Efficient Stereoselective Syntheses of Cyclic Amino Acids *via* Michael Induced Ring Closing Reactions

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Supplementary material

General: NMR-spectra were recorded in CDCl₃ using Bruker DRX 250, Bruker AC-300, Bruker Avance 300 and Bruker DRX 500 with XWIN-NMR software. CI-MS analyses were performed using a Finnigan MAT 90. The enantiomeric and diastereomeric ratios were determined with HP 5890, HP 5890 Series II and Varian CP3380 gas chromatographs using Chirasil-*L*-Val and Permethyl- γ -Cyclodextrin capillary columns. Helium was used as carrier gas. Optical rotations were measured with a Perkin-Elmer polarimeter PE 241. THF was distilled over Na/benzophenone.

Typical procedure for conjugate addition of chelated glycine ester enolate (described for the synthesis of **9** and **10** from **7b**):

The reaction was carried out under Ar atmosphere using oven-dried glassware. 147 mg (0.65 mmol) TFA-Gly-*O*tBu were dissolved in dry THF and cooled to -78°C . A LHMDs-solution which was freshly prepared from 293 mg HMDS (1.82 mmol) and 1.05 ml of a 1.6 M solution of *n*-BuLi (1.68 mmol) in hexane in 2.5 ml of dry THF was added dropwise at this temperature. The solution was stirred for 15 min. Then a solution of 99 mg (0.73 mmol) ZnCl₂, which had been dried by heating *in vacuo*, in 1 ml of dry THF was added and stirring was continued for 30 min at -78°C . 145 mg (0.60 mmol) of methyl (2*Z*)-5-iodo-pentenoate (**7b**) was added and the solution was stirred overnight under warm-up to room temperature. The solution was diluted with diethyl ether and 1 M KHSO₄ was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica (hexane/ethyl acetate 88:12) and give 159 mg (0.47 mmol) **9** and 24 mg (0.07 mmol) **10**.

(*S*)-*tert*-Butyl 5-methoxycarbonyl-2-trifluoroacetyl-amino-4(*E*)-pentenoate [**3**]:

According to the general procedure for Michael additions **3** was obtained as the minor product in reactions of (*E*)-configured unsaturated bromoester **2a**.

¹H-NMR (300 MHz): δ = 1.45 (s, 9H, 9-H), 2.74 (m, 2H, 5-H), 3.70 (s, 3H, 1-H), 4.57 (m, 1H, 6-H), 5.87 (d, $J_{3,4}$ = 15.4 Hz, 1H, 3-H), 6.74 (dt, $J_{4,3}$ = 15.4 Hz, $J_{4,5}$ = 7.5 Hz, 1H, 4-H), 7.11 (s, 1H, N-H).

¹³C-NMR (75 MHz): δ = 27.9 (q, C-9), 34.2 (t, C-5), 51.6, 52.1 (q,d, C-1, C-6), 84.1 (s, C-8), 115.5 (q, $J_{11,\text{F}}$ = 287.7 Hz, C-11), 125.1 (d, C-3), 141.0 (d, C-4), 156.7 (q, $J_{10,\text{F}}$ = 156.7 Hz, C-10), 165.9 (s, C-2), 168.6 (s, C-7).

()-tert.-Butyl 2-(2'-methoxycarbonylcyclopropyl)-2-trifluoroacetyl-glycinate [()-4]:

According to the general procedure for Michael additions **4** was obtained as the major product in reactions of (*E*)-configured bromoester **2a**, and as the sole product from (*Z*)-configured unsaturated phosphates **2b**.

Data of the *anti*-diastereomer:

¹H-NMR (300 MHz): δ = 1.06 (ddd, $J_{4cis,5}$ = 8.9 Hz, $J_{4cis,3} = J_{4cis,4trans}$ = 5.7 Hz, 1H, 4-*H_{cis}*), 1.29 (ddd, $J_{4trans,3}$ = 9.2 Hz, $J_{4trans,5} = J_{4trans,4cis}$ = 5.2 Hz, 1H, 4-*H_{trans}*), 1.49 (s, 9H, 9-H), 1.73 (m, 1H, 5-H), 1.84 (dt, $J_{3,4trans}$ = 8.8 Hz, $J_{3,4cis} = J_{3,5}$ = 4.6 Hz, 1H, 3-H), 3.67 (s, 3H, 1-H), 4.10 (dd, $J_{6,5} = J_{6,N-H}$ = 7.9 Hz, 1H, 6-H), 6.98 (d, $J_{N-H,6}$ = 6.3 Hz, N-H).

¹³C-NMR (75 MHz): δ = 12.7 (t, C-4), 17.7 (d, C-3), 23.6 (d, C-5), 27.5 (q, C-9), 51.8 (q, C-1), 54.3 (d, C-6), 83.8 (s, C-8), 115.4 (q, $J_{11,F}$ = 287.8 Hz, C-11), 156.6 (q, $J_{10,F}$ = 37.6 Hz, C-10), 168.2 (s, C-7), 173.0 (s, C-2).

Selected data of the *syn*-diastereomer:

¹³C-NMR (75 MHz) δ = 12.9 (t, C-4), 18.6 (d, C-3), 24.0 (d, C-5), 52.5 (q, C-1), 54.8 (d, C-6).

