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Asymmetric Syntheses of α-Aminophosphonic Acids, V[1]

Synthesis of Enantiomerically Pure Diethyl 2-Pyrrolidinyl- and 5-Oxo-2-pyrrolidinylphosphonates

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Enantiomerically pure 3- and 4-substituted phosphonic acid derivatives **5** of pyroglutamic acid were prepared by a Michael addition of the lithiated (+)-camphor derivative **2** to α,β-unsaturated esters and subsequent hydrolysis. The reduction of the lactams **5** with $LiBH_4/BF_3 \cdot OEt_2$ afforded substituted phosphonic acid analogues **7** of proline.

α-Aminophosphonic acids, the phosphonic acid analogues of α-amino acids, are finding increasing interest[2,3] because of their potential or proven biological activity[4]. Due to the tetrahedral structure of the phosphonic moiety, they act as "transition-state analogues"[5] and thus serve as models for enzyme reactions[6] or as components in enzyme inhibitors[7]. Recently, we reported on the synthesis of enantiomerically pure phosphonic acid analogues of pyroglutamic acid and proline[1]. Encouraged by those results, we were interested in the asymmetric synthesis of substituted derivatives.

The Michael addition of the lithiated (+)-camphor derivative **2** to substituted acrylic esters proceeds smoothly with a high degree of stereoselectivity. In many cases, only two out of the four possible stereoisomers were detectable by ^1H-, ^{13}C- and ^{31}P-NMR spectroscopy.

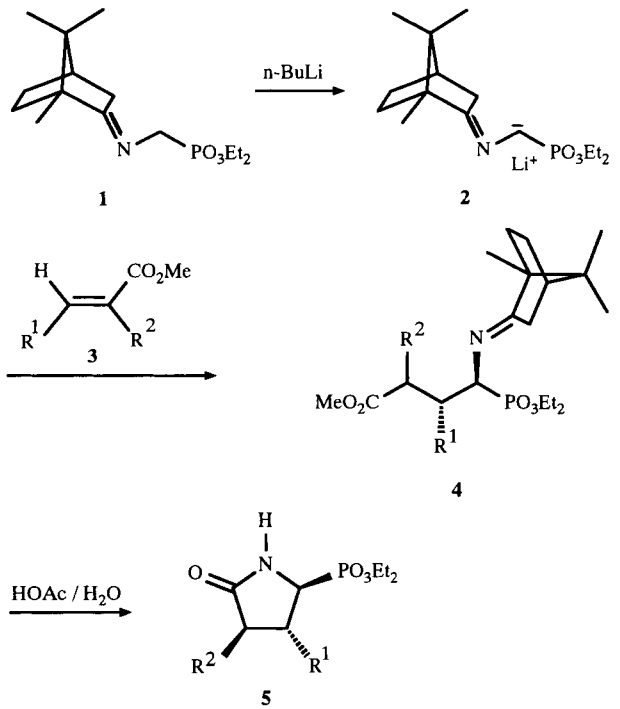

Table 1. Michael adducts **4** generated via the lithiated imine **2** and *trans*-acrylates **3**

3-5	R^1	R^2	yield of 4 (%)	ratio of diastereomers (1S,2S):(1S,2R):(1R,2R):(1R,2S)				yield of 5 (%) [a]
a	C_6H_5	H	91	100	<2	14	<2	74
b	CH_3	H	85	5	100	3	12.5	81
c	p-Br-C_6H_4	H	86	100	3	12	<2	72
d	C_6H_5	CO_2CH_3	84	100	4	4	<2	41
e	p-C_5H_4N	H	78	100	3	23	<2	
f	CH_3	CO_2CH_3	92	6	100	3	16	

[a] Diastereomerically pure after one recrystallization or chromatography.

In all cases, (1*S*) configuration was assigned to the predominantly formed stereoisomer due to the characteristic absorption of its protons 8′-H_3 in the ^1H-NMR spectra[1,8]. The relative configuration at C-1 and C-2 of the major diastereomers was determined to be *anti*[9] (see below). The predominantly formed stereoisomers are therefore (1*S*,2*S*)-configurated[10].

The minor diastereomers of the 1,4-adducts **4a–f** obtained from the reaction of **2** with *trans*-substituted acrylic esters **3a–f** possess the (1*R*) configuration (Table 1). This was confirmed again by the absorption of their protons 8′-H_3 in the ^1H-NMR spectra[8]. After removal of the chiral auxiliary only enantiomers of the major (1*S*,2*S*) stereoisomers were obtained, therefore the minor diastereomers must possess the (1*R*,2*R*) configuration[10].

Upon reaction of **2** with *cis*-substituted acrylic esters **6a** and **b**, only (1*S*) stereoisomers are formed. The minor

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diastereomers of adducts **4a** and **g** consequently exhibit (*1S,2R*) configuration (Table 2).

