Synthesis of Amino Acids with Modified Principal Properties 1. Amino Acids with Fluorinated Side Chains

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The synthesis and characterization of chiral fluorinated analogues of norvaline and norleucine from commercially available starting materials are presented. Full experimental details for the synthesis of the following amino acids are given: (S)-4,4-difluoronorvaline, (S)-4,4,5,5,5-pentafluoronorvaline, (S)-5,5-difluoronorleucine, (S)-5,5,6,6,6-pentafluoronorleucine, and (S)-4,4,5,5,6,6,6-heptafluoronorleucine.

These compounds were prepared with a view to obtaining new amino acids which possess physical and chemical properties so that their principal properties would be outside the range of variation of hitherto known amino acids. The principal properties are determined as latent variables in principal component analysis of molecular property descriptors. Two of the fluorinated amino acids, (S)-5,5,6,6,6-pentafluoronorleucine and (S)-4,4,5,5,6,6,6-heptafluoronorleucine were found to have principal properties outside the variation of previously characterized natural and synthetic amino acids. The principal properties, z parameters, for the five new fluorinated amino acids are given.

Proteins and peptides which are synthesized on the ribosomes of cells are made from a set of 20 natural amino acids. The information of the peptide chain structure is coded in the genetic material and these amino acids are therefore often referred to as coded amino acids. In certain microorganisms other types of amino acid can be found in peptide structures, and such peptides often have interesting physiological properties, e.g., antibiotic activity.

With a view to finding efficient pharmaceutical agents with minimum side-effects, an increased interest in peptide-type compounds has been demonstrated in recent years.

In this context, quantitative structure–activity relations, QSARs, play important roles. A very efficient method for obtaining peptide QSARs is to use PLS modelling (Projections to Latent Structures) for relating the physiological activity of the peptide to the principal properties of the amino acids in the peptide chain, see Ref. 1–9 for thorough discussions. The general concept of principal properties is discussed in Ref. 10 and no details are given here.

Principal properties of amino acids

The first determination of principal properties of coded amino acids was accomplished from a data set which contained 20 different physical and chemical descriptors to characterize the amino acids.[1] It was then shown that the

corresponding principal component scores (principal properties) could be used for PLS modelling to derive QSARs which relate the structure of peptides to their pharmacological activity.[2]

The data set for determining the principal properties has then been augmented by the inclusion of more property descriptors and also of other types of amino acid (non-coded amino acids as well as purely synthetic amino acids).[7,8] The utility of the principal properties for QSAR modelling through PLS has been demonstrated in many cases now.[4]

It is, however, rather cumbersome to measure a large number of physical and chemical properties for every new amino acid that becomes available and a rapid method of screening based on thin layer chromatography (TLC) with a set of different eluent systems has been developed.[6] The R_f values obtained in the TLC screening can be used as descriptors and have been found to produce a very similar result upon principal components analysis to that produced by the physical and chemical property descriptors.

A plot of the principal properties (a score plot of the first two principal components) from a set of 48 amino acids is shown in Fig. 1. This plot was available when the present study was initiated.[6]

It is seen in Fig. 1 that the data points corresponding to the amino acids are unevenly spread over the plot; there are 'white spots' on the map. These white spots correspond to certain combinations of molecular properties which are not represented in the set of amino acids

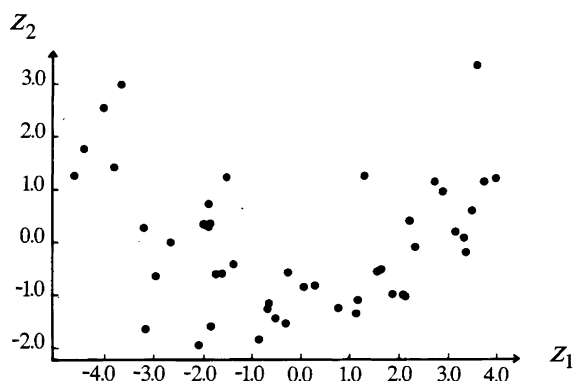---

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Fig. 1. Principal component score plot of the 48 amino acids described in Ref. 6.

covered by the study in Ref. 6. This inspired us to try to synthesize a set of modified amino acids which would have such properties that they would be projected in the white spots of the amino acid principal property map.

A subsequent study on an augmented data set of 55 amino acids afforded three principal components but this did not change the overall picture as regards the white spots in any significant way.[8] Analysis of the principal components model obtained from this augmented data set showed that the first principal component largely accounts for lipophilic–hydrophilic properties of the side chain of the amino acids, whereas the second and third components describe variations related to the bulk of the side-chain and to properties related to the electronic distribution. The score values were used to define scales (z_1, z_2, z_3) for the principal properties.[8]

From these results it was concluded that structural modifications which alter the lipophilic and electronic properties while leaving the steric bulk relatively unper-
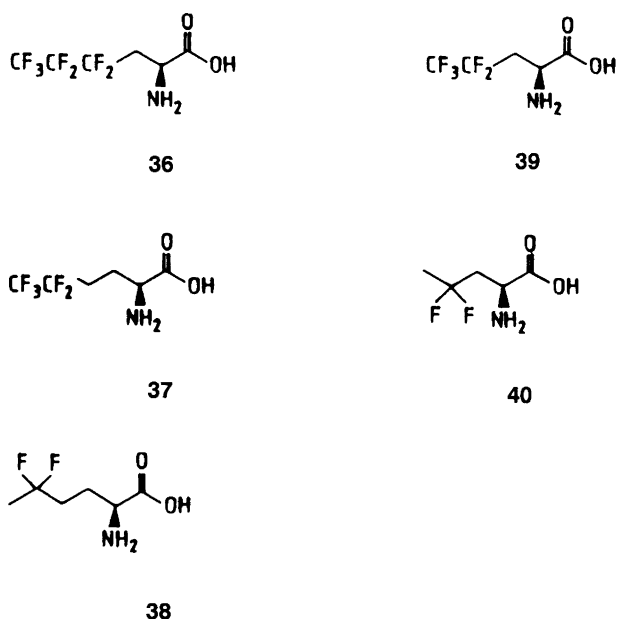
turbed might give amino acids which would be projected with a shift along the z axes related to lipophilic and electronic variations. One way to accomplish such a structural modification would be to replace hydrogen atoms of methylene and methyl groups on the side-chain by fluorine. The present paper presents the synthesis and the characterization of five fluorinated amino acids, shown in Fig. 2.

Methods and results

Synthesis of the amino acids. The amino acids were obtained in chiral form (S configuration) from the corresponding fluorinated carboxylic acid by the method of Evans,[11] see Scheme 1. The fluorinated carboxylic acid precursors were prepared by the routes summarized in Schemes 2–5. Details of the synthetic procedure and physical data are given in the Experimental section. The compounds have been numbered in the order they appear in the Experimental section. 5,5-Difluorohexanoic acid (8) and 4,4-difluoropentanoic acid (15) were prepared from the corresponding oxoester by treatment with sulfur tetrafluoride,[12] see Scheme 2.

4,4,5,5,5-Pentafluoropentanoic acid (13) was prepared according to the sequence summarized in Scheme 3. The first step was an addition of pentafluoroiodoethane to allyl acetate using azoisobutyronitrile, AIBN, as a radical initiator to yield 2-iodo-4,4,5,5,5-pentafluoropentyl acetate (10). The reaction was carried out in sealed glass ampoules. It was found that an almost quantitative conversion into the desired product (10) was achieved when the reaction was run without evacuating the ampoule prior to sealing, whereas prior evacuation afforded poor yields, in the range 30–35%.[13] The increased yield is probably an effect of pressure. The volume of the ampoules was 13 ml and this permits a fairly high pressure to build up during the course of the reaction.
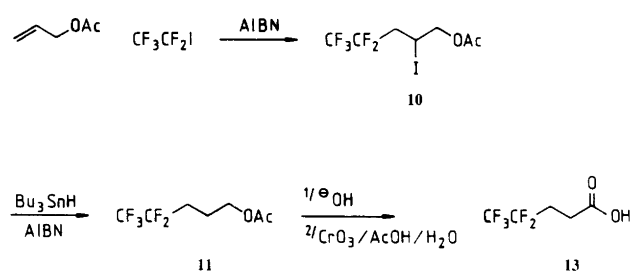
Deiodination of the iodo ester (10) was accomplished through reaction with tributyltin hydride.[14] Hydrolysis of the resulting 4,4,5,5,5-pentafluoropentyl acetate yielded

