Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 245–250

First 1,3-dipolar cycloaddition of *Z*-α-phenyl-*N*-methylnitrone with allylic fluorides: a stereoselective route to enantiopure fluorine-containing isoxazolidines and amino polyols

Luca Bernardi, Bianca F. Bonini, Mauro Comes-Franchini,* Mariafrancesca Fochi, Mahena Folegatti, Stefano Grilli, Andrea Mazzanti and Alfredo Ricci

Dipartimento di Chimica Organica 'A. Mangini', Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy

Received 24 September 2003; accepted 4 November 2003

Abstract—Enantiopure fluorinated isoxazolidines and amino polyols were obtained from the 1,3-dipolar cycloaddition of allylic fluorides and *Z*-α-phenyl-*N*-methylnitrone under environment-friendly conditions.

1. Introduction

The introduction of a fluorine atom into biologically active compounds often induces strong modifications of their chemical, physical and biological properties. Due to this, the interest in fluorine-containing compounds has greatly increased over the last few decades,[1] since enantiopure fluorine-containing heterocycles and fluorinated amino polyols[2] have shown great potential as drug candidates.

As part of our ongoing interest in the stereoselective synthesis of enantiopure isoxazolidines containing a carbon–fluorine centre, we herein report on the 1,3-dipolar cycloaddition[3] of *Z*-α-phenyl-*N*-methylnitrone **1** with allylic fluorides, focusing on the use of environment-friendly conditions,[4] such as microwave irradiation and metal triflate catalysis. Moreover, since the reductive opening of isoxazolidine is a well known method for obtaining amino alcohols, this protocol might provide an easy entry to enantiopure fluorinated amino polyols. Our approach is based on the utilization of allylic fluorides as dipolarophiles. Very little is known at present about the effect of these moieties on stereoselective organic transformations.[5]

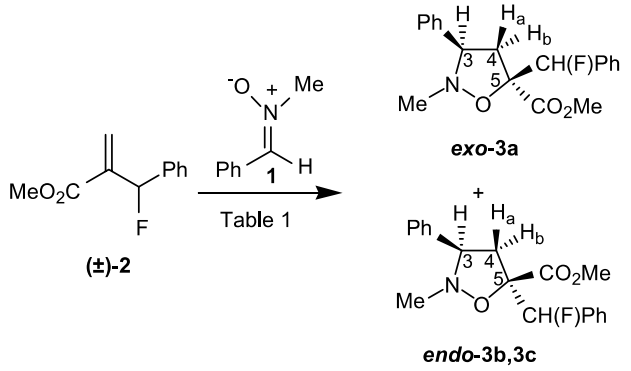
2. Results and discussion

The reaction of **1** with racemic methyl 2-[fluoro-(phenyl)methyl]acrylate **2**[5a] has been investigated as a model reaction, with the final aim of applying this protocol to allylic fluorides derived from the natural pool. In toluene as solvent under $In(OTf)_3$ catalysis (5 mol%), complete conversion of the starting materials was achieved after 24 h at reflux. Analysis of the crude mixtures using ^{19}F NMR showed three new sets of doublets for the CH–F signals, thus indicating the formation of three cycloadducts **3a**–**c**, in a 10:60:30 ratio. As far as the regiochemistry was concerned, after separation of the three diastereoisomers,[6] obtained in 46% overall yield, NMR analysis (COSY and gHSQC) confirmed that the three products were 5,5′-disubstituted isoxazolidines in agreement with the majority of the literature findings.[7]

Stereochemical assignment of the three adducts was based upon 1D-NOE experiments. Selective excitation[8] of the CH(F) signal in the first isolated adduct **3a** revealed a positive NOE effect only on one of the two diastereotopic CH_2 signals (H_{4a} in Scheme 1). This result is compatible with a structure in which the phenyl group and the CH(F)Ph group are on the same side of the ring **3a** (*exo*-structure). On the other hand, excitation of the CH(F) signals in the remaining adducts, **3b** and **3c**, showed NOE enhancements of the benzylic proton H_3 and of the other diastereotopic CH (H_{4b}) in line with arrangements in which the phenyl group and the CH(F)Ph group are on the opposite side of the ring. The

Keywords: Allylic fluorides; Nitrone; 1,3-Dipolar cycloaddition; Isoxazolidines; Amino polyols.
* Corresponding author. Tel.: +39-05-12093626; fax: +39-05-120936-54; e-mail: comes@ms.fci.unibo.it

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All right reserved.
doi:10.1016/j.tetasy.2003.11.008



Scheme 1.

unambiguous assignment of the two diastereotopic CH (H_{4a} and H_{4b}) was possible because of the long range (^4J) coupling constant of H_{4a} with the fluorine atom. This coupling constant can be observed only when the 'W' path is available.[10] Since **3b** and **3c** differ only in the stereochemistry at the carbon–fluorine bond and the starting allylic fluoride **2** being racemic, an overall *endo*/*exo* ratio of 90:10 can be calculated for this reaction.