Elemental analysis:

C ₁₃ H ₁₈ F ₃ NO ₅	calcd	C 48.00	H 5.58	N 4.31
325.28	found	C 48.25	H 5.46	N 4.33

()-tert.-Butyl (2*R*,1'*R*,2'*R*,3'*R*)-2-(2'-methoxycarbonyl-3'-methylcyclopropyl)-2-trifluoroacetyl-glycinate [6a]:

According to the general procedure for Michael additions **6a** was obtained as the sole product from (*Z*)-configured unsaturated phosphate **5**. $[\alpha]_D^{25} = -90.1^\circ$ (c = 1.8, CHCl₃)

¹H-NMR (500 MHz): δ = 1.18 (d, $J_{5,4}$ = 6.4 Hz, 3H, 5-H), 1.47 (sh, 10H, 10-H, 4-H), 1.56 (ddd, $J_{6,7}$ = 8.4 Hz, $J_{6,4} = J_{6,3}$ = 5.5 Hz, 1H, 6-H), 1.89 (dd, $J_{3,4}$ = 9.4 Hz, $J_{3,6}$ = 4.7 Hz, 1H, 3-H), 3.65 (s, 3H, 1-H), 4.04 (dd, $J_{7,6} = J_{7,N-H}$ = 8.4 Hz, 1H, 7-H), 7.04 (d, $J_{N-H,7}$ = 6.7 Hz, 1H, N-H).

¹³C-NMR (125 MHz): δ = 11.1 (q, C-5), 21.2 (d, C-4), 23.5 (d, C-3), 27.7 (q, C-10), 29.5 (d, C-6), 51.6 (q, C-1), 54.7 (d, C-7), 83.4 (s, C-9), 115.4 (q, $J_{12,F}$ = 287.7 Hz, C-12), 156.7 (q, $J_{11,F}$ = 37.9 Hz, C-11), 168.4 (s, C-8), 171.3 (s, C-2).

Elemental analysis:

C ₁₄ H ₂₀ F ₃ NO ₅	Calcd	C 49.55	H 5.94	N 4.13
339.31	found	C 49.60	H 6.00	N 4.14

(*E*)-**1-tert.-Butyl 3-(2'-methoxycarbonyl-3'-methylecyclopropyl)-2-trifluoroacetylaminopentane-1,5-dicarboxylate** [**6b**]:

According to the general procedure for Michael additions **6b** was obtained as the major isomer from (*E*)-configured unsaturated phosphate **5**. [α_D^{25}] = +63.5° (c = 0.8, CHCl₃) (mixture *syn/anti*-diast.)

¹H-NMR (500 MHz): δ = 1.29 (d, *J*_{5,4} = 6.0 Hz, 3H, 5-H), 1.46 (s, 9H, 10-H), 1.59 (dd, *J*_{3,4} = *J*_{3,6} = 5.0 Hz, 1H, 3-H), 1.62 (m, 1H, 4-H), 1.68 (ddd, *J*_{6,7} = *J*_{6,4} = 10.0 Hz, *J*_{6,3} = 4.4 Hz, 1H, 6-H), 3.61 (s, 3H, 1-H), 4.16 (dd, *J*_{7,6} = 10.5 Hz, *J*_{7,N-H} = 8.2 Hz, 1H, 7-H), 7.35 (s, 1H, N-H).

¹³C-NMR (125 MHz): δ = 12.9 (q, C-5), 22.1 (d, C-4), 25.7 (d, C-3), 27.8 (q, C-10), 29.6 (d, C-6), 51.7, 51.9 (2d, C-1, C-7), 83.6 (s, C-9), 115.7 (q, *J*_{12,F} = 287.6 Hz, C-12), 156.9 (q, *J*_{11,F} = 38.0 Hz, C-11), 168.7 (s, C-8), 173.5 (s, C-2).

HRMS (CI+)	calcd	found
C ₁₄ H ₂₀ NF ₃ O ₅ [M+H] ⁺	339.1294	339.1296

(*E*)-**1-tert.-Butyl-5-methyl 3-(2'-bromoethyl)-2-trifluoroacetylaminopentane-1,5-dicarboxylate** [**8**]:

According to the general procedure for Michael additions **8** was obtained at −78°C from (*E*)-configured unsaturated bromide **7a**.

¹H-NMR (500 MHz): δ = 1.48 (s, 9H, 10-H), 1.93 (m, 2H, 5-H), 2.38 (dd, *J*_{3a,3b} = 16.1 Hz, *J*_{3a,4} = 5.7 Hz, 1H, 3-Ha), 2.46 (dd, *J*_{3b,3a} = 16.4 Hz, *J*_{3b,4} = 6.3 Hz, 1H, 3-Hb), 2.79 (m, 1H, 4-H), 3.43 (ddd, *J*_{6a,6b} = 10.7 Hz, *J*_{6a,5a} = *J*_{6a,5b} = 6.5 Hz, 1H, 6-Ha), 3.49 (ddd, *J*_{6b,6a} = 10.6 Hz, *J*_{6b,5a} = 7.3 Hz, *J*_{6b,5b} = 6.3 Hz, 1H, 6-Hb), 3.69 (s, 3H, 1-H), 4.58 (dd, *J*_{7,N-H} = 8.5 Hz, *J*_{7,4} = 4.1 Hz, 1H, 7-H), 7.80 (d, *J*_{N-H,7} = 7.9 Hz, 1H, N-H).

¹³C-NMR (125 MHz): δ = 27.9 (q, C-10), 30.0, 33.5, 34.3 (3t, C-3, C-5, C-6), 35.6 (d, C-4), 52.3 (q, C-1), 54.6 (d, C-7), 83.9 (s, C-9), 115.7 (q, *J*_{12,F} = 287.7 Hz, C-12), 157.4 (q, *J*_{11,F} = 37.6 Hz, C-11), 168.7, 172.8 (2s, C-2, C-8).

Elemental analysis:

C ₁₄ H ₂₁ BrF ₃ NO ₅	calcd	C 40.02	H 5.04	N 3.33
420.22	found	C 40.31	H 5.18	N 3.48

()-tert.-Butyl 2-(2'-methoxycarbonylcyclobutyl)-2-trifluoroacetyl-glycinate [()-9]:

According to the general procedure for Michael additions **9** was obtained as the major product from (Z)-configured unsaturated iodide **7b**.

