Supporting Information File 1

For

A novel family of (1-aminoalkyl)(trifluoromethyl)- and -(difluoromethyl)phosphinic acids – analogues of α-amino acids

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Experimental procedures, elemental analysis and NMR data.

[(Dibenzylamino)(phenyl)methyl](trifluoromethyl)phosphinic acid (13b). Following the general procedure (I) using benzaldehyde (2.12 g, 20 mmol) 13b was obtained as a white solid (2.35 g, 28%); mp 280ºC; [Found: C, 62.88; H, 5.21; N. 3.50. C_{22}H_{21}F_{3}NO_{2}P requires C, 63.00; H, 5.05; N, 3.34%]; NMR (DMSO-d₆) δH (300 MHz) 4.02 (2H, d, J_{AB} 12.5, CH₂Ph), 4.07 (1H, d, J_{HP} 11.1, PCH), 4.14
(2H, d, J_{AB} 12.5, CH_2Ph), 7.37-7.39 (15 H, m, H_{arom.}); \( \delta_p \) (121 MHz) 6.4 (qd, \( 2J_{PF} \) 79, \( 2J_{PH} \) 11); \( \delta_F \) (188 MHz) -74.8 (d, \( 2J_{FP} \)).

[1-(Dibenzylamino)ethyl](trifluoromethyl)phosphinic acid (13c). 13c was synthesized according to the general procedure (I) and was characterized in a mixture with Bn_2NH-HCl (~1:7) by NMR spectroscopy. NMR (DMSO-d_6): \( \delta_H \) (300 MHz) 5.9 (qd, \( 2J_{HP} \) 6.9, \( 3J_{HH} \) 7.9, CH_3), 3.08 (1H, m, PC), 4.28 (1H, d, J_{AB} 13.5, CH_2Ph), 7.38-7.63 (m, H_{arom}), 9.81 (br s, NH); \( \delta_P \) (81 MHz) 5.9 (qm, \( 2J_{PF} \)).

Ammonium [hydroxy(phenyl)methyl](trifluoromethyl)phosphinate (15). The filtrate after separating of 13b was evaporated to the dryness. The addition to the residue of an excess of ethanolic ammonia solution gave the precipitate, which was filtered, crystallized and dried to give 15 as a white solid (3.1 g, 60%); mp 210ºC (dec.)(from EtOH); [Found: C, 37.55; H, 3.72; N, 5.42. C_8H_11F_3NO_3P requires C, 37.66; H, 3.56; N, 5.49%]; NMR (D_2O): \( \delta_H \) (300 MHz) 4.88 (1H, d, \( 2J_{HP} \) 6.9, PC), 7.22-7.31 (5H, m, H_{arom}); \( \delta_P \) (121 MHz) 6.8 (qd, \( 2J_{PF} \) 76, \( 2J_{PH} \)); \( \delta_F \) (188 MHz) -74.2 (d, \( 2J_{FP} \)).

[Amino(phenyl)methyl](trifluoromethyl)phosphinic acid (14b). Following the general procedure (II) 14b was obtained as a white powder (1.08 g, 90%); mp 263ºC (dec.); [Found: C, 39.96; H, 3.60; N, 5.69. C_8H_9F_3NO_2P requires C, 40.18; H, 3.79; N, 5.86%]; NMR (D_2O): \( \delta_H \) (300 MHz) 4.57 (1H, d, \( 2J_{HP} \) 9.3, PCH), 7.2-7.25 (5H, m, H_{arom}); \( \delta_P \) (121 MHz) 11.5 (qd, \( 2J_{PF} \) 82, \( 2J_{PH} \) 9); \( \delta_F \) (188 MHz) -75.5 (d, \( 2J_{FP} \) 82); \( \delta_C \) (125 MHz) 51.9 (d, \( 1J_{CP} \) 102.5, PCH), 122.5 (qd, \( 1J_{CP} \) 316.8, \( 1J_{CP} \) 176.2, CF_3), 128.4, 128.5, 129.4, 129.7, 130.0, 130.1.

[(Benzylamino)methyl](trifluoromethyl)phosphinic acid (17a) (Table 1, entry 1). Following the general procedure (III) a crude solid, obtained from 1 (1.28 g, 9.6 mmol) and 16a (1.14 g, 3.2 mmol) was purified by recrystallization to give 17a as a white solid (2.0 g, 83%); mp 282°C (from water); [Found: C, 42.93; H, 4.51; N, 5.66. C_9H_11F_3NO_2P requires C, 42.70; H, 4.38; N, 5.53%]; NMR (DMSO-d_6): \( \delta_H \) (300 MHz) 2.85 (2H, d, \( 2J_{HP} \) 9.6, PCH_2), 4.16 (2H, s, CH_2Ph), 7.42 (3H, m,
[(Benzylamino)(phenyl)methyl](trifluoromethyl)phosphinic acid (17b) (Table 1, entry 2). Following the general procedure (III) a crude solid, obtained from 1 (0.13 g, 1.0 mmol) and 16b (0.20 g, 1.0 mmol) was purified by recrystallization to give 17b as a white solid (0.29 g, 87%); mp 293°C (from EtOH / water); [Found: C, 54.80; H, 4.62; N. 4.17. C_{15}H_{15}F_{3}NO_{2}P requires C, 54.72; H, 4.59; N, 4.25%]; NMR (DMSO-d$_6$): $\delta$H (300 MHz) 3.95 (1H, d, $J_{AB}$ 12.3, C$_2$H$_2$Ph), 4.05 (1H, d, $J_{HP}$ 10.0, PC$_2$H), 4.12 (1H, d, $J_{AB}$ 12.3, C$_2$H$_2$Ph), 7.33-7.42 (10H, m, H$_{arom}$); $\delta$P (121 MHz) 7.9 (qd, $J_{PF}$ 79, $J_{PH}$ 10); $\delta$F (188 MHz) -74.2 (d, $J_{FP}$ 85).