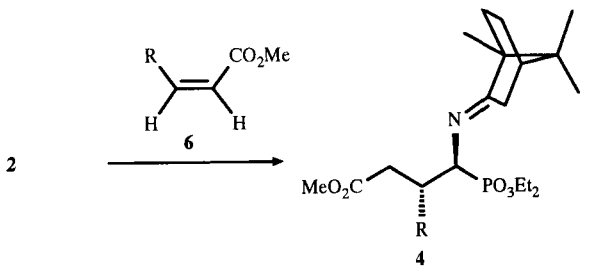

Table 2. Michael adducts **4** generated via the lithiated imine **2** and *cis*-acrylates **6**

4,6	R	yield of 4 (%)	ratio of diastereomers (1S,2S):(1S,2R):(1R,2R):(1R,2S)			
a	C_6H_5	89	100	16	<2	<2
g	CO_2CH_3	88	100	49	<2	<2

These surprising stereochemical results may be explained by different structures of the transition states. For the Michael addition of **2** to *cis*-substituted acrylic esters, we assume a *cisoid* conformation for the unsaturated ester. Addition should proceed via a cyclic transition state where the Li^+ cation complexes the carbonyl oxygen of the ester[11]. Due to the compact structure of the resulting transition states, the attack of the ester takes place exclusively from the sterically less hindered *si* side of the lithio compound **2**. Consequently, only (*1S*)-configurated products were formed.

trans-Substituted vinylogous esters should prefer a *transoid* conformation[12]. Cyclic transition states where the carbonyl oxygen is complexed by the cation are disfavored for steric reasons. The adducts **4a–f** are formed via the less hindered, non cyclic transition states, and predominantly (*1S,2S*)- and (*1R,2R*)-configurated stereoisomers are generated[10]. Hydrolysis of adducts **4a–d** was carried out with 90% aqueous acetic acid and afforded exclusively the *trans*-substituted lactams **5a–d**. After hydrolysis of the adduct **4a** [obtained from the lithiated (+)-camphor derivative **2** and methyl *cis*-cinnamate (**6a**)], the *cis*-substituted lactam **5a** was isolated in 10% yield besides 65% of the *trans* isomer. Both isomers could easily be separated by flash chromatography.

The relative configuration of lactams **5a–c** were not directly assignable because of insignificant ^1H-^1H and ^{13}C-^{31}P coupling constants and indefinite NOE signals. Therefore, the lactam **5c** was converted into the corresponding *N*-Boc-lactam which assumes a different and apparently more rigid conformation. The configuration of this *N*-Boc-lactam derivative was established by spin-decoupling experiments and by analyzing the ^1H-^1H and ^{13}C-^{31}P coupling constants.

The adduct **4d** was obtained diastereomerically pure[13] after flash chromatography. After removal of the chiral auxiliary by hydrolysis, a third stereogenic center is formed at C-4 upon ring closure. Two diastereomers in a 6:1 ratio were isolated after column filtration. Recrystallization from ether/chloroform afforded the diastereomerically and enantiomerically pure[14] lactam **5d** in 41% yield. The relative configuration of C-2 and C-3 was shown to be *trans* by analysis of ^1H-^1H and ^{13}C-^{31}P coupling constants. The proton 3-H absorbs at significant lower field ($\Delta\delta$ = 0.46 ppm) than the proton 3-H of the lactam **5a**. This downfield shift should be the result of the anisotropic effect of the ester carbonyl group *cis* to proton 3-H. Therefore, the (*2S,3S,4S*) configuration was assigned to the lactam **5d**.

The substituted pyroglutamic acid analogs **5a** and **b** were reduced to the phosphoprolines **7a** and **b** by $LiBH_4$/$Et_2O \cdot BF_3$[1,15]. The reduction proceeds without epimerization nor formation of phosphanes, and persisting, boron-containing impurities were removed with ammonia/methanol. The diastereomerically pure phosphoprolines **7a** and **b** were obtained in 68–71% yield with an enantiomeric excess of 77–95% (Table 3).

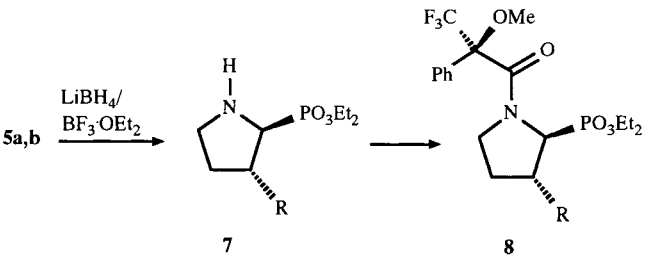

Table 3. 3-Substituted phosphoprolines 7

5,7,8	R	yield of 7 (%)	e.e. of 7 (%)
a (via **2** and **6a**)	C_6H_5	69	95
a (via **2** and **3a**)	C_6H_5	71	84
b	CH_3	68	77

The optical purity of the phosphoprolines **7a** and **b** and thus of the lactams **5a** and **b** was determined by conversion of the pyrrolidines **7a** and **b** into the amides **8a** and **b**[16]. According to the analysis of the ^1H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra, the pyrrolidine **7a**, which was obtained from the lithiated (+)-camphor derivative **2** and methyl *cis*-cinnamate (**6a**), and thus the lactam **5a** were obtained enantiomerically pure. The enantiomeric purity of the pyrrolidines **7a** and **b**, which were prepared from the lithiated (+)-camphor derivative **2** and the *trans*-acrylic esters **3**, reflects the ratio of the predominantly formed diastereomers of the adducts **4a** and **b**[17].

