Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 1119-1126, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00143-X

Biocatalytic Resolution of β-Fluoroalkyl-β-Amino Acids

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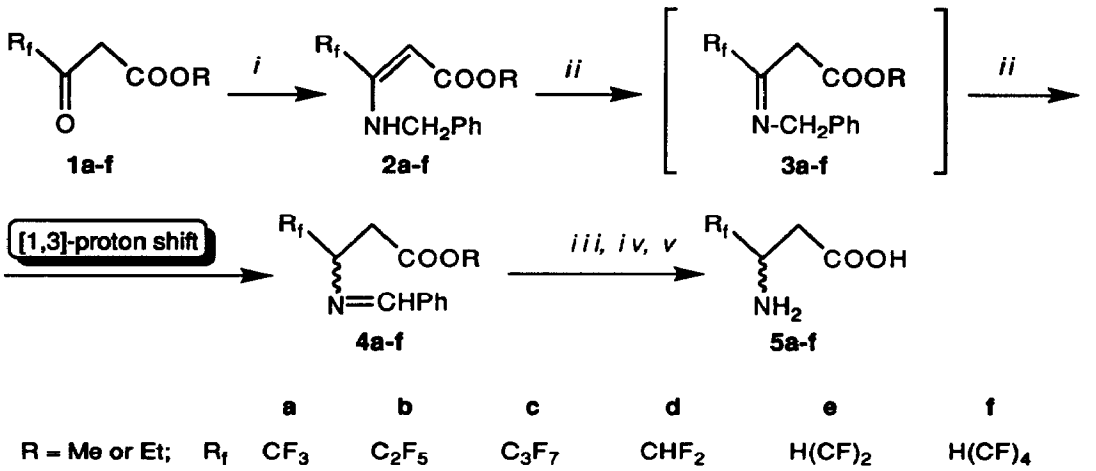
Abstract: *N*-Phenylacetyl derivatives of β-fluoroalkyl-β-alanines **6** were synthesized and biocatalytically resolved to the corresponding enantiopure β-amino acids **7, 9** with the aid of penicillin acylase (EC 3.5.1.11) from *Escherichia coli*. In substrates **6** the enantioselectivity of the biocatalytic process was practically uninfluenced by the nature of the fluoroalkyl chain. Thus, β-fluoroalkyl-β-alanines **7, 9** bearing short (R = CF_3, CHF_2) or long [C_3F_7, $H(CF_2)_4$] chains were prepared in high enantiomeric purity. The (*R*)-enantiomer was the fast-reacting enantiomer in all cases.

Introduction.

In recent decades, organofluorine chemistry has made a marked impact on the design and synthesis of many kinds of biologically active molecules such as steroids, carbohydrates, amino acids, peptides, and other natural products.[2] The progress in fluorine-containing amino acid chemistry has revealed that this type of unnatural amino acids, especially those which are CF_3 branched or possess fluorine atom(s) in the β-position to amino group, are highly biologically active molecules with a wide range of potential applications.[3] However, most of the research in the field has been focused on the chemistry of fluorinated α-amino acids. Conversely, there are relatively few methods for the synthesis of optically pure fluorine-containing β-amino acids.[3] To our knowledge, only one type, namely, α-fluoro-β-amino acids are potentially available in optically active form by the Welch chemistry.[4] On the other hand, in recent years, there has been a substantial interest in the synthesis of β-amino acids. Thus, being important constituents of many classes of natural products,[5] β-amino acids attract considerable interest as useful chiral structural units for the synthesis of compounds of pharmaceutical interest.[6] In view of beneficial medicinal effects that fluorine can impart to biologically active molecules the importance of fluorine-containing β-amino acids as a potentially biologically active compounds became clear. Our strategy on this project involves a two-ponged approach which includes asymmetric synthesis[7] and biocatalytic resolution[8] of racemates. In this paper we report a convenient method for the preparation of β-fluoroalkyl-β-amino acids in optically pure form *via* resolution of their racemic *N*-phenylacetyl derivatives by means of penicillin acylase (EC 3.5.1.11) from *Escherichia coli*.