[1-(Benzylamino)ethyl](trifluoromethyl)phosphinic acid (17c) (Table 1, entry 3). Following the general procedure (III) a crude solid, obtained from 1 (0.5 g, 3.7 mmol) and the freshly prepared 16c (0.99 g, 7.4 mmol) was dissolved in acetone. Upon standing at 5 °C overnight 17c crystallized, the crystals were filtered, dissolved in water and passed down an ion-exchange column to give after the evaporation of water 17c as a white solid (0.58 g, 59%); mp 212ºC; [Found: C, 45.09; H, 5.01; N, 5.08. C$_{10}$H$_{13}$F$_{3}$NO$_{2}$P requires C, 44.95; H, 4.90; N, 5.24%]; NMR (DMSO-d$_6$): $\delta$H (300 MHz) 1.33 (3H, dd, $J_{HH}$ 13.5, $J_{HP}$ 7.5, CH$_3$), 2.86-2.94 (1H, m, PCH), 4.21 (1H, d, $J_{AB}$ 13.3, CH$_2$Ph), 4.29 (1H, d, $J_{AB}$ 13.3, CH$_2$Ph), 7.38-7.46 (3H, m, H$_{arom}$), 7.50-7.54 (2H, m, H$_{arom}$), 8.88 (1H, br s, NH); $\delta$P (81 MHz) 4.6 (qm, $J_{PF}$ 79). $\delta$F (188 MHz) -72.8 (d, $J_{FP}$ 79).

[1-(Benzylamino)-2-methylpropyl](trifluoromethyl)phosphinic acid (17d) (Table 1, entry 4). Following the general procedure (III) a crude solid, obtained from 1 (0.20 g, 1.5 mmol) and 16d (0.24 g, 1.5 mmol) was triturated with acetone to afford 17d of a sufficient purity as a white solid (0.40 g, 92%), mp 207ºC; [Found: C, 48.77; H, 5.79; N, 4.78. C$_{12}$H$_{17}$F$_{3}$NO$_{2}$P requires C, 48.82; H, 5.80; N, 4.74%]; NMR (DMSO-d$_6$): $\delta$H (300 MHz) 1.03 (3H, d, $J_{HH}$ 6.6, CH$_3$), 1.09 (3H, d, $J_{HH}$ 6.6, CH$_3$), 2.24 (1H, m, CHMe$_2$), 2.81 (1H, m, PCH), 3.25 (1H, br s, NH), 4.24 (1H, d, $J_{AB}$ 13.5, CH$_2$Ph), 4.37 (1H, d, $J_{AB}$ 13.5, CH$_2$Ph), 7.34-7.46 (3H, m,
H<sub>arom</sub>), 7.51-7.55 (2H, m, H<sub>arom</sub>), 8.64 (1H, br s, OH); δ<sub>P</sub> (81 MHz) 6.2 (qm, 2<sup>J<sub>PF</sub></sup> 79); δ<sub>F</sub> (188 MHz) -74.2 (d, 2<sup>J<sub>FP</sub></sup> 79).