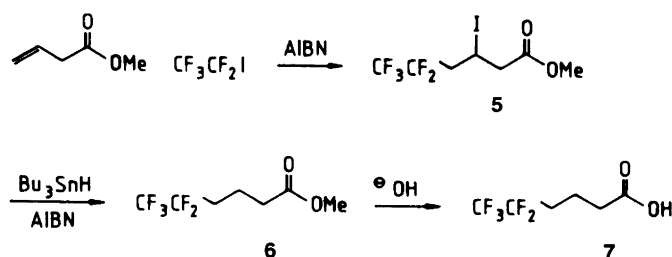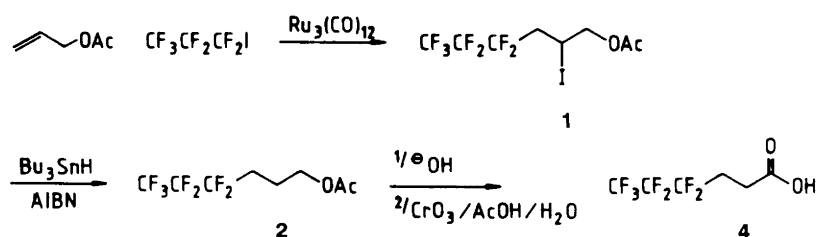*Fig. 2.* Structures of the fluorinated amino acids synthesized in the present work.
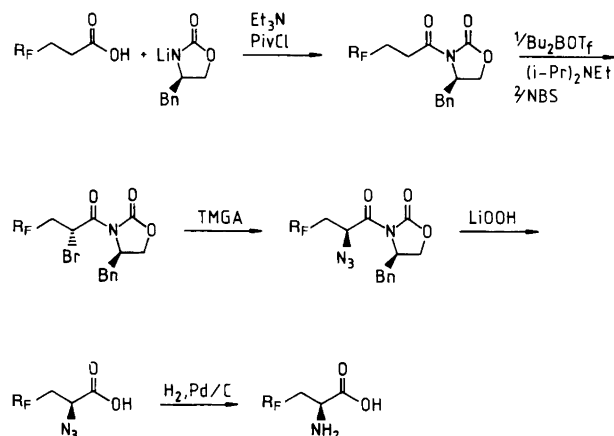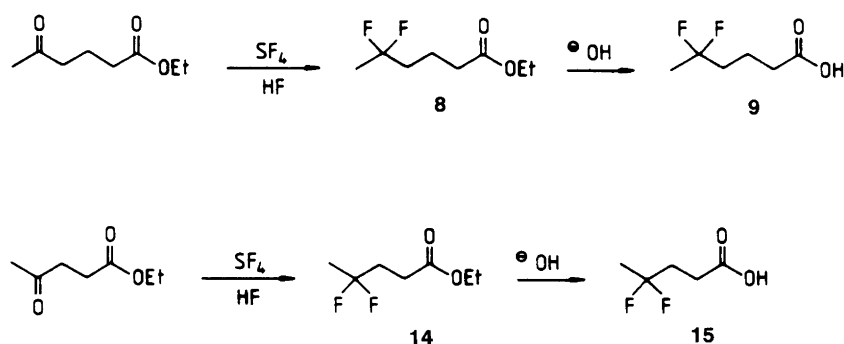
Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

4,4,5,5,5-pentafluoropentanol (**12**) which was oxidized with chromium trioxide in aqueous acetic acid to yield the desired carboxylic acid.

5,5,6,6,6-Pentafluorohexanoic acid (**7**) was prepared as summarized in Scheme 4. The first step was a radical addition of pentafluoroiodoethane to methyl 3-butenoate yielding the methyl ester of 3-iodo-5,5,6,6,6-pentafluoro-hexanoic acid (**5**). Deiodination, as given above, followed by saponification afforded the fluorinated carboxylic acid.

4,4,5,5,6,6,6-Heptafluorohexanoic acid (**4**) was prepared according to Scheme 5. Addition of heptafluoro-1-iodopropane to allyl acetate in the presence of tri-ruthenium dodecacarbonyl was carried out according to Fuchikami and Ojima.[15] The subsequent steps were carried out as given above.

Characterization and principal properties of the fluorinated amino acids. To determine the principal properties of the

Table 1. Descriptors and principal property scores of the fluorinated amino acids.

Amino acid		Descriptors[a]												Principal property scores		
No.	C_nF_m	1	2	3	4	5	6	7	8	9	10	11	12	z_1	z_2	z_3
36	C_6F_7	94	65	50	62	88	73	88	60.1	257.1	—[b]	—[b]	3.66	5.78	0.81	2.46
37	C_6F_5	97	63	49	56	89	66	89	56.6	221.1	3.97	3.63	3.50	4.33	1.52	−1.79
38	C_6F_2	88	55	48	40	74	50	88	48.9	167.1	4.09	3.78	3.26	2.83	0.27	−1.08
39	C_5F_5	91	61	44	55	81	64	89	46.3	207.1	—[b]	4.15	3.64	4.62	−0.39	2.16
40	C_5F_2	81	44	45	33	65	44	85	38.7	153.1	4.37	4.01	3.49	2.25	−0.97	1.06

[a] Descriptors: 1–7 are hR_f values determined from a test battery of seven eluents,[6] 8 is the van der Waal's radius (Å) of the side-chain, 9 is the molar mass (10^{-3} kg mol^{-1}) 10–12 are the chemical shifts of the α proton in ^{1}H NMR spectrum recorded in deuterium oxide at different pD, 10 (pD 2), 11 (pD 7), 12 (pD 12.5). [b] Not determined, the amino acid was not soluble at these pD.

fluorinated amino acids the following descriptors were used for characterization:[8] hR_f values from the TLC test battery,[6] van der Waals radius of the side-chain, molar mass, and the chemical shift of the α proton in the ^{1}H NMR spectrum recorded at varying pD in deuterium oxide. These descriptors are summarized in Table 1. The descriptor variables are the same as these used by Johnsson *et al.* in their characterization of 55 amino acids.[8] Their data are given in Ref. 8 and are not reproduced here.

The estimated principal property parameters, z_1–z_3, of the fluorinated amino acids are also given in Table 1. These parameters are the scores for the first three principal components determined from the data set obtained by appending the descriptors in Table 1 to the data of the 55 amino acids given in Ref. 8. Two-dimensional projections of the principal properties thus determined are shown in Fig. 3, and a three-dimensional projection is shown in Fig. 4.
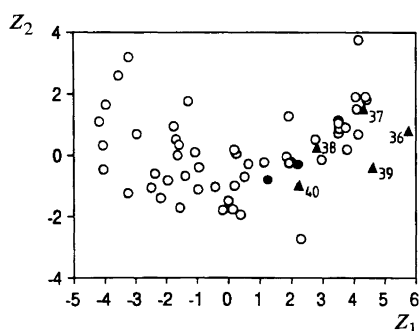

Fig. 3. Score plot showing the projection of the fluorinated amino acids (▲) down to the plane spanned by the two first principal components (z_1 and z_2 scales) of the amino acids (○) given in Ref. 8. The variation in hydrophobic–hydrophilic properties is mainly described by the z_1 axis and the variation in the size of the side-chains of the amino acids is spanned by the z_2 axis. The filled circles show norvaline (left) and norleucine (right). The points from these amino acids have been marked to permit a comparison with their fluorinated analogues.
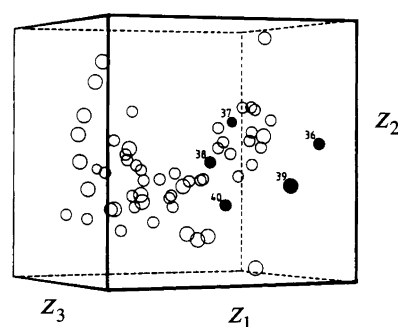

Fig. 4. Three-dimensional score plot showing the variation of the principal properties along the z_1–z_3 axes. The fluorinated amino acids have been marked with filled circles.