A screening aimed at the optimization of the reaction conditions was then performed with the results shown in Table 1.

The use of microwave irradiation as an alternative method of heating reaction mixtures in cycloaddition reactions has been reported to dramatically reduce reaction times and affect product ratios and yields.[10] We applied this technique to the reaction shown in Scheme 1 performed in various reaction media such as water, ionic liquids (RTILs) and under solvent-free conditions with the aim of finding the optimal reaction conditions leading to **3a**–**c**. The use of these reaction media was inspired by the well known acceleration of cycloadditions in water[4,11] and the recently reported great potential of ionic liquids (RTILs)[12] as novel and environmentally benign solvents for transition metal catalyzed organic transformations. Catalytic amounts of triflates (5 mol%) were used throughout. As shown in Table 1 neither the yields nor the *exo*/*endo* ratio could be substantially improved by running the reaction in different media.[13] A remarkably shorter reaction time was obtained under microwave irradiation without affecting the yields (entries 2, 4, 6). A substantial improvement was finally achieved when the reaction of **1** with **2** was performed under microwave activation without any solvent in the presence of a catalytic amount of metal triflates. In two cases (entries 7 and 8), the cycloaddition proceeded smoothly to afford **3a**–**c** in 72–75% yields after 15 min.

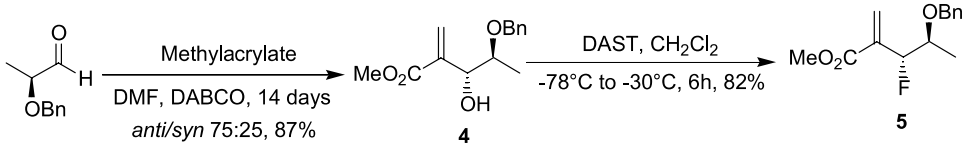
The final goal of this research was the development of asymmetric routes to unknown enantiomerically pure fluorinated isoxazolidines and to fluorinated amino polyols. For this, we applied this synthetic protocol to an enantiopure allylic fluoride. (*S*)-2-Benzyloxypropanal, a very useful building block for stereoselective synthesis, was the starting material of choice. Its Baylis–Hilmann[14] reaction with methyl acrylate in DMF gave, after 14 days, an 87% yield of the allylic alcohols **4** in an *anti*/*syn* ratio of 75:25.[15] Fluorination of the isolated *anti*-alcohol with DAST in CH_2Cl_2 yielded the enantiopure allylic fluoride **5** in 82% yield with retention of configuration[5a] (Scheme 2).

Cycloaddition of **5** with **1** in the presence of 5% $In(OTf)_3$ took place under the optimized solvent-free conditions and microwave irradiation at 60 W for 25 min to give a mixture of the 5,5′-isoxazolidine isomers **6a**–**b** in 61% overall yield in a 90:10 ratio (Scheme 3).

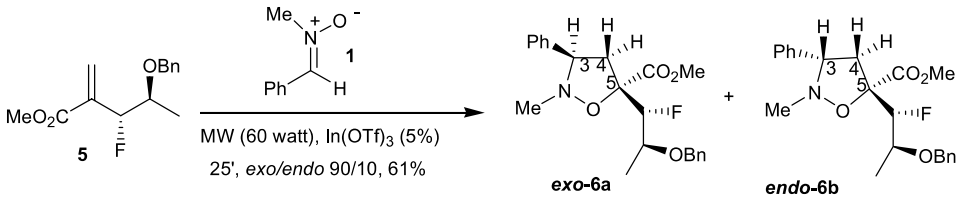
Semi-preparative HPLC allowed the separation of the two compounds with the relative assignment of **6a** and **6b** obtained from NOE data. Selective saturation[9] of the H_F hydrogen shows a positive NOE on one of the two diastereotopic H's at position 4 (H_a in Fig. 1). Selective irradiation of the latter reveals an NOE on the ortho

Table 1. 1,3-Dipolar cycloaddition reactions of **1** with **2**

Entry	Solvent	MW (W)	*T* (°C)/Time	Yield (%)	Lewis acid (5%)	Ratio **3a/3b/3c**
1	Toluene	—	110/24 h	46	$In(OTf)_3$	10:60:30
2	Toluene	120	110/10 min	48	$In(OTf)_3$	10:60:30
3	H_2O	—	rt/72 h	50	$Yb(OTf)_3$	10:60:30
4	H_2O	90	100/7 min	49	$Yb(OTf)_3$	10:60:30
5	$BimimBF_4$	—	80/16 h	19	$In(OTf)_3$	10:60:30
6	Toluene/$BimimBF_4$	90	165/10 min	39	$In(OTf)_3$	10:60:30
7	None	60	100/15 min	73	$Sc(OTf)_3$	10:60:30
8	None	60	100/15 min	75	$In(OTf)_3$	10:60:30



Scheme 2.



