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Complete Diastereocontrol in [3+2] Cycloaddition Reactions: Synthesis of Enantiomerically Pure Fluoromethyl Substituted β-Amino Acids

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Abstract: The intramolecular reaction of nitrones of crotonic and cinnamic esters of (*S*)-3-fluoro-2-hydroxypropanal afforded corresponding cycloadducts in good chemical yields and complete stereoselection.

Fluorine-containing amino acids (FAAs) have found applications as mechanistic tracers, biochemical probes, pharmacological tools, medicinal agents.[1] These diverse uses derive from the peculiar and advantageous effects induced by fluorine introduction. The replacement of hydrogen by fluorine typically results in an enhanced binding of the amino acid to the target enzyme and has afforded potent agonists and antagonists of natural amino acids. The superior leaving group ability of fluorine relative to hydrogen allows potent enzyme-activated irreversible inhibitors of various amino acid processing enzymes to be obtained and the high electronegativity of fluorine permits the rational design and construction of ground-state and transition-state analogue enzyme inhybitors.[2] These biological, pharmacological, and medicinal results rest on the availability of stereochemically defined FAAs and a great demand for effective methodologies for the synthesis of enantiomerically and diastereoisomerically pure FAAs was thus induced.

We have already reported how fluoromethyl derivatives of α-amino-β-hydroxy acids[3] can be obtained through an aldol condensation between a glycine anion equivalent and enantiopure 1-fluoro-3-tolylsulfinylacetone. Here we describe how some fluoromethyl derivatives of β-amino-γ-hydroxy acids are prepared in enantiomerically and diastereoisomerically pure form starting from the (2*R*,S_S)-1-fluoro-3-sulfinyl-2-propanol (**1**) which is obtained with complete chemo- and diastereoselectively when the above cited enantiopure (*S*)-1-fluoro-3-tolylsulfinylacetone is reduced with diisobutylaluminium hydride.[4]

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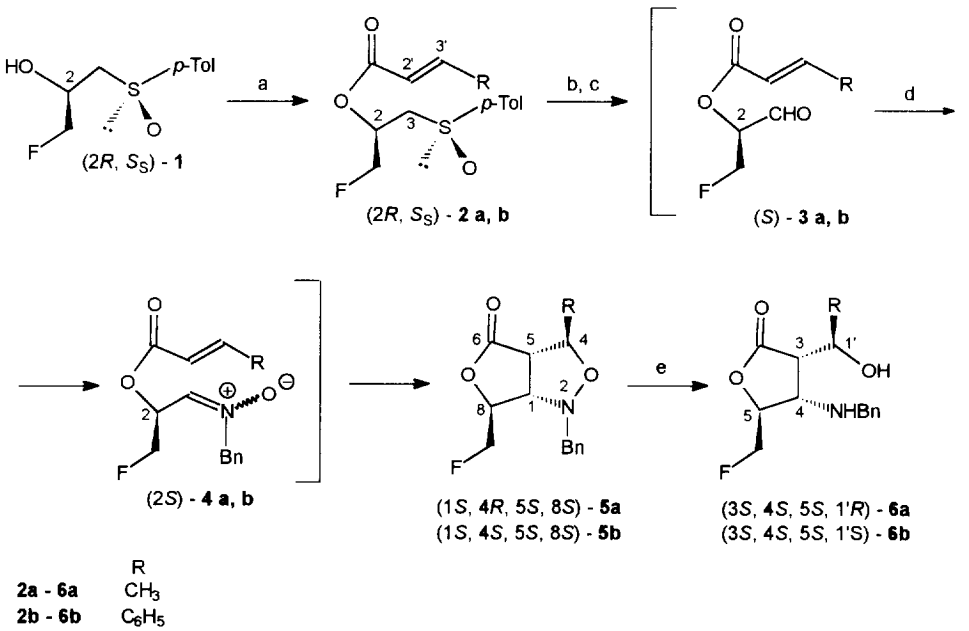
The key step in the synthetic sequence described in this paper is an intramolecular [3+2] cycloaddition reaction of a δ,ε-unsaturated nitrone[5] and it is noteworthy that this cycloaddition occurs with complete diastereoselection.