Discussion

This paper presents the synthesis of modified chiral amino acids. (S)-5,5,6,6,6-Pentafluoronorleucine (**37**) and (S)-4,4-difluoronorvaline (**40**) are new compounds. The syntheses of racemic 4,4,5,5,5-pentafluoronorvaline,[16,17] 5,5-difluoronorleucine[18] and 4,4,5,5,6,6,6-heptafluoronorleucine[16,17] have previously been reported.

The structural modifications were made with the intention of altering the principal properties of the amino acids so that the new compounds would possess properties which were not found in hitherto known amino acids.

Two of the newly synthesized amino acids, (S)-4,4,5,5,6,6,6-heptafluoronorleucine (**36**), and (S)-4,4,5,5,5-pentafluoronorvaline (**39**) were indeed found to be projected outside the range of the principal properties of previously known amino acids.

The remaining fluorinated amino acids were projected with a displacement compared with their hydrogen analogues along the principal component vectors related to liphilic and electronic properties. This confirms our initial assumptions as to the effects of fluorine substitution.

Experimental

Caution: sulfur tetrafluoride is highly toxic and experiments carried out with this gas were conducted in an efficient hood.

General techniques. ^1H and ^{13}C NMR spectra were recorded on Bruker AC80, AC200 and ACP250 instruments, using deuteriochloroform as the solvent. The NMR spectra of the amino acids were recorded using deuterium oxide as the solvent. Electron impact ionization (EI) mass spectra were obtained using an HP GC/MSD 5830/5970 system and chemical ionization (CI) mass spectra were obtained using a Finnigan INCOS 500 instrument. Mass spectra are reported as follows: m/z (% relative abundance) [assignment]. IR spectra were recorded on a Perkin-Elmer 681 spectrometer and are reported in cm^{-1}. GLC analyses were carried out on a Carlo-Erba Fractovap 4130 using 30 m × 0.53 mm i.d. capillary columns coated with SPB-20 or Supelcowax 10. Peak areas were measured with a Spectra Physics integrator or a Carlo-Erba DP700 instrument. The optical rotation was measured on a Perkin-Elmer 141 polarimeter using chloroform as the solvent. Boiling points in Kugelrohr distillations refer to the oven temperature.

Chemicals and material. Starting materials, reagents and solvents were *puriss.* or *p.a.* grade and were supplied by Aldrich, Merck or Janssen. Sulfur tetrafluoride was obtained from Matheson (USA). Reactions involving sulfur tetrafluoride were carried out in an autoclave made of Monel® which is a fluorine-resistant copper–nickel alloy.

4,4,5,5,6,6,6-Heptafluoro-2-iodohexyl acetate (1). Allyl acetate (1.69 g, 16.9 mmol), perfluoropropyl iodide (5 g, 16.9 mmol) and $Ru_3(CO)_{12}$, (0.3 mol%), were placed in a 13 ml ampoule fitted with a Teflon stopper and flushed with argon before sealing.[15] The ampoule was placed in an oil bath at 60°C for 3 h after which 95% conversion of the starting material had been achieved. The product (1) was isolated in 73% yield by Kugelrohr distillation of the reaction mixture, b.p. 100°C/15mmHg. MS (EI): 396 (1) [M^+], 336 (40), 317 (5), 269 (100), 209 (8), 190 (7), 145 (10), 127 (19), 69 (25). ^1H NMR (80 MHz): δ 4.53–4.27 (m, 3 H), 3.12–2.60 (m, 2 H), 2.11 (s, 3 H). ^{13}C NMR (20.15 MHz): δ 170.1, 131.4–104.5 (m, 3 C), 68.7, 38.2 (t, J 21.4 Hz), 20.0, 16.7. IR (neat): 1753, 1355, 1225, 735.

4,4,5,5,6,6,6-Heptafluorohexyl acetate (2). A dry 50 ml two-necked round-bottomed flask fitted with a dropping funnel and a reflux condenser was flushed with argon. The flask was charged with 1 (14.2 g, 35.85 mmol) and azoisobutyronitrile (AIBN, 20 mg) and was placed in an argon atmosphere.[14] The flask was heated to 55–65°C and tributyltin hydride (11.03 g, 37.96 mmol) was added dropwise over a period of 3.5 h at 55–65°C. The product 2 was distilled from the reaction mixture at 92–93°C/58 mmHg which yielded 8.52 g (87%) of 2. MS (EI): 270 (1) [M^+], 227 (5), 207 (4), 190 (8), 145 (13), 119 (9), 91 (18), 69 (48), 61 (100). MS (CI): 299 [$(M+C_2H_5)^+$], 271 [$(M+H)^+$], 190. ^1H NMR (80

MHz): δ 4.15 (t, 2 H, J 6.0 Hz), 2.43–1.76 (m, 7 H). ^{13}C NMR (21.15 MHz): δ 171.0, 130–105 (m, 3 C), 63.1, 27.9 (t, J 23.7 Hz), 20.8, 20.2 (t, J 3.9 Hz).

4,4,5,5,6,6,6-Heptafluorohexanol (3). Saponification of (2) was accomplished by refluxing 2 (8.52 g, 37.4 mmol) in a solution of sodium hydroxide (3.0 g, 74.8 mmol) in 70 ml of water for 3 h. After being cooled, the mixture was extracted with ether. The combined ether extracts were washed with brine and dried ($MgSO_4$). The ether was removed by distillation at atmospheric pressure and the residual crude product was purified by Kugelrohr distillation, b.p. 90°C/130 mmHg, to yield 7.73 g (91%) of 3. MS (EI): 227 (100) [M^+], 207 (26), 159 (26), 139 (27), 127 (20), 95 (27), 69 (28). ^1H NMR (80 MHz): δ 3.66 (t, 2 H, J 5.9 Hz), 2.80 (s, 1 H), 2.50–1.61 (m, 4 H). IR (neat): 3600–3100, 3000–2800, 1455, 1355, 1220, 1170, 1115, 1060, 1020, 725.

4,4,5,5,6,6,6-Heptafluorohexanoic acid (4). A 250 ml two-necked round-bottomed flask fitted with a dropping funnel was charged with a mixture of chromium trioxide (14.05 g, 140.5 mmol), acetic acid (125 ml) and water (14 ml). The flask was placed in an ice bath and 3 (8.01 g, 35.3 mmol) was slowly added with stirring. When the addition was complete the reaction mixture was maintained at 0°C for another 2 h and after that at room temperature for 24 h. The resulting reaction mixture was diluted with saturated aqueous sodium chloride and was extracted several times with ether. The combined ether extracts were treated with saturated sodium hydrogen carbonate until the combined aqueous layers showed a basic reaction on litmus paper. The combined aqueous layers were washed with ether and then acidified with 5 M HCl. The acidified aqueous phase was then extracted with several portions of ether and the combined organic layers were dried ($MgSO_4$). The ether was removed by evaporation at reduced pressure followed by fractional distillation of the residual crude product to yield 5.42 g (64%) of 4; m.p. 33°C, (lit.[19] 38.5°C); b.p. 100–101°C/20 mmHg, (lit.[19] 101–102°C/25 mmHg). MS (CI): 271 [$(M+C_2H_5)^+$], 243 [$(M+H)^+$], 223. ^1H NMR (80 MHz): δ 12.00 (s, 1 H), 2.82–2.09 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 178.5, 135.4–103.5 (m, 3 C), 26.5 (t, J 22.3 Hz), 25.8 (t, J 4.3 Hz).

Methyl 5,5,6,6,6-pentafluoro-3-iodohexanoate (5). Pentafluoroiodoethane (2.36 g, 20.0 mmol) was condensed at −78°C in an ampoule (13 ml) fitted with a Teflon stopper. Methyl 3-butenoate (2.00 g, 20.0 mmol) and AIBN (98 mg, 3 mol%) were added to the ampoule which was sealed and placed in an oil bath at 70°C for 24 h. Kugelrohr distillation of the reaction mixture afforded 5.52 g (80%) of 5, b.p. 100°C/10 mmHg. The product was further purified by fractional distillation, b.p. 85–87°C/12 mmHg. MS (EI): 346 [M^+], 287 (12), 219 (21), 177 (19), 127 (13), 59 (100). ^1H NMR (80 MHz): δ 4.58 (quintet, 1 H, J 6.3 Hz), 3.75 (s, 3 H), 3.18–2.64

(m, 4 H). ^{13}C NMR (20.15 MHz): δ 170.4, 129.0–97.6 (m, 3 C), 52.2, 45.2, 40.7 (t, J 20.8 Hz), 8.8. IR (neat): 3020–2850, 1740, 1438, 1320, 1190, 1023, 725.