Scheme 3.

hydrogens of the phenyl group in one of the two diastereoisomers **6a** (in Fig. 1), and on the H at position 3 (HN) for the other diastereoisomer **6b** (Fig. 1).

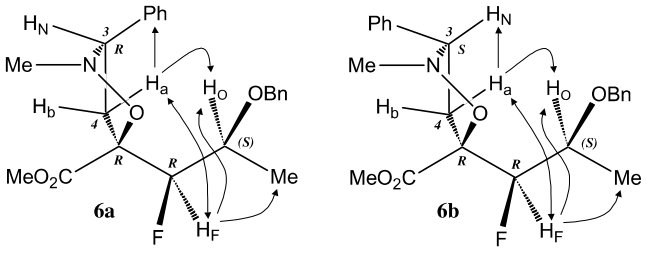
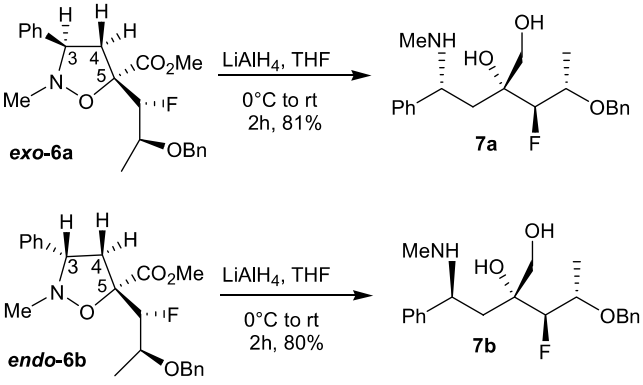


Figure 1.

These results imply an *exo*-structure for the major isomer **6a** and an *endo*-structure for the minor isomer **6b**. The absolute structure can be confirmed by the following NOE data. In the case of **6a**, selective saturation of H_a shows NOE effects also on H_F and H_O signals; saturation of H_F shows NOE effects on the signal of H_O and on the methyl group. NOE ratios show that the distances H_a–H_F and H_a–H_O are very similar, as well as the distances H_F–H_O and H_F–Me. Of the four obtainable diastereoisomers, only the 5(*R*)-CHF(*R*) structure matched the experimental NOE data (the *exo* relationship of the cycle is defined, and one stereogenic carbon, indicated as (*S*) in Fig. 1, is fixed). By applying the *exo* relationships, the configuration (3*R*,5*R*,*R*,*S*) can be assigned to **6a**. The same approach was used for **6b** and structure (3*S*,5*R*,*R*,*S*) assigned. This further confirms the retention of configuration in the DAST fluorination.

It has been claimed that the stereoselectivity in the 1,3-dipolar cycloaddition is very much affected by the structure of the substrates.[3] The explanation for the reversed stereoselectivity observed for **6a**–**b** in comparison with **3a**–**c** is currently under investigation, while as far as the influence of the fluorine on the reactivity and stereoselectivity is concerned, we can only rely on comparison with other structurally similar, non-fluorinated dipolarophiles. It has been reported that chiral allylic alcohols and ethers react with nitrones to give the 5,5′-disubstituted cycloadducts.[16] The stereochemical outcome of these cycloadditions is rationalized by an 'inside alkoxy' transition state model that always leads to *exo*/*endo* mixtures with a preference for the *exo*-cycloadduct. This outcome was ascribed to the electronegativity of the OR group in the allylic position, which prefers the inside to the outside position in the transition state to avoid the repulsive interaction between the allylic oxygen and the nitrone oxygen.[16] Accordingly, even though our understanding is at a preliminary level, we propose that also the strong electron-withdrawing fluorine atom might also increase the *exo*-preference in the transition state. Further studies are currently in progress to rationalize the chemical behaviour of allylic fluorides in 1,3-dipolar cycloadditions.