¹H-NMR (500 MHz): δ = 1.43 (s, 9H, 10-H), 1.98 (m, 2H, 5-H), 2.14 (m, 2H, 4-H), 2.78 (m, 1H, 6-H), 3.03 (dt, $J_{3,6} = J_{3,4} = 9.4$ Hz, 3-H), 3.66 (s, 3H, 1-H), 4.32 (dd, $J_{7,6} = 10.1$ Hz, $J_{7,N-H} = 6.9$ Hz, 1H, 7-H), 7.33 (s, 1H, N-H).

¹³C-NMR (125 MHz): δ = 21.7 (t, C-4), 22.4 (t, C-5), 27.9 (q, C-10), 40.7 (d, C-6), 41.7 (d, C-3), 52.0 (q, C-1), 57.4 (d, C-7), 83.1 (s, C-9), 115.7 (q, $J_{12,F} = 286.9$ Hz, C-12), 157.2 (q, $J_{11,F} = 37.1$ Hz, C-11), 168.2 (s, C-8), 174.6 (s, C-2).

Elemental analysis:

$C_{14}H_{20}F_3NO_5$	calcd	C 49.55	H 5.94	N 4.13
339.31	found	C 49.30	H 5.96	N 4.27

()-tert.-Butyl syn 2-methoxycarbonylmethyl-N-trifluoroacetyl-prolinate [()-10]:

According to the general procedure for Michael additions **9** was obtained as the minor product from (Z)-configured unsaturated bromide **7a**.

data of the major rotamer:

¹H-NMR (500 MHz): δ = 1.43 (s, 9H, 10-H), 1.87 (m, 1H, 2-Ha), 2.15 (m, 1H, 2-Hb), 2.38 (dd, $J_{4a,4b} = 17.3$ Hz, $J_{4a,3} = 7.3$ Hz, 1H, 4-Ha), 2.49 (dd, $J_{4b,4a} = 17.0$ Hz, $J_{4b,3} = 7.9$ Hz, 1H, 4-Hb), 2.80 (m, 1H, 3-H), 3.61 (m, 1H, 1-Ha), 3.69 (s, 3H, 6-H), 3.94 (m, 1H, 1-Hb), 4.52 (d, $J_{7,3} = 8.5$ Hz, 1H, 7-H).

¹³C-NMR (125 MHz): δ = 27.8 (q, C-10), 29.9 (t, C-2), 34.2 (t, C-4), 36.2 (d, C-3), 46.2 (tq, $J_{1,F} = 3.5$ Hz, C-1), 51.9 (q, C-6), 63.1 (d, C-7), 82.9 (s, C-9), 116.1 (q, $J_{12,F} = 287.1$ Hz, C-12), 155.8 (q, $J_{11,F} = 37.1$ Hz, C-11), 168.2 (s, C-8), 171.4 (s, C-5).

Selected data of the minor rotamer:

¹H-NMR (500 MHz): δ = 1.42 (s, 9H, 10-H), 1.73 (m, 1H, 2-Ha), 2.09 (m, 1H, 2-Hb), 2.89 (m, 1H, 3-H), 3.70 (s, 3H, 6-H), 3.80 (m, 1H, 1-Hb), 4.62 (d, $J_{7,3} = 7.9$ Hz, 1H, 7-H).

¹³C-NMR (125 MHz): δ = 26.6 (t, C-2), 27.8 (q, C-10), 34.5 (t, C-4), 39.3 (d, C-3), 47.2 (t, C-1), 51.9 (q, C-6), 62.0 (dq, $J_{7,F} = 2.9$ Hz, C-7), 83.3 (s, C-9), 116.0 (q, $J_{12,F} = 287.9$ Hz, C-12), 155.4 (q, $J_{11,F} = 37.1$ Hz, C-11), 168.5 (s, C-8), 171.3 (s, C-5).

Elemental analysis:

$C_{14}H_{20}F_3NO_5$	Calcd	C 49.55	H 5.94	N 4.13
339.31	found	C 49.40	H 5.93	N 4.18

Synthesis and spectroscopic data of substrates:

The compound (**Z**)-**5** was synthesized from *rac* methyl 4-(tetrahydro-pyran-2-yloxy)-pent-2-ynoate by a sequence of deprotection, enzymatic kinetic resolution, phosphatation and Lindlar-hydrogenation:

Procedure for deprotection and enzymatic, kinetic resolution:

3.92 g (18.5 mmol) *rac* methyl 4-(tetrahydro-pyran-2-yloxy)-pent-2-ynoate were dissolved in methanol and two drops conc. hydrochloric acid were added. After completion of the reaction, NaHCO₃ was added and the solvent was removed under reduced pressure. The residue was diluted with dichloromethane and a small amount of water was added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na₂SO₄ and the solvent was removed under reduced pressure. 24 ml of vinyl acetate and 400 mg Novozym 435 were added. The mixture was shaken and the conversion was monitored by GC. After approximately 20 h the (*R*)-enantiomer of the alcohol was completely consumed. The solution was filtered from the immobilized enzyme and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica (hexane/ethyl acetate 90:10). The fraction which contained the enantiomerically pure methyl (4*S*)-hydroxy-pent-2-ynoate was evaporated and used for the synthesis of the phosphate.

Procedure for phosphatation:

The methyl (4*S*)-hydroxy-pent-2-ynoate was dissolved in dichloromethane. At 0 °C 1.8 ml (23 mmol) pyridine and 225 mg (1.85 mmol) 4-dimethylaminopyridine (DMAP) were added, followed by 2.7 ml (18.5 mmol) diethylchlorophosphate dissolved in dichloromethane. The solution was stirred until the conversion was completed. 1 N KHSO₄ was added, the layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica (hexane/ethyl acetate 1:1) and gave 982 mg (3.75 mmol) methyl (4*S*)-(diethoxy-phosphoryloxy)-pent-2-ynoate.