Methyl 5,5,6,6,6-pentafluorohexanoate (6). The deiodination of 5 with tributyltin hydride and AIBN was achieved by the same procedure as for 1. Kugelrohr distillation of the reaction mixture at 79–80°C/59 mmHg gave 89% of 6. MS (El): 220 (2) [M^+], 200 (9), 189 (100), 161 (25), 141 (12), 121 (19), 74 (53), 59 (65). ^{1}H NMR (80 MHz): δ 3.69 (s, 3 H), 2.43 (t, 2 H, J 6.4 Hz), 2.10–1.80 (m, 2 H). IR (neat): 3050–2820, 1740, 1438, 1370, 1185, 1115, 1075, 1020, 720.

5,5,6,6,6-Pentafluorohexanoic acid (7). Saponification of 6 was accomplished by refluxing a mixture of 6 (10.12 g, 46.0 mmol) and 150 ml of aqueous sodium hydroxide (3.61 g, 91.9 mmol) for 1 h. The work-up procedure was the same as for 4. Kugelrohr distillation at 95°C/15 mmHg gave 8.64 g (91%) of 7, m.p. 26°C. MS (Cl): 235 [$(M+C_2H_5)^+$], 207 [$(M+H)^+$], 187, 167. ^{1}H NMR (80 MHz): δ 12.0 (s, 1 H), 2.49 (t, 2 H, J 6.9), 2.20–1.80 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 179.8, 130–105 (m, 2 C), 33.3, 30.3 (t, J 22.2 Hz), 16.2 (t, J 4.1 Hz).

Ethyl 5,5-difluorohexanoate (8). Ethyl 5-oxohexanoate (20.37 g, 128.6 mmol), dichloromethane (77 ml) and water (1.5 ml) were mixed in a Monel autoclave. The bomb was closed and flushed three times with nitrogen and then cooled to −78°C. To the cooled reactor were added 20.85 g (193 mmol) of sulfur tetrafluoride. The bomb was heated to 95°C for 10 h and then allowed to cool to room temperature over a period of 8 h. The bomb was cautiously flushed with nitrogen to remove unchanged SF$_4$ and volatile products. After opening, the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate and extracted several times with ether. The combined ether layers were dried. After removal of the ether by evaporation under reduced pressure the residue of the crude product was distilled bulb-to-bulb to yield 20.0 g of impure product, b.p. 110–130°C/10 mmHg. Analysis by ^{1}H NMR of the product showed a 45 : 55 mixture of two components, one of which showed a triplet at 2.5 ppm indicating a methyl group α to a difluoro methylene group. Fractionation using a spinning band column afforded 6.46 g (28%) of pure 8, b.p. 102°C/40 mmHg (lit.^{20} 102°C/40 mmHg). MS (El): 160 (7) [M^+], 135 (57), 115 (21), 87 (75), 65 (100). ^{1}H NMR (200 MHz): δ 4.07 (q, 2 H), 2.29 (t, 2 H, J 7.1 Hz), 1.86–1.72 (m, 4 H), 1.89 (t, 3 H, J 18.4 Hz), 1.19 (t, 3 H). ^{13}C NMR (50.32 MHz): δ 172.88, 123.70 (t, J 238.3 Hz), 60.07, 36.64 (t, J 25.8 Hz), 33.26, 22.90 (t, J 28.0 Hz), 17.95 (t, J 4.9 Hz), 13.88. IR: (neat) 2960, 1710, 1385, 1180, 1035, 910.

5,5-Difluorohexanoic acid (9). A mixture of 5.66 g (35.4 mmol) of 8 and 30 ml of 10% aqueous sodium

hydroxide were refluxed for 1 h whereupon the aqueous phase was extracted several times with ether. The combined organic layers were dried and the ether was removed by evaporation. Bulb-to-bulb distillation afforded 4.92 g (95%) of 9, b.p. 90°C/15 mmHg; m.p. 31–33°C (lit.^{20} 34–35°C). ^{1}H NMR (250 MHz): δ 10.02 (s, 1 H), 2.47 (t, 2 H, J 7.3 Hz), 2.02–1.82 (m, 2 H), 1.64 (t, 3 H, J 18.4 Hz). ^{13}C NMR (62.89 MHz): δ 180.05, 124.14 (t, J 238.3 Hz), 37.10 (t, J 25.5 Hz), 33.45, 23.31 (t, J 27.7 Hz), 18.0 (t, J 5.0 Hz). IR (neat): 3400–2400, 1705, 1385, 900.

4,4,5,5,5-Pentafluoro-2-iodopentyl acetate (10). Freshly distilled allyl acetate (2.00 g, 20.0 mmol) and 2.5 ml (20.0 mmol) of 2,2,3,3,3-pentafluoroiodopropane were allowed to react in the presence of 3 mol% AIBN at 70°C for 10 h following the same procedure as for 5. Kugelrohr distillation of the reaction mixture at 90°C/10 mmHg followed by fractional distillation afforded 5.76 g (83%) of pure 10, b.p. 84.5–85.5°C/12 mmHg. MS (El): 346 (1) [M^+], 286 (40), 219 (78), 159 (25), 127 (16), 95 (16), 43 (43). ^{1}H NMR (80 MHz): δ 4.49–4.20 (m, 3 H), 3.08–2.57 (m, 2 H), 2.11 (s, 3 H). ^{13}C NMR (20.15 MHz): δ 170.0, 130–105 (m, 2 C), 68.6, 38.2 (t, J 21.2 Hz), 20.6, 12.0. IR (neat): 3050–2850, 1745, 1430, 1320, 1193, 1030, 720.

4,4,5,5,5-Pentafluoropentyl acetate 11. Deiodination of 10 (18.48 g, 53.4 mmol) was performed by the same procedure as for 1. Kugelrohr distillation of the reaction mixture afforded 14.21 g (78%) of 11, b.p. 78–79°C/56 mmHg. MS (El): 220 [M^+], 177 (3), 91 (18), 73 (50), 61 (100). ^{1}H NMR (80 MHz): δ 4.07 (t, 2 H, J 5.8 Hz), 2.20–1.80 (m, 4 H), 1.98 (s, 3 H). ^{13}C NMR (20.15 MHz): δ 171.0, 130–105 (m, 2 C), 63.1, 27.9 (t, J 22.4 Hz), 20.8, 20.4 (t, J 3.8 Hz). IR (neat): 3000–2850, 1745, 1370, 1235, 1190, 1030, 717.

4,4,5,5,5-Pentafluoropentanol (12). Saponification of 11 was accomplished by refluxing a mixture of 14.21 g (64.6 mmol) of 11 and 150 ml of an aqueous solution of 5.16 g (129.1 mmol) of sodium hydroxide for 1 h followed by extraction with ether. After drying and removal of the ether by evaporation, the residue was fractionated to yield 10.58 g (92%) of 12, b.p. 89–90°C/140 mmHg. MS (El): 178 (13) [M^+], 177 (10), 121 (19), 109 (27), 91 (86), 77 (75), 69 (93), 59 (100). ^{1}H NMR (80 MHz): δ 3.69 (t, 2 H, J 6.1 Hz), 2.38 (s, 1 H), 2.48–1.72 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 130–105 (t, 2 C), 61.5, 27.6 (t, J 22.4 Hz), 23.8 (t, J 3.2 Hz). IR (neat): 3600–3100, 3000–2850, 1455, 1360, 1315, 1190, 1010, 714.

4,4,5,5,5-Pentafluoropentanoic acid (13). Oxidation of (12) (10.0 g, 56.1 mmol) with chromium trioxide was carried out as for 3. After distillation using a Kugelrohr apparatus, 6.79 g (63%) of 13 were obtained, b.p. 90°C/13 mmHg. The compound was semi-solid at room temperature. MS (Cl): 221 [$M+C_2H_5)^+$], 193 [$(M+H)^+$]. 173, 153. ^{1}H NMR (80 MHz): δ 11.6 (s, 1

H), 2.73–2.10 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 178, 130–105 (m, 2 C), 26.3 (t, *J* 22.2 Hz), 23.8 (t, *J* 3.2 Hz). IR (neat): 3600–2340, 1720, 1435, 1295, 1192, 1110.

