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Enantiomerically Pure α-Fluoroalkyl-α-Amino Acids: Synthesis of (*R*)-α-Difluoromethyl-Alanine and (*S*)-α-Difluoromethyl-Serine

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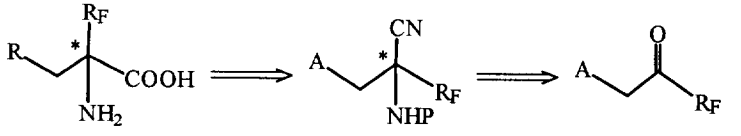
Abstract: Hydrocyanation of enantiomerically pure *N*-Cbz α-fluoroalkyl β-sulfinylenamines **1** occurs smoothly by treatment with KCN or by addition of trimethylsilylcyanide or diethyl phosphorocyanidate to preformed sodium derivatives of **1**. The diastereoisomeric difluoro α-aminonitriles **2b** have been transformed in the unnatural amino acids (*R*)-α-difluoromethyl-alanine and (*S*)-α-difluoromethyl-serine.

The interest in organofluorine fine chemicals is continually growing. In particular, the area of fluorinated amino acids (FAAs) presents several attractive aspects, mainly due to the proven value of some FAAs as suicide inhibitors of pyridoxal phosphate-dependent α-aminoacid decarboxylases and aminotransferases. Due to these properties they have been successfully employed as probes for investigations on the mechanisms of action of enzymes.[1a] Moreover, FAAs can play an important role in the control of blood pressure, allergies and tumor growth,[1b-d] and for these reasons they have been object of intense synthetic activity.[2] Relatively few approaches to enantiomerically pure (e.p.) FAAs have been reported,[3] although a wide variety of methods have been developed for the synthesis of the racemic compounds. The asymmetric Strecker reaction requires common starting materials, namely a chiral aldehyde or ketone, an amine hydrochloride and an alkali metal cyanide salt, therefore it is a straightforward and useful method for the synthesis of enantiomerically pure α-aminoacids.[4] It is well known that the reaction generally proceeds *via* formation of an α-hydroxynitrile, which reacts with the amine hydrochloride affording the desired α-aminonitrile.[5]



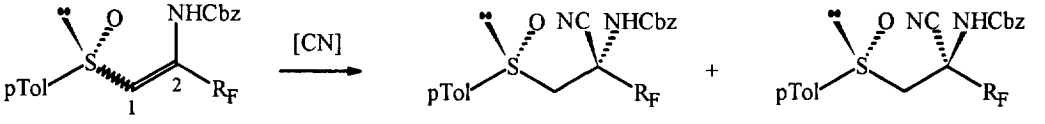
A = Chiral Auxiliary
R_F = Fluoroalkyl group
P = Protecting group
R = Amino acid residue

Retrosynthetic Scheme

However, the Strecker reaction on highly electron-deficient ketones frequently stops at the stage of the corresponding cyanohydrins or is characterized by low yields. For these reasons it has found a limited application in the synthesis of FAAs.[6] In order to prepare chiral and enantiomerically pure α-fluoroalkyl-α-amino acids we submitted enantiomerically pure γ-fluorosubstituted-β-ketosulfoxides (mainly existing in *gem*-diolic form) to the classical Strecker protocol (NH_4Cl, KCN) or to the Bucherer-Bergs modification [$(NH_4)_2CO_3$, KCN], that usually produces the corresponding hydantoins. Not surprisingly, in our hands the γ-difluoro and γ-trifluoro-β-ketosulfoxides did not afford the desired products. When the reactions were carried out at room temperature unchanged starting materials were mainly recovered, while complex reaction mixtures formed by moderately heating for several hours.[7]

We have recently reported the synthesis of enantiomerically pure α-fluoroalkyl-β'-sulfinylenamines **1** and the reactivity of these versatile building blocks have been studied in detail.[8] In particular, it has been found that *N*-, *O*-, *S*- and *C*-centred nucleophiles add smoothly at C-2, affording the corresponding β-substituted β-sulfinylamines. Now we report that hydrocyanation of trifluoro-, difluoro- and chlorodifluoro-β-sulfinylenamines **1a-c** produces excellent yields of the fluorinated α-aminonitriles **2a-c**. The synthesis of enantiomerically pure (*R*)-α-difluoromethyl-alanine **5** and (*S*)-α-difluoromethyl-serine **8** can be efficiently accomplished by elaboration of the diastereoisomeric hydrocyanation products, *i.e.* the difluoro α-aminonitriles (R_S,2*R*)- and (R_S,2*S*)-**2b**.[9]

Upon treatment of the trifluoro, difluoro and chlorodifluoro *N*-Cbz-β-sulfinylenamines (*Z*)-**1a-c** with KCN in a THF/H_2O 4:1 mixture at room temperature (rt) and overnight, the *N*-Cbz-α-amino-nitriles **2a** formed in excellent yield, but with modest diastereoselectivity (from 10 % to 30 % d.e. for the *syn* diastereoisomer, as shown in Table 1, entry 1, 2 and 6, respectively).



1 **a**: $R_F = CF_3$
b: $R_F = CF_2H$
c: $R_F = CF_2Cl$

syn-**2**

anti-**2**

Scheme 1

Scheme 1 and Table 1. Hydrocyanation of α-fluoroalkyl-β'-sulfinylenamines **1**.