Reductive opening of the cycloadducts with $LiAlH_4$ in THF took place cleanly in 2 h affording **7a** and **7b** in 80–81% yields in which the ester functionality was also reduced (Scheme 4). These fluorinated enantiopure amino polyols are important structures containing up to four stereocentres, with one of them being quaternary.



Scheme 4.

3. Conclusions

In summary, the cycloadditions of the allylic fluorides with nitrone **1** reported herein allow the synthesis of enantiopure fluorine-containing isoxazolidines and amino polyols. To the best of our knowledge, this is the first 1,3-dipolar cycloaddition using allylic fluorides. The optimization of the reaction has been achieved under environment-friendly conditions and its extension to the synthesis of other fluorinated compounds of pharmaceutical interest is currently being investigated.

4. Experimental

Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions at 300, 400

and 600 MHz for 1H and 75.46, 100.6 and 150.92 MHz for ^{13}C. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$ for ^1H and $\delta = 77.0$ for ^{13}C or 7.24 and 128.0 ppm for C_6D_6) and relative to $CF_3C_6H_5$ ($\delta = -163.0$ ppm for ^{19}F). J values are given in Hz. ^1H NMR and ^{13}C NMR spectral assignments were made by DEPT, gCOSY and gHSQC experiments. IR spectra were recorded on a Perkin–Elmer model 257 grating spectrometer. Mass spectra were obtained using a VG 7070-E spectrometer at an ionizing voltage of 70 eV. HPLC analysis has been performed with a Kromasil column KR100-5SIL (25 cm, id = 4.6 mm) and semi-preparative separation with a Kromasil 100-10 silica (25 cm, id = 20 mm). $[\alpha]_D^{20}$ values were determined with Perkin–Elmer polarimeter 341. Reactions under microwave irradiation have been run in a monomode reactor, with a Synthwave 402 Prolabo focused MW at 2.45 GHz. Reactions were conducted in oven-dried (120 °C) glassware under a positive Ar atmosphere. Transfers of anhydrous solvents or mixtures were accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Toluene was distilled from sodium. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with bp 40–60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed with Merck silica gel 60 (70–230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1 mm layer of Merck silica gel 60 Pf 254. All chemicals were used as obtained or purified by distillation as needed. Lithium aluminium hydride (1 M THF) was purchased from Aldrich.

4.1. Methyl 2-[(1*R*,2*S*)-2-(benzyloxy)-1-fluoropropyl]-acrylate 2

To a stirred solution of DAST (1.0 ml, 7.6 mmol) in 5.0 ml of CH_2Cl_2 at −78 °C under argon, methyl 2-[hydroxy(phenyl)methyl]acrylate (1.46 g, 7.6 mmol) in 0.5 ml of CH_2Cl_2 was added. Stirring was continued at −78 °C for 5 min and then for 30 min at room temperature. The reaction was diluted with CH_2Cl_2 (20 ml) and washed with water, $NaHCO_3$ and brine. The resulting organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to give a dark orange oil, which was purified by silica gel column chromatography (petroleum ether/Et_2O 10:1) to give 736 mg (57%) of **2** as a pale yellow oil. IR (KBr): ν 3036, 1728, 1100–1000 cm^{-1}. m/z (ESI): 217 (M^++Na). ^1H NMR (300 MHz, $CDCl_3$): δ 3.37 (s, 3H, $COOCH_3$), 6.04 (s, 1H, CH_2=), 6.42 (d, 1H, $J = 46.0$ Hz, CH–Ph), 6.47 (d, 1H, $J = 2.0$ Hz, CH_2=), 7.35 (s, 5H, ArCH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 51.9 (CH_3O), 90.7 (d, $J = 173.4$ Hz, CH–F), 127.1–128.9 (ArCH), 137.4 (d, $J = 20.5$ Hz, C_q), 139.4 (d, $J = 22.5$ Hz, C_q), 165.2 (d, $J = 6.2$ Hz, $COOCH_3$) ppm. ^{19}F NMR (470.38 MHz, $CDCl_3$): δ −171.48 ppm.

4.2. General procedure for the 1,3-dipolar cycloaddition of 2

2-[Fluoro(phenyl)methyl]acrylate **2** (150 mg, 0.77 mmol), $In(OTf)_3$ (22 mg, 0.04 mmol) and *Z*-α-phenyl-*N*-methylnitrone **1** (104 mg, 0.77 mmol) were mixed in a cylindrical Pyrex sealed vessel. The mixture was introduced into the reactor and irradiated as described in Table 1. In the cases where toluene or water was used as solvent, 2 ml of them was added. After cooling, the mixture was extracted with ethyl acetate (3 × 20 ml), washed with water (2 × 20 ml) and dried over anhydrous sodium sulfate. After filtration, removal of the solvent and purification by column chromatography on silica gel (CH_2Cl_2/EtOAc 80:1), the three cycloadducts **3a–c** were obtained as pale yellow oils and fully characterized.