Scheme 1



Reagents and Conditions: *i*, benzene or toluene, Dowex-50 or *p*-Tol-SO_3H, reflux; *ii*, base (NEt_3 or 1,8-diazabicyclo[5.4.0]undec-7-ene); *iii*, 2 N HCl, room temperature, 2 hr.; *iv*, 6 N HCl, 90 °C, 6 hr.; *v*, Dowex-50, 0.2 N NH_4OH

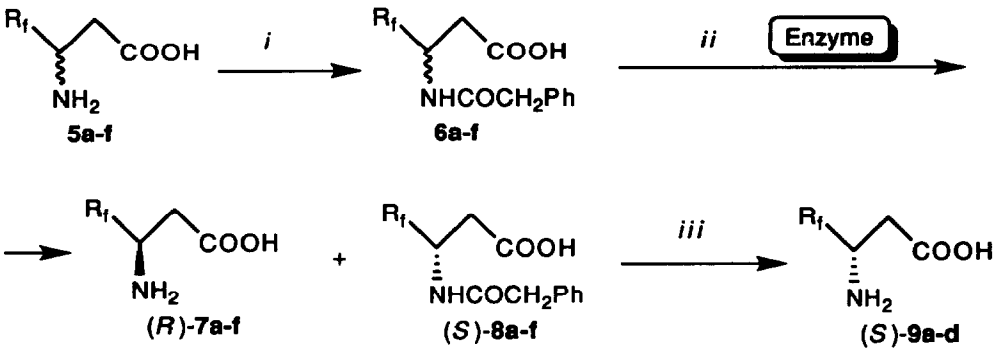
Results and Discussion

***Synthesis of Racemic β-Fluoroalkyl-β-Amino Acids* 5a-f.** Recently, we have developed a general method for synthesis of racemic β-fluoroalkyl-β-amino acids starting from readily available ketoesters **1a-f** and benzylamine (Scheme 1).[9] Two sequential base-catalyzed [1,3]-proton transfers lead to facile conversions of enamines **2a-f** into the *N*-benzylidene derivatives of β-amino acids **4a-f** which were deprotected by an acidic hydrolysis to give free amino acids **5a-f** in good overall yield. Following this procedure all starting amino acids **5a-f** were prepared on a multi-gram scale and were used for further transformation after isolation by cation exchange resin without additional purification.

***Synthesis of Racemic N-Phenylacetyl-β-Fluoroalkyl-β-Amino Acids* 6a-f.**

From the viewpoint of synthetic convenience and reagent availability the procedure of Schotten and Baumann for the acylation of amino acids was regarded as the most attractive for the preparation of *N*-phenylacetyl derivatives **6a-f**. However, previously we have shown that the presence of trifluoromethyl group in the α-position of α-amino carboxylic acids strongly influences on the amino function decreasing its reactivity in acylation reactions.[10] Thus, the $pK(NH_2)$ value of β-trifluoromethyl-β-alanine (**5a**) was found to be 6.3 which is substantially lower than that for fluorine-free β-amino acids.[5] Nevertheless, as experiments revealed, treatment of water-acetone solutions of β-amino acids **5a-f** in the presence of potassium bicarbonate with phenylacetyl chloride at low temperature (-5 °C) provide the desired *N*-phenylacetyl derivatives **6a-f** with good-to-excellent (73-98%) isolated yields (Scheme 2). Analytically pure samples of **6a-f** for biocatalytic resolution were obtained by single recrystallizations of crude *N*-phenylacetyl derivatives **6a-f** from toluene.

Scheme 2



	a	b	c	d	e	f
R_f	CF_3	C_2F_5	C_3F_7	CHF_2	$H(CF)_2$	$H(CF)_4$
R	CH_3	C_2H_5	C_2H_5	C_2H_5	CH_3	CH_3

Reagents and Conditions: *i*, water/acetone (1/1), $KHCO_3$, phenylacetyl chloride, –5 °C, 2 hr., then room temp., 1 h; *ii*, penicillin acylase, 22-25 °C, pH 7.4-7.6; *iii*, 6 N HCl, 70 °C, 11 hr.