Procedure for Alkine-hydrogenation:

346 mg (1.32 mmol) methyl (4*S*)-(diethoxy-phosphoryloxy)-pent-2-ynoate were dissolved in a mixture of 8 ml hexane and 2.5 ml *tert*-butanol. 50 mg Pd (5 % on BaSO₄) and 75 mg quinoline were added. The solution was stirred vigorously under of hydrogen (1 atm) until the calculated amount of hydrogen was consumed. The reaction mixture was filtered on Celite and the solvent was removed under reduced pressure. The residue was purified by flash-chromatography on silica (hexane/ethyl acetate 1:1) and gave 253 mg (0.96 mmol) methyl (2*Z*)-(4*S*)-(diethoxy-phosphoryloxy)-pentenoate.

The phosphatation and hydrogenation reactions leading to (*E*)-**2b**, (*Z*)-**2b**, and (*E*)-**5** were carried out in analogy to these procedures.

Methyl (2*E*)-(diethoxy-phosphoryloxy)-butenoate [(*E*)-**2b**]:

¹H-NMR (300 MHz): δ = 1.33 (t, $J_{7,6}$ = 7.1 Hz, 6H, 7-H), 3.74 (s, 3H, 1-H), 4.12 (dq, $J_{6,P}$ = 8.1 Hz, $J_{6,7}$ = 7.0 Hz, 4H, 6-H), 4.68 (m, 2H, 5-H), 6.11 (dt, $J_{3,4}$ = 15.8 Hz, $J_{3,5}$ = 1.9 Hz, 1H, 3-H), 6.92 (dtd, $J_{4,3}$ = 15.8 Hz, $J_{4,5}$ = 4.2 Hz, $J_{4,P}$ = 1.8 Hz, 1H, 4-H).

¹³C-NMR (75 MHz): δ = 16.1 (qd, $J_{7,P}$ = 6.8 Hz, C-7), 51.7 (q, C-1), 64.1 (td, $J_{6,P}$ = 6.2 Hz, C-6), 65.3 (td, $J_{5,P}$ = 5.1 Hz, C-5), 121.6 (d, C-3), 141.6 (dd, $J_{4,P}$ = 7.4 Hz, C-4), 166.2 (s, C-2).

³¹P-NMR: δ = -2.38.

Elemental analysis:

C ₉ H ₁₇ PO ₆	calcd	C 42.87	H 6.79
252.19	found	C 42.90	H 6.74

Methyl (Z)-(diethoxy-phosphoryloxy)-butenoate [(Z)-2b]:

¹H-NMR (300 MHz): δ = 1.32 (td, $J_{7,6}$ = 7.2 Hz, $J_{7,P}$ = 0.9 Hz, 6H, 7-H), 3.70 (s, 3H, 1-H), 4.14 (dq, $J_{6,P}$ = 7.7 Hz, $J_{6,7}$ = 7.2 Hz, 4H, 6-H), 5.12 (ddd, $J_{5,P}$ = 8.8 Hz, $J_{5,4}$ = 4.8 Hz, $J_{5,3}$ = 2.6 Hz, 2H, 5-H), 5.84 (dt, $J_{3,4}$ = 11.8 Hz, $J_{3,5}$ = 2.4 Hz, 1H, 3-H), 6.37 (dt, $J_{4,3}$ = 11.7 Hz, $J_{4,5}$ = 4.8 Hz, 1H, 4-H).

¹³C-NMR (75 MHz): δ = 16.1 (qd, $J_{7,P}$ = 6.8 Hz, C-7), 51.1 (q, C-1), 63.9 (td, $J_{6,P}$ = 5.4 Hz, C-6), 65.3 (td, $J_{5,P}$ = 5.0 Hz, C-5), 119.9 (d, C-3), 145.6 (dd, $J_{4,P}$ = 7.4 Hz, C-4), 166.0 (s, C-2).

³¹P-NMR: δ = -0.64.

Elemental analysis:

C ₉ H ₁₅ PO ₆	calcd	C 42.87	H 6.79	P 12.28
252.19	found	C 42.66	H 6.80	P 11.99

Methyl (2Z,4S)-(diethoxy-phosphoryloxy)-pentenoate [(Z)-5]:

¹H-NMR (300 MHz): δ = 1.29 (t, $J_{8,7}$ = 7.2 Hz, 6H, 8-H), 1.43 (d, $J_{6,5}$ = 6.6 Hz, 3H, 6-H), 3.70 (s, 3H, 1-H), 4.07 (m, 4H, 7-H), 5.76 (dd, $J_{3,4}$ = 11.6 Hz, $J_{3,5}$ = 1.3 Hz, 1H, 3-H), 5.94 (m, 1H, 5-H), 6.26 (dd, $J_{4,3}$ = 11.6 Hz, $J_{4,5}$ = 7.5 Hz, 1H, 4-H).

¹³C-NMR (75 MHz): δ = 15.8 (qd, $J_{8,P}$ = 1.7 Hz, C-8), 15.9 (qd, $J_{8,P}$ = 1.1 Hz, C-8), 21.2 (qd, $J_{6,P}$ = 5.7 Hz, C-6), 51.3 (q, C-1), 63.5 (td, $J_{7,P}$ = 6.2 Hz, C-7), 63.5 (td, $J_{7,P}$ = 5.7 Hz, C-7), 71.7 (dd, $J_{5,P}$ = 5.1 Hz, C-5), 118.6 (d, C-3), 148.8 (dd, $J_{4,P}$ = 5.1 Hz, C-4), 165.4 (s, C-2).

³¹P-NMR: δ = -1.82.