Ethyl 4,4-difluoropentanoate (**14**). Ethyl 4-oxopentanoate (20.00 g, 138.8 mmol), dichloromethane (80 ml) and water (1.5 ml) were mixed in a Monel autoclave and were allowed to react with sulfur tetrafluoride at 95°C for 12 h in the same way as for **8**. Evaporation of the solvent and purification of the crude product by flash chromatography yielded 7.84 g (34%) of (**14**). MS (El): 166 (1) [*M*$^+$], 146 (5), 121 (96), 101 (20), 99 (19), 73 (69), 65 (100). ^{1}H NMR (80 MHz): δ 4.16 (q, 2 H), 2.52–1.6 (m, 4 H), 1.61 (t, 3 H, *J* 18.3 Hz), 1.28 (t, 3 H). ^{13}C NMR (20.15 MHz): δ 172.4, 123.4 (t, *J* 238.6 Hz), 60.8, 33.2 (t, *J* 26.1 Hz), 27.7 (t, *J* 4.9 Hz), 23.5 (t, *J* 27.8 Hz), 14.2. IR (neat): 3000–2800, 1723, 1377, 1178, 1100, 890.

4,4-Difluoropentanoic acid (**15**). A mixture of **14** (6.62 g, 39.8 mmol) and 32 ml of 10% sodium hydroxide solution was refluxed for 1.5 h. After being cooled the reaction mixture was extracted with ether, dried and evaporated. Bulb-to-bulb distillation of the residue gave 5.11 g (93%) of **15**, m.p. 29–31°C. ^{1}H NMR (80 MHz): δ 11.74 (s, 1 H), 2.70–2.00 (m, 4 H), 1.62 (t, 3 H, *J* 18.3 Hz). ^{13}C NMR (20.15 MHz): δ 179.2, 123.3 (t, *J* 238.2 Hz), 32.9 (t, *J* 26.1 Hz), 27.5 (t, *J* 5.0 Hz), 23.5 (t, *J* 27.7 Hz). IR (neat): 3400–2400, 1695, 1422, 1395, 1215, 1170, 900, 805.

General procedure for the preparation of N-*Acyloxazolidinones.* The method is according to Evans.[11a] A typical procedure was as follows.

(4R)-*3-(4,4,5,5,6,6,6-Heptafluoro-1-oxohexyl)-4-(phenyl-methyl)-2-oxazolidinone* (**16**). The reactions were conducted under an argon atmosphere. To a solution of **4** (2.42 g, 10 mmol) in 200 ml of dry tetrahydrofuran (THF) at −78°C were added 2.09 ml (15 mmol) of freshly distilled triethylamine followed by pivaloyl chloride (1.35 ml, 11 mmol). The reaction mixture was warmed to 0°C over a period of 20 min and then recooled to −78°C. A solution of (+)-(*R*)-4-benzyl-2-oxazolidinone (3.72 g, 21 mmol) in 100 ml of dry THF was prepared in another flask protected by argon and cooled to −78°C. Butyllithium (12.5 ml of a 1.6 M solution in hexane; 20 mmol) was added via a Teflon cannula to the solution of (+)-(*R*)-4-benzyl-2-oxazolidinone. This solution was then rapidly added to the solution of mixed anhydrides from **4**. The resulting slurry was kept at −78°C for 20 min whereafter it was quenched by addition of 1 M aqueous sodium hydrogen sulfate. The organic solvent was evaporated and the residual aqueous phase was extracted several times with dichloromethane. The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated. Purification by flash chromatography on Silica

gel 60 (hexane–ethyl acetate, 3.75 : 1) yielded 3.51 g of **16** (87%) as a viscous oil. MS (Cl): 430 [(*M* + C$_2$H$_5$)$^+$], 402 [(*M* + H)$^+$], 382. ^{1}H NMR (80 MHz): δ 4.41–7.13 (m, 5 H), 4.75–4.39 (m, 1 H), 4.04 (m, 2 H), 3.61–2.21 (m, 6 H). ^{13}C NMR (62.89 MHz): δ 170.7, 153.7, 135.4, 129.6, 129.2, 127.7, 125–107 (m, 3 C), 66.7, 55.5, 38.0, 27.4, 25.6 (t, *J* 21.8 Hz). IR (neat): 3100–2850, 1785, 1705, 1390, 1355, 1225, 1115, 900. [α]$_D^{25}$ = −38.4° (*c* 0.20).

(4R)-*3-(5,5,6,6,6-Pentafluoro-1-oxohexyl)-4-(phenyl-methyl)-2-oxazolidinone* (**17**). Treatment of **7** (2.06 g, 10 mmol) with (+)-(*R*)-4-benzyl-2-oxazolidinone according to the general procedure afforded 3.47 g (95%) of **17** as a white solid after purification by flash chromatography on Silica gel 60 using hexane–ethyl acetate (4 : 1) as the eluent, m.p. 57–58°C. MS (El): 366 (12) [*M*$^+$], 189 (100), 121 (16), 91 (30). ^{1}H NMR (80 MHz): δ 7.27–7.14 (m, 5 H), 4.82–4.53 (m, 1 H), 4.27 (m, 2 H), 3.28 (dd, 2 H, *J* 3.4 and 13.3 Hz), 3.11–2.80 (m, 4 H), 2.48–1.96 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 172.0, 153.6, 135.3, 129.5, 129.1, 127.5, 120–105 (m, 2 C), 66.5, 55.2, 38.0, 34.6, 30.0 (t, *J* 22.1 Hz), 15.3 (t, *J* 4.3 Hz). IR (neat): 3100–2850, 1780, 1702, 1387, 1350, 1190, 990, 760, 700. [α]$_D^{25}$ = −46.7° (*c* 0.75).

(4R)-*3-(5,5-Difluoro-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone* (**18**). Reaction of **9** (1.52 g, 10 mmol) with (+)-(*R*)-4-benzyl-2-oxazolidinone according to the general procedure and purification by column chromatography on Silica gel 60 using a gradient of hexane–ethyl acetate (7 : 1–3 : 1) as the eluent afforded 2.71 g (87%) of pure **18** as a viscous oil. MS (El): 311 (7) [*M*$^+$], 220 (7), 178 (4), 135 (100), 115 (30), 91 (22), 87 (45), 65 (37). ^{1}H NMR (250 MHz, CDCl$_3$): δ 7.35–7.18 (m, 5 H), 4.69–4.62 (m, 1 H), 4.21–4.12 (m, 2 H), 3.26 (dd, 1 H, *J* 3.3 and 13.4 Hz), 2.97 (m, 2 H), 2.78 (dd, 2 H, *J* 9.3 and 13.4 Hz), 1.91 (m, 2 H), 1.60 (t, 3 H, *J* 18.6). ^{13}C NMR (62.89 MHz): δ 172.20, 153.23, 135.23, 129.20, 128.70, 127.09, 123.90 (t, *J* 237.3 Hz), 66.04, 54.80, 37.56, 36.80 (t, *J* 25.9 Hz), 34.64, 22.97 (t, *J* 28.6 Hz), 17.23. IR (neat): 3100–2800, 1775, 1690, 1380, 1200, 900, 753, 694. [α]$_D^{25}$ = −56.7° (*c* 0.77).

(4R)-*3-(4,4,5,5,5-Pentafluoro-1-oxopentyl)-4-(phenyl-methyl)-2-oxazolidinone* (**19**). Reaction of **13** (1.92 g, 10 mmol) with (+)-(*R*)-4-benzyl-2-oxazolidinone according to the general procedure afforded 3.22 g (92%) of **19** as a viscous oil after purification by flash chromatography on Silica gel 60 using hexane–ethyl acetate (4 : 1) as the eluent. MS (El): 351 (15) [*M*$^+$], 175 (100), 127 (13), 86 (75), 65 (34). ^{1}H NMR (80 MHz): δ 7.36–7.13 (m, 5 H), 4.80–4.53 (m, 1 H), 4.18 (m, 2 H), 3.39–2.27 (m, 6 H). ^{13}C NMR (20.15 MHz): δ 180.2, 153.6, 135.3, 129.6, 129.2, 127.6, 125–105 (m, 2 C), 66.7, 55.4, 38.0, 27.6 (t, *J* 3.2 Hz), 25.5 (t, *J* 21.9 Hz). IR (neat): 3100–2850, 1785, 1705, 1390, 1352, 1315, 1190, 1100, 1022, 760, 700. [α]$_D^{25}$ = −46.4° (*c* 0.73).