***Biocatalytic Resolution of N-Phenylacetyl-β-Fluoroalkyl-β-Amino Acids* 6a-f.** Due to the low pK(NH_2) values of β-fluoroalkyl-β-amino acids **5a-f** it was impossible to use the common spectrophotometric *o*-phthalaldehyde method[11] to determine the concentration of biocatalytically produced amino acid. For instance, to achieve a value of the molar extinction coefficient as high as 2070 M^{-1} x cm^{-1}, the reaction mixture was kept for 3 h at 70 °C. So, this method is too time consuming and not sensitive enough to follow the time dependence of β-fluoroalkyl-β-amino acids concentration. Instead, we took advantage of the fact, that at pH 7.5 the amino group of β-fluoroalkyl-β-amino acid is fully protonated, and used continuous automatic titration (pH-stat) at the constant pH (7.5) to follow the rate of enzymatic reaction. The course of the biocatalytic hydrolysis was monitored by consumption of 20% NH_4OH and was stopped by acidification of reaction mixture with 2 N HCl at an appropriate point to obtain 50% conversion of starting material. The reaction rate slowed down significantly or even stopped when a conversion of 50% was reached. Regarding the reactivity, it is worth noting, that the rate of penicillin acylase-catalyzed hydrolytic reaction decreased with an increase in the length of the fluoroalkyl chain in the *N*-phenylacetyl derivatives **6a-f**. Thus, a reaction time for 50% conversion varied from 4.5 hr. for **6a** to about 48 hr. for **6f**. However, the enantioselectivity of the biocatalytic process was practically uninfluenced by the nature of fluoroalkyl chain. Chiral HPLC analysis[12] of crude amino acids **7a-f**, released by the enzyme and isolated by means of cation exchange resin Dowex-50, has shown that their enantiomeric purities are, at least (the sensitivity limit of the method), 95% ee. The enzymatically unconverted *N*-phenylacetyl derivatives **8a-f** were isolated from the water solutions by extraction with ethyl acetate (see experimental part) and without purification were hydrolyzed by 6 N HCl to give after dehydrochlorination with cation exchange resin Dowex-50 free amino acids **9a-d**, which enantiomeric purity, according to HPLC analysis, is more than 90% ee.

These results show the high reactivity and enantioselectivity of the penicillin acylase on *N*-phenylacetyl derivatives **6a-f**. Preliminary experiments on the ratio of the second-order rate constants of the enzyme-catalyzed hydrolysis of (*R*)- and (*S*)-*N*-phenylacetyl derivative of β-trifluoromethyl-β-alanine has revealed that the enzyme stereoselectivity is 500, i.e. $(k_{cat}/K_M)_R/(k_{cat}/K_M)_S = 500$.

Determination of Absolute Configuration of β-Fluoroalkyl-β-Amino Acids. Since it is well known that penicillin acylase does not cleave (*D*)-α-amino carboxylic[13] or α-amino alkylphosphonic acids[14], as well as (*D*)-enantiomers of fluorine-free β-amino[8a,15] and γ-amino acids,[16] we expected that our biocatalytically prepared β-fluoroalkyl-β-amino acids would be members of the (*L*)-series. We have confirmed this for the (*R*)-β-trifluoromethyl-β-alanine (**7a**) with X-ray analysis.[8b] Taking into account that the sense of enantioselection during the enzymatic hydrolysis[13] should be the same for all *N*-phenylacetyl derivatives **6a-f** and the fact of similarity in the order of elution in conditions of chiral HPLC analysis of biocatalytically reactive enantiomers and enzymatically unreactive ones (Table 1), we can attribute (*R*)-absolute configuration for all biocatallytically prepared amino acids **7a-f** and (*S*)-absolute configuration for enantiomers **9a-d** obtained by chemical hydrolysis of *N*-phenylacetyl derivatives **8a-f**.

Table 1. Chromatographic Behavior of β-Fluoroalkyl-β-Amino Acids

Entry	β-amino acid	Retention Times of Enantiomers (min)[a]	
		(*R*)	(*S*)
1	CF_3-CH(NH_2)-CH_2COOH	5.8	6.7
2	C_2F_5-CH(NH_2)-CH_2COOH	11.7	13.1
3	C_3F_7-CH(NH_2)-CH_2COOH	18.5	22.1
4	CHF_2-CH(NH_2)-CH_2COOH	5.6	5.9
5	H(CF_2)$_2$-CH(NH_2)-CH_2COOH	8.0	9.0
6	H(CF_2)$_4$-CH(NH_2)-CH_2COOH	13.4	15.9

[a] Column: Nucleosil Chiral [(*L*)-Hydroxy-Pro)] - (250 x 4.0 mm), Macherey-Nagel, Germany. The mobile phase: 5.0 mM cooper sulfate solutions at a flow-rate of 0.5 ml/min.