Pyrrolidin-2-yl-(trifluoromethyl)phosphinic acid (14e) (Table 1, entry 5). Following the general procedure (III) a crude product, obtained from 1 (1.0 g, 7.5 mmol) and 16e (0.52 g, 2.5 mmol) was dissolved in ethanolic ammonia solution until pH 8–9 and this solution was evaporated to the dryness. The residue was triturred with acetone affording a solid, which was dissolved in water and passed down an ion-exchange column to give after the evaporation of water 14e as a white solid (1.0 g, 66%); mp 293ºC; [Found: C, 29.40; H, 4.52; N, 6.89. C<sub>5</sub>H<sub>9</sub>F<sub>3</sub>NO<sub>2</sub>P requires C, 29.52; H, 4.47; N, 6.89%]; NMR (D<sub>2</sub>O): δ<sub>H</sub> (500 MHz) 1.9–2.3 (4H, m, C<sub>2</sub>H–C<sub>2</sub>H), 3.34 (2H, m, C<sub>2</sub>H–N), 3.74 (1H, m, C–P); δ<sub>P</sub> (81 MHz) 12.1 (qm, 2<sup>J<sub>PF</sub></sup> 94); δ<sub>F</sub> (188 MHz) -76.4 (d, 2<sup>J<sub>FP</sub></sup> 94); δ<sub>C</sub> (125 MHz) 23.8 (d, 2<sup>J<sub>CP</sub></sup> 8, C–3), 24.9 (C–4), 47.8 (d, 3<sup>J<sub>CP</sub></sup> 5, C–5), 53.4 (d, 1<sup>J<sub>CP</sub></sup> 107.2, C–2), 122.2 (qd, 1<sup>J<sub>CP</sub></sup> 316.2, 1<sup>J<sub>CP</sub></sup> 177.3, CF<sub>3</sub>) [(Benzylamino)methyl](difluoromethyl)phosphinic acid (19a) (Table 2, entry 1). Following the general procedure (III) a mixture of 5 (0.56 g, 3.9 mmol) and 16a (0.46 g, 1.3 mmol) in DME (10 mL) was heated at 50°C for 24 h to give a complex mixture with a major product ethyl [(benzylamino)methyl](difluoromethyl)phosphinate (18a) according to 31P NMR: δ<sub>P</sub> (121 MHz, DME) 33.7 (tm, 2<sup>J<sub>PF</sub></sup> 73). This mixture was chromatographed on SiO<sub>2</sub> with eluent ethylacetate-methanol (1:3) to afford 19a as a white solid (0.62 g, 68%); mp 226ºC; [Found: C, 46.13; H, 5.33; N. 5.79. C<sub>9</sub>H<sub>12</sub>F<sub>2</sub>NO<sub>2</sub>P requires C, 45.94; H, 5.14; N, 5.96%]; NMR (DMSO-d<sub>6</sub>): δ<sub>H</sub> (300 MHz) 2.75 (2H, d, 2<sup>J<sub>HP</sub></sup> 7.2, PCH<sub>2</sub>), 4.10 (2H, s, CH<sub>2</sub>Ph), 5.88 (1H, td, 2<sup>J<sub>HF</sub></sup> 48.7, 2<sup>J<sub>HP</sub></sup> 21.5, CHF<sub>2</sub>), 7.37-7.41 (3H, m, H<sub>arom</sub>), 7.51-7.55 (2H, m, H<sub>arom</sub>), 9.21 (1H, br s, NH); δ<sub>P</sub> (81 MHz) 11.8 (tm, 2<sup>J<sub>PF</sub></sup> 70); δ<sub>F</sub> (188 MHz) -135.8 (dd, 2<sup>J<sub>FP</sub></sup> 70, 2<sup>J<sub>HF</sub></sup> 49).

Ethyl [1-(benzylamino)ethyl](difluoromethyl)phosphinate (18c) (Table 2, entry 3). Following the general procedure (III) a crude product from 5 (0.30 g, 2.1 mmol) and 16c (0.28 g, 2.1 mmol) was worked up as described above for 18b to afford 18c as a yellowish semisolid (0.27 g, 46%), as a mixture of two
diastereoisomers in an approximately 3:2 ratio due to NMR (CDCl₃): δH (300 MHz) 1.24-1.38 (6H, m, OCH₂CH₃ and PCHCH₃), 2.95-3.15 (1H, m, PCH), 3.64-4.07 (2H, m, CH₂Ph), 4.15-4.30 (2H, m, OCH₂), 6.14 (0.6H, td, 2J_HF 49.5, 2J_HP 25.4, CHF₂, major isomer), 6.22 (0.4 H, td, 2J_HF 49.3, 2J_HP 26.0, CHF₂, minor isomer), 7.18-7.32 (5H, m, H_arom); δp (81 MHz) 35.7 (m); δF (188 MHz) -130 ÷ -142 (complex multiplet). From the residue after extraction of 18c [1-(benzylamino)ethyl](difluoro-methyl)phosphinic acid (19c) was obtained by the analogy with 19b as a white solid (0.22 g, 42%); mp 216ºC; [Found: C, 47.96; H, 5.72; N, 5.68. C₁₀H₁₄F₂NO₂P requires C, 48.12; H, 5.66; N, 5.62%]; NMR (DMSO-d₆): δH (300 MHz) 1.35 (3H, dd, 3J_HP 12.9, 3J_HH 7.4, CH₃), 2.98 (1H, dq, 2J_HP 15.0, 3J_HH 7.4, PCH), 4.23 (1H, d, J_AB 9.1, CH₂Ph), 4.32 (1H, d, J_AB 9.1, CH₂Ph), 5.91 (1H, td, 2J_HF 49.2, 2J_HP 20.4, CHF₂), 7.39-7.45 (3H, m, H_arom), 7.52-7.59 (2H, m, H_arom); δp (81 MHz) 16.6 (tm, 2J_PF 75); δF (188 MHz) -134.5 (1F, ddd, J_AB 349, 2J_FP 75, 2J_HF 49), -136.5 (1F, ddd, J_AB 349, 2J_FP 75, 2J_HF 49). By hydrolysis of 18c (0.27 g, 0.98 mmol) the additional quantity of 19c (0.20 g, 83%) was obtained. The overall yield of 19c is 0.42 g (80%).