(4R)-*3-(4,4-Difluoro-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone* (**20**). A round-bottomed flask fitted with a reflux condenser was charged with **15** (2.76 g, 20.0 mmol) and thionyl chloride (2.92 g, 29.5 mmol). The mixture was allowed to stand at room temperature for 15 min after which it was refluxed for 0.5 h. Unchanged thionyl chloride was removed by fractional distillation.

In a 100 ml dry reaction flask was placed (+)-(R)-4-benzyl-2-oxazolidinone (3.72 g, 21.0 mmol) dissolved in 50 ml of dry tetrahydrofuran under argon. The flask was cooled to −78°C and 13.1 ml of 1.6 M butyllithium (21 mmol) in hexane were added. The acid chloride dissolved in 10 ml of dry tetrahydrofuran was then added to the lithiated oxazolidinone solution over a period of 2 min via a Teflon cannula. The mixture was allowed to stand at room temperature for 3 h after which it was quenched by the addition of aqueous sodium hydrogen carbonate. Tetrahydrofuran was removed by evaporation and the residual aqueous mixture was extracted several times with dichloromethane. The combined organic layers were washed with brine, dried and evaporated. Purification by flash chromatography on Silica gel 60 using hexane–ethyl acetate (3 : 1) yielded 4.02 g (70%) of **20** as a viscous oil. MS (El): 297 (10) $[M^+]$, 277 (3), 206 (6), 121 (100), 91 (11), 65 (28). ¹H NMR (80 MHz): δ 7.40–7.09 (m, 5 H), 4.81–4.52 (m, 1 H), 4.15 (m, 2 H), 3.29 (dd, 1 H, J 3.4, 10.7 Hz), 3.21–1.97 (m, 5 H), 1.63 (t, 3 H, J 18.4 Hz). ¹³C NMR (20.15 MHz): δ 171.7, 153.4, 135.3, 129.4, 129.0, 127.4, 123.6 (t, J 238.3 Hz), 66.4, 55.2, 37.8, 32.3 (t, J 22.0 Hz), 29.2 (t, J 4.8 Hz), 23.5 (t, J 27.7 Hz). IR (neat): 3100–2850, 1780, 1705, 1390, 1355, 1210, 900, 760, 745, 700. $[\alpha]_D^{25} = -53.6°$ (c 0.63).

General procedure for the bromination and azide displacement of N-*acyloxazolidinones.*[11b] (4R)-*3-[(2S)-2-azido-4,4,5,5,6,6,6-heptafluoro-1-oxohexyl]-4-(phenylmethyl)-2-oxazolidinone* (**21**). A solution of **16** (3.51 g, 8.75 mmol) in 35 ml of dry dichloromethane under argon was cooled to −78°C and dry, freshly distilled diisopropylethylamine (1.83 ml, 10.5 mmol) was added followed by a slow addition (via a Teflon cannula) of 9.20 ml (9.19 mmol) of 1 M dibutylboron triflate. The reaction mixture was kept at −78°C for 15 min and then at 0°C for 1 h. Meanwhile, a second dried flask under argon was charged with recrystallized N-bromosuccinimide (NBS) (1.71 g, 9.63 mmol). The flask was cooled to −78°C and 25 ml of dry dichloromethane were added. The boron enolate solution was recooled to −78°C and then rapidly added to the magnetically stirred NBS slurry via a Teflon cannula. The reaction mixture was kept at −78°C for 1.25 h and then quenched by the addition of 0.5 M sodium hydrogen carbonate/brine solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed in sequence with, 0.5 M sodium thiosulfate/brine and brine. After drying and evaporation of the solvent, the crude product **22** showed a diastereomeric distribution of (R,R : S,R) = 7 : 3 according to GLC analysis. The mass spectrum is given below.

The crude α-bromo carboximide was transferred to a dry reaction flask, flushed with argon, and 40 ml of dry dichloromethane were added. The solution was cooled in an ice bath and tetramethylguanidinium azide (4.15 g, 26.23 mmol) was added in one portion. The resulting solution was maintained at 0°C for 3 h and was then quenched by the addition of saturated aqueous sodium hydrogen carbonate. The reaction mixture was extracted several times with dichloromethane and the combined organic layers were washed with brine and dried. The crude product after evaporation of the solvent was purified by flash chromatography on Silica gel 60 using hexane–ethyl acetate (4.5 : 1) as the eluent. This afforded a mixture of both diastereomers in 72% yield. Column chromatography on Silica gel 60 using a hexane–ethyl acetate gradient yielded 1.40 g (36%) of pure **21**. ¹H NMR (80 MHz): δ 7.35–7.14 (m, 5 H), 5.06 (m, 1 H), 4.80–4.58 (m, 1 H), 4.23 (m, 2 H), 3.31 (dd, 1 H, J 3.3 and 13.5 Hz), 2.84 (dd, 1 H, J 8.8 and 13.5 Hz), 2.45–2.00 (m, 4 H). ¹³C NMR (20.15 MHz): δ 167.9, 153.0, 134.7, 129.6, 129.5, 127.8, 125–105 (m, 3 C), 67.1, 55.6, 54.0, 37.6, 31.9 (t, J 6.7 Hz). IR (neat): 3100–2850, 2110, 1785, 1710, 1395, 1352, 1220, 1115, 760, 732, 700. $[\alpha]_D^{25} = -37.9°$ (c 0.67).

(2R,4R)-*3-(2-Bromo-4,4,5,5,6,6,6-heptafluoro-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone* (**22**). MS (El): 482 (3) $[(M+2)^+]$, 480 (3) $[M^+]$, 357 (8), 277 (23), 275 (22), 207 (6), 205 (6), 126 (94), 91 (100), 86 (89).

(2R,4R)-*3-(2-Bromo-5,5,6,6,6-pentafluoro-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone* (**23**). Bromination of **17** (3.47 g) according to the general procedure afforded 87% conversion to yield a 88.4 : 11.6 mixture of diastereomeric α-bromo carboximides 2R : 2S. The composition of the diastereomeric mixture was determined by capillary GLC and GC–MS. MS (El): 446 (4) $[(M+2)^+]$, 444 (4) $[M^+]$, 354, 352 (4), 321 (11), 269, 267 (15), 241, 239 (30), 159 (25), 133 (99), 91 (100), 86 (77).

(2R,4R)-*3-(2-Bromo-5,5-difluoro-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone* (**24**). Bromination of **18** (2.68 g) by the general procedure afforded 95% conversion and an isomeric ratio of 2R : 2S = 85 : 15 according to GLC/GC–MS analysis. Purification by flash chromatography using hexane–ethyl acetate (5 : 1) as the eluent yielded 2.47 g (70%) of **24**. MS: 391 (8) $[(M+2)^+]$, 389 (9) $[M^+]$, 290 (16), 215 (43), 213 (43), 133 (100), 91 (85), 65 (69).

(2R,4R)-*3-(2-Bromo-4,4,5,5-pentafluoro-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone* (**25**). Bromination of **19** (3.13 g), by the general procedure and analysis by GLC showed a 2R : 2S ratio of 80 : 20. MS (El): 432 (2) $[(M+2)^+]$, 430 (2) $[M^+]$, 306 (8), 225, 223 (21), 133 (84), 91 (98), 86 (100).