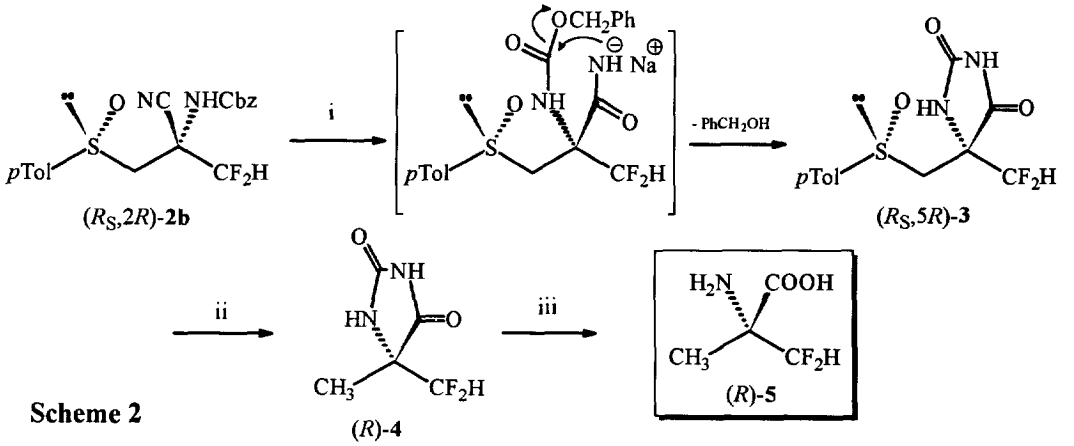
Entry	Enamine	R_F	Reagents and Conditions	Yield	*syn*/*anti*-**2**[c]
1[a]	(*Z*)-**1a**	CF_3	KCN, rt	90 %	65 : 35
2[a]	(*Z*)-**1b**	CF_2H	KCN, rt	92 %	65 : 35
3[a]	(*E*)-**1b**	CF_2H	KCN, rt	90 %	65 : 35
4[b]	(*Z*)- or (*E*)-**1b**	CF_2H	1. NaH, 0°C 2. $(EtO)_2P(O)CN$, rt	93 %	70 : 30
5[b]	(*Z*)- or (*E*)-**1b**	CF_2H	1. NaH, 0°C 2. TMSCN, rt	93 %	70 : 30
6[a]	(*Z*)-**1c**	CF_2Cl	KCN, rt	90 %	55 : 45

[a] THF:H_2O = 4:1 as solvent. [b] DMF as solvent. [c] Determined by HPLC, ^1H and ^{19}F NMR of the crude reaction mixtures.

The same results were obtained with the difluoro enamine (*E*)-**1b** (Table 1, entry 3), showing that the geometry of the double bond has little influence on the reaction, probably because of *cis-trans* isomerization occurring in basic media.[8b] Though the Strecker reaction is often a thermodynamically controlled process,[4b] the addition of cyanide anion to the β-sulfinylenamines **1** was found to be kinetically controlled. In fact, treating both the diastereoisomerically pure α-amino-nitriles **2** with KCN and moderately heating for several hours, no epimerization at C-2 was observed.

A very efficient route to the difluoro α-amino-nitriles **2b** was found to be the addition of the electrophilic cyanide reagents $(EtO)_2P(O)CN$ and trimethylsilylcyanide (TMSCN) to a preformed sodium derivative of the difluoro β-sulfinylenamines (*Z*)- or (*E*)-**1b** (NaH, DMF).[10] The desired products formed in excellent yields after one night at room temperature, with a 40% d.e. for the *syn*-(R_S,2*R*)-**2b** diastereoisomer (Table 1, entry 4 and 5). Probably the reaction involves the attack of the negatively charged nitrogen atom of the sulfinylenamines **1b** on the P or Si atom of the electrophilic reagent, with subsequent delivery of the cyanide group. No reaction was observed after several days, when the aforementioned cyanide releasing reagents were added to **1b** without preliminary NaH treatment, probably owing to the extreme electron-deficiency of the substrate.

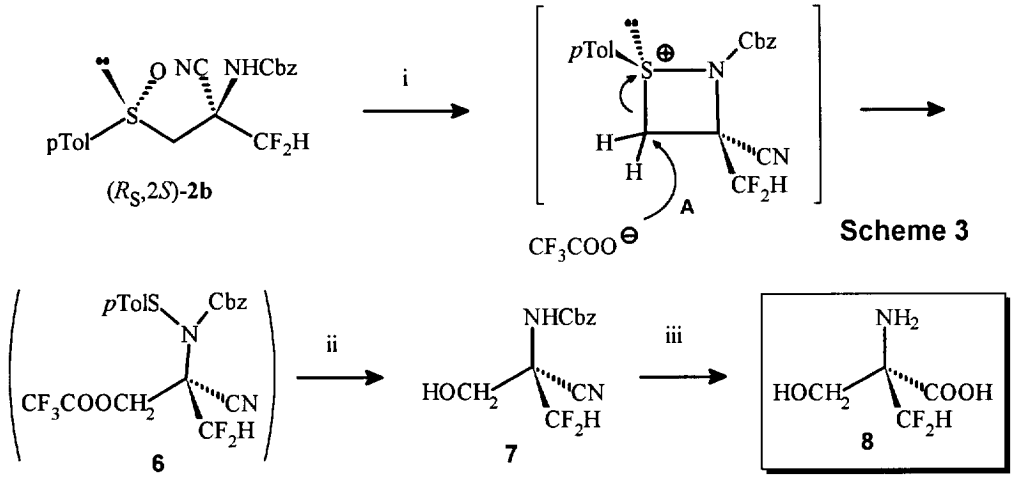
The enantiomerically pure α-amino-β-sulfinylnitriles **2** are valuable templates for the synthesis of α-fluoroalkyl-α-amino acids, as shown in the straightforward syntheses of (*R*)-α-difluoromethyl-alanine **5** and (*S*)-α-difluoromethyl-serine **8**. The α-aminonitrile (R_S,2*R*)-**2b** (easily obtained in diastereoisomerically pure form by flash chromatography from the diastereomeric mixture) was submitted to basic hydrolysis (KOH 1N). The 5-sulfinylmethylene-5-difluoromethyl hydantoin (R_S,5*R*)-**3**, formed via intramolecular attack of the intermediate amide moiety on the carbamoyl group, and benzyl alcohol were obtained as main reaction products (Scheme 2). Small amounts of the corresponding difluoro β-ketosulfoxide and methyl-*p*-tolylsulfoxide, the hydrolysis and the deacylation products respectively, were also isolated.