4.2.1. *exo*-Methyl 5-[fluoro(phenyl)methyl]-2-methyl-3-phenyltetrahydro-5- isoxazolecarboxylate 3a. m/z (ESI): 352 (M^++Na). (Found: C, 69.37; H, 6.19; N, 4.33; $C_{19}H_{20}FNO_3$ requires C, 69.29; H, 6.12; N, 4.25.) ^1H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3–N), 2.55 (dd, 1H, $J = 13.3$ Hz, $J = 10.6$ Hz, CH_2), 2.75 (dd, 1H, $J = 13.3$ Hz, $J = 6.50$ Hz, CH_2), 2.90 (dd, 1H, $J = 10.6$ Hz, $J = 6.5$ Hz, CH), 3.36 (s, 3H, CH_3O), 5.67 (d, 1H, $J = 45.1$ Hz, CH–F), 6.92–7.35 (m, 10H, ArCH) ppm. ^{13}C NMR (75.46 MHz, $CDCl_3$, +25 °C): δ 43.3 (CH_3–N), 45.1 (CH_2), 52.6 (CH_3O), 72.5 (CH–N), 85.9 (d, $J = 22.6$ Hz, C_q), 94.4 (d, $J = 183.9$ Hz, CH–F), 127.1–128.9 (ArCH), 134.7 (d, $J = 21.9$ Hz, Ar–C_q), 137.0 (Ar–C_q), 170.8 (C=O) ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ −174.8 (d, $J = 45.1$ Hz) ppm.

4.2.2. *endo*-Methyl 5-[fluoro(phenyl)methyl]-2-methyl-3-phenyltetrahydro-5-isoxazolecarboxylate 3b. m/z (ESI): 352 (M^++Na). ^1H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3–N), 2.68 (dd, 1H, $J = 13.2$ Hz, $J = 8.4$ Hz, CH_2), 2.75 (dd, 1H, $J = 13.2$ Hz, $J = 1.6$ Hz, CH_2), 2.96 (t, 1H, $J = 8.4$ Hz, CH), 3.40 (s, 3H, CH_3O), 5.64 (d, 1H, $J = 46.0$ Hz, CH–F), 6.95–7.15 (m, 10H, ArCH) ppm. ^{13}C NMR (50.30 MHz, $CDCl_3$): δ 42.5 (CH_3–N), 43.5 (CH_2), 52.4 (CH_3O), 72.9 (CH–N), 86.1 (d, $J = 22.6$ Hz, C_q), 93.9 (d, $J = 183.5$ Hz, CH–F), 127.2–129.2 (ArCH), 134.5 (d, $J = 20.5$ Hz, ArC_q), 137.5 (ArC_q), 172.1 (C=O) ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ −181.05 (d, $J = 46.0$ Hz) ppm.

4.2.3. *endo*-Methyl 5-[fluoro(phenyl)methyl]-2-methyl-3-phenyltetrahydro-5-isoxazolecarboxylate 3c. m/z (ESI): 352 (M^++Na). ^1H NMR (300 MHz, $CDCl_3$, +25 °C): δ 2.43 (s, 3H, CH_3–N), 2.74 (dd, 1H, $J = 12.6$ Hz, $J = 7.8$ Hz, CH_2), 2.92 (dd, 1H, $J = 12.6$ Hz, $J = 9.4$ Hz, CH_2), 3.03 (t, 1H, $J = 7.6$ Hz, CH), 3.31 (s, 3H, CH_3O), 5.82 (d, 1H, $J = 45.7$ Hz, CH–F), 6.90–7.20 (m, 10H, ArCH) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 42.6 (CH_3–N), 43.7 (CH_2), 52.9 (CH_3O), 72.7 (CH–N), 85.9 (d, $J = 29.6$ Hz, C_q), 94.4 (d, $J = 182.6$ Hz, CH–F), 127.9–129.9 (ArCH), 133.6 (Ar–C_q), 136.5 (Ar–C_q), 172.2 (C=O) ppm. ^{19}F NMR (283 MHz, $CDCl_3$): δ −172.59 ($J = 45.7$ Hz) ppm.