Ethyl [1-(benzylamino)-2-methylpropyl](difluoromethyl)phosphinate (18d) (Table 2, entry 4). Following the general procedure (III) a crude solid, obtained from 5 (0.29 g, 2.0 mmol) and 16d (0.32 g, 2.0 mmol) was worked up as described above for 18b to afford 18d as a yellowish semisolid (0.22 g, 36%) as a mixture of two diastereoisomers in an approximately 3:2 ratio due to NMR (CDCl₃): δH (300 MHz) 1.05 (6H, m, PCHCH₃), 1.29 (3H, m, OCH₂CH₃), 2.19 (1H, m, CHMe₂), 2.86 (0.6H, ddm, 2J_HP 12.9, 3J_HH 5.2, PCH, major isomer), 2.96 (0.4H, ddm, 2J_HP 11.6, 3J_HH 4.8, PCH, minor isomer), 3.72-3.95 (2H, m, CH₂Ph), 4.02-4.30 (2H, m, OCH₂), 6.08 (0.4H, td, 2J_HP 49.6, 2J_HP 24.8, CHF₂, minor isomer), 6.18 (0.6H, td, 2J_HF 49.6, 2J_HP 25.2, CHF₂, major isomer), 7.18-7.32 (5H, m, H_arom); δp (81 MHz) 35.4 (0.4P, m, minor isomer), 36.8 (0.6P, m, major isomer); δF (188 MHz) -132 ÷ -140.5 (complex multiplet). From the residue after extraction of 18d [1-(benzylamino)-2-methylpropyl](difluoromethyl)phosphinic acid (19d) was obtained by analogy with 19b as a white solid (0.27 g, 48%); mp 242ºC; [Found: C, 52.16; H, 6.69; N, 4.89.
C_{12}H_{18}F_{2}NO_{2}P requires C, 51.99; H, 6.54; N, 5.05%; NMR (DMSO-d_{6}): \delta_{H} (300 MHz) 0.98 (3H, d, \text{j}_{HH} 6.9, CH_{3}), 1.06 (3H, d, \text{j}_{HH} 6.9, CH_{3}), 2.10-2.30 (1H, m, CHMe_{2}), 2.68-2.78 (1H, m, PCH), 4.20 (1H, d, J_{AB} 13.1, CH_{2}Ph), 4.30 (1H, d, J_{AB} 13.1, CH_{2}Ph), 5.72 (1H, td, J_{HF} 49.5, J_{HP} 19.4, CHF_{2}), 7.36-7.44 (3H, m, H_{arom}), 7.48-7.56 (2H, m, H_{arom}); \delta_{P} (81 MHz) 12.3 (tm, J_{PF} 81); \delta_{F} (188 MHz) -132.8 (1F, ddd, J_{AB} 348, J_{FP} 81, J_{FH} 49), -134.1 (1F, ddd, J_{AB} 348, J_{FP} 81, J_{HF} 49). By hydrolysis of 18d (0.22 g, 0.72 mmol) the additional quantity of 19d (0.19 g, 95%) was obtained. The overall yield of 19d is 0.46 g (82%).

(Difluoromethyl)pyrrolidin-2-ylphosphinic acid (20e) (Table 2, entry 5). Following the general procedure (III) a crude product, obtained from 5 (0.54 g, 3.8 mmol) and 16e (0.26 g, 1.25 mmol) was worked up as described for 14e to afford 20e as a white solid (0.54 g, 79%); mp 246ºC; [Found: C, 32.30; H, 5.52; N, 7.68. C_{5}H_{10}F_{2}NO_{2}P requires C, 32.44; H, 5.45; N, 7.57%;] NMR (D_{2}O): \delta_{H} (500 MHz) 1.90-2.02 (1H, m, CH_{2}), 2.04-2.12 (2H, m, CH_{2}), 2.20-2.30 (1H, m, CH_{2}), 3.33 (2H, t, \text{j}_{HH} 6.5, C_{2}H_{5}N), 3.71 (1H, m, PC_{2}H); \delta_{P} (121 MHz) 15.2 (qm, J_{PF} 91); \delta_{F} (188 MHz) -73.8 (d, J_{FP} 91); \delta_{C} (125 MHz) 31.8 (C-3), 44.1 (d, J_{CP} 105.5, PCH), 122.1 (qd, J_{CF} 316.2, J_{CP} 177.3, CF_{3}).

(1-Aminoethyl)( trifluoromethyl)phosphinic acid (14c) (Table 1, entry 3). Following the general procedure (II) 14c was obtained as a white powder, mp 255ºC (dec.); [Found: C, 20.28; H, 3.89; N, 7.79. C_{3}H_{7}F_{3}NO_{2}P requires C, 20.35; H, 3.98; N, 7.91%]; NMR (D_{2}O): \delta_{H} (300 MHz) 1.30 (3H, d, \text{j}_{HH} 14.7, \text{j}_{HP} 7.5, C_{2}H_{5}), 3.46 (1H, m, PCH); \delta_{P} (121 MHz) 15.2 (qm, J_{PF} 91); \delta_{F} (188 MHz) -73.8 (d, J_{FP} 91); \delta_{C} (125 MHz) 31.8 (CH_{3}); 44.1 (d, J_{CP} 105.5, PCH), 122.1 (qd, J_{CF} 316.9, J_{CP} 179.8, CF_{3}).