CONCLUSIONS

We have disclosed that some β-fluoroalkyl-β-amino acids can be obtained in enantiomerically pure form in good yield by penicillin acylase-catalyzed resolution of their racemic *N*-phenylacetyl derivatives. The results obtained revealed a significant decrease in reaction rate of enzymatic hydrolysis with increasing a length of fluoroalkyl group, whereas the enantiodifferentiation remains very high and almost constant with a change in the size of fluoroalkyl chain and so it possesses no limitation on the generality of the method in view of optical purity of desired amino acids. Taking into account that this method employs an inexpensive, commercially available enzyme and cheap readily accessible starting racemic material, it could be practically useful for production of enantiomerically pure β-fluoroalkyl-β-amino acids on a preparative scale.

ACKNOWLEDGMENT

We thank the Ukrainian Academy of Sciences and the JSPS Foundation (Japan) for financial support.

EXPERIMENTAL

General. ^{1}H-NMR was performed on a Varian VXR-300 (299.94 MHz) or Gemini-200 (199.98 MHz) spectrometer. ^{19}F-NMR spectra were recorded on Bruker WP-200 (188.98 MHz). Tetramethylsilane and $CFCl_3$ were used as internal standards in organic solvents and sealed in a glass capillary for D_2O solutions. NMR data are reported in δ units. HPLC analyses were performed on LKB (Sweden) liquid chromatographic system consisting of a model 2150 HPLC pump, a model 7410 injector, a model 2140 detector, a model 2200 recording integrator and model 2155 column oven. Chiral stationary phase column Nucleosil Chiral [(*L*)-Hydroxy-Pro) - (250 x 4.0 mm), Macherey-Nagel, Germany. Eluent: 5.0 mM $CuSO_4$, flow-rate 0.5 mL/min, 35 °C, detection at 235 nm. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Determination of the β-trifluoromethyl-β-alanine amino group pK value was performed on RTS-622 automatic titration system (Radiometer, Copenhagen, Denmark) using a stepped titration curve technique described in RTS-622 Operating Instructions.

Melting points (mp) are uncorrected and were obtained on a capillary apparatus.

Penicillin acylase (EC 3.5.1.11) from *E. coli* was used in soluble form.[14]

General procedure for the synthesis of racemic N-phenylacetyl derivatives **6a-f.** Phenylacetyl chloride (0.21 mol) in acetone (70 mL) was added to the solution of racemic β-amino acid (0.13 mol) and potassium bicarbonate (0.356 mol) in aqueous acetone (1/1, 600 mL) under stirring at –5 °C. The resulted solution was stirred for 2 h at -5 °C and 1 h at room temperature. The reaction mixture was filtered, acetone evaporated and washed with diethyl ether (3 x 50 mL). The aqueous phase was acidified with 2N HCl up to pH 2.0 and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with $MgSO_4$ and concentrated. The residue was subjected to recrystallization from toluene.

***rac*-4,4,4-Trifluoro-3-(*N*-Phenylacetylamino)butanoic acid (6a):** 85%, mp144-146 °C; ^{1}H-NMR (CD_3SOCD_3): 2.66, 2.86 (ABX, J_{AB} = 16.4 Hz, J_{AX} = 9.1, J_{BX} = 4.6 Hz, 2H, CH_2), 3.57 (s, 2H, $CH_2C_6H_5$), 5.11 (dddq, J_{HH} = 9.1 Hz, J_{HH} = 4.6 Hz, J_{HH} = 8.4 Hz, J_{HF} = 7.5 Hz, 1H, CH), 7.27 (m, 5H, C_6H_5), 7.80 (d, J_{HH} = 8.4 Hz, 1H, NH). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.40; F, 20.71. Found: C, 52.34; H, 4.38; F, 20.77.