Scheme 2

Key: i) KOH 1N, MeOH/H_2O 1:1, rt, 4 days (65%). ii) Ni-Raney, EtOH, 60°C, 5 days (72%). iii) a: $Ba(OH)_2 \cdot 8H_2O$, H_2O, reflux, 24 h; b: HCl 1N; c: DOWEX 50W (90%).

Desulfinylation of the hydantoin (R_S,5*R*)-**3** by treatment with Ni-Raney afforded the 5-difluoromethyl-5-methyl-hydantoin (*R*)-**4**, that was hydrolyzed to (*R*)-α-difluoromethyl-alanine hydrochloride by refluxing with aqueous $Ba(OH)_2 \cdot 8H_2O$ and subsequent HCl acidification of the reaction mixture. The free aminoacid α-difluoromethyl alanine (*R*)-**5** was obtained by chromatography of the hydrochloride salt on DOWEX 50W.

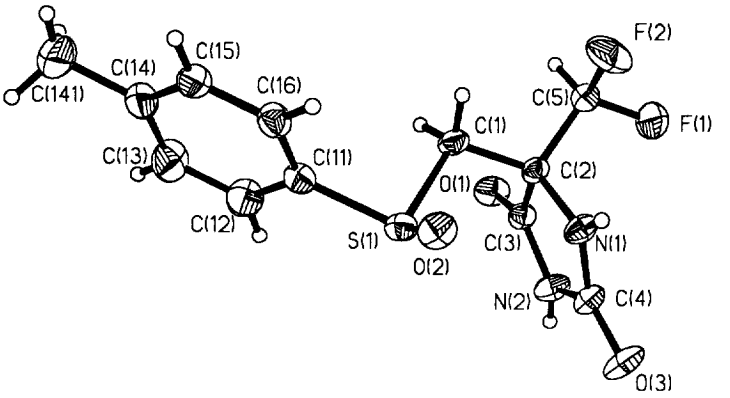


Key: i) *Sym*-collidine, trifluoroacetic anhydride, CH_3CN, 0°C. ii) a: K_2CO_3/H_2O; b: $NaBH_4$ (96% from **2**). iii) a: $Ba(OH)_2 \cdot 8H_2O$, H_2O, reflux, 8 h; b: HCl 1N; c: DOWEX 50W (55%).

We next proceeded toward the synthesis of α-trifluoromethyl-serine **8** (scheme 3). The α-aminonitrile (R_S,2*S*)-**2b** underwent elimination of the chiral sulfinyl auxiliary and simoultaneus introduction of the oxygen functionality in its place under Pummerer reaction conditions. Indeed, treatment of (R_S,2*S*)-**2b** with *sym*-collidine and trifluoroacetic anhydride (TFAA) afforded the α-trifluoroacetoxy-sulfenamide (*R*)-**6**, that is the product of a "non-oxidative" rearrangement. As already reported for the TFAA promoted Pummerer reaction of *N*-Cbz-γ-trifluoro-β-aminosulfoxides,[11] this unusual outcome should involve the formation of the intermediate cyclic four membered acylaminosulfonium ion **A**. *One-pot* addition of aqueous K_2CO_3 to the trifluoroacetate (*R*)-**6**, followed by $NaBH_4$ reduction of the sulfenamide moiety, delivered in high yield the β-hydroxy-α-aminonitrile (*R*)-**7**. The latter was hydrolyzed directly to enantiomerically pure α-difluoromethyl-serine (*S*)-**8** by treatment with $Ba(OH)_2 \cdot 8H_2O$.

Structural Assignments. The stereochemistry of the above described products was confirmed by X-Ray crystallographic analysis of the 5-sulfinylmethylene-5-difluoromethyl hydantoin (R_S,5*R*)-**3b**. In Fig. 1 the ORTEP[12] drawing of (R_S,5*R*)-**3b** with the appropriate atomic labelling is shown. The heterocyclic ring presents a very nearly planar conformation, hardly distorted by the difluoromethyl and the sulfinyl substituents.

Fig.1: ORTEP view of compound (R_S,5*R*)-**3**.



Pertinent bond distances and angles (Table 2) correspond closely to those recently reported for a differently substituted hydantoin.[13] The crystalline conformation of (R_S,5*R*)-**3** is characterized by a nearly *trans* planar arrangement of the C(11)-S(1)-C(1)-C(2)-C(5)-F(1) sequence, which is nearly perpendicular to both the phenyl and the heterocyclic ring planes.

Table 2. Selected molecular dimensions of (R_S,5*R*)-**3b** with estimated standard deviations in parentheses.