(1-Amino-2-methylpropyl)( trifluoromethyl)phosphinic acid (14d) (Table 1, entry 4). Following the general procedure (II) 14d was obtained as a white powder, mp 225ºC (dec.); [Found: C, 29.22; H, 5.31; N, 6.78. C_{5}H_{11}F_{3}NO_{2}P requires C, 29.28; H, 5.41; N, 6.83%]; NMR (D_{2}O): \delta_{H} (500 MHz) 1.06 (3H, d,
(Aminomethyl)(difluoromethyl)phosphinic acid (20a) (Table 2, entry 1). Following the general procedure (II) 20a was obtained as a white powder, mp 242°C; [Found: C, 16.62; H, 4.29; N 9.59. C$_2$H$_6$F$_2$NO$_2$P requires C, 16.56; H, 4.17; N 9.66%]; NMR (D$_2$O): $\delta$H (300 MHz) 3.03 (2H, d, $^2$J$_{HP}$ 10.4, CH$_2$), 5.77 (1H, td, $^2$J$_{HF}$ 49.2, $^2$J$_{HP}$ 22.2, CHF$_2$); $\delta$P (121 MHz) 16.1 (tdt, $^2$J$_{PF}$ 78, $^2$J$_{PH}$ 22 and 10); $\delta$F (188 MHz) -136.7 (dd, $^2$J$_{FP}$ 78, $^2$J$_{FH}$ 49); $\delta$C (125 MHz) 35.3 (d, $^1$J$_{CP}$ 103.2, CH$_2$), 114.5 (td, $^1$J$_{CP}$ 246.8, $^1$J$_{CP}$ 129.3, CHF$_2$).

[Amino(phenyl)methyl](difluoromethyl)phosphinic acid (20b) (Table 2, entry 2). Following the general procedure (II) 20b was obtained as a white powder, mp 256°C; [Found: C, 43.59; H, 4.68; N 6.29. C$_8$H$_{10}$F$_2$NO$_2$P requires C, 43.45; H, 4.56; N, 6.33%]; NMR (D$_2$O): $\delta$H (300 MHz) 4.48 (1H, d, $^2$J$_{HP}$ 9.6, PCH), 5.78 (1H, td, $^2$J$_{HF}$ 48.9, $^2$J$_{HP}$ 22.5, CHF$_2$), 7.27-7.30 (5H, m, H$_{arom}$); $\delta$P (121 MHz) 15.9 (td, $^2$J$_{PF}$ 88, $^2$J$_{PH}$ 22 and 10); $\delta$F (376 MHz) -135.8 (symm. complex multiplet); $\delta$C (125 MHz) 51.5 (d, $^1$J$_{CP}$ 94.2, PCH), 114.8 (td, $^1$J$_{CP}$ 257.8, $^1$J$_{CP}$ 138.3, CF$_3$), 128.1, 129.3, 129.4, 130.5.

(1-Aminomethyl)(difluoromethyl)phosphinic acid (20c) (Table 2, entry 3). Following the general procedure (II) 20c was obtained as a white powder, mp 255°C; [Found: C, 22.48; H, 4.96; N 8.92. C$_3$H$_8$F$_2$NO$_2$P requires C, 22.65; H, 5.07; N, 8.81%]; NMR (D$_2$O): $\delta$H (500 MHz) 1.41 (3H, dd, $^3$J$_{HP}$ 13.5, $^3$J$_{HH}$ 7.5, CH$_3$), 3.52 (1H, m, PCH), 5.97 (1H, td, $^2$J$_{HF}$ 48.5, $^2$J$_{HP}$ 22.5, CHF$_2$); $\delta$P (121 MHz) 18.6 (tm, $^2$J$_{PF}$ 75); $\delta$F (376 MHz) -133.6 (1F, ddd, J$_{AB}$ 348.8, $^2$J$_{FP}$ 74.9, $^2$J$_{FH}$ 48.5), -143.9 (1F, ddd, J$_{AB}$ 348.8, $^2$J$_{FP}$ 74.9, $^2$J$_{FH}$ 48.5); $\delta$C (125 MHz) 12.1 (CH$_3$); 43.3 (d, $^1$J$_{CP}$ 100, PCH), 114.5 (td, $^1$J$_{CP}$ 248.2, $^1$J$_{CP}$ 136.3, CHF$_2$).

(1-Amino-2-methylpropyl)(difluoromethyl)phosphinic acid (20d) (Table 2, entry 4). Following the general procedure (II) 20d was obtained as a white powder, mp 232°C; [Found: C, 32.12; H, 6.37; N 7.61. C$_5$H$_{12}$F$_2$NO$_2$P requires C,
The reaction of the acid 1 with the imine 21. A mixture of 1 (0.10 g, 0.75 mmol) and 21 [1] (0.15 g, 0.75 mmol) in DME (5 mL) was heated at 50 °C under stirring for 48 h. After cooling to room temperature the formed precipitate was filtered, washed with acetone and dried to give 14b (0.06 g, 32%).

The reactions of the acids 1 and 6 with the imines 22 and 27 (general procedure IV). An equimolar mixture of 1 or 6 and 22 or 27 in DME (5 mL per 1 mmol) was stirred at 50 °C under monitoring with 31P NMR until the signals of 1 or 6 disappeared. After cooling to room temperature the formed precipitate was filtered, thoroughly washed with acetone and dried in vacuo.

(1-Amino-2-ethoxy-2-oxoethyl)(trifluoromethyl)phosphinic acid (23). Following the general procedure (IV) using 1 (0.95 g, 7.1 mmol) and 22 [2] (11.42 g, 7.1 mmol) 23 was obtained as a white solid (1.13 g, 68%), mp 241°C (dec.).

Sodium salt of 23. NMR (D2O): δH (500 MHz) 1.22 (3H, t, 3JHH 7.0, CH3), 4.20 (2H, q, 3JHH 7.0, CH2); δC (125 MHz) 13.3 (CH3), 53.9 (CH), 63.0 (CH2), 122.4 (qd, 1JCF 318, 1JCP 171, CF3), 171.3 (O=C).