(2R,4R)-3-(2-Bromo-4,4-difluoro-1-oxopentyl)-4-(phenyl-methyl)-2-oxazolidinone (**26**). Bromination of **20** (3.31 g, 11.1 mmol) by the general procedure and analysis by GLC and GC–MS showed a 86.0 : 14.0 (*2R* : *2S*) ratio. Purification by flash chromatography on Silica gel 60 [hexane–ethyl acetate (5 : 1)] yielded 3.09 g (73%) of **26**. MS (EI): 377 (12) [$(M + 2)^+$], 375 (12) [M^+], 286 (11), 284 (11), 201 (45), 199 (46), 133 (100), 91 (88), 65 (96). ^{1}H NMR (80 MHz): 7.35–7.15 (m, 5 H), 5.96 (dd, 1 H *J* 4.2 and 9.4 Hz), 4.76–4.54 (m, 1 H), 4.16 (m, 2 H), 3.33–2.40 (m, 4 H), 1.63 (t, 3 H, *J* 16.3 Hz). ^{13}C NMR (20.15 MHz): 168.3, 152.4, 134.8, 129.5, 128.9, 127.4, 122.6 (t, *J* 239.9 Hz), 66.2, 55.1, 42.2 (t, *J* 25.0 Hz), 36.8, 34.9 (t, *J* 4.2 Hz), 23.8 (t, *J* 26.8 Hz). IR (neat): 3100–2850, 1780, 1705, 1390, 1355, 1195, 1105, 758, 700. $[\alpha]_D^{25} = -61.6°$ (*c* 0.65).

(2S,4R)-3-(2-Azido-5,5,6,6,6-pentafluoro-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone (**27**). The crude α-bromo-carboximide **23** was treated with azide according to the general procedure. Purification by column chromatography on Silica gel 60 using a gradient of hexane–dichloromethane (1.5 : 1–1 : 2) yielded **27** (2.88 g, 75%) as a viscous oil. ^{1}H NMR (80 MHz): 7.36–7.10 (m, 5 H), 5.03–4.60 (m, 2 H), 4.26 (m, 2 H), 3.24 (dd, 1 H, *J* 3.6 and 13.5 Hz), 2.83 (dd, 1 H, *J* 8.7 and 13.5 Hz), 2.60–1.90 (m, 4 H). ^{13}C NMR (20.15 MHz): 169.8, 153.2, 134.7, 129.6, 129.2, 127.8, 120–105 (m, 2 C), 67.3, 60.0, 55.3, 37.9, 27.7 (t, *J* 22.3 Hz), 23.1. IR (neat): 3100–2850, 2210, 1780, 1705, 1387, 1190, 1110, 995, 760, 700. $[\alpha]_D^{25} = -59.0°$ (*c* 0.63).

(2S,4R)-3-(2-Azido-5,5-difluoro-1-oxohexyl)-4-(phenyl-methyl)-2-oxazolidinone (**28**). Treatment of 2.28 g of **24** with azide according to the general procedure followed by column chromatography on Silica gel 60 using a gradient of hexane–dichloromethane (2 : 1–1 : 2) gave 1.21 g (59%) of pure **28** as a viscous oil. ^{1}H NMR (80 MHz): 7.35–7.12 (m, 5 H), 5.0–4.62 (m, 2 H), 4.22 (m, 2 H), 3.23 (dd, 1 H, *J* 3.55 and 13.5 Hz), 2.82 (dd, 1 H, *J* 8.72 and 13.37 Hz), 2.3–1.89 (m, 4 H), 1.61 (t, 3 H, *J* 18.42 Hz). ^{13}C NMR (20.15 MHz): 170.3, 153.0, 134.9, 129.5, 129.0, 127.5, 123.7 (t, *J* 162.7 Hz), 67.1, 60.1, 55.1, 37.7, 34.4 (t, *J* 26.0 Hz), 24.9 (t, *J* 4.8 Hz), 23.4 (t, *J* 27.6 Hz). IR: 3060–2810, 2105, 1780, 1705, 1390, 1215, 1115, 910, 760, 700. $[\alpha]_D^{25} = -43.3°$ (*c* 0.36).

(2S,4R)-3-(2-Azido-4,4,5,5,5-pentafluoro-1-oxopentyl)-4-(phenylmethyl)-2-oxazolidinone (**29**). Crude **25** was treated with azide according to the general procedure. Column chromatography on Silica gel 60 using a gradient of hexane–dichloromethane (1 : 0.6–1 : 15) yielded 2.07 g (59%) of **29** as a viscous oil. ^{1}H NMR (80 MHz): 7.30–7.12 (m, 5 H), 5.47 (dd, 1 H, *J* 5.4, 7.7 Hz), 4.78–4.55 (m, 1 H), 4.18 (m, 2 H), 3.26 (dd, 1 H, *J* 3.1 and 13.2 Hz), 2.92–2.30 (m, 3 H). ^{13}C NMR (20.15 MHz): 167.9, 153.0, 134.8, 129.0, 127.6, 120–105 (m, 2 C), 67.1, 55.4, 54.1, 37.4, 31.8 (t, *J* 21.0 Hz). IR (neat): 3100–2850, 2105, 1780, 1705, 1390, 1195, 1123, 760, 700. $[\alpha]_D^{25} = -41.5°$ (*c* 0.65).

(2S,4R)-3-(2-Azido-4,4-difluoro-1-oxopentyl)-4-(phenyl-methyl)-2-oxazolidinone (**30**). The general procedure was employed with 3.05 g (8.11 mmol) of **26**. Purification by flash chromatography on Silica gel 60 using hexane–ethyl acetate (4.25 : 1) as the eluent yielded 2.08 g (76%) of **30** as a viscous oil. ^{1}H NMR (80 MHz): 7.37–7.12 (m, 5 H), 5.30 (dd, 1 H, *J* 5.8 and 7.4 Hz), 4.81–4.57 (m, 1 H), 4.21 (m, 2 H), 3.31 (dd, 1 H, *J* 3.4 and 13.4 Hz), 2.88–2.21 (m, 3 H), 1.72 (t, 3 H, *J* 18.7 Hz). ^{13}C NMR (20.15 MHz): 169.3, 152.9, 134.9, 129.4, 129.1, 127.6, 122.5 (t, *J* 239.5 Hz), 66.9, 55.4, 38.6 (t, *J* 26.1 Hz), 37.5, 23.6 (t, *J* 27.1 Hz). IR (neat): 3100–2850, 2108, 1785, 1708, 1390, 1235, 1130, 1110, 760, 700. $[\alpha]_D^{25} = -10.9°$ (*c* 0.51).

General procedure for hydrolysis of the α-azido carboximides using LiOOH: (S)-2-azido-4,4,5,5,6,6,6-heptafluorohexanoic acid (**31**).[11b] A solution of **21** (0.90 g, 3.03 mmol) in 45 ml of tetrahydrofuran and 14 ml of water was cooled to 0°C. To this solution were added 1.21 ml (12.12 mmol) of 31% hydrogen peroxide and solid lithium hydroxide (145 mg, 6.06 mmol). The reaction was maintained at 0°C for 0.5 h whereafter it was treated with sodium bisulfite, (1.68 g, 13.3 mmol) dissolved in 9 ml of water, followed by the addition of 30 ml aqueous 0.5 M sodium hydrogen carbonate. The reaction mixture was evaporated under reduced pressure to remove tetrahydrofuran and the residual aqueous layer was diluted to 200 ml with water and then extracted with several portions of dichloromethane. The combined organic layers contained the chiral auxiliary which was recovered after evaporation. The aqueous layer was acidified to pH = 1–2 by the addition of 5 M hydrochloric acid and then extracted with ethyl acetate. After drying and evaporation of the solvent, 0.85 g (94%) of **31** was obtained. ^{1}H NMR (80 MHz): 12.0 (s, 1 H), 4.38 (dd, 1 H, *J* 4.5 and 8.1 Hz), 2.97–2.13 (m, 2 H). ^{13}C NMR (20.15 MHz): 174.9, 129–100 (m, 3 C), 55.9, 32.6 (t, *J* 21.5 Hz). IR (neat): 3500–2400, 2112, 1730, 1352, 1220, 1117, 919, 720. $[\alpha]_D^{25} = -51.2°$ (*c* 0.63).

(S)-2-Azido-5,5,6,6,6-pentafluorohexanoic acid (**32**). Hydrolysis of **27** (2.88 g) according to the general procedure yielded 1.53 g (87%) of pure (TLC) **32** as an oil. ^{1}H NMR (80 MHz): 11.9 (s, 1 H), 4.11 (m, 1 H), 2.45–2.00 (m, 4 H). ^{13}C NMR (20.15 MHz): 176.3, 130–105 (m, 2 C), 61.1, 27.3 (t, *J* 22.3 Hz), 22.9 (t, *J* 3.9 Hz). IR (neat): 3500–2400, 2110, 1725, 1190, 1015, 997. $[\alpha]_D^{25} = -79.9°$ (*c* 0.45).