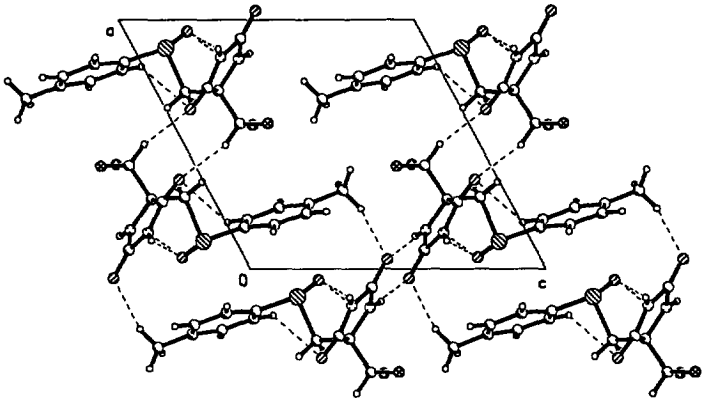
Bond lengths (Å)		Bond angles (°)		Torsion angles (°)	
S(1)-O(1)	1.496(2)	O(1)-S(1)-C(1)	105.19(11)	C(3)-C(2)-C(1)-S(1)	79.0(2)
S(1)-C(11)	1.781(3)	O(1)-S(1)-C(11)	107.11(11)	C(11)-S(1)-C(1)-C(2)	-166.9(2)
S(1)-C(1)	1.819(2)	C(1)-S(1)-C(11)	96.89(10)	C(12)-C(11)-S(1)-C(1)	99.1(2)
C(1)-C(2)	1.542(3)	N(1)-C(2)-C(5)	112.0(2)	C(1)-C(2)-C(5)-F(1)	-178.0(2)
C(2)-C(3)	1.526(4)	N(1)-C(2)-C(3)	101.4(2)	C(1)-C(2)-C(5)-F(2)	65.1(2)
C(2)-C(5)	1.516(3)	C(3)-C(2)-C(1)	111.4(2)	N(1)-C(2)-C(1)-S(1)	-35.1(2)
C(3)-O(2)	1.210(3)	C(2)-C(1)-S(1)	110.99(14)	O(1)-S(1)-C(1)-C2()	83.2(2)
C(4)-O(3)	1.209(3)	F(2)-C(5(-F(1)	106.7(2)	N(2)-C(3)-C(2)-N(1)	2.52(2)
F(1)-C(5)	1.339(3)	F(1)-C(5)-C(2)	109.9(2)	N(1)-C(4)-N(2)-C(3)	0.75(3)
F(2)-C(5)	1.353(4)	F(2)-C(5)-C(2)	109.5(2)	C(4)-N(1)-C(2)-C(3)	-2.21(2)
N(1)-C(2)	1.440(3)	N(2)-C(3)-C(2)	106.6(2)	C(4)-N(2)-C(3)-C(2)	-2.11(2)
N(1)-C(4)	1.343(3)	N(1)-C(4)-N(2)	107.3(2)	C(2)-N(1)-C(4)-N(2)	1.08(3)
N(2)-C(3)	1.353(3)	C(3)-N(2)-C(4)	112.1(2)	C(4)-N(1)-C(2)-C(5)	117.6(2)
N(2)-C(4)	1.388(3)	C(4)-N(1)- C(2)	112.7(2)	S(1)-C(1)-C(2)-C(5)	161.3(2)

Only intermolecular hydrogen bonds (details in Table 3) result which, as shown by the packing plot in Fig. 2, give rise to a tridimensional network.

Table 3. Hydrogen bonding geometry for (R_S,5*R*)-**3b**.

D-H····A	D····A (Å)	H····A (Å)	D-H····A (°)	Asymmetric unit of A
N(1)-H(1N)····O(3)	2.753	1.89	163.4	*-x, -1/2+y, 1-z*
N(2)-H(2N)····O(1)	2.913	2.11	154.3	*x, -1+y, z*

Fig. 2. Projection of the packing of (R_S,5*R*)-**3b** on the ***a c*** plane.



The stereochemistry of the β-sulfinyl-α-aminonitriles **2a** and **2c** was assigned assuming a common stereochemical course for the formation of **2** from the corresponding enamines **1**. This hypothesis is supported by a clear correspondence in the ^{1}H and ^{19}F NMR spectra of both the series of diastereoisomeric α-aminonitriles **2a-c** which are assumed to have the same *anti* or *syn* stereochemistry (see experimental).[14]

Conclusions. In summary, (*R*)-α-difluoromethyl-alanine **5** and (*S*)-α-difluoromethyl-serine **8** have been synthesized for the first time in enantiomerically pure form from the e.p. fluorinated β-sulfinyl-α-aminonitriles **2**, readily available from the corresponding α-fluoroalkyl-β'-sulfinylenamines **1**. This method could be applied to the synthesis of other enantiomerically pure α-fluoroalkyl-α-aminoacids.