(1-Amino-2-ethoxy-2-oxoethyl)(difluoromethyl)phosphinic acid (24). Following the general procedure (IV) using 6 (0.83 g, 7.2 mmol) and 22 [2] (1.44 g, 7.2 mmol) 24 was obtained as a white solid (0.95 g, 61%), mp 223°C (dec.).

[Found: C, 27.77; H, 4.74; N, 6.40. C5H10F2NO4P requires C, 27.66; H, 4.64; N, 6.45%]; NMR (D2O): δH (300 MHz) 1.11 (3H, t, 3JHH 6.9, CH3), 4.08 (2H, q, 3JHH 6.9, CH2).
6.9, CH2), 4.31 (1H, d, 2JHP 14.1, PCH), 5.9 (1H, td, 2JHF 48.5, 2JHP 25.8, CHF2); δp (121 MHz) 12.1 (tdd, 2JPF 80, 2JPH 26 and 14); δF (282 MHz) -135.3 (1F, ddd, 2JFP 80, 2JFH 49), -137.1 (1F, ddd, JAB 347, 2JFP 80, 2JFH 49); δC (125 MHz) 13.2 (C3H6), 51.4 (d, 1JCP 78, CH), 64.1 (C7H14F2), 114.0 (td, 1JCF 259, 1JCP 148, CHF2), 166.4 (O=C).

Amino[(difluoromethyl)(hydroxy)phosphoryl]acetic acid (25). A mixture of 24 (0.52 g, 2.4 mmol) and Me3SiONa (0.54 g, 4.8 mmol) in DME (10 mL) was stirred at 50 °C for 24 h. After cooling to room temperature the formed precipitate was filtered, washed with acetone and dissolved in water. The resulting solution was discolored with charcoal and then passed down an ion-exchange column. Water was evaporated under reduced pressure, the residue was thoroughly dried in vacuo to afford 25 as a white powder (0.16 g, 35 %), mp 265°C (dec.). [Found: C, 18.98; H, 3.25; N. 7.38. C3H6F2NO4P requires C, 19.06; H, 3.20; N, 7.41%]; NMR (D2O): δH (300 MHz) 3.48 (1H, d, 2JHP 12.5, PCH), 5.9 (1H, td, 2JHF 50.7, 2JHP 25.2, C3H6); δp (121 MHz) 18.2 (tdd, 2JPF 78, 2JPH 51, 2JCP 148, CHF2); δF (282 MHz) -133.1 (1F, ddd, JAB 338, 2JFP 78, 2JFH 51), -135.0 (1F, ddd, JAB 338, 2JFP 78, 2JFH 51).

Methyl 2-[hydroxy(trifluoromethyl)phosphoryl]valinate (27). Following the general procedure (IV) using 1 (1.0 g, 7.4 mmol) and 26 [3] (0.96 g, 7.4 mmol) 27 was obtained as a white solid (1.24 g, 63 %), mp 218°C (dec.). [Found: C, 31.99; H, 5.10; N. 5.29. C7H13F3NO4P requires C, 31.95; H, 4.98; N, 5.32%]; NMR (D2O): δH (300 MHz) 0.76 (3H, d, 3JHH 7.0, CC3H), 0.99 (3H, d, 3JHH 7.0, CCH3), 2.69 (1H, septet of doublets, 3JHH 7.0, 3JHP 5.9, CHMe2), 3.70 (3H, s, OCH3); δp (121 MHz) 10.4 (dq, 2JPF 95, 3JPH 6); δF (282 MHz) -72.1 (d, 2JFP 95).

Methyl 2-[(difluoromethyl)(hydroxy)phosphoryl]valinate (28). Following the general procedure (IV) using 6 (0.45 g, 3.9 mmol) and 26 [3] (0.50 g, 3.9 mmol) 28 was obtained as a white solid (0.38 g, 40 %), mp 209°C (dec.). [Found: C, 34.30; H, 5.80; N. 5.80. C7H14F2NO4P requires C, 34.29; H, 5.76; N, 5.71%]; NMR (D2O): δH (300 MHz) 0.78 (3H, d, 3JHH 6.8, CCH3), 1.00 (3H, d, 3JHH 6.8, CCH3), 2.70 (1H, septet of doublets, 3JHH 6.8, 3JHP 6.0, CHMe2), 3.72 (3H, s, OCH3), 5.82 (1H, td, 2JHF 48.6, 2JHP 25.2, CHF2); δp (121 MHz) 14.7 (tdd, 2JPF 76,
$\delta_F$ (282 MHz): -133.2 (1F, ddd, $J_{AB}$ 349, $J_{FP}$ 76, $J_{FH}$ 49), -135.3 (1F, ddd, $J_{AB}$ 349, $J_{FP}$ 76, $J_{FH}$ 49).

The reaction of the acid 1 with aminoacrylate 29. Following the general procedure (IV) using 1 (0.51 g, 3.8 mmol) and 29 [4] (0.81 g, 3.8 mmol) ethyl 2-[(hydroxy(trifluoromethyl))phosphoryl]alaninate (31) was obtained as a white solid (0.56 g, 59%), mp 242ºC (dec.). [Found: C, 28.79; H, 4.38; N, 5.66. C$_6$H$_{11}$F$_3$NO$_4$P requires C, 28.93; H, 4.45; N, 5.62 %]; NMR (DMSO-$d_6$): $\delta_H$ (300 MHz) 1.20 (3H, t, $J_{HH}$ 6.9, CH$_2$C$_3$H$_3$), 1.55 (3H, d, $J_{HP}$ 12.9, PCC$_3$H$_3$), 4.13 (2H, q, $J_{HH}$ 6.9, C$_3$H$_2$); $\delta_P$ (121 MHz) 7.2 (qq, $J_{PF}$ 84, $J_{PH}$ 13); $\delta_F$ (282 MHz) -69.3 (d, $J_{FP}$ 84).

