun*., 1988, 9; *J. Chem. Soc., Perkin Trans. 1*, 1989, 2215.
3 M. Ihara, T. Kawabuchi, Y. Tokunaga and K. Fukumoto, *Heterocycles*, 1995, **40**, 97.
4 (*a*) M. Ihara, N. Taniguchi, T. Kai, K. Satoh and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1992, 221; (*b*) M. Ihara, T. Kawabuchi, Y. Tokunaga and K. Fukumoto, *Tetrahedron: Asymmetry*, 1994, **5**, 1041.
5 J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem*., 1969, **34**, 2543.
6 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl*., 1978, **17**, 522.
7 M. Ihara, M. Suzuki, A. Hirabayashi, Y. Tokunaga and K. Fukumoto, *Tetrahedron: Asymmetry*, 1995, **6**, 2053.
8 M. Hudlicky, *Org. React*., 1988, **35**, 513.
9 M. Simizu and H. Yoshioka, *Tetrahedron Lett*., 1988, **29**, 4101.
10 D. B. Dess and J. C. Martin, *J. Am. Chem. Soc*., 1991, **113**, 7277.
11 The results are consistent with the frontier orbital theory: I. Fleming, *Frontier Orbitals and Organic Reactions*, Wiley, Chichester, 1976, p. 148.
12 R. H. Baker, K. H. Cornell and M. J. Cron, *J. Am. Chem. Soc*., 1948, **70**, 1490.
13 N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom and G. Saucy, *J. Org. Chem*., 1976, **41**, 3505.
14 P. Grisenti, P. Ferraboschi, A. Manzocchi and E. Santaniello, *Tetrahedron*, 1992, **48**, 3827.
15 M. Ihara, F. Setsu, M. Shohda (*née* Hosoda), N. Taniguchi, Y. Tokunaga and K. Fukumoto, *J. Org. Chem*., 1994, **59**, 5317.

Paper 7/02810E
Received 24*th April* 1997
Accepted 14*th July* 1997