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EXPERIMENTAL

General Details:

^{1}H, ^{19}F and ^{13}C nuclear magnetic resonance samples were prepared as dilute solutions in $CDCl_3$ or D_2O and spectra recorded on Bruker spectrometers: CXP 300 or AC 250L. Chemical shifts (δ) are reported in parts per million (ppm) of the applied field. Me_4Si was used as internal standard (δ_H and δ_C = 0.00) for ^{1}H and ^{13}C nuclei, while C_6F_6 was used as external standard (δ_F = −162.90) for ^{19}F nuclei. Peak multiplicities are

abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m. Coupling constants (*J*) are reported in hertz (Hz). $[\alpha]^{20}_{D}$ and $[\alpha]^{20}_{365}$ values were taken on a Jasco-Dip polarimeter. FT-IR spectra were registered on a Perkin Elmer System 2000 spectrophotometer. Melting points are uncorrected and were obtained on a capillary apparatus. Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness were used. Merck silica gel 60 (230-400 ASTM mesh) was employed for flash column chromatography (FC). HPLC analyses were performed on a Waters 600E instrument using LiChrosorb Si60 (5 μm, Merck) prepacked columns and hexane and ethyl acetate HPLC-grade solvents (Merck). Combustion microanalyses were performed by Redox SNC, Cologno M. (Milano). Mass spectra were registered on a Hitachi-Perkin-Elmer ZAB 2F instrument. Commercially available reagent-grade solvents were employed without purification. The synthesis of *N*-Cbz α-fluoroalkyl β'-sulfinylenamines **1** has been already described.[8b]

X-ray diffraction data for (*R*$_S$,5*R*)-**3b** were collected from colourless prismatic crystal measuring 0.8 x 0.6 x 0.4 mm on a Siemens P4 diffractometer using graphite-monocromated Cu-Kα radiation (λ = 1.5418Å). Cell parameters were obtained by least-square refinement on the 2θ values of 20 reflections with 2θ > 40°. Two octants of intensity data were collected by the θ/2θ scan technique in the range 4.50° < 2θ < 57.24° for a number of 1878 independent reflections (R_{int} = 0.0118).

Three standard reflections were monitored every 97 reflections to check crystal orientation and stability. Data were corrected for Lorentz and polarization effects but no absorption correction was deemed necessary.

The structure was solved by direct methods using SIR92[15] and refined by full matrix least-squares on F2 with SHELXL93[16]. The absolute configuration was established refining the Flack'x parameter.[17]

The two amidic hydrogens were located with a difference-Fourier map and refined with a common thermal parameter, while the others were included at calculated positions and refined in the riding mode with group temperature factors.

CAUTION!!! KCN and cyanide releasing reagents TMSCN, $(ETO)_2POCN$ are poisons.

Synthesis of the α-aminonitriles **2**: *Method A.* To a solution of sulfinylenamine **1** (5.9 mmol) in a THF/H_2O 4:1 mixture (15 ml) potassium cyanide (6.3 mmol) was added at rt. The solution was stirred overnight at the same temperature. After evaporation of the organic solvent, the solution was extracted with CH_2Cl_2. The collected organic layers were dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. FC of the residue (Hex/AcOEt = 4:1) afforded the pure (*R*$_S$,2*R*) and (*R*$_S$,2*S*) diastereoisomeric α-aminonitriles.

Method B. To a solution of sulfinylenamine **1** (0.25 mmol) in DMF (4 ml) was added, under nitrogen atmosphere at 0°C, a 55% sodium hydride dispersion (0.25 mmol). The solution was stirred at rt until the gas evolution ceased. Neat diethylphosphorocyanidate (0.25 mmol) was added at 0°C and the solution was kept at rt overnight. The reaction was quenched with a saturated aqueous ammonium chloride solution and extracted with AcOEt. The collected organic layers were worked-up as described above and the crude submitted to FC.

Method C. To a solution of sulfinylenamine **1** (0.083 mmol) in DMF (1 ml) was added, under nitrogen atmosphere at 0°C, a 55% sodium hydride dispersion (0.083 mmol). The solution was stirred at rt until the gas

evolution ceased. Neat trimethylsilylcyanide (0.167 mmol) was added at 0°C and the solution was kept at rt overnight. The reaction was quenched and worked-up as described above and the crude submitted to FC.

The trifluoro α-aminonitriles **2a** were obtained in 90% yield and (R_S,2*R*)/(R_S,2*S*) = 65:35 ratio using *Method A*. We were not able to isolate diastereoisomerically pure **2a**, but only enriched mixtures.

(R_S,2*R*)-**2a**: R_f (3:1 hexane/AcOEt) 0.37; ^{1}H NMR ($CDCl_3$): δ 7.60-7.25 (7H, m, ArH), 5.27 (1H, d, , J = 12.5 Hz, OHC<u>H</u>Ph), 5.12 (1H, d, J = 12.5 Hz, O<u>H</u>CHPh), 3.35 (1H, d, J = 15 Hz, SHC<u>H</u>), 3.25 (1H, d, J = 15 Hz, S<u>H</u>CH), 2.46 (3H, s, ArC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 153.8, 143.5, 138.4, 135.1, 130.7, 130.6, 128.6, 128.4, 124.0, 121.4 (q, $J_{C\text{-}F}$ = 289 Hz, CF_3), 112.3 (s, CN), 68.3 (s, OC<u>H</u>$_2$), 60.2 (s, SC<u>H</u>$_2$), 56.5 (q, $J_{C\text{-}F}$ = 34.3 Hz, <u>C</u>-CF_3), 21.5 (s, ArC<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$): δ −77.4 (s, CF_3); FT IR: cm^{-1} 3436, 1744; MS (EI, 70 eV) m/Z (%) 411 (M^++1, 41), 139 (pTolSO$^+$, 90), 91 ($C_7H_7^+$, 100).

(R_S,2*S*)-**2a**: R_f (3:1 hexane/AcOEt) 0.37; ^{1}H NMR ($CDCl_3$): δ 7.60-7.25 (7H, m, ArH), 5.17 (2H, s, OC<u>H</u>$_2$Ph), 3.52 (1H, d, J = 15 Hz, SHC<u>H</u>); 3.36 (1H, d, J = 15 Hz, S<u>H</u>CH), 2.45 (3H, s, ArC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) main signals: δ 122.0 (q, $J_{C\text{-}F}$ = 289 Hz, CF_3), 111.8 (s, CN), 68.2 (s, OC<u>H</u>$_2$), 57.1 (s, SC<u>H</u>$_2$), 56.3 (q, $J_{C\text{-}F}$ = 34.3 Hz, <u>C</u>-CF_3), 21.5 (s, ArC<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$): δ −75.5 (s, CF_3).