2-[(Hydroxy(trifluoromethyl))phosphoryl]alanine (32). Hydrolysis of 31 (1.2 g, 4.8 mmol) with 5 N HCl (10 mL) was performed at room temperature for 48 h under stirring. Resulting solution was evaporated to the dryness, the residue was dissolved in the ethanolic ammonia solution at 0 ºC until pH 7–8. Ethanol was evaporated to the dryness and the residue was triturated with acetone to afford yellowish solid. This solid was dissolved in water; the resulting solution was discolored with charcoal and then passed down an ion-exchange column. After the evaporation of water the residue was thoroughly dried in vacuo to afford 32 as a white powder (0.58 g, 54%), mp 266ºC (dec.). [Found: C, 21.56; H, 3.24; N, 6.32. C$_4$H$_7$F$_3$NO$_4$P requires C, 21.73; H, 3.19; N, 6.34 %]; NMR (D$_2$O): $\delta_H$ (500 MHz) 1.58 (3H, d, $J_{HP}$ 14.5, CH$_3$); $\delta_P$ (121 MHz) 21.0 (qq, $J_{PF}$ 82, $J_{PH}$ 14); $\delta_F$ (282 MHz) -70.3 (d, $J_{FP}$ 82); $\delta_C$ (125 MHz) 20.8 (CH$_3$), 75.3 (d, $J_{CP}$ 115, PC), 122.9 (qd, $J_{CF}$ 318, $J_{CP}$ 166, CF$_3$), 175.2 (O=C).

The reaction of a mixture of the esters 3 and 4 with aminoacrylic acid 33. The freshly distilled mixture of 3 (3.69 g, 19.4 mmol) and 4 (2.10 g, 12.9 mmol) (bp 65–75 ºC, 70 mm Hg) [5] and 33 (1.66 g, 12.9 mmol) was stirred at 20 ºC for 72 h under the $^{31}$P NMR control. The resulting viscous mixture was diluted with 25 ml ether and the formed precipitate was filtered, washed with acetone and dried in vacuo to afford [1-(acetylamino)ethyl](trifluoromethyl)phosphinic acid (37) as a white solid (0.75 g, 18%), mp 199ºC (dec.). [Found: C, 27.41; H, 4.14; N, 6.39.
C₃H₉F₃NO₅P requires C, 27.62; H, 4.24; N, 6.16 %]. NMR (D₂O): δₓ (300 MHz) 1.07 (3H, dd, 3ⱼ_HP 14.7, 3ⱼ_HH 7.5, CHCH₃), 1.75 (3H, s, O=CC₃H), 4.07 (1H, dq, 2ⱼ_HP 10.3, 3ⱼ_HH 7.5, PCH); δₚ (121 MHz) 19.4 (qqd, 2ⱼ_PF 85, 3ⱼ_PH 15, 2ⱼ_PH 10); δ₇ (282 MHz) -73.3 (d, 2ⱼ_F₇ 85).

All volatiles from the filtrate after the isolation of 37 were removed by heating to 50 °C at a pressure of 0.1 mm Hg. The residue was fractionated by the silica gel column chromatography (hexane/EtOAc 10:1 to EtOAc/EtOH 1:1, gradient).

Ethyl N-acetyl-2-[hydroxy(trifluoromethyl)phosphoryl]alaninate (35) was isolated with the eluent EtOAc/EtOH 2:1 as a white solid (0.26 g, 7%), mp 203°C (dec.). [Found: C, 33.22; H, 4.68; N, 4.70. C₈H₁₃F₃NO₅P requires C, 33.00; H, 4.50; N, 4.81 %]. NMR (DMSO-d₆): δₓ (300 MHz) 1.11 (3H, t, 3ⱼ_HH 7.0, CH₂C₃H), 1.48 (3H, d, 3ⱼ_HP 14.1, PCC₃H), 1.81 (3H, s, O=CC₃H), 4.18 (2H, q, 3ⱼ_HH 7.0, CH₂); δₚ (121 MHz) 19.2 (qq, 2ⱼ_PF 81, 3ⱼ_PH 14); δ₇ (282 MHz) -74.1 (d, 2ⱼ_F₇ 81).