$[\alpha]_D^{25} = 12.3^\circ$ (c = 0.7, CHCl₃)

HRMS (FAB+)

	calcd	found
C ₁₀ H ₂₀ PO ₆ [M+1] ⁺	267.0998	267.0995

Methyl (2E,4S)-(diethoxy-phosphoryloxy)-pentenoate [(E)-5]:

¹H-NMR (300 MHz): δ = 1.30 (td, $J_{8,7}$ = 7.2 Hz, $J_{8,P}$ = 0.9 Hz, 3H, 8-H), 1.31 (td, $J_{8,7}$ = 7.0 Hz, $J_{8,P}$ = 0.9 Hz, 3H, 8-H), 1.43 (d, $J_{6,5}$ = 6.6 Hz, 3H, 6-H), 3.72 (s, 3H, 1-H), 4.08 (m, 4H, 7-H), 5.04 (m, 1H, 5-H), 6.02 (dd, $J_{3,4}$ = 15.6 Hz, $J_{3,5}$ = 1.7 Hz, 1H, 3-H), 6.86 (ddd, $J_{4,3}$ = 15.6 Hz, $J_{4,5}$ = 5.0 Hz, $J_{4,P}$ = 1.1 Hz, 1H, 4-H).

¹³C-NMR (75 MHz): δ = 15.8 (qd, $J_{8,P}$ = 1.1 Hz, C-8), 15.9 (qd, $J_{8,P}$ = 1.1 Hz, C-8), 21.3 (qd, $J_{6,P}$ = 4.0 Hz, C-6), 51.5 (q, C-1), 63.6 (td, $J_{7,P}$ = 5.7 Hz, C-7), 63.7 (td, $J_{7,P}$ = 5.7 Hz, C-7), 72.8 (dd, $J_{5,P}$ = 5.1 Hz, C-5), 120.5 (d, C-3), 146.4 (dd, $J_{4,P}$ = 6.2 Hz, C-4), 166.2 (s, C-2).

³¹P-NMR: δ = -3.41. $[\alpha]_D^{25} = -10.5^\circ$ (c = 0.9, CHCl₃)

HRMS (FAB+)	calcd	found
C ₁₀ H ₂₀ PO ₆ [M+1] ⁺	267.0998	267.1003

Methyl (2Z)-5-bromo-pentenoate [7a]

Methyl (2Z)-5-bromo-pentenoate (**7a**) was prepared from methyl 5-bromo-pent-2-ynoate in analogy to the procedure reported above.

¹H-NMR (500 MHz): δ = 3.22 (dt, $J_{5,4}$ = 6.8 Hz, $J_{5,6}$ = 6.6 Hz, 2H, 5-H), 3.46 (t, $J_{6,5}$ = 6.6 Hz, 2H, 6-H), 3.70 (s, 3H, 1-H), 5.90 (dt, $J_{3,4}$ = 11.4 Hz, $J_{3,5}$ = 1.6 Hz, 1H, 3-H), 6.27 (dt, $J_{4,3}$ = 11.4 Hz, $J_{4,5}$ = 7.0 Hz, 1H, 4-H).

¹³C-NMR (125 MHz): δ = 31.7 (2t, C-5, C-6), 51.2 (q, C-1), 121.5 (d, C-3), 146.2 (d, C-4), 166.4 (s, C-2).

Elemental analysis:

C ₆ H ₉ BrO ₂	calcd	C 37.33	H 4.70
193.04	found	C 37.20	H 4.47

Methyl (2Z)-5-iodo-pentenoate (7b)

514 mg (2.66 mmol) Methyl (2Z)-5-bromo-pentenoate (**7a**) were dissolved in 2.2 ml acetone, 481 mg (3.21 mmol) NaI was added and the mixture was heated to reflux. The mixture was cooled to room temperature and dichloromethane and water were added. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified

by flash-chromatography on silica (hexane/ethyl acetate 96:4) yielding 495 mg (2.06 mmol) **7b** and 52 mg (0.22 mmol) of its (*E*)-isomer.

¹H-NMR (500 MHz): δ = 3.20–3.28 (sh, 4H, 5-H, 6-H), 3.70 (s, 3H, 1-H), 5.90 (d, $J_{3,4}$ = 11.7 Hz, 1H, 3-H), 6.19 (dt, $J_{4,3}$ = 11.4 Hz, $J_{4,5}$ = 6.3 Hz, 1H, 4-H).

¹³C-NMR (125 MHz): δ = 3.8 (t, C-6), 32.5 (t, C-5), 51.2 (q, C-1), 121.2 (d, C-3), 147.9 (d, C-4), 166.4 (s, C-2).

Elemental analysis:

C ₆ H ₉ IO ₂	calcd	C 30.02	H 3.78
240.04	found	C 30.07	H 3.76

XRAY DATA OF 6

Table 1. Crystal data and structure refinement for 6.

Identification code	shelxs1909	
Empirical formula	C14 H20 F3 N O5	
Formula weight	339.31	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.853(2) Å	= 90°.
	b = 12.771(3) Å	= 108.07(3)°.
	c = 13.273(3) Å	= 90°.
Volume	1748.9(7) Å ³	
Z	4	
Density (calculated)	1.289 Mg/m ³	
Absorption coefficient	0.117 mm ⁻¹	
F(000)	712	
Crystal size	0.7 x 0.5 x 0.4 mm ³	
Theta range for data collection	1.97 to 23.50°.	
Index ranges	-12<=h<=11, 0<=k<=14, 0<=l<=14	
Reflections collected	2592	
Independent reflections	2592 [R(int) = 0.0000]	
Completeness to theta = 23.50°	100.0 %	
Absorption correction	N/A	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2592 / 0 / 208	
Goodness-of-fit on F ²	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0666, wR2 = 0.1744	
R indices (all data)	R1 = 0.0769, wR2 = 0.1860	
Largest diff. peak and hole	0.564 and -0.425 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	8957(3)	3658(2)	-48(2)	73(1)
O(2)	9231(3)	2183(2)	-847(2)	83(1)
O(3)	7806(2)	6231(2)	-3976(2)	64(1)
O(4)	8878(2)	7234(2)	-2576(2)	71(1)
O(5)	11733(3)	4931(2)	-3206(2)	87(1)
N(1)	10817(2)	5699(2)	-2070(2)	51(1)
C(1)	9482(3)	5432(2)	-2648(2)	47(1)
C(2)	8828(3)	4872(2)	-1944(2)	47(1)
C(3)	8880(3)	3693(2)	-1858(2)	51(1)
C(4)	7617(3)	4262(2)	-2422(3)	56(1)
C(5)	6504(4)	4309(4)	-1965(3)	84(1)
C(6)	9029(3)	3208(3)	-825(2)	56(1)
C(7)	9354(6)	1612(4)	129(3)	116(2)
C(8)	8706(3)	6425(2)	-3061(2)	51(1)
C(9)	6807(4)	7019(3)	-4511(3)	77(1)
C(10)	7449(5)	7969(4)	-4819(4)	113(2)
C(11)	6032(5)	7302(5)	-3792(5)	120(2)
C(12)	6016(5)	6425(5)	-5484(4)	126(2)
C(13)	11796(3)	5451(3)	-2425(3)	58(1)
C(14)	13102(4)	5876(3)	-1779(4)	77(1)
F(1)	13055(3)	6656(3)	-1147(3)	159(2)
F(2)	13752(3)	6262(4)	-2359(3)	159(2)
F(3)	13833(3)	5191(3)	-1200(4)	198(2)