Results and Discussion

Coupling of (2*R*,*S*$_S$)-fluoropropanol **1** with *trans*-crotonic and -cinnamic acids to give corresponding esters **2a,b** was best performed by using 1,1'-carbonyldiimidazole as other procedures (carboxylic acid/dicyclohexylcarbodiimide/4-dimethylaminopyridine or acid chloride/pyridine) which had proven effective with saturated acids gave poor yields with the α,β-unsaturated acids employed here (Scheme).[6] The sulfinyl residue of **2a,b** was oxidatively removed through a Pummerer rearrangement performed by treatment with trifluoroacetic anhydride and 2,4,6-trimethylpyridine.[7] 1-[(Trifluoroacetyl)oxy)]-1-toluenesulfenyl-2-oxycarbonyl-3-fluoropropanes were formed cleanly and these masked aldehydes were hydrolyzed to (*S*)-2-oxycarbonyl-3-fluoropropanals **3a,b** with copper(II) chloride in basic medium. Crude **3a,b** were refluxed in methanol with *N*-benzylhydroxylamine to give nitrones **4a,b** which underwent *in situ* [3+2] cycloaddition reaction to afford bicyclo[3.3.0]octane derivatives (1*S*,4*R*,5*S*,8*S*)-**5a** and (1*S*,4*S*,5*S*,8*S*)-**5b** which were formed as single isomers (d.e. >98%)[8] and isolated in 63 and 69% overall yields, respectively, starting from esters **2a**



Scheme: (a) 1,1' carbonyldiimidazole, sodium hydride, dimethylformamide/tetrahydrofuran; (b) trifluoroacetic anydride, 2,4,6-trimethylpyridine, acetonitrile; (c) copper(II) chloride, water; (d) *N*-benzyl hydroxylamine hydrochloride, sodium carbonate, methanol, reflux; (e) Ni-Raney, hydrogen, methanol.

and 2b. Selective cleavage of the isoxazolidine ring of bicycles **5** to give furan-2-ones **6** in nearly quantitative yields was performed with hydrogen and Raney nickel, other metal catalysts (e.g. platinum and palladium) which worked well on strictly related compounds being uneffective.[9]

The structures of compounds **5** and **6** are supported by spectroscopic data (Experimental). In bicyclic derivatives **5a,b** the absolute configuration at C-8 comes from that of the starting alcohol **1**[4] and the *trans* relationship between H-8 and H-1 is supported by the small observed coupling constant (J = 1.0 Hz for both compounds). The *cis* orientation of H-1 and H-5 is revealed by the mutual NOEs observed between these protons (4 and 3.5%, respectively for **5a**) while the chirality at C-4 comes as a consequence of the stereoconservative mechanism of 1,3-dipolar cycloadditions which retains in the cycloadducts **5** the *trans* geometry of the starting alkenes **4**. Aminoalcohols **6** have been unequivocally identified by the presence of two exchangeable protons presenting vicinal coupling constants (ranging between 4.5 and 7.0 Hz) with H-1', H-4, and benzylic protons.

A four contiguous stereogenic centre moiety has been generated under complete control of the stereochemistry at C-2 of starting nitrones **4**. The observed stereochemical course is preferred over the alternative pathways as it allows to avoid steric congestion in bicyclic products **5**. In fact, the relative stereochemistry at C-8, C-1, C-5, and C-4 in compounds **5** is determined by the minimization of steric hindrance which occurs when the ring appendages on C-8 and C-4 reside on the less congested convex side of bicyclic products **5**, namely when products **5** having the fluoromethyl chain *trans* to the *cis*-fused isoxazolidine ring are exclusively formed. The ability of the stereochemistry in the α position of starting unsaturated nitrones to control the stereochemical course of intramolecular cycloaddition reactions has already been observed on *N*-methylnitrones of sugar derived 5-hexenals.[10] Moreover, stereochemical courses similar to that described above have been observed by others and us in [3+2] cycloaddition reactions of structurally different δ,ε-unsaturated nitrones (NH,[11] NAlky,[12] NBenzyl,[13] NAryl[14] nitrones) in which the tether connecting the dipole and the dipolarophile can also contain an heteroatom (nitrogen,[11a-d, 13a] oxygen,[12b,c, 13b,d, 14a,] sulfur[14b])