Ethyl [1-(acetylamino)ethyl](trifluoromethyl)phosphinate (36) was isolated with the eluent hexane/ethyl acetate 2:1 as a yellowish viscous liquid (1.28 g, 40%) as a mixture of two diastereoisomers in an approximately 7:8 ratio due to NMR (CDCl₃): δₓ (300 MHz) 1.25-1.45 (6H, m, CHCH₃ and CH₂CH₃), 1.96 (1.4H, s, O=CC₃H, minor isomer), 1.99 (1.6H, s, O=CC₃H, major isomer), 4.15-4.42 (2H, m, OCH₂), 4.68-4.84 (1H, m, PCH), 7.55 (0.45H, br s, NH, minor isomer), 7.76 (0.55 H, br s, NH, major isomer); δₚ (121 MHz) 27.6 (qm, minor isomer), 28.4 (qm, major isomer); δ₇ (282 MHz) -72.1 (1.6 F, d, 2ⱼ_F₇ 87, major isomer), -72.9 (1.4F, d, 2ⱼ_F₇ 87, minor isomer). Hydrolysis of 36 (1.28 g, 5.2 mmol) with 5N HCl (15 mL) at room temperature for 24 h gave 37 (1.07 g, 95%). The overall yield of 37 from 33 was 1.82 g (65%). The N-deprotection of 37 (1.5 g, 6.9 mmol) was performed with 5 N HCl (20 mL) in an ampoule with Teflon stopcock at 130°C for 8 h to give 14c (0.41 g, 34%).

The reaction of the acid 1 with the malonate 38. A mixture of 1 (1.05 g, 7.8 mmol) and 38 (1.79 g, 7.8 mmol) in CH₃CN (15 mL) was stirred at room temperature for a week under the ³¹P NMR control and then cooled to −20 °C. The formed precipitate was filtered and recrystallized to give [1-(acetylamino)-3-
ethoxy-2-(ethoxycarbonyl)-3-oxopropyl][trifluoromethyl]phosphinic acid (39)
as a white solid (1.26 g, 44%), mp 176°C (dec.) (from a wet dioxane). [Found: C, 36.24; H, 4.84; N, 3.90. C_{11}H_{17}F_{3}NO_{7}P requires C, 36.37; H, 4.72; N, 3.86 %];
NMR (DMSO-d_{6}): \(\delta_H\) (300 MHz) 1.16 (3H, t, \(^3J_{HH} 6.9, CH_2CH_3\)), 1.18 (3H, t, \(^3J_{HH} 6.9, CH_2CH_3\)), 1.81 (3H, s, O=CCCH_{3}), 3.72 (1H, t, \(^3J_{HH} = ^3J_{HP} = 8.0, PCHCH\)), 4.07 (4H, q, \(^3J_{HH} 6.9, C\)), 4.87 (1H, dd, \(^2J_{HP} 17.1, ^3J_{HH} 8.0, PCH\)), 7.62 (1H, br s, NH); \(\delta_P\) (121 MHz) 12.5 (qm, \(^2J_{PF} 87\)); \(\delta_F\) (282 MHz) -73.2 (d, \(^2J_{FP} 87\)).

3-(Acetylamino)-3-[hydroxy(trifluoromethyl)phosphoryl]propanoic acid (40).
A suspension of 39 (0.84 g, 2.3 mmol) in 5N HCl (10 mL) was heated to reflux for 12 h. The resulting solution was evaporated to the dryness, and the residue was triturated with acetone and dried in vacuo to afford 40 as a white solid (0.50 g, 82%), mp 178°C (dec.). [Found: C, 27.48; H, 3.57; N, 5.20. C_{6}H_{9}F_{3}NO_{5}P requires C, 27.39; H, 3.45; N, 5.32 %]; NMR (DMSO-d_{6}): \(\delta_H\) (300 MHz) 2.01 (3H, s, O=CCCH_{3}), 2.78 (1H, ddd, \(^3J_{AB} 17.5, ^3J_{HP} 10.8, ^3J_{HH} 4.5, CH_2\)), 2.94 (1H, ddd, \(^3J_{AB} 17.5, ^3J_{HH} 4.5, ^3J_{HP} 2.7, CH_2\)), 4.42-4.50 (1H, m, PCH); \(\delta_P\) (121 MHz) 7.9 (qm, \(^2J_{PF} 91\)); \(\delta_F\) (282 MHz) -73.8 (d, \(^2J_{FP} 91\)).

3-Amino-3-[hydroxy(trifluoromethyl)phosphoryl]propanoic acid (41). A mixture of 40 (0.50 g, 1.9 mmol) and 5N HCl (5 mL) was stirred in an ampoule with Teflon stopcock at 130 °C for 5 h. The resulting solution was evaporated under reduced pressure and co-evaporated with water to the dryness. The crude product was triturated with acetone, dissolved in water and passed down an ion-exchange column to give 41 as a white powder (0.18 g, 43%), mp 210°C (dec.). [Found: C, 21.67; H, 3.09; N, 6.32. C_{4}H_{7}F_{3}NO_{4}P requires C, 21.73; H, 3.19; N, 6.34 %]; NMR (D_{2}O): \(\delta_H\) (500 MHz): 2.81 (1H, ddd, \(^3J_{AB} 18.1, ^3J_{HP} 10.0, ^3J_{HH} 8.1, CH_2\)), 2.97 (1H, ddd, \(^3J_{AB} 18.1, ^3J_{HP} 12.5, ^3J_{HH} 4.5, CH_2\)), 3.84-3.92 (1H, m, PCH); \(\delta_P\) (121 MHz) 12.4 (qm, \(^2J_{PF} 93\)); \(\delta_F\) (282 MHz) -74.3 (d, \(^2J_{FP} 93\)); \(\delta_C\) (125 MHz) 31.8 (CH_2), 44.1 (d, \(^1J_{CP} 105, PCH\)), 122.2 (qd, \(^1J_{CF} 316, ^1J_{CP} 179, CF_3\)), 173.7 (COOH).
References