Table 3. Bond lengths [Å] and angles [°] for **6**.

O(1)-C(6)	1.204(4)	C(3)-C(2)-C(1)	120.2(2)
O(2)-C(6)	1.329(4)	C(6)-C(3)-C(2)	118.8(3)
O(2)-C(7)	1.456(4)	C(6)-C(3)-C(4)	118.7(3)
O(3)-C(8)	1.324(4)	C(2)-C(3)-C(4)	58.76(19)
O(3)-C(9)	1.488(4)	C(2)-C(4)-C(5)	121.2(3)
O(4)-C(8)	1.202(4)	C(2)-C(4)-C(3)	60.0(2)
O(5)-C(13)	1.215(4)	C(5)-C(4)-C(3)	122.1(3)
N(1)-C(13)	1.327(4)	O(1)-C(6)-O(2)	123.0(3)
N(1)-C(1)	1.454(4)	O(1)-C(6)-C(3)	125.5(3)
C(1)-C(2)	1.517(4)	O(2)-C(6)-C(3)	111.5(3)
C(1)-C(8)	1.527(4)	O(4)-C(8)-O(3)	126.9(3)
C(2)-C(4)	1.490(4)	O(4)-C(8)-C(1)	123.0(3)
C(2)-C(3)	1.509(4)	O(3)-C(8)-C(1)	110.0(3)
C(3)-C(6)	1.468(4)	O(3)-C(9)-C(11)	109.2(3)
C(3)-C(4)	1.527(4)	O(3)-C(9)-C(12)	101.8(3)
C(4)-C(5)	1.511(5)	C(11)-C(9)-C(12)	112.5(4)
C(9)-C(11)	1.499(7)	O(3)-C(9)-C(10)	109.9(3)
C(9)-C(12)	1.514(6)	C(11)-C(9)-C(10)	111.9(4)
C(9)-C(10)	1.517(6)	C(12)-C(9)-C(10)	111.0(4)
C(13)-C(14)	1.511(5)	O(5)-C(13)-N(1)	126.4(3)
C(14)-F(3)	1.268(5)	O(5)-C(13)-C(14)	118.4(3)
C(14)-F(2)	1.292(5)	N(1)-C(13)-C(14)	115.2(3)
C(14)-F(1)	1.313(5)	F(3)-C(14)-F(2)	105.6(4)
		F(3)-C(14)-F(1)	106.1(5)
C(6)-O(2)-C(7)	116.3(3)	F(2)-C(14)-F(1)	103.2(4)
C(8)-O(3)-C(9)	122.2(3)	F(3)-C(14)-C(13)	113.4(4)
C(13)-N(1)-C(1)	122.3(3)	F(2)-C(14)-C(13)	112.9(4)
N(1)-C(1)-C(2)	111.5(2)	F(1)-C(14)-C(13)	114.8(3)
N(1)-C(1)-C(8)	110.1(2)		
C(2)-C(1)-C(8)	107.6(2)	Symmetry transformations used to generate	
C(4)-C(2)-C(3)	61.2(2)	equivalent atoms:	
C(4)-C(2)-C(1)	120.3(2)		

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **6**. The anisotropic displacement factor exponent takes the form: $-2 \sum_{i,j} h_i h_j U^{ij} + \dots + 2 \sum_i h_i U^{1i}$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	105(2)	73(2)	45(1)	-4(1)	28(1)	1(1)
O(2)	145(3)	55(2)	52(1)	9(1)	35(2)	7(2)
O(3)	64(1)	61(1)	54(1)	2(1)	1(1)	5(1)
O(4)	80(2)	53(1)	71(2)	-7(1)	9(1)	2(1)
O(5)	89(2)	94(2)	92(2)	-23(2)	49(2)	5(2)
N(1)	49(1)	62(2)	43(1)	-4(1)	17(1)	-1(1)
C(1)	50(2)	51(2)	41(2)	-3(1)	15(1)	-1(1)
C(2)	50(2)	48(2)	43(2)	-3(1)	15(1)	1(1)
C(3)	64(2)	47(2)	43(2)	-2(1)	19(1)	2(1)
C(4)	55(2)	61(2)	51(2)	1(2)	13(1)	-5(2)
C(5)	55(2)	107(3)	95(3)	14(2)	29(2)	-5(2)
C(6)	65(2)	54(2)	48(2)	-2(2)	18(2)	-1(2)
C(7)	212(6)	73(3)	66(3)	25(2)	47(3)	6(3)
C(8)	53(2)	53(2)	47(2)	2(2)	16(1)	-2(1)
C(9)	62(2)	77(3)	77(2)	14(2)	0(2)	12(2)
C(10)	106(4)	98(3)	121(4)	51(3)	16(3)	19(3)
C(11)	83(3)	143(5)	134(4)	29(4)	36(3)	44(3)
C(12)	104(4)	128(4)	99(4)	-2(3)	-35(3)	18(3)
C(13)	59(2)	57(2)	66(2)	2(2)	30(2)	7(2)
C(14)	54(2)	88(3)	94(3)	3(2)	30(2)	7(2)
F(1)	68(2)	208(4)	199(4)	-108(3)	40(2)	-42(2)
F(2)	103(2)	235(4)	156(3)	2(3)	65(2)	-62(3)
F(3)	96(2)	157(3)	271(5)	82(3)	-47(3)	-12(2)

XRAY DATA OF 9

Table 5. Crystal data and structure refinement for **9**.