The difluoro α-aminonitriles **2b** were obtained in 92% yield and (R_S,2*R*)/ (R_S,2*S*) = 65:35 ratio using *Method A*, 93% yield and (R_S,2*R*)/ (R_S,2*S*) = 7:3 ratio using *Method B and C*.

(R_S,2*R*)-**2b**: R_f (3:1 hexane/AcOEt) 0.36; t_r 4.13 (4:1 hexane/AcOEt, 1.0 ml/min); $[\alpha]^{20}_D$ + 153.0 (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.60-7.30 (9H, m, ArH), 7.15 (1H, br s, N<u>H</u>), 6.71 (1H, t, $J_{H\text{-}F}$ = 56 Hz, C<u>H</u>F_2), 5.25 (1H, d, J = 12 Hz, OHC<u>H</u>Ph); 5.15 (1H, d, J = 12 Hz, O<u>H</u>CHPh), 3.22 (1H, d, J = 14 Hz, SHC<u>H</u>), 3.12 (1H, d, J = 14 Hz, SO<u>H</u>CH), 2.45 (3H, s, ArC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 154.7, 143.3, 138.2, 135.0, 130.5, 128.6, 128.5, 128.2, 123.9, 109.9 (t, $J_{C\text{-}F}$ = 253 Hz, CHF_2), 114.0 (s, CN), 68.1 (s, OC<u>H</u>$_2$), 56.8 (t, $J_{C\text{-}F}$ = 27 Hz, <u>C</u>-CF_3), 55.9 (s, SC<u>H</u>$_2$), 21.4 (s, ArC<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$): δ −135.5 (1F, dd, $J_{H\text{-}F}$ = 56 Hz and $J_{F\text{-}F}$ = 280 Hz), ~ 129.3 (1F, dd, $J_{H\text{-}F}$ = 56 Hz and $J_{F\text{-}F}$ = 280 Hz); IR: cm^{-1} 3250, 2215, 1720. Anal. Calcd. for $C_{19}H_{18}F_2N_2O_3S$: C, 58.15; H, 4.62; N, 7.14. Found: C, 57.68; H, 4.68; N, 7.03.

(R_S,2*S*)-**2b**: R_f (3:1 hexane/AcOEt) 0.24; t_r 6.33 (4:1 hexane/AcOEt, 1.0 ml/min); m.p. 110-112 °C (AcOEt); $[\alpha]^{20}_D$ + 178.6 (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.60-7.25 (9H, m, ArH), 7.15 (1H, br s, NH), 6.61 (1H, t, $J_{H\text{-}F}$ = 56 Hz, C<u>H</u>F_2), 5.20 (1H, d, J = 12 Hz, OHC<u>H</u>Ph), 5.12 (1H, d, J = 12 Hz, O<u>H</u>CHPh), 3.45 (1H, d, J = 14 Hz, SHC<u>H</u>); 3.18 (1H, d, J = 14 Hz, S<u>H</u>CH), 2.45 (3H, s, ArC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 154.4, 143.4, 137.9, 135.1, 130.6, 128.7, 128.6, 128.4, 124.1, 113.5 (t, $J_{C\text{-}F}$ = 6 Hz, *C*N), 111.0 (t, $J_{C\text{-}F}$ = 252 Hz, *C*HF_2), 68.0, 56.2 (t, $J_{C\text{-}F}$ = 27 Hz, <u>C</u>CHF_2), 54.1, 21.6; ^{19}F NMR ($CDCl_3$): δ −130.5 (1F, dd, $J_{H\text{-}F}$ = 56 Hz and $J_{F\text{-}F}$ = 280 Hz), −128.5 (1F, dd, $J_{H\text{-}F}$ = 56 Hz and $J_{F\text{-}F}$ = 280 Hz).

The chlorodifluoro α-aminonitriles **2c** were obtained in 80% yield and (R_S,2*S*)/(R_S,2*R*) = 55:45 ratio using *Method A*.

(R_S,2*S*)-**2c**: R_f (7:3 hexane/AcOEt) 0.31; we were not able to obtain this compound pure enough for a polarimetric analysis; ^{1}H NMR ($CDCl_3$): δ 7.65-7.30 (9H, m, ArH), 5.30 (1H, d, J = 11.6 Hz, OHC<u>H</u>Ph), 5.15 (1H, d, J = 11.5 Hz, O<u>H</u>CHPh); 3.30 (2H, s, SOCH_2), 2.46 (3H, s, ArC<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$): δ 153.7, 143.4, 138.5, 135.2, 130.6, 128.6, 128.4, 128.3, 124.1, 126.6 (t, $J_{C\text{-}F}$ = 304.5 Hz, $CClF_2$), 112.6 (s, CN), 68.2 (s, OC<u>H</u>$_2$), 61.8 (s, SC<u>H</u>$_2$), 60.8 (t, $J_{C\text{-}F}$ = 29.0 Hz, <u>C</u>-$CClF_2$), 21.5 (s, ArC<u>H</u>$_3$); ^{19}F NMR ($CDCl_3$): δ −63.0 (1F, d, $J_{F\text{-}F}$ = 147 Hz), −62.3 (1F, d, $J_{F\text{-}F}$ = 147 Hz).