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Experimental

Infrared (IR) spectra were obtained using a Perkin-Elmer 298 spectrometer. – NMR spectra were measured with a Varian XL

200, VXR 200 or XI 500 spectrometer for ^1H and ^{13}C NMR, a Bruker WP 80 SY spectrometer for ^{19}F NMR and a Bruker AM 250 spectrometer for ^{31}P NMR. Chemical shifts are given in δ values by using tetramethylsilane as internal standard for ^1H- and ^{13}C NMR, $CFCl_3$ for ^{19}F NMR and orthophosphoric acid (85%) as external standard for ^{31}P NMR. – Mass spectra were recorded with Varian MAT 731 or 311 A spectrometers. – Optical rotations were measured with a Perkin Elmer Mod. 141 polarimeter. – Melting points are uncorrected. – TLC analyses were performed on Polygram Sil G/UV_{254} silica gel plates. Silica gel (30–60 μm) from Baker was used for flash chromatography. – Combustion analyses were carried out by the microanalytical laboratory of the University of Göttingen. – The (+)-camphor derivative **1** was prepared as described previously[3a]. All reactions were carried out under nitrogen or argon except those involving hydrolysis. All reagents were purified and dried if necessary prior to use.

Michael Additions of the Methyl Acrylates **3** *and* **6** *to the Lithio Compound* **2**. – *Compounds* **4**. – *General Procedure:* To a stirred solution of **1** (0.90 g, 3.0 mmol) in THF (15 ml), *n*-butyllithium in hexane (1.6 N, 2.1 ml, 3.3 mmol) was added at –70°C. After stirring for 15 min at –70°C, 3.3 mmol of a cooled solution of the vinylogous ester **3** or **6** in THF (5 ml) was added dropwise, and stirring was continued for 2 h at –70°C. Then acetic acid (0.21 g) was added, and the solvent was removed in vacuo. The residue was dissolved in diethyl ether (30 ml) and washed with 30-ml portions of aqueous 5% $NaHCO_3$ and saturated NaCl solution. The aqueous layers were reextracted with diethyl ether (2 portions of 20 ml each), and the combined organic layers were dried with $MgSO_4$. The solvent was removed in vacuo and the crude products **4** were purified by bulb-to-bulb distillation or flash chromatography on silica gel.

Diethyl (1S,1′R,2S,4′R)-3-Methoxycarbonyl-2-phenyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4a**] (*via* **2** *and* **6a**): From 0.54 g (3.3 mmol) of methyl *cis*-cinnamate (**6a**), 1.24 g (89%) of (1*S*,1′*R*,2*S*,4′*R*)-**4a** was obtained after bulb-to-bulb distillation. – B.p. 150°C/0.01 Torr. – IR (neat): $\tilde{\nu}$ = 1735 (C=O), 1670 (C=N), 1250 (P=O), 1040 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): a) (1*S*,2*S*)-**4a**: δ = 0.76 (s; 3H, 8′-H_3), 0.87 and 0.97 (2s; 6H, 9′- and 10′-H_3), 1.24–1.41 (m; 2H, aliph. H), 1.27 and 1.32 (2dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, OCH_2CH_3), 1.50–1.98 (m; 4H, aliph. H), 2.16–2.34 (m; 1H, 4′-H), 3.08 and 3.30 (ABM system; J_{AB} = 17 Hz, J_{AM} = 11 Hz, J_{BM} = 4 Hz; 2H, 3-H_2), 3.53 (s; 3H, OCH_3), 3.81–3.98 (m; 2H, 1-H and 2-H), 3.99–4.25 (m; 4H, OCH_2), 7.13–7.34 (m; 5H, C_6H_5). b) (1*S*,2*R*)-**4a**: δ = 0.85 and 0.95 (2s; 6H, 9′- and 10′-H_3), 3.55 (s; 3H, OCH_3). – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*S*)-**4a**: δ = 11.46 (C-10′), 16.42 and 16.52 (2d, J = 5 Hz; OCH_2CH_3), 18.92 and 19.34 (C-8′ and C-9′), 27.10 (C-5′), 31.98 (d, J = 3 Hz; C-6′), 34.43 (d, J = 4 Hz; C-3), 35.74 (d, J = 2 Hz; C-3′), 42.53 (d, J = 2.5 Hz; C-2), 43.48 (C-4′), 47.39 (d, J = 2 Hz; C-7′), 51.31 (OCH_3), 54.60 (d, J = 7 Hz; C-1′), 62.40 and 62.84 (2 d, J = 7 Hz; OCH_2), 65.14 (d, J = 154 Hz; C-1), 126.64, 127.93 and 128.10 (arom. C), 142.02 (d, J = 14.5 Hz; C-1″), 172.92 (C=O), 187.63 (d, J = 15 Hz; C=N). b) (1*S*,2*R*)-**4a**: δ = 11.15 (C-10′), 19.45 (C-9′), 43.64 (C-4′), 47.04 (d, J = 2 Hz; C-7′), 51.31 (OCH_3), 127.63 and 129.19 (arom. C), 141.22 (d, J = 14.5 Hz; C-1″), 172.12 (C=O), 186.15 (d, J = 14 Hz; C=N). Further ^1H- and ^{13}C-NMR signals of (1*S*,2*R*)-**4a** were covered by the signals of (1*S*,2*S*)-**4a**. – ^{31}P NMR ($CDCl_3$): δ = 23.50 [16.5%, (1*S*,2*R*)-**4a**], 23.60 [100%, (1*S*,2*S*)-**4a**]. – MS (70 eV): *m/z* (%) = 463 (14) [M^+], 326 (65) [M^+ – PO_3Et_2], 300 (100) [M^+ – $PhCH=CHCO_2CH_3$].