The intramolecular cycloaddition of nitrones is a powerful tool to construct nitrogen-substituted carbon frameworks with high regio- and stereoselectivity.[15] This methodology has been the key-step in the asymmetric synthesis of alkaloids, prostaglandins, sugars and here we have described how it can be usefully employed to prepare polyhydroxylated and fluorine containing β-amino acids. In general, fluorinated β-amino acids have recently received considerable attention[16] and the molecular array here obtained is particularly interesting as lactones **6** can be transformed into 3-(1'-hydroxyethyl)-4-(2'-fluoro-1'-hydroxyethyl)-β-lactams, a typical framework of monobactam antibiotics.[17]

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Experimental

General. ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded on a Bruker AC 250L spectrometer. Mass spectra were registered with a Finnigan Mat TSQ 70. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR and frequencies are reported in cm^{-1}. TMS and $CFCl_3$ were used as internal standards. Optical rotations were determined on a Jasco DIP-181 polarimeter. TLC were run on silica gel 60 F_{254} Merck; flash column cromatographies were performed with silica gel 60 (60-200 μm, Merck). A detailed procedure is described for compounds obtained starting from (2*R*, S_S)-**2a**. The same conditions were used for elaboration of (2*R*,S_S)-**2b**.

(*E*)-But-2-enoic acid (2*R*)-1-fluoro-3-(S_S)-[(4-methylphenyl)sulphinyl]2-propyl ester (2a). A solution of 1,1'-carbonyldiimidazole (1.46 g, 9.0 mmol) in DMF (10 mL) was added to a solution of *trans* crotonic acid (0.6 g, 6.9 mmol) in THF (10 mL) with stirring at 0 °C under nitrogen. After 30 min a solution of the sodium alcoholate of (2*S*,S_S)-**1** (prepared by treating (2*S*,S_S)-**1** (1.0 g, 4.6 mmol with NaH (0.14 g, 6.0 mmol) in THF (10 mL) was dropped maintaining the temperature at 0 °C. The resulting mixture was left at room temperature overnight then saturated water solution of ammonium chloride was added, volatiles were evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The combined organic phases were dried (Na_2SO_4), evaporated under reduced pressure and the resulting crude product was flash cromatographed (hexane/ethyl acetate 50 : 50) to give 1.1 g (79% yield) of pure (2*R*, S_S)-**2a**: $[\alpha]_D^{22}$ -133.05 (c 0.7, $CHCl_3$); IR (KBr/ν_{max}) 2928, 1724, 1655, 1626, 1309, 1254, 1103, 1087, 1048; ^{1}H NMR ($CDCl_3$), δ: 7.55 and 7.35 (4H, m, ArH), 7.08 (1H, dq, *J* = 15.6 and 7.0 Hz, H-3'), 5.89 (1H, dq, *J* = 15.6 and 1.9 Hz, H-2'), 5.52 (1H, ddddd, *J* = 24.6, 8.1, 4.5, 3.6 and 2.8 Hz, H-2), 4.71 (1H, ddd, *J* = 47.9, 10.3 and 2.8 Hz, CH_aF), 4.51 (1H, ddd, *J* = 46.5, 10.3 and 3.6 Hz, CH_bF), 3.11 (1H, brdd, *J* = 13.7 and 8.1 Hz, H-3a), 3.03 (1H, dd, *J* = 13.7 and 4.5 Hz, H-3b), 2.41 (3H, brs, ArMe), and 1.93 (3H, dd, *J* = 7.0 and 1.9 Hz, H_3-4')); ^{19}F NMR ($CDCl_3$), δ: -233.84 (ddd, *J* = 47.9, 46.5, and 24.6 Hz, CH_2F); m/z (EI) 139 (*p*-tol-SO), 145 (M - *p*-tol-SO), 182, 225, 265 (M - F), 285 (M+1).