(R_S,2*R*)-**2c**: R_f (7:3 hexane/AcOEt) 0.32; m.p. 158-160 °C (AcOEt); ^{1}H NMR ($CDCl_3$): δ 7.60-7.25 (9H, m, ArH), 7.1 (1H, br s, NH), 5.20 (2H, s, OCH_2Ph), 3.65 (1H, d, *J* = 14 Hz, SHCH); 3.35 (1H, d, J = 14 Hz, SHCH), 2.45 (3H, s, $ArCH_3$); ^{13}C NMR ($CDCl_3$) main signals: δ 126.8 (t, J_{C-F} = 304.5 Hz, $CClF_2$), 112.3 (s, CN), 68.1 (s, OCH_2), 61.8 (s, SCH_2), 60.9 (t, J_{C-F} = 29.0 Hz, C-$CClF_2$), 21.5 (s, $ArCH_3$); ^{19}F NMR ($CDCl_3$): δ −62.3 (1F, d, J_{F-F} = 165 Hz), −61.4 (1F, d, J_{F-F} = 165 Hz); FT IR: cm^{-1} 3436, 1744; MS (CI, 70 eV) m/Z (%) 426 (M^+, 100).

Synthesis of the hydantoin sulfoxide. The α-aminonitrile (R_S,2*R*)-**2b** (3.6 mmol) was dissolved in a 1*N* KOH MeOH/H_2O 1:1 mixture (15 ml) and stirred four days at rt. AcOH was added until neutral pH was reached. The resulting solution was extracted with AcOEt, the collected organics layers were dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure. FC of the residue (6:4 AcOEt/hexane) afforded the hydantoin (R_S,5*R*)-**3**, as a white solid (65% yield).

(R_S,5*R*)-**3**: R_f (7:3 AcOEt/hexane) 0.26; $[\alpha]^{20}_D$ + 119.6 (c 0.70, MeOH); m.p. 223-224°C (AcOEt); ^{1}H NMR (CD_3OD): δ 7.5 (4H, m, ArH), 6.08 (1H, t, J_{H-F} = 55 Hz, CHF_2), 3.55 (1H, d, *J* = 14 Hz, SHCH), 3.35 (1H, d, *J* = 14 Hz, SOHCH), 2.45 (3H, s, $ArCH_3$); ^{19}F NMR (CD_3OD): δ −130.6 (1F, dd, J_{H-F} = 55 Hz and J_{F-F} = 285 Hz), −128.2 (dd, J_{H-F} = 55 Hz and J_{F-F} = 285 Hz); MS (CI, 70 eV) m/Z (%) 303 (M^++1, 100). Anal. Calcd. for $C_{12}H_{12}N_2F_2O_3S$: C, 47.63; H, 4.00; N, 9.22. Found: C, 47.68; H, 4.00; N, 9.27.

Crystal data for (R_S,5*R*)-**3** : $C_{12}H_{12}F_2N_2O_3S$, f.w. 302.30, monoclinic, space group P 2_1, a = 10.580(1)Å, b = 6.632(1)Å, c = 11.113(1)Å, β = 117.86(1)°, V = 689.34(10)Å^3, Z = 2, D_c = 1.456 Mg/m^3, μ = 2.411 mm^{-1}, F(000) = 312, index ranges −11 ≤ h ≤ 11, −7 ≤ k ≤7, −12 ≤ l ≤ 12, 205 parameters, S = 1.069, final R1 = 0.0274 for 1871 data with I > 2σ(I), final wR2=0.0749 (all data), Flack'x parameter = 0.01(2).

Desulfinylation reaction. To a solution of hydantoin sulfoxide (R_S,5*R*)-**3** (1.90 mmol) in ethanol (20 ml), Ni-Raney (2 g) was added. The slurry was vigorously stirred for 64 h under hydrogen atmosphere at rt. After complete disappearance of the starting material (TLC), a substantial amount of the corresponding sulfide was still detected. Other Ni-Raney (1 g) was added and the stirring continued for other 48 h at rt and then for 6 h at 60°C. The slurry was cooled and filtered on a Celite pad. The residue was submitted to FC (7:3 to 4:6 hexane/AcOEt) giving the desired hydantoin (*R*)-**4** as a white solid (72% yield).

(*R*)-**4**: R_f (1:1 hexane/AcOEt) 0.47; $[\alpha]^{20}_D$ −21.9 (c 1.02, MeOH); m.p. 178-179 °C (AcOEt); ^{1}H NMR (CD_3OD): δ 5.95 (1H, t, J_{H-F} = 55 Hz, CHF_2), 1.47 (3H, s, CH_3); ^{13}C NMR (CD_3OD): δ 174.9, 159.0, 115.8 (t, J_{C-F} = 245 Hz), 65.6 (t, J_{C-F} = 21 Hz), 17.6 (t, J_{C-F} = 2 Hz); ^{19}F NMR (CD_3OD): −132.3 (1F, dd, J_{H-F} = 55 Hz and J_{F-F} = 283.5 Hz), −127.1 (1F, dd, J_{H-F} = 55 Hz and J_{F-F} = 283.5 Hz); MS (CI, 70 eV) m/Z (%) 164 (M^+, 100). Anal. Calcd. for $C_5H_6N_2F_2O_2$: C, 36.33; H, 3.55; N, 16.98. Found: C, 36.59; H, 3.69; N, 17.07.