4.3. Methyl 2-[2(*S*)-(benzyloxy)-1-fluoropropyl]acrylate 5

To a solution of (*S*)-2-benzyloxypropanal (3.22 g, 19.7 mmol) in DMF (20 ml), methyl acrylate (2.66 ml, 29.5 mmol) and DABCO (2.42 g, 21.7 mmol) were added and the mixture allowed to stir at room temperature for 14 days. The reaction mixture was diluted with EtOAc (50 ml) and washed with water (2×20 ml). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/CH_2Cl_2/EtOAc 10:10:1) to afford 4.28 g (87%) of **4** in a 75:25 *anti*/*syn* ratio. To a stirred solution of the isolated ***anti*-4** (1.28 g, 5.15 mmol) in dichloromethane (7.0 ml) at 0 °C, DAST (0.60 ml, 5.15 mmol) was added dropwise as a neat liquid. After 1 min, the cold bath was removed and the reaction mixture allowed to reach −30 °C. Upon completion (6 h) the reaction was worked up by the slow addition of sodium bicarbonate solution (2 ml) followed by washing with water (3 ml). Pure product **5** (1.06 mg, 82%) was isolated by column chromatography on silica gel (petroleum ether/Et_2O 8:1). $[\alpha]_D = +3.15$ ($c = 4.33$, $CHCl_3$). m/z (ESI): 275 (M^++Na). (Found: C, 66.71; H, 6.87; $C_{14}H_{17}FO_3$ requires C, 66.65; H, 6.79.) ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.18 (dd, $J = 6.5$ Hz, $J = 1.5$ Hz, 3H, CH_3–CH), 3.73 (s, 3H, CH_3–O), 3.76–3.84 (m, 1H, CH–O), 4.63 (s, 2H, CH_2–Ph), 5.48 (m, $J = 47.1$ Hz, 1H, CH–F), 5.99 (dd, $J = 1.5$ Hz, $J = 1.0$ Hz, 1H, CH_2=), 6.42 (ddd, $J = 3.4$ Hz, $J = 1.0$ Hz, $J = 1.0$ Hz, 1H, CH_2=), 7.26–7.36 (m, 5H, C_6H_5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.3 (d, $J = 6.9$ Hz, CH_3–CH), 51.9 (CH_3O), 70.9 (CH_2–Ph), 75.1 (d, $J = 22.9$ Hz, CH–O), 91.1 (d, $J = 180.9$ Hz, CH–F), 127.1 (d, $J = 9.9$ Hz, CH_2=), 127.6 (C_6H_5), 127.7 (C_6H_5), 128.3 (C_6H_5), 136.8 (*C*=CH_2), 138.2 (ArCH), 165.4 (CO_2Me). ^{19}F NMR (282 MHz, $CDCl_3$): δ −200.25 (dd, $J = 21.7$ Hz, $J = 46.6$ Hz).

4.4. 1,3-Dipolar cycloaddition with chiral allylic fluoride 5

The cycloaddition was performed following the general procedure starting from **5** (200 mg, 0.79 mmol), $In(OTf)_3$ (44 mg, 0.079 mmol) and **1** (107 mg, 0.79 mmol). Microwave irradiation (60 W) for 25 min gave 185 mg (61%) of **6a/6b** in a 95:5 ratio. After column chromatography (petroleum ether/EtOAc 4:1), the two cycloadducts were isolated together and subjected to semi-preparative HPLC separation.

4.4.1. *exo*-Methyl (3*R*,5*R*)-5-[(1*R*,2*S*)-2-(benzyloxy)-1-fluoropropyl]-2-methyl-3-phenyltetrahydro-5-isoxazolecarboxylate 6a.

HPLC (hexane/*i*-PrOH 99.5:0.5): elution time 9.78 min. $[\alpha]_D = +7.3$ ($c = 1.0$, MeOH). m/z (ESI): 410 (M^++Na). (Found: C, 68.31; H, 6.84; N, 3.70; $C_{22}H_{26}FNO_4$ requires C, 68.20; H, 6.76; N, 3.62.) ^{1}H NMR (C_6D_6, 600 MHz): δ 1.40 (dd, $J = 6.1$ Hz, $J = 3.1$ Hz, 3H, CH_3–CH), 2.74 (s, 3H, N–CH_3), 3.01–3.04 (m, 1H, CH_2), 3.47–3.51 (m, 1H, CH_2), 3.52 (s, 3H, CH_3–O), 3.68–3.76 (m, 2H, CH–Ph+C*H*–CH_3), 4.33 (d, $J = 11.1$ Hz, 1H, CH_2–O), 4.45 (d, $J = 11.1$ Hz, 1H, CH_2–O), 5.17 (dd, $J = 47.8$ Hz, $J = 7.6$ Hz, 1H, CH–F), 7.28–7.33 (m, 2H, Ph), 7.35–7.39 (m, 4H, Ph), 7.47–7.48 (m, 2H, Ph), 7.60–7.62 (m, 2H, Ph). ^{13}C NMR (C_6D_6, 100.6 MHz): δ 15.7 (d, $J = 5.0$ Hz, CH_3–CH), 42.3 (N–CH_3), 42.6 (CH_2), 52.1 (CH_3–O), 70.8 (CH_2–O), 73.6 (CH–Ph), 73.8 (d, $J =$ 25.9 Hz, *C*H–Me), 85.4 (d, $J = 20.1$ Hz, O–*C*–C=O), 93.3 (d, $J = 183.9$ Hz, CH–F), 127.7, 127.9, 128.3, 128.4, 128.5, 128.8, 138.2, 139.2, 171.9 (d, $J = 7.6$ Hz, CO_2Me) ppm. ^{19}F NMR (C_6D_6, 282 MHz): δ −198.6 (m, $J = 50.2$ Hz).