(*E*)-Cinnamic acid (2*R*)-1-fluoro-3-(S_S)-[(4-methylphenyl)sulphinyl]2-propyl ester (2b). Yield 81%; $[\alpha]_D^{22}$ -108.5 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$), δ: 7.74 (1H, brd, *J* = 15.9 Hz, H-3'), 7.6-7.2 (9H, m, ArH), 6.45 (1H, brd, *J* = 15.9 Hz, H-2'), 5.61 (1H, ddddd, *J* = 24.7, 7.9, 4.8, 3.4 and 2.8 Hz, H-2), 4.74 (1H, ddd, *J* = 48.3, 10.5 and 2.8 Hz, CH_aF), 4.55 (1H, ddd, *J* = 46.6, 10.5 and 3.4 Hz, CH_bF), 3.18 (1H, dd, *J* = 13.6 and 7.9 Hz, H-3a), 3.13 (1H, dd, *J* = 13.6 and 4.8 Hz, H-3b), and 2.39 (3H, brs, ArMe); ^{19}F NMR ($CDCl_3$), δ: -233.49 (ddd, *J* = 48.3, 46.6, and 24.7 Hz, CH_2F); m/z (EI) 131, 139 (*p*-tol-SO),182, 207 (M - *p*-tol-SO), 347 (M+1). Anal. Calcd for $C_{19}H_{19}FO_3S$: C, 65.89; H, 5.49; S, 9.26; found: C, 65.97; H, 5.35; S, 9.45.

(1*S*,4*R*,5*S*,8*S*)-2-Benzyl-8-fluoromethyl-4-methyl-3,7-dioxa-1-azabicyclo[3.3.0]octan-6-one (5a). A solution of trifluoroacetic anhydride (0.53 mL, 3.8 mmol) in acetonitrile (0.5 mL) was added dropwise to a solution of (2*R*,S_S)-**2a** (0.5 g, 1.9 mmol) and of 2,4,6-trimethylpyridine (0.76 mL, 5.7 mmol) in the same solvent (5 mL) with stirring at 0 °C under nitrogen. After 30 min at room temperature a suspension of copper (II) chloride (0.38 g, 2.9 mmol) and potassium carbonate (0.39 g, 2.9 mmol) in water was added. The resulting mixture was stirred at room temperature for 2 h and then evaporated under reduced pressure. The residue was dissolved in water (10 mL), extracted with ethyl acetate (3x20 mL) and the combined organic phases were dried (Na_2SO_4). Evaporation under reduced pressure gave a residue containing the crude (*E*)-but-2-enoic ester of (*S*)-3-fluoro-2-hydroxypropanal **3a** which was used in successive reactions without further purification. A solution of crude (*S*)-**3a**, obtained as described above starting from 0.5 g (2*R*,S_S)-**2a** (1.9 mmol), in methanol (5 mL) was added to a suspension of *N*-benzyl hydroxylamine hydrochloride (0.91 g, 5.7 mmol) and sodium carbonate (0.6 g, 5.7 mmol) in the same solvent (5 mL) under nitrogen. The reaction mixture was refluxed for 2 h, then it was evaporated under reduced pressure. The residue was dissolved in water (10 mL) and extracted with ethyl acetate (3x20 mL). The combined organic phases were dried (Na_2SO_4), evaporated under reduced