(S)-2-Azido-5,5-difluorohexanoic acid (**33**). Hydrolysis of 1.21 g of **28** by the general procedure yielded 0.51 g (77%) of **33** as an oil. ^{1}H NMR (80 MHz): 11.37 (s, 1 H), 4.02 (m, 1 H), 2.61–1.73 (m, 4 H), 1.62 (t, 3 H, *J* 18.37 Hz). ^{13}C NMR (20.15 MHz): 176.2, 123.7 (t, *J* 238.2 Hz), 61.4, 34.0 (t, *J* 26.1 Hz), 24.7 (t, *J* 4.8 Hz), 23.5 (t, *J* 27.7 Hz). IR (neat): 3600–2350, 2080, 1705, 1380, 1220, 895. $[\alpha]_D^{25} = -66.9°$ (*c* 0.11).

(−)-(S)-2-Azido-4,4,5,5,5-pentafluoropentanoic acid (34). Hydrolysis of 29 (2.07 g) by the general procedure yielded 0.86 g (70%) of 34 as an oil. ^{1}H NMR (80 MHz): δ 11.32 (s, 1 H), 4.38 (dd, 1 H, J 4.4, 8.3 Hz), 2.90–2.10 (m, 4 H). ^{13}C NMR (20.15 MHz): δ 178.2, 130–105 (m, 2 C), 56.0, 32.6 (t, J 21.4 Hz). IR (neat): 3700–2400, 2115, 1730, 1435, 1345, 1195. $[α]_D^{25} = -52.5°$ (c 0.60).

(S)-2-Azido-4,4-difluoropentanoic acid (35). Hydrolysis of 2.08 g of 30 by the general procedure afforded 0.94 g (82%) of 35 as an oil. The product was pure according to TLC. ^{1}H NMR (80 MHz): δ 11.39 (s, 1 H), 4.23 (dd, 1 H, J 4.8 and 8.0 Hz), 2.69–2.10 (m, 2 H), 1.70 (t, 3 H, J 18.7 Hz). ^{13}C NMR (20.15 MHz): δ 175.7, 122.5 (t, J 239.5 Hz), 57.2 (t, J 4.5 Hz), 39.0 (t, J 26.2 Hz), 23.9 (t, J 27.1 Hz). IR (neat): 3600–2400, 2110, 1725, 1395, 1230, 1130, 900. $[α]_D^{25} = -63.2°$ (c 0.37).

General procedure for catalytic hydrogenation of α-azido-carboxylates: (−)-(S)-4,4,5,5,6,6,6-Heptafluoronorleucine (36).[11b] A 500 ml glass hydrogenation vessel was charged with 31 (0.63 g, 2.12 mmol), 25 ml of water–acetic acid (3 : 1) and 15 mg of 10% Pd on carbon. Hydrogenation was carried out using a Parr hydrogenation apparatus under a hydrogen pressure of about 40 psi for 22 h. The reaction was monitored by TLC on silica gel using n-butanol–acetic acid–water (40 : 10 : 10) as the eluent. After completion, the reaction mixture was filtered through a sintered-glass filter and the solvent was removed under reduced pressure. The residual white precipitate was dissolved in water and the solution was treated with ether to remove impurities. Evaporation of the aqueous layer followed by drying of the white residue over P_2O_5 at 10 mmHg yielded 0.44 g (80%) of 36 as a white crystalline product, m.p. 200–205°C (decomp.). ^{1}H NMR (80 MHz, D_2O, pD 12.5): δ 3.66 (dd, 1 H, J 5.0 and 7.1 Hz), 3.0–2.1 (m, 2 H). IR (KBr): 3200–2400, 1620, 1590, 1358, 1225, 1178, 1117.

(−)-(S)-5,5,6,6,6-Pentafluoronorleucine (37). Hydrogenation of 32 (1.09 g) by the general procedure for 20 h yielded 0.80 g (82%) of 37 as a white solid, m.p. 200–210°C (decomp.). ^{1}H NMR (80 MHz, D_2O, pD 12.5), 3.30 (m, 1 H), 1.7–2.7 (m, 4 H). IR (KB$_r$): 3200–2400, 1590, 1520, 1405, 1200, 1115.

(−)-(S)-5,5-Difluoronorleucine (38). Hydrogenation of 33 (0.51 g) for 23 h by the general procedure yielded 0.43 g (97%) of 26 as a white solid, m.p. 210–220°C (decomp.). ^{1}H NMR (80 MHz, D_2O, pD 12.5): δ 3.26 (m, 1 H), 1.62 (t, 3 H, J 19.3 Hz), 2.2–1.5 (m, 4 H). IR (KBr): 3200–2400, 1580, 1510, 1412, 1320, 1225, 890.

(−)-(S)-4,4,5,5,5-Pentafluoronorvaline (39). Hydrogenation of 34 (0.86 g) for 21 h by the general procedure yielded 0.55 g (77%) of 39 as a white solid, m.p. 190–200°C (decomp.). IR (KBr): 3300–2300, 1620, 1590, 1525, 1400, 1340, 1190.

(−)-(S)-4,4-Difluoronorvaline (40). Hydrogenation of 35 (0.91 g) for 23 h by the general procedure yielded 0.63 g (81%) of 40 as a white solid, m.p. 195–205°C (decomp.). ^{1}N NMR (80 MHz, D_2O, pD 12.5): δ 4.02 (dd, 1 H J 4.0 and 8.5 Hz), 2.86–2.28 (m, 2 H), 1.73 (t, 3 H, J 19.4 Hz). IR (KBr): 3300–2400, 1600, 1510, 1400, 1238, 1124, 905.

General procedure for determination of enantiomeric purity of the amino acids.[21] (+)-Methyl (N-MTPA)-4,4,5,5,6,6,6-heptafluoro-2-aminohexanoate (41). A dry two-necked round-bottomed flask was fitted with a reflux condenser and flushed with argon. The flask was charged with 36 (0.1 g, 0.39 mmol) and 4 ml of dry methanol. The resulting slurry was cooled in an ice bath and thionyl chloride (0.10 ml, 1.2 mmol) was added. The solutions was protected with argon and heated to 70°C for 3 h. The solvent was removed by evaporation and the residual solid was dissolved in 4 ml of dry dichloromethane and cooled to 0°C. To this solution was added triethylamine (0.19 ml, 1.36 mmol) and (+)-MTPA chloride,[21] (0.20 g, 0.78 mol). The reaction temperature solution was maintained at 0°C for 15 min and the raised to room temperature at which the reaction was allowed to proceed for 5 h. The reaction was quenched by the addition of aqueous 1 M sodium hydrogen sulfate, followed by extractions with several portions of ether. The combined ether layers were washed with brine, dried and evaporated. The enantiomeric purity was determined by capillary GLC which indicated a 2S : 2R ratio of 92.4 : 7.6. MS (EI): 456 (3), 428 (3), 376 (3), 298 (36), 270 (100), 225 (38), 105 (47).

(+)-Methyl (N-MTPA)-5,5,6,6,6-pentafluoro-2-amino-hexanoate (42). Reaction of 37 with (+)-MTPA according to the general procedure and analysis by capillary GLC showed a 2S : 2R ratio of 98.0 : 2.0. MS (EI): 420 (2), 392 (6), 262 (24), 234 (100), 190 (32), 189 (45), 105 (30).

(+)-Methyl (N-MTPA)-5,5-difluorohexanoate (43). Capillary GLC and GC–MS showed a 2S : 2R ratio of 98.2 : 1.8 after the reaction of 38 with (+)-MTPA chloride by the general procedure. MS (EI): 338 (11), 208 (24), 189 (48), 180 (100), 160 (61), 105 (39).

(+)-Methyl (N-MTPA)-4,4,5,5,5-pentafluoropentanoate (44). Reaction of 39 with (+)-MTPA chloride, followed by GLC/GLC–MS analysis showed a 2S : 2R ratio of 88.9 : 11.1. MS (EI): 406 (3), 378 (4), 248 (39), 220 (100), 189 (63), 105 (45).

Methyl (N-MTPA)-2-amino-4,4-difluoropentanoate (45). Reaction of 40 with (+)-MTPA chloride, followed by analysis on GC/GC–MS showed a 99.4 : 0.6 2S : 2R ratio. MS (EI): 324 (5), 194 (30), 189 (38), 166 (100), 105 (28).

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