Identification code	shelxs1879	
Empirical formula	C14 H20 F3 N O5	
Formula weight	339.31	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 11.083(2) Å	= 90°.
	b = 9.304(2) Å	= 91.78(3)°.
	c = 16.856(3) Å	= 90°.
Volume	1737.3(6) Å ³	
Z	4	
Density (calculated)	1.297 Mg/m ³	
Absorption coefficient	0.117 mm ⁻¹	
F(000)	712	
Crystal size	0.2 x 0.18 x 0.14 mm ³	
Theta range for data collection	2.23 to 24.13°.	
Index ranges	-12<=h<=12, -9<=k<=9, -19<=l<=19	
Reflections collected	10554	
Independent reflections	2592 [R(int) = 0.0690]	
Completeness to theta = 24.13°	93.5 %	
Absorption correction	N/A	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2592 / 0 / 235	
Goodness-of-fit on F ²	2.576	
Final R indices [I>2sigma(I)]	R1 = 0.1160, wR2 = 0.3605	
R indices (all data)	R1 = 0.1378, wR2 = 0.3669	
Largest diff. peak and hole	0.376 and -0.288 e.Å ⁻³	

Table 6. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **9**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	1843(5)	290(6)	6180(3)	69(2)
O(2)	4476(4)	1137(6)	7667(3)	59(1)
O(3)	3473(4)	2828(6)	6927(3)	66(1)
N(1)	1272(5)	1551(7)	7255(3)	55(2)
O(5)	-463(5)	2123(9)	9772(3)	92(2)
O(6)	-410(5)	2596(8)	8477(3)	91(2)
C(1)	2352(5)	1175(8)	7736(3)	47(2)
C(2)	2248(6)	1752(9)	8575(4)	59(2)
C(3)	1193(6)	1204(9)	9090(4)	61(2)
C(4)	2067(8)	1277(14)	9815(5)	94(3)
C(5)	3128(7)	1243(13)	9239(4)	87(3)
C(6)	1128(6)	1056(8)	6513(4)	56(2)
C(7)	14(7)	1626(11)	6060(5)	75(2)
C(8)	3493(5)	1805(8)	7386(4)	52(2)
C(9)	5722(6)	1657(9)	7513(5)	65(2)
C(10)	32(7)	2046(10)	9062(5)	68(2)
C(11)	-1574(9)	2948(16)	9822(6)	115(4)
C(12)	6509(8)	581(12)	7976(7)	93(3)
C(13)	5952(8)	1585(14)	6646(6)	98(3)
C(14)	5859(8)	3147(11)	7865(7)	93(3)
F(1A)	-828(12)	2070(20)	6555(10)	107(5)
F(2A)	-644(9)	632(11)	5728(6)	94(3)
F(3A)	380(20)	2410(20)	5426(12)	125(7)
F(1B)	160(50)	2900(70)	5770(30)	118(17)
F(2B)	-590(40)	2680(40)	6342(18)	110(14)
F(3B)	-400(40)	650(50)	5560(20)	190(30)

Table 7. Bond lengths [Å] and angles [°] for **9**.