***rac*-5,5,5,4,4-Pentafluoro-3-(*N*-Phenylacetylamino)pentanoic acid (6b):** 77%, mp155-156 °C; ^{1}H-NMR (CD_3COCD_3): 2.67, 2.91 (ABX, J_{AB} = 16.2 Hz, J_{AX} = 8.7, J_{BX} = 4.5 Hz, 2H, CH_2), 3.63 (s, 2H, $CH_2C_6H_5$), 5.26 (m, 1H, CH), 7.23-7.40 (m, 5H, C_6H_5), 7.80 (m, 1H, NH). Anal. Calcd for $C_{13}H_{12}F_5NO_3$: C, 48.00; H, 3.72; F, 29.21. Found: C, 48.17; H, 3.75; F, 29.00.

***rac*-6,6,6,5,5,4,4-Heptafluoro-3-(*N*-Phenylacetylamino)hexanoic acid (6c):** 80%, mp163-164 °C; ^{1}H-NMR (CD_3COCD_3): 2.64, 2.80 (ABX, J_{AB} = 15.6 Hz, J_{AX} = 8.7, J_{BX} = 4.8 Hz, 2H, CH_2), 3.64 (s, 2H, $CH_2C_6H_5$), 5.30 (m, 1H, CH), 7.25-7.35 (m, 5H, C_6H_5), 7.80 (m, 1H, NH). Anal. Calcd for $C_{14}H_{12}F_7NO_3$: C, 44.81; H, 3.22; F, 35.44. Found: C, 45.02; H, 3.31; F, 35.37.

***rac*-4,4-Difluoro-3-(*N*-Phenylacetylamino)butanoic acid (6d):** 98%, mp163-165 °C; ^{1}H-NMR ($CDCl_3$): 2.69, 2.75 (ABX, J_{AB} = 16.8 Hz, J_{AX} = 9.0, J_{BX} = 4.5 Hz, 2H, CH_2), 3.56 (s, 2H, $CH_2C_6H_5$), 4.25 (m, 1H, CH), 5.03 (td, J_{HF} = 56.1 Hz, J_{HH} = 3.0, 1H, CHF_2), 7.26-7.30 (m, 5H, C_6H_5),

7.55 (m, 1H, NH). Anal. Calcd for $C_{12}H_{13}F_2NO_3$: C, 56.03; H, 5.09; F, 14.77. Found: C, 56.01; H, 5.03; F, 14.75.

***rac*-5,5,4,4-Tetrafluoro-3-(*N*-Phenylacetylamino)pentanoic acid (6e)**: 83%, mp125-128 °C; ^{1}H-NMR (CD_3COCD_3): 2.63, 2.88 (ABX, J_{AB} = 14.4 Hz, J_{AX} = 9.3, J_{BX} = 5.4 Hz, 2H, CH_2), 3.57 (s, 2H, $CH_2C_6H_5$), 5.20 (m, 1H, CH), 6.18 (tdd, J_{HF} = 52.3 Hz, J_{HF} = 3.3 Hz, J_{HF} = 8.1 Hz, 1H, CHF_2), 7.30-7.35 (m, 5H, C_6H_5), 7.78 (d, J_{HH} = 8.8 Hz, 1H, NH). Anal. Calcd for $C_{13}H_{13}F_4NO_3$: C, 50.82; H, 4.26; F, 24.74. Found: C, 50.95; H, 4.38; F, 24.77.

***rac*-7,7,6,6,5,5,4,4-Oktafluoro-3-(N-Phenylacetylamino)heptanoic acid (6f)**: 73%, mp135-138 °C; ^{1}H-NMR (CD_3COCD_3): 2.67, 2.90 (ABX, J_{AB} = 16.5 Hz, J_{AX} = 9.0, J_{BX} = 4.8 Hz, 2H, CH_2), 3.58 (s, 2H, $CH_2C_6H_5$), 5.42 (m, 1H, CH), 6.69 (tt, J_{HF} = 51.0 Hz, J_{HF} = 5.4 Hz, 1H, CHF_2), 7.25-7.40 (m, 5H, C_6H_5), 7.82 (m, 1H, NH). Anal. Calcd for $C_{15}H_{13}F_8NO_3$: C, 44.23; H, 3.22. Found: C, 44.42; H, 3.37.