pressure and the resulting crude oil was flash cromatographed (hexane/ethyl acetate 70 : 30) to give 0.3 g (63% yield) of pure (1*S*,4*R*,5*S*,8*S*)-**5a**: $[\alpha]_D^{22}$ -61.4 (c 0.8, $CHCl_3$); IR (KBr/ν_{max}) 2914, 1760; ^{1}H NMR ($CDCl_3$), δ: 7.5 - 7.3 (5H, m, ArH), 4.39 and 3.81 (2H, brd each, J = 12.1 Hz, NCH_2Ph), 4.33 (1H, ddd, J = 48.1, 10.5 and 2.0 Hz, CH_aF), 4.24 (1H, dq, J = 6.1 and 6.2 Hz, H-4), 3.95 (1H, ddd, J = 45.8, 10.5 and 1.9 Hz, CH_bF), 3.90 (1H, dddd, J = 32.5, 2.0, 1.9 and 1.0 Hz, H-8), 3.63 (1H, ddd, J = 8.4, 1.1, and 1.0 Hz, H-1), 3.21 (1H, ddd, J = 8.4, 6.1 and 2.0 Hz, H-5), and 1.46 (3H, d, J = 6.2 Hz, Me); ^{19}F NMR ($CDCl_3$), δ: -236.33 (brddd, J = 48.1, 45.8 and 32.5 Hz, CH_2F); ^{13}C NMR ($CDCl_3$), δ: 175.45 (C-6); 134.97, 129.57, 128.80 and 128.43 (ArC); 82.47 (CH_2F; $J_{C,F}$ = 173.9 Hz); 79.91 (C-8; $J_{C,F}$ = 18.5 Hz); 76.68 (C-4); 69.62 (C-1; $J_{C,F}$ = 3.8 Hz); 61.97 (NCH_2Ph); 56.43 (C-5); and 19.16 (Me); m/z (EI) 91 (C_7H_7), 265 (M). Anal. Calcd for $C_{14}H_{16}FNO_3$: C, 63.40; H, 6.04; N, 5.28; found: C, 63.65; H, 6.28; N, 5.01.

(1*S*,4*S*,5*S*,8*S*)-2-Benzyl-8-fluoromethyl-4-phenyl-3,7-dioxa-1-azabicyclo[3.3.0]octan-6-one (5b). Yield 69%; $[\alpha]_D^{22}$ -41.4 (c 0.7, $CHCl_3$); IR (KBr/ν_{max}) 1763; ^{1}H NMR ($CDCl_3$), δ: 7.5 - 7.2 (10H, m, ArH), 5.18 (1H, brd, J = 5.8 Hz, H-4), 4.51 and 3.95 (2H, brd each, J = 12.2 Hz, NCH_2Ph), 4.38 (1H, ddd, J = 48.0, 10.6 and 2.0 Hz, CH_aF), 4.06 (1H, ddd, J = 45.8, 10.6 and 1.9 Hz, CH_bF), 3.97 (1H, dddd, J = 32.6, 2.0, 1.9 and 1.0 Hz, H-8), 3.78 (1H, ddd, J = 8.3, 1.1, and 1.0 Hz, H-1), 3.60 (1H, ddd, J = 8.3, 5.8, and 2.2 Hz, H-5); ^{19}F NMR ($CDCl_3$), δ: -236.09 (brddd, J = 48.0, 45.8 and 32.6 Hz, CH_2F); ^{13}C NMR ($CDCl_3$), δ: 175.38 (C-6); 138.01, 134.80, 129.71, 129.00, 128.83, 128.72, 128.53 and 126.30 (ArC); 82.48 (CH_2F; $J_{C,F}$ = 173.9 Hz), 81.51 (C-4); 79.69 (C-8; $J_{C,F}$ = 18.5 Hz); 69.66 (C-1; $J_{C,F}$ = 3.7 Hz); 61.88 (NCH_2Ph); and 57.50 (C-5); m/z (EI) 91 (C_7H_7), 327 (M).