$C_{25}H_{38}NO_5P$ (463.6) Calcd. C 64.78 H 8.26
Found C 64.57 H 8.21

Diethyl (1S,1′R,2S,4′R)-3-Methoxycarbonyl-2-phenyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4a**] (*via* **2** *and* **3a**): From 0.54 g (3.3 mmol) of methyl *trans*-cinnamate (**3a**), 1.27 g (91%) of (1*S*,1′*R*,2*S*,4′*R*)-**4a** was obtained after bulb-to-bulb distillation. – B.p. 150°C/0.01 Torr. – ^1H NMR ($CDCl_3$): a) (1*S*,2*S*)-**4a**: See above. b) (1*R*,2*R*)-**4a**; δ = 0.43 (s; 3H, 8′-H_3), 0.87 and 0.99 (2 s; 6H, 9′- and 10′-H_3), 1.23–1.40 (m; 2H, aliph. H), 1.26 and 1.31 (2 dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, OCH_2CH_3), 1.52–1.92 (m; 4H, aliph. H), 2.16–2.34 (m; 1H, 4′-H), 3.05 and 3.28 (ABM system, J_{AB} = 17 Hz; J_{AM} = 11 Hz, J_{BM} = 4 Hz: 2H, 3-H_2), 3.51 (s; 3H, OCH_3), 3.80–3.96 (m; 2H, 1-H and 2-H), 3.97–4.19 (m; 4H, OCH_2), 7.12–7.26 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*S*)-**4a**: See above. b) (1*R*,2*R*)-**4a**: δ = 11.35 (C-10′), 18.81 (C-8′), 35.27 (d, J = 4 Hz; C-3), 43.72 (C-4′), 46.77 (d, J = 2 Hz; C-7′), 54.77 (d, J = 7 Hz; C-1′), 62.16 and 62.60 (2 d, J = 7 Hz; OCH_2), 187.13 (d, J = 15 Hz; C=N). Further signals of (1*R*,2*R*)-**4a** were covered by the signals of (1*S*,2*S*)-**4a**. – ^{31}P NMR ($CDCl_3$): δ = 23.41 [14.5%, (1*R*,2*R*)-**4a**], 23.60 [100%, (1*S*,2*S*)-**4a**]. – For further experimental data see above.

Diethyl (1S,1′R,2R,4′R)-3-Methoxycarbonyl-2-methyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*R*,4′*R*)-**4b**]: From 0.33 g (3.3 mmol) of methyl *trans*-crotonate (**3b**), 1.02 g (85%) of (1*S*,1′*R*,2*R*,4′*R*)-**4b** was obtained after bulb-to-bulb distillation. – B.p. 140°C/0.01 Torr. – IR (neat): $\tilde{\nu}$ = 1735 (C=O), 1670 (C=N), 1245 (P=O), 1050 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): a) (1*R*,2*S*) **4b**: δ = 0.88 (s; 3H, 8′-H_3), 0.94 and 0.97 (2 s; 6H, 9′- and 10′-H_3), 1.04 (d, J = 6.5 Hz; 3H, CH_3), 1.33 (t, J = 7 Hz; 6H, OCH_2CH_3), 1.15–2.10 (m; 7H, aliph. H), 3.66 (s; 3H, OCH_3), 3.64 (dd, J_{PH} = 13 Hz, J_2 = 8 Hz; 1H, 1-H), 3.96–4.30 (m; 4H, OCH_2). b) (1*S*,2*R*)-**4b**: δ = 0.77 (s; 3H, 8′-H_3). – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*R*)-**4b**: δ = 11.32 (C-10′), 16.45 and 16.56 (OCH_2CH_3), 18.15 (d, J = 11 Hz; CH_3), 19.05 and 19.53 (C-8′ and C-9′), 27.49 (C-5′), 32.00 (d, J = 3 Hz; C-2), 32.64 (d, J = 3 Hz; C-6′), 36.22 (d, J = 2 Hz; C-3′), 37.06 (d, J = 7 Hz; C-3), 43.89 (C-4′), 47.39 (d, J = 1 Hz; C-7′), 51.30 (OCH_3), 54.63 (d, J = 2 Hz; C-1′), 62.20 and 62.56 (2 d, J = 6.5 Hz; OCH_2), 64.64 (d, J = 153 Hz; C-1), 173.71 (C=O), 186.64 (d, J = 14 Hz; C=N). b) (1*R*,2S)-**4b**: δ = 11.40 (C-10′), 18.46 and 18.84 (C-8′ and C-9′), 27.34 (C-5′), 31.76 (d, J = 2 Hz; C-2), 35.61 (d, J = 1.5 Hz; C-3′), 186.06 (d, J = 13.5 Hz; C=N). Further ^1H- and ^{13}C-NMR signals of (1*R*,2*S*)-**4b** were covered by the signals of (1*S*,2*R*)-**4b**. – ^{31}P NMR ($CDCl_3$): δ = 24.40 [12.5%, (1*R*,2*S*)-**4b**, 24.58 [3%, (1*S*,2*S*)-**4b**], 24.69 [100%, (1*S*,2*R*)-**4b**], 24.75 [5%, (1*R*,2*R*)-**4b**]. – MS (70 eV): *m/z* (%) = 401 (12) [M^+], 328 (26) [M^+ – $CH_2CO_2CH_3$], 264 (100) [M^+ – PO_3Et_2].

$C_{20}H_{36}NO_5P$ (401.5) Calcd. C 59.83 H 9.04
Found C 59.69 H 9.07

Diethyl (1S,1′R,2S,4′R)-2-(4-Bromophenyl)-3-methoxycarbonyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4c**]: From 0.80 g (3.3 mmol) of the methyl acrylate **3c**, 1.54 g (86%) of (1*S*,1′*R*,2*S*,4′*R*)-**4c** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether) = 0.24. – IR (neat): $\tilde{\nu}$ = 1730 (C=O), 1660 (C=N), 1240 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): a) (1*S*,2*S*)-**4c**: δ = 0.79 (s; 3H, 8′-H_3), 0.89 and 0.98 (2 s; 6H, 9′- and 10′-H_3), 1.00–1.95 (m; 6H, aliph. H), 1.28 and 1.32 (2 dt, J_1 = 7.5 Hz, J_{PH} = 1 Hz; 6H, OCH_2CH_3), 2.23–2.41 (m; 1H, 4′-H), 3.04 and 3.30 (ABM system, J_{AB} = 18 Hz, J_{AM} = 6 Hz, J_{BM} = 16 Hz; 2H, 3-H_2), 3.56 (s; 3H, OCH_3), 3.56–4.28 (m; 6H, OCH_2, 1-H and 2-H), 7.28 (AA′BB′ system, J_{AB} = 9 Hz; 4H, C_6H_4). b) (1*R*,2*R*)-**4c**: δ = 0.45 (s; 3H, 8′H_3), 1.00 (s; 3H, 9′-H_3) 3.55 (s; 3H, OCH_3). Further signals of (1*R*,2*R*)-**4c** were covered by the signals of (1*S*,2*S*)-**4c**. – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*S*)-**4c**: δ = 11.43 (C-10′), 16.38 and 16.49 (2

d, J = 5.5 Hz; OCH_2CH_3) 18.92 and 19.36 (C-8′ and C-9′), 32.14 (d, J = 3 Hz; C-6′), 34.55 (d, J = 4 Hz; C-3), 36.00 (d, J = 2 Hz; C-3′), 42.17 (d, J = 2.5 Hz; C-2), 43.52 (C-4′), 47.46 (C-7′), 51.49 (OCH_3), 54.77 (d, J = 2 Hz; C-1′), 62.47 (d, J = 7.5 Hz; OCH_2), 63.10 (d, J = 6.5 Hz, OCH_2), 64.77 (d, J = 156 Hz; C-1), 120.55 (C-4″), 129.80 and 131.17 (arom. C), 141.03 (d, J = 14.5 Hz; C-1″), 172.75 (C=O), 180.28 (d, J = 15 Hz; C=N). b) (1*R*,2*R*)-**4c**: δ = 11.52 (C-10′), 18.80 and 18.92 (C-8′ and C-9′) 31.83 (d, J = 4.5 Hz; C-6), 35.22 (d, J = 5.5 Hz; C-3), 35.62 (C-3′), 43.73 (C-4′), 46.70 (C-7′), 54.89 (d, J = 2 Hz; C-1′), 62.19 (OCH_2), 62.71 (d, J = 5.5 Hz; OCH_2), 130.64 (arom. C), 141.13 (d, J = 13.5 Hz; C-1″), 172.90 (C=O), 187.72 (d, J = 13 Hz; C=N). c) (1*S*,2*R*)-**4c**: 18.71 (C-8′), 31.99 (C-6′). Further signals of (1*R*,2*R*)-**4c** and (1*S*,2*R*)-**4c** were covered by the signals of (1*S*,2*S*)-**4c**. – ^{31}P NMR ($CDCl_3$): δ = 22.91 [3%, (1*S*,2*R*)-**4c**], 22.99 [12%, (1*R*,2*R*)-**4c**], 23.18 [100%, (1*S*,2*S*)-**4c**]. – MS (70 eV): *m/z* (%) · 543 and 541 (0.02 and 0.02) [M^+].

$C_{25}H_{37}BrNO_5P$ Calcd. 541.1593
Found 541.1593 [HRMS (70eV)]

Diethyl (1S,1′R,2S,4′R)-3,3-Bis(methoxycarbonyl)-2-phenyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4d**]: From 0.73 g (3.3 mmol) of dimethyl benzylidene malonate (**3d**), 1.25 g (80%) of diastereomerically pure (1*S*,1′*R*,2*S*,4′*R*)-**4d** was obtained after flash chromatography on silica gel (100 g). – R_f (ethyl acetate/petroleum ether, 1:1) = 0.40. – IR (neat): $\tilde{\nu}$ = 1755 (C=O), 1730 (C=O), 1675 (C=N), 1245 (P=O), 1050 cm^{-1} (P–O). – ^{1}H NMR: ($Cl_2DC-CDCl_2$, 120°C): δ = 0.83 (s; 3H, 8′-H_3), 0.90 and 0.92 (2 s; 6H, 9′- and 10′-H_3), 0.96 and 1.15 (2 dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, OCH_2CH_3), 1.10–1.46 (m; 2H, aliph. H), 1.56–2.04 (m; 4H, aliph. H), 2.46–2.65 (m; 1H, 4-H), 3.45 and 3.64 (2 s; 6H, OCH_3), 3.59–4.46 (m; 7H, 1-H, 2-H, 3-H, and OCH_2), 7.30 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 11.33 (C-10′), 15.85 and 16.41 (2 d, J = 6 Hz; OCH_2CH_3), 19.12 and 19.48 (C-8′ and C-9′), 27.36 (C-5′), 31.57 (d, J = 3.5 Hz; C-6′), 36.59 (d, J = 2 Hz; C-3′), 43.91 (C-4′), 46.67 (C-2), 47.95 (C-7′), 51.92 and 52.14 (OCH_3), 54.75 (C-1′), 54.89 (d, J = 8.5 Hz; C-3), 61.33 and 63.12 (2d, J = 7 Hz; OCH_2), 63.25 (d, J = 152 Hz; C-1), 126.96, 127.68 and 129.45 (arom. C), 139.13 (d, J = 3 Hz; C-1″), 168.35 and 168.53 (C=O), 188.52 (d, J = 12 Hz; C=N). – ^{31}P NMR ($CDCl_3$): δ = 23.22 [4%, (1*R*,2*R*)-**4d**], 23.53 [100%, (1*S*,2*S*)-**4d**], 23.65 [4%, (1*S*,2*R*)-**4d**]. – MS (70 eV): *m/z* (%) = 521 (7) [M^+], 390 (25) [M^+ – OCH_3], 384 (42) [M^+ – PO_3Et_2], 300 [M^+ – $PhCH=C(CO_2CH_3]$, 163 (100) [M^+ – PO_3Et_2 – $PhCH=C(CO_2CH_3)_2$].

$C_{27}H_{40}NO_7P$ (521.6) Calcd. C 62.17 H 7.73
Found C 62.34 H 7.61

Diethyl (1S,1′R,2S,4′R)-3-Methoxycarbonyl-2-(4-pyridyl)-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4e**]: From 0.54 g (3.3 mmol) of the methyl acrylate **3e**, 1.09 g (78%) of (1*S*,1′*R*,2*S*,4′*R*)-**4e** was obtained after flash chromatography on silica gel (80 g). – R_f (ethyl acetate/methanol, 10:1) = 0.25. – IR (neat): $\tilde{\nu}$ = 1740 (C=O), 1680 (C=N), 1600 (C=C), 1250 cm^{-1} (P=O), 1050 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): a) (1*S*,2*S*)-**4e**: δ = 0.80 (s; 3H, 8′-H_3), 0.89 and 0.99 (2 s; 6H, 9′- and 10′-H_3), 1.26 and 1.43 (2 t, J = 7 Hz; 6H, OCH_2CH_3), 0.90–2.13 (m; 6H, aliph. H), 2.20–2.50 (m; 1H, 4′-H), 2.90–3.45 (m; 2H, 3-H_2), 3.56 (s; 3H, OCH_3), 3.70–4.10 (m; 2H, 1-H and 2-H), 3.86–4.30 (m; 4H, OCH_2), 7.16 and 8.50 (AA′BB′ system, J_{AB} = 6 Hz; 4H, C_5H_4). b) (1*R*,2*R*)-**4e**: δ = 0.43 (s; 3H, 8′-H_3), 1.00 (s; 3H, 9′-H_3). Further signals of (1*R*,2*R*)-**4e** were covered by the signals of (1*S*,2*S*)-**4e**. – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*S*)-**4e**: δ = 11.41 (C-10′), 16.38 and 16.51 (2 d, J = 6 Hz; OCH_2CH_3), 18.93 and 19.36 (C-8′ and C-9′), 27.19 (C-5′), 32.22 (d, J = 3 Hz; C-6′), 34.05 (d, J = 4 Hz; C-3), 36.13 (d, J = 2 Hz; C-3′), 42.26 (d, J = 2 Hz; C-2), 43.53 (C-4′), 47.49 (C-7′), 51.53 (OCH_3), 54.83 (d, J = 2 Hz; C-1′), 62.32 and 63.14 (2 d, J = 7 Hz; OCH_2), 64.13 (d, J = 156 Hz; C-1), 123.39 and 149.60 (arom. C), 151.21 (d, J = 14 Hz; C-1″), 172.43 (C=O), 188.55 (d, J = 14 Hz; C=N). b) (1*R*,2*R*)-**4e**: δ = 11.36 (C-10′), 18.76 and 19.26 (C-8′ and C-9′), 31.32 (d, J = 5 Hz; C-6′), 34.45 (d, J = 5 Hz; C-3), 35.61 (d, J = 2 Hz; C-3′), 43.70 (C-4′), 46.64 (C-7′), 54.93 (d, J = 2 Hz; C-1′), 62.22 and 62.89 (2 d, J = 7 Hz; OCH_2), 64.24 (d, J = 153 Hz; C-1), 151.36 (d, J = 14 Hz; C-1″), 172.50 (C=O), 187.92 (d, J = 12 Hz; C=N). Further signals of (1*R*,2*S*)-**4e** were covered by the signals of (1*S*,2*S*)-**4e**. – ^{31}P NMR ($CDCl_3$): δ = 22.38 [3%, (1*S*,2*R*)-**4e**], 22.47 [23%, (1*R*,2*R*)-**4e**], 22.65 [100%, (1*S*,2*S*)-**4e**]. – MS (70 eV): *m/z* (%) = 464 (14) [M^+], 391 (11) [M^+ – $CH_2CO_2CH_3$], 327 (100) [M^+ – PO_3Et_2], 300 (50) [M^+ – $C_5H_5NCH=CHCO_2CH_3$].

$C_{24}H_{37}N_2O_5P$ (464.5) Calcd. C 62.05 H 8.03
Found C 62.16 H 8.05

Diethyl (1S,1′R,2S,4′R)-3,3-Bis(methoxycarbonyl)-2-methyl-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4f**]: From 0.52 g (3.3 mmol) of dimethyl ethylidene malonate (**3f**), 1.27 g (92%) of (1*S*,1′*R*,2*S*,4′*R*)-**4f** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether/petroleum ether, 3:1) = 0.15. – IR (neat): $\tilde{\nu}$ = 1750 (C=O), 1735 (C=O), 1675 (C=N), 1250 (P=O), 1050 cm^{-1} (P–O). – ^{1}H NMR: ($CDCl_3$): a) (1*S*,2*S*)-**4f**: δ = 0.86 (s; 3H, 8′-H_3), 0.91 and 0.93 (2 s; 6H, 9′- and 10′-H_3), 1.10–1.42 (m; 2H, aliph. H), 1.25 (d, J = 7 Hz; 3H, CH_3), 1.31 and 1.32 (2 t, J = 7 Hz; 6H, OCH_2CH_3), 1.56–2.10 (m; 4H, aliph. H), 2.41–2.58 (m; 1H, 4′-H), 2.76–3.04 (m; 1H, 2-H), 3.56–3.95 (m; 2H, 1-H and 3-H), 3.65 and 3.67 (2 s; 6H, OCH_3), 4.01–4.25 (m; 4H, OCH_2). b) (1*R*,2*S*)-**4f**: δ = 0.73 (s; 3H, 8′-H_3). – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*R*)-**4f**: δ = .11.30 (C-10′), 14.54 (d, J = 3 Hz; CH_3), 16.45 (d, J = 6 Hz; 2 OCH_2CH_3), 19.09 and 19.52 (C-8′ and C-9′), 27.36 (C-5′), 32.09 (d, J = 3.5 Hz; C-6′), 35.68 (C-2), 36.18 (d, J = 2 Hz; C-3′), 43.90 (C-4′), 47.62 (C-7′), 51.93 and 52.28 (OCH_3), 52.53 (C-3), 54.67 (d, J = 2 Hz; C-1′), 63.21 (d, J = 152 Hz; C-1), 62.28 and 62.68 (2 d, J = 7 Hz; OCH_2), 168.85 and 169.75 (C=O), 187.54 (d, J = 13 Hz; C=N). b) (1*R*,2*S*)-**4f**: δ = 11.38 (C-10′), 14.39 (d, J = 4 Hz; CH_3), 18.87 and 19.33 (C-8′ and C-9′), 27.24 (C-5′), 31.62 (d, J = 5 Hz; C-6′), 35.53 (C-2), 44.00 (C-4′), 46.60 (C-7′), 51.76 (OCH_3), 63.10 (d, J = 150 Hz; C-1), 62.36 (d, J = 6 Hz; OCH_2), 187.15 (d, J = 11.5 Hz; C=N). Further signals of (1*R*,2*S*)-**4f** were covered by the signals of (1*S*,2*R*)-**4f**. Signals of (1*S*,2*S*)-**4f** were not detectable. – ^{31}P NMR ($CDCl_3$): δ = 23.83 [3%, (1*R*,2*R*)-**4f**], 23.93 [6%, (1*S*,2*S*)-**4f**], 24.43 [16%, (1*R*,2*S*)-**4f**], 24.88 [100%, (1*S*,2*R*)-**4f**]. – MS (70 eV): *m/z* (%) = 459 (4) [M^+], 328 (46) [M^+ – $CH(CO_2CH_3)_2$], 322 (100) [M^+ – PO_3Et_2].

$C_{22}H_{36}NO_7P$ (459.5) Calcd. C 57.50 H 8.33
Found C 57.38 H 8.39

Diethyl (1S,1′R,2S,4′R)-2,3-Bis(methoxycarbonyl)-1-(1′,7′,7′-trimethylbicyclo[2.2.1]hept-2′-ylideneamino)propylphosphonate [(1*S*,1′*R*,2*S*,4′*R*)-**4g**]: From 0.48 g (3.3 mmol) of dimethyl maleate (**6g**), 1.18 g (88%) of (1*S*,1′*R*,2*S*,4′*R*)-**4g** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether) = 0.25. – IR (neat): $\tilde{\nu}$ = 1735 (C=O), 1670 (C=N), 1245 (P=O), 1045 cm^{-1} (P–O). – ^{1}H NMR: ($CDCl_3$); a) (1*S*,2*S*)-**4g**: δ = 0.85 (s; 3H, 8′-H_3), 0.91 (s; 6H, 9′- and 10′-H_3), 1.10–1.40 (m; 2H, aliph. H), 1.31 (t, J = 7 Hz; 6H, OCH_2CH_3), 1.58–2.00 (m; 4H, aliph. H), 2.47–2.65 (m; 1H, 4′-H), 2.78–3.62 (m; 3H, 2-H and 3-H_2), 3.66 and 3.69 (2 s; 6H, OCH_3), 4.00–4.25 (m; 5H, 1-H and OCH_2). Signals of (1*S*,2*R*)-**4g** were covered by the signals of (1*S*,2*S*)-**4g**. – ^{13}C NMR ($CDCl_3$): a) (1*S*,2*S*)-**4g**: δ = 11.19 (C-10′), 16.35 and 16.51

(2d, J = 2.5 Hz; OCH_2CH_3), 19.06 and 19.51 (C-8′ and C-9′), 27.31 (C-5′), 32.29 (d, J = 3 Hz; C-3), 32.94 (d, J = 2 Hz; C-6′), 36.21 (d, J = 2 Hz; C-3′), 43.89 (C-4′), 44.00 (d, J = 3 Hz; C-2), 47.59 (d, J = 5 Hz; C-7′), 51.73 (2 OCH_3), 54.79 (d, J = 2 Hz; C-1′), 61.07 (d, J = 153 Hz; C-1), 62.56 and 63.21 (2 d, J = 5 Hz; OCH_2), 172.66 (d, J = 5 Hz; C=O), 172.93 (d, J = 3 Hz; C=O), 187.99 (d, J = 13.5 Hz; C=N). b) (1*S*,2*R*)-**4g**: δ = 27.47 (C-5′), 31.88 (d, J = 5 Hz; C-3), 32.45 (d, J = 3 Hz; C-6′), 42.68 (d, J = 2 Hz; C-2), 47.45 (C-7′), 51.65 and 51.91 (2 OCH_3), 54.65 (d, J = 2 Hz; C-1′), 60.42 (d, J = 157 Hz; C