***Typical procedure for the enzymatic hydrolysis of rac-N-phenylacetyl derivatives* 6a-f. (*R*)-4,4,4-Trifluoro-3-aminobutanoic acid (7a).** The pH of the solution of 30 g (0.11 mol) of *N*-phenylacetyl derivative **6a** in water (500 mL) was adjusted with 20 % NH_4OH to 7.5 and 15 mL of 10^{-6} M penicillin acylase solution was added. The mixture was stirred at 22-25 °C, and pH was constantly adjusted in the limits of 7.4-7.6 by dropwise addition of 20 % NH_4OH. On the reaching of 50% convertion of starting material the reaction mixture was acidified by 2 N HCl up to pH 2.0 and extracted with ethyl acetate (3 x 100 mL). The aqueous phase was evaporated in vacuum (50 °C, 30-40 mm Hg). Dowex-50 (H^+-form) column chromatography yielded 7.4 g (86%) of (+)-(*R*)-**7a**, after recristallyzation from methanol mp 173-174 °C; $[\alpha]_D^{25}$ = +27.6, $[\alpha]_{578}^{25}$ = +28.5, $[\alpha]_{546}^{25}$ = +32.4, $[\alpha]_{436}^{25}$ = +53.2, $[\alpha]_{365}^{25}$ = +72.6 (*c* 2.6 6 N HCl). ^{1}H-NMR (CD_3SOCD_3): 2.78, 3.01 (ABX, J_{AB} = 17.8 Hz, J_{AX} = 8.8 Hz, J_{BX} = 4.2 Hz, 2H, CH_2), 4.39 (qdd, *J* = 8.8 Hz, *J* = 4.2 Hz, *J* = 10.8 Hz, 1H, CH). Anal. Calcd for $C_4H_6F_3NO_2$: C, 30.58; H, 3.85; F, 36.28; N, 8.92. Found: C, 30.42; H, 3.91; F 36.13; N, 8.96.

(*S*)-4,4,4-Trifluoro-3-aminobutanoic acid (9a). The ethyl acetate extracts, obtained after *rac*-*N*-phenylacetyl derivative **6a** enzymatic hydrolysis, were combined, dried with $MgSO_4$ and evaporated. The recrystallization of the residue from toluene yielded 12.3 g (82%) of (*S*)-**8a**; mp 163-166 °C, $[\alpha]_D^{25}$ = +4.6 (*c* 1.0 CH_3COCH_3). The ^{1}H-NMR spectrum of (*S*)-**8a** is identical to that of *rac*-**6a**. 1.8 g (6.5 mmol) of (*S*)-**8a** was dissolved in 6 N HCl (30 mL) and heated at 70 °C for 11 hr. The reaction mixture was evaporated in vacuum (50 °C, 30-40 mm Hg) to dryness. The residue was dissolved in water (50 mL) and washed with ethyl acetate (3 x 20 mL). Free (-)-(*S*)-**9a** was isolated from the aqueous phase using Dowex-50 column chromatography. The yield was 0.91 g (88.6%), after recrystallization from methanol, mp 170-173 °C; $[\alpha]_D^{25}$ = –27.1, $[\alpha]_{578}^{25}$ = –28.2, $[\alpha]_{546}^{25}$ = –31.4, $[\alpha]_{436}^{25}$ = –52.6, $[\alpha]_{365}^{25}$ = –79.2 (*c* 1.4 6 N HCl). The ^{1}H-NMR spectrum of (-)-(*S*)-**9a** is identical to that of (+)-(*R*)-**7a**.

The other biocatalytic resolutions were done in the same way. (*S*)-Amino acids **9b-d** were prepared from crude enzymatically unreactive *N*-phenylacetyl derivatives **8b-d** which structure and chemical purety were controlled by ^{1}H NMR analysis. ^{1}H NMR Spectra of **8b-d** are similar to racemic patterns.

(*R*)-5,5,5,4,4-Pentafluoro-3-aminopentanoic acid (7b): 82%, mp 135-140 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = +37.1 (*c* 0.3 H_2O). ^{1}H-NMR (0.1 N DCl in D_2O): 2.75, 2.97 (ABX, J_{AB} = 18.2 Hz, J_{AX} = 9.2 Hz, J_{BX} = 4.0 Hz, 2H, CH_2), 4.46 (qdd, *J* = 9.2 Hz, *J* = 4.2 Hz, *J* = 12.8 Hz, 1H, CH). ^{19}F-NMR

(D_2O): -83.8 (s, 3F, CF_3), -121.5, -125.5 (AB, J_{AB} = 256 Hz, 2F, CF_2). Anal. Calcd for $C_5H_6F_5NO_2$: C, 28.99; H, 2.92; F, 45.87; N, 6.76. Found: C, 29.13; H, 2.98; F, 45.64; N, 6.86.