(3*S*,4*S*,5*S*,1'*R*)-4-Benzylamino-5-fluoromethyl-3-(1'hydroxyethyl)dihydro-furan-2-one (6a). A solution of (1*S*,4*R*,5*S*,8*S*)-**5a** (0.05 g, 0.2 mmol) in methanol was stirred with Raney-Ni under hydrogen for 30 min. The catalyst was filtered off, the solvent was removed under reduced pressure, and the residue was flash cromatographed (hexane/ethyl acetate 70 : 30) to give 47 mg (93% yield) of pure (3*S*,4*S*,5*S*,1'*R*)-**6a**: $[\alpha]_D^{22}$ -45.1 (c 0.55, $CHCl_3$); IR (KBr/ν_{max}) 3449, 1763; ^{1}H NMR (DMSO-d_6), δ: 7.4 - 7.2 (5H, m, ArH), 5.27 (1H, brd, J = 4.5 Hz, OH), 4.62 (1H, ddd, J = 48.3, 10.5 and 4.7 Hz, CH_aF), 4.61 (1H, dddd, J = 28.3, 5.0, 4.7 and 2.3 Hz, H-5), 4.56 (1H, ddd, J = 47.5, 10.5 and 5.0 Hz, CH_bF), 3.99 (1H, brddq, J = 7.5, 4.5, and 6.1 Hz, H-1'), 3.82 (1H, brdd, J = 13.4 and 5.0 Hz, NCH_aPh), 3.71 (1H, brdd, J = 13.4, and 4.5 Hz, NCH_bPh), 3.49 (1H, ddd, J = 6.9, 5.5 and 2.3 Hz, H-4), 2.90 (1H, brddd, J = 5.5, 5.0 and 4.5 Hz, NH), 2.74 (1H, brdd, J = 7.5 and 6.9 Hz, H-3), and 1.30 (3H, d, J = 6.1 Hz, Me); ^{19}F NMR ($CDCl_3$), δ: -233.44 (brddd, J = 48.3, 47.5 and 28.3 Hz, CH_2F). Anal. Calcd for $C_{14}H_{18}FNO_3$: C, 62.92; H, 6.74; N, 5.24; found: C, 63.01; H, 6.58; N, 5.37.

(3*S*,4*S*,5*S*,1'*S*)-4-Benzylamino-5-fluoromethyl-3-(1'-hydroxybenzyl)dihydro-furan-2-one (6b). Yield 90%; $[\alpha]_D^{22}$ -39.05 (c 0.8, $CHCl_3$); IR (KBr/ν_{max}) 3328, 1763; ^{1}H NMR (DMSO-d_6), δ: 7.5 - 7.1 (10H, m, ArH), 6.20 (1H, brd, J = 5.0 Hz, OH), 5.10 (1H, brdd, J = 5.0 and 4.4 Hz, H-1'), 4.59 and 4.53 (2H, m, CH_2F), 4.55 (1H, m, H-5), 3.41 (1H, brdd, J = 13.2 and 7.0 Hz, NCH_aPh), 3.39 (1H, ddd, J = 7.7, 5.5 and 4.6 Hz, H-4), 3.33 (1H, brdd, J = 7.7 and 4.4 Hz, H-3), 3.24 (1H, brdd, J = 13.2 and 5.5 Hz, NCH_bPh), and 2.68 (1H, brddd, J = 7.0, 5.5, 5.5 Hz, NH); ^{19}F NMR ($CDCl_3$), δ: -233.36 (brddd, J = 48.0, 46.0 and 28.0 Hz, CH_2F); ^{13}C NMR ($CDCl_3$), δ: 175.15 (C-2); 141.38, 138.18, 128.70, 128.42, 128.16, 127.74, 127.66 and 125.59 (ArC); 82.33 (CH_2F; $J_{C,F}$ = 174.8 Hz); 81.87 (C-5; $J_{C,F}$ = 19.5 Hz); 71.42 (C-1'), 57.47 (C-4; $J_{C,F}$ = 3.8 Hz); 52.15 (NCH_2Ph); and 49.28 (C-3); m/z (EI) 91 (C_7H_7), 106 (C_7H_6O), 160, 330 (M+1). Anal. Calcd for $C_{19}H_{20}FNO_3$: C, 69.30; H, 6.07; N, 4.26; found: C, 69.43; H, 5.98; N, 4.37.

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