4.4.2. *endo*-Methyl (3*S*,5*R*)-5-[(1*R*,2*S*)-2-(benzyloxy)-1-fluoropropyl]-2-methyl-3-phenyltetrahydro-5-isoxazolecarboxylate 6b.

HPLC (hexane/*i*-PrOH 99.5:0.5): elution time 13.99 min. $[\alpha]_D = +7.95$ ($c = 1.0$, MeOH). m/z (ESI): 410 (M^++Na). ^{1}H NMR (C_6D_6, 600 MHz): δ 1.52 (dd, $J = 6.2$ Hz, $J = 3.0$ Hz, 3H, CH_3–CH), 2.80 (s, 3H, N–CH_3), 3.05 (dd, $J = 12.4$ Hz, $J = 11.0$ Hz, 1H, CH_2), 3.24 (dd, $J = 12.4$ Hz, $J = 6.0$ Hz, 1H, CH_2), 3.54 (s, 3H, CH_3–O), 3.88–3.94 (bm, 1H, CH–Ph), 4.02–4.07 (m, 1H, CH_3–CH), 4.46 (d, $J = 11.4$ Hz, 1H, CH_2–O), 4.53 (d, $J = 11.4$ Hz, 1H, CH_2–O), 5.32 (dd, $J = 47$ Hz, $J = 6.5$ Hz, 1H, CH–F), 7.29–7.34 (m, 4H, Ph), 7.36–7.39 (m, 2H, Ph), 7.46–7.49 (m, 4H, Ph). ^{13}C NMR (C_6D_6, 100.6 MHz): δ 15.8 (d, $J = 6.1$ Hz, *C*H$_3$–CH), 43.6 (N–CH_3), 44.2 (CH_2), 51.9 (CH_3–O), 70.8 (CH_2–O), 73.1 (CH–Ph), 73.7 (d, $J = 25.1$ Hz, *C*H–Me), 84.8 (d, $J = 20.1$ Hz, O–*C*–C=O), 95.4 (d, $J = 184.7$ Hz, CH–F), 127.7, 127.8, 128.1, 128.2, 128.4, 128.8, 138.1, 138.5, 170.7 (d, $J = 7.6$ Hz, CO_2Me) ppm. ^{19}F NMR (C_6D_6, 282 MHz): δ −197.4 (m, $J = 45.9$ Hz).

4.5. Lithium aluminium hydride opening reactions: (2*R*,3*R*,4*S*)-4-(benzyloxy)-3-fluoro-2-[(2*R*)-2-(methylamino)-2-phenylethyl]-1,2-pentanediol 7a