O(1)-C(6)	1.216(8)	F(2A)-C(7)-F(3B)	17(2)
O(2)-C(8)	1.329(8)	F(2B)-C(7)-F(3A)	93(2)
O(2)-C(9)	1.493(8)	F(1B)-C(7)-F(3A)	34(2)
O(3)-C(8)	1.226(9)	F(2A)-C(7)-F(3A)	102.6(12)
N(1)-C(6)	1.337(9)	F(3B)-C(7)-F(3A)	89(3)
N(1)-C(1)	1.468(8)	F(2B)-C(7)-F(1A)	32.0(19)
O(5)-C(10)	1.334(9)	F(1B)-C(7)-F(1A)	93(2)
O(5)-C(11)	1.455(11)	F(2A)-C(7)-F(1A)	95.4(11)
O(6)-C(10)	1.201(10)	F(3B)-C(7)-F(1A)	112(2)
C(1)-C(2)	1.520(9)	F(3A)-C(7)-F(1A)	123.6(13)
C(1)-C(8)	1.528(9)	F(2B)-C(7)-C(6)	120.2(17)
C(2)-C(5)	1.537(11)	F(1B)-C(7)-C(6)	114(3)
C(2)-C(3)	1.564(9)	F(2A)-C(7)-C(6)	113.9(9)
C(3)-C(10)	1.506(11)	F(3B)-C(7)-C(6)	110(2)
C(3)-C(4)	1.537(11)	F(3A)-C(7)-C(6)	109.0(11)
C(4)-C(5)	1.548(11)	F(1A)-C(7)-C(6)	111.3(9)
C(6)-C(7)	1.527(11)	O(3)-C(8)-O(2)	125.9(6)
C(7)-F(2B)	1.29(3)	O(3)-C(8)-C(1)	122.8(6)
C(7)-F(1B)	1.30(6)	O(2)-C(8)-C(1)	111.2(6)
C(7)-F(2A)	1.294(13)	C(13)-C(9)-O(2)	110.1(7)
C(7)-F(3B)	1.31(3)	C(13)-C(9)-C(14)	114.0(8)
C(7)-F(3A)	1.36(3)	O(2)-C(9)-C(14)	108.1(6)
C(7)-F(1A)	1.336(18)	C(13)-C(9)-C(12)	111.1(8)
C(9)-C(13)	1.491(12)	O(2)-C(9)-C(12)	102.4(6)
C(9)-C(14)	1.514(14)	C(14)-C(9)-C(12)	110.6(8)
C(9)-C(12)	1.527(12)	O(6)-C(10)-O(5)	123.0(8)
F(1A)-F(2B)	0.73(4)	O(6)-C(10)-C(3)	125.0(6)
F(1A)-F(1B)	1.91(6)	O(5)-C(10)-C(3)	112.0(7)
F(2A)-F(3B)	0.40(5)	F(2B)-F(1A)-C(7)	70(4)
F(3A)-F(3B)	1.86(6)	F(2B)-F(1A)-F(1B)	28(4)
F(3A)-F(1B)	0.78(5)	C(7)-F(1A)-F(1B)	42.7(17)
F(1B)-F(2B)	1.32(7)	C(7)-F(2A)-F(3B)	83(5)
F(1B)-F(3B)	2.21(7)	F(3B)-F(3A)-F(1B)	106(7)
		F(3B)-F(3A)-C(7)	44.5(12)
C(8)-O(2)-C(9)	122.6(6)	F(1B)-F(3A)-C(7)	68(6)
C(6)-N(1)-C(1)	120.4(6)	F(3A)-F(1B)-F(2B)	132(9)
C(10)-O(5)-C(11)	116.9(7)	F(3A)-F(1B)-C(7)	78(6)
N(1)-C(1)-C(2)	110.2(5)	F(2B)-F(1B)-C(7)	59(3)
N(1)-C(1)-C(8)	111.4(5)	F(3A)-F(1B)-F(3B)	54(6)
C(2)-C(1)-C(8)	108.1(5)	F(2B)-F(1B)-F(3B)	78(4)
C(1)-C(2)-C(5)	120.3(7)	C(7)-F(1B)-F(3B)	32.2(18)
C(1)-C(2)-C(3)	118.8(6)	F(3A)-F(1B)-F(1A)	118(8)
C(5)-C(2)-C(3)	87.9(6)	F(2B)-F(1B)-F(1A)	15(2)
C(10)-C(3)-C(4)	121.3(7)	C(7)-F(1B)-F(1A)	44(2)
C(10)-C(3)-C(2)	117.8(7)	F(3B)-F(1B)-F(1A)	64(2)
C(4)-C(3)-C(2)	87.9(5)	F(1A)-F(2B)-F(1B)	137(6)
C(3)-C(4)-C(5)	88.5(6)	F(1A)-F(2B)-C(7)	78(4)
C(2)-C(5)-C(4)	88.5(6)	F(1B)-F(2B)-C(7)	60(3)
O(1)-C(6)-N(1)	125.0(6)	F(3A)-F(3B)-C(7)	47.0(18)
O(1)-C(6)-C(7)	120.0(6)	F(3A)-F(3B)-F(1B)	19.8(15)
N(1)-C(6)-C(7)	114.8(7)	C(7)-F(3B)-F(1B)	32.0(18)
F(2B)-C(7)-F(1B)	61(3)	F(3A)-F(3B)-F(2A)	117(7)
F(2B)-C(7)-F(2A)	114(2)	C(7)-F(3B)-F(2A)	79(4)
F(1B)-C(7)-F(2A)	124(3)	F(1B)-F(3B)-F(2A)	97(7)
F(2B)-C(7)-F(3B)	126(3)	Symmetry transformations used to generate	
F(1B)-C(7)-F(3B)	116(3)	equivalent atoms:	

Table 8. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **9**. The anisotropic displacement factor exponent takes the form: $-2 \sum [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	74(3)	80(4)	54(3)	-7(2)	8(2)	19(3)
O(2)	42(2)	68(3)	68(3)	5(2)	8(2)	3(2)
O(3)	62(3)	66(3)	70(3)	15(3)	10(2)	3(2)
N(1)	44(3)	69(4)	53(3)	-8(3)	3(2)	3(2)
O(5)	72(4)	147(6)	57(3)	5(3)	23(3)	23(3)
O(6)	77(4)	135(6)	62(3)	6(3)	15(3)	33(3)
C(1)	38(3)	57(4)	47(3)	3(3)	4(2)	3(3)
C(2)	56(4)	68(5)	53(4)	-5(3)	6(3)	-13(3)
C(3)	59(4)	77(5)	49(4)	1(3)	8(3)	-3(3)
C(4)	78(5)	144(9)	59(5)	8(5)	9(4)	9(5)
C(5)	64(5)	146(9)	51(4)	-4(5)	-2(3)	-1(5)
C(6)	53(4)	60(5)	54(4)	1(3)	3(3)	-2(3)
C(7)	61(5)	83(7)	81(5)	1(5)	-5(4)	9(4)
C(8)	43(3)	53(4)	61(4)	-6(3)	10(3)	2(3)
C(9)	39(3)	76(5)	79(5)	6(4)	10(3)	-2(3)
C(10)	65(4)	87(6)	53(4)	-5(4)	15(3)	-6(4)
C(11)	84(6)	189(13)	74(6)	-7(6)	28(5)	44(7)
C(12)	55(5)	103(7)	122(7)	23(6)	3(4)	13(4)
C(13)	68(5)	141(10)	86(6)	6(6)	27(5)	5(5)
C(14)	66(5)	76(7)	138(9)	-3(6)	3(5)	-14(4)
F(1A)	66(5)	162(15)	92(9)	-7(8)	-16(5)	42(7)
F(2A)	76(5)	100(7)	104(7)	-9(6)	-25(5)	-5(4)
F(3A)	103(8)	160(18)	109(14)	73(11)	-20(9)	0(10)
F(1B)	120(40)	150(40)	90(40)	60(30)	-30(30)	-20(20)
F(2B)	160(30)	100(20)	64(16)	-24(15)	-34(17)	70(20)
F(3B)	180(40)	260(50)	110(30)	-160(40)	-80(30)	30(40)