(*S*)-5,5,5,4,4-Pentafluoro-3-aminopentanoic acid (9b): 73%, mp 133-137 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = –36.7 (*c* 0.1 H_2O). The ^{1}H-NMR spectrum of (-)-(*S*)-**9b** is identical to that of (+)-(*R*)-**7b**.

(*R*)-6,6,6,5,5,4,4-Heptafluoro-3-aminohexanoic acid (7c): 80%, mp 155-157 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = +27.0 (*c* 0.1 H_2O). ^{1}H-NMR (0.1 N DCl in D_2O): 2.76, 2.99 (ABX, J_{AB} = 18.0 Hz, J_{AX} = 9.3 Hz, J_{BX} = 3.3 Hz, 2H, CH_2), 4.50 (m, 1H, CH). Anal. Calcd for $C_6H_6F_7NO_2$: C, 28.03; H, 2.35. Found: C, 28.31; H, 2.33.

(*S*)-6,6,6,5,5,4,4-Heptafluoro-3-aminohexanoic acid (9c): 61%, mp 153-156 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = –26.1 (*c* 0.05 H_2O). The ^{1}H-NMR spectrum of (-)-(*S*)-**9c** is identical to that of (+)-(*R*)-**7c**.

(*R*)-4,4-Difluoro-3-aminobutanoic acid (7d): 88%, mp 200-203 °C (decomp.) from H_2O. $[\alpha]_D^{25}$ = +19.5 (*c* 0.2 H_2O). ^{1}H-NMR (D_2O): 2.20, 2.39 (ABX, J_{AB} = 16.2 Hz, J_{AX} = 9.0 Hz, J_{BX} = 4.8 Hz, 2H, CH_2), 3.28 (m, 1H, CH), 5.86 (td, J_{HF} = 56.7 Hz, J_{HH} = 3.6 Hz, 1H, CHF_2). ^{19}F-NMR (D_2O): -127.5 (d, J = 56.7 Hz, CHF_2). Anal. Calcd for $C_4H_7F_2NO_2$: C, 34.54; H, 5.07; F, 27.32; N, 10.07. Found: C, 34.57; H, 5.12; F, 27.28; N, 10.11.

(*S*)-4,4-Difluoro-3-aminobutanoic acid (9d): 72%, mp 201-203 °C (decomp.) from H_2O. $[\alpha]_D^{25}$ = –17.5 (*c* 0.06 H_2O). The ^{1}H-NMR spectrum of (-)-(*S*)-**9d** is identical to that of (+)-(*R*)-**7d**.

(*R*)-5,5,4,4-Tetrafluoro-3-aminopentanoic acid (7e): 74%, mp 126 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = +23.2 (*c* 0.4 MeOH). ^{1}H-NMR (CD_3OD): 2.40-3.00 (m, 2H, CH_2), 4.53 (m, 1H, CH), 6.11 (tdd, J_{HF} = 53.0 Hz, J_{HF} = 7.5 Hz J_{HF} = 4.2 Hz, 1H, CHF_2). Anal. Calcd for $C_5H_7F_4NO_2$: C, 31.75; H, 3.73; F, 40.19; N, 7.41. Found: C, 31.64; H, 3.69; F, 40.25; N, 7.34.

(*R*)-7,7,6,6,5,5,4,4-Octafluoro-3-aminoheptanoic acid (7f): 63%, mp 138-140 °C (decomp.) from H_2O. $[\alpha]_D^{22}$ = +12.2 (*c* 0.1 MeOH). ^{1}H-NMR (CD_3OD): 2.80, 3.15 (ABX, J_{AB} = 18.1 Hz, J_{AX} = 8.4 Hz, J_{BX} = 4.2 Hz, 2H, CH_2), 4.66 (m, 1H, CH), 6.69 (tt, $^2J_{HF}$ = 51.0 Hz, $^3J_{HF}$ = 5.4 Hz, 1H, CHF_2). Anal. Calcd for $C_7H_7F_8NO_2$: C, 29.08; H, 2.44. Found: C, 29.13; H, 2.49.

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(*Received* 4 *April* 1994)