Hydantoin hydrolysis. The hydantoin (*R*)-**4** (0.33 mmol) was dissolved in an aqueous 1*N* $Ba(OH)_2 \cdot 8H_2O$ solution (3 ml) and refluxed for 24 h. An aqueous 1*N* HCl solution was added until strongly acidic pH was reached. The solvent was removed under reduced pressure, affording a white solid, that was chromatographed on strongly acidic resin DOWEX 50W X8-400. Water was used as eluant until the collected fractions reached an almost neutral pH, then an aqueous 7.5% ammonia solution. After solvent removal, the free aminoacid was obtained as a white powder (90% yield).

(*R*)-α-Difluoromethyl-alanine 5: R_f (3:1:1 BuOH/AcOH/H_2O) 0.46; $[\alpha]^{20}_D$ +15.35 (c 0.85, H_2O); m.p. 194-196 °C (decomposes). ^1H NMR (D_2O): δ 6.20 (1H, t, J_{H-F} = 53 Hz, CHF_2), 1.50 (3H, s, CH_3). ^{13}C NMR (D_2O): δ 174.9, 118.4 (t, J_{C-F} = 240 Hz, *C*HF_2), 64.3, 20.2; ^{19}F NMR (D_2O): δ −131.95 (1F, dd, J_{H-F} = 53.2 Hz and J_{F-F} = 275.4 Hz), −126.1 (1F, dd, J_{H-F} = 53 Hz and J_{F-F} = 275.5 Hz). FT IR: cm^{-1} 3423 (broad), 1628; MS (CI, 70eV) m/Z (%) 140 (M^++1, 100).

Pummerer reaction. To a stirred solution of α-aminonitrile (*R*$_S$,2*S*)-**2b** (1.95 mmol) and *sym*-collidine (5.85 mmol) in acetonitrile (25 ml) under a nitrogen atmosphere at 0°C, neat trifluoroacetic anhydride (9.75 mmol) was added dropwise. The reaction mixture was stirred at 0°C and after 10 min a drop of water and potassium carbonate were added until neutral pH was reached. After 10 min at 0°C, sodium borohydride (about 5 mmol) was added portionwise. After 5 min the reaction was quenched with a saturated aqueous ammonium chloride solution and extracted with AcOEt. The collected organic layers were treated twice with 1N HCl solution, in order to remove the excess of *sym*-collidine. The organic layers were dried over anhydrous sodium sulphate, filtered, and the solvent was removed under reduced pressure. The residue was submitted to FC (7:3 hexane/AcOEt) to give the α-aminoalcohol **7** (95% yield).

(*R*)-**7**: R_f (8:2 hexane/AcOEt) 0.25; $[\alpha]^{20}_D$ −19.6 (c 0.82, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.35 (5H, m, ArH); 6.38 (1H, t, J_{H-F} = 55 Hz, CHF_2), 5.70 (1H, br s, NH), 5.15 (2H, s, PhC$\underline{H}_2$O), 4.15 (2H, s, C$\underline{H}_2$OH); ^{13}C NMR ($CDCl_3$): δ 154.9, 134.9, 128.7, 128.4, 114.5 (br s, CN), 111.2 (t, J_{C-F} = 252.3 Hz, *C*HF_2), 68.3 (s, OC$\underline{H}_2$), 60.8 (t, J_{C-F} = 3.2 Hz, HO*C*H_2), 58.4 (t, J_{C-F} = 25.0 Hz, $\underline{C}$-*C*HF_2). ^{19}F NMR ($CDCl_3$): δ −133 (1F, dd, J_{H-F} = 55 Hz and J_{F-F} = 288 Hz); −131.2 (1F, dd, J_{H-F} = 55 Hz and J_{F-F} = 288 Hz); FT IR: cm^{-1} 3414, 3350 (broad), 1730.

Hydrolysis of the β-hydroxy-α-aminonitrile. The (*R*)-aminoalcohol **6** (0.48 mmol) was dissolved in an aqueous 1*N* $Ba(OH)_2 \cdot 8H_2O$ solution (4.4 ml) and refluxed for 24 h. An aqueous 1*N* HCl solution was added until strongly acidic pH was reached. The solvent was removed under reduced pressure, affording a white solid, that was chromatographed on strongly acidic resin DOWEX 50W X8-400. Water was used as eluant until the collected fractions reached an almost neutral pH, then an aqueous 7.5% ammonia solution. After solvent removal the free amino acid was obtained as a white powder (55% yield).

(*S*)-α-difluoromethyl-serine 8: R_f (3:1:1 *t*BuOH/AcOH/H_2O) 0.53; $[\alpha]^{20}_D$ −4.99 (c 1.263, MeOH); m.p. 156°C (decomposes); ^1H NMR (D_2O): δ 6.27 (1H, t, J_{H-F} = 54 Hz, CHF_2), 4.00 (1H, d, J_{H-F} = 12 Hz, HC$\underline{H}$OH), 3.85 (1H, d, J_{H-F} = 12 Hz, $\underline{H}$CHOH); ^{13}C NMR (D_2O): δ 172.1, 117.0 (dt, J_{C-F} = 247.5 Hz, J_{C-H} = 198 Hz, *C*HF_2), 68.8 (t, J_{C-F} = 16.5 Hz, $\underline{C}$CHF_2), 65.6 (t, J_{C-H} = 148.5 Hz, *C*H_2OH); ^{19}F NMR (D_2O): δ −128.9 (1F, dd, J_{H-F} = 54 Hz and J_{F-F} = 288 Hz), −126.3 (1F, dd, J_{H-F} = 54 Hz and J_{F-F} = 288 Hz); FT IR: cm^{-1} 3400 (broad), 3135, 3050, 1643.

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