Cycloadduct **6a** (190 mg, 0.57 mmol) was dissolved in THF (2 ml) and cooled to 0 °C. $LiAlH_4$ (2.3 ml, 2.3 mmol) was slowly added and the mixture stirred for 10 min after which the flask was warmed to room temperature and allowed to stir for a further 1 h. The reaction was quenched at 0 °C with the slow addition of 20% NaOH (2 ml) and stirring continued for 2 h. The aqueous solution was extracted three times with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered and evaporated to give a light yellow oil which was purified by silica gel column chromatography (EtOAc/petroleum ether 2:1) to give **7a** (59 mg, 81%) as a colourless oil. $[\alpha]_D = +6.3$ ($c = 0.5$, MeOH). m/z (ESI): 384 (M^++Na). HRMS for $C_{21}H_{28}FNO_3$ [$M+NH_4^+$] requires 361.2053, found 361.2051. ^{1}H NMR (C_6D_6, 600 MHz): δ 1.25 (dd, $J = 6.0$ Hz, $J = 2.8$ Hz, 3H, CH_3–CH), 2.28–2.35 (m, 1H, CH_2CHN), 2.45 (s, 3H, NMe), 2.55–2.75 (m, 3H, C*H*N+CH_2CHN), 3.60–3.65 (m, 1H, CHMe), 3.80 (t, 2H, $J = 8.9$ Hz, CH_2O), 3.90 (bs, 3H, 2OH+NH), 4.22 (dd, $J = 12.0$ Hz, 1H, CH_2Ph), 4.30 (dd, 1H, $J = 12.0$ Hz, CH_2Ph), 4.95 (d, 1H, $J = 44.1$ Hz, CHF), 7.05–7.40 (m, 10H, ArCH) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz): δ 12.6 (d, $J = 6.0$ Hz, *C*H$_3$–CH), 41.6 (CH_2), 42.6 (N–CH_3), 66.6 (CH_2OH), 73.8 (CHN), 83.1 (C_q, d, $J = 25.0$ Hz), 73.1 (CH–Ph), 73.1 (d,

$J = 23.3$ Hz, *C*H–Me), 91.6 (d, $J = 188.7$ Hz, CH–F), 127.0–128.6 (ArCH), 135.1 (ArC_q) ppm. ^{19}F NMR (C_6D_6, 282 MHz): δ −181.0–181.6 (m).

Acknowledgements

We acknowledge the financial support by the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' 2002–2003 and from the RTN project 'Design, Analysis and Computation for Catalytic Organic Reactions' (contract HPRN-CT-2001-00172). Dr. John M. Brown of the Dyson Perrins Laboratory (Oxford, UK) is also acknowledged for useful discussions.

References and notes

1. (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds. Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: USA, 1999; (b) Myers, A. G.; Barbay, J. K.; Zhang, B. J. *J. Am. Chem. Soc.* **2001**, *123*, 7207–7219.
2. Asensio, A.; Bravo, P.; Crucianelli, M.; Farina, A.; Fustero, S.; Soler, J. G.; Meille, S. V.; Panzeri, W.; Viani, F.; Volonterio, A.; Zanda, M. *Eur. J. Org. Chem.* **2001**, 1449–1458.
3. Gothelf, K. V. In *Cycloaddition Reaction in Organic Synthesis*; Kobayashi, S., Jorgensen, K. V., Eds.; Wiley-VCH: New York, 2001, Chapter 6.
4. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998.
5. (a) Brown, J. M.; Comes-Franchini, M.; Farrington, E. *Chem. Commun.* **1998**, 277–278; (b) Gree, D.; Vallerie, L.; Gree, R. *J. Org. Chem.* **2001**, *66*, 2374–2387; (c) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 3291–3294.
6. Despite a careful investigation, we did not find any trace of the fourth possible *exo*-cycloadduct.
7. (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 1; (b) Herrera, R.; Nagarajan, N.; Morales, M.; Méndez, F.; Jiménez-Vásquez, H. A.; Zepeda, L.-G.; Tamariz, J. *J. Org. Chem.* **2001**, *66*, 1252–1263.
8. Obtained at 600 MHz using a DPFGSE-NOE sequence with either a 25 or 75 Hz 'r-snob' pulse and a mixing time of 2 s. See: Claridge, T. D. W. In *High-Resolution NMR Techniques in Organic Chemistry*; Pergamon Press: Amsterdam, 1999 Shaka, A. J.; Van, Q. N.; Smith, E. M. *J. Magn. Res*. p 191–198.
9. Wasylingen, R. E.; Barfield, M. *J. Am. Chem. Soc.* **1975**, *97*, 4545–4552.
10. de La Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3573–3659.
11. Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299–307.
12. Wilkes, J. S. *Green Chemistry* **2002**, *4*, 73–80.
13. In particular, serious problems were encountered with RTILs under microwave irradiation because of difficult temperature control (entry 5). The use of ionic liquids as aids for microwave heating of non-polar solvents turned out to slightly improve the isolated yield of **3a**–**c** (entry 6). See: Leadbeater, N. E.; Terenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145–3148.
14. Aggarwal, V. D.; Dean, D. K.; Meren, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510–514.
15. Bernardi, A.; Cardani, S.; Colombo, S.; Poli, G.; Schimperna, G.; Scolastico, C. *J. Org. Chem.* **1988**, *52*, 888–891.
16. Ito, M.; Maeda, M.; Kibayashi, C. *Tetrahedron Lett.* **1992**, *33*, 3765–3768; Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Raimondi, L. *Tetrahedron Lett.* **1991**, *32*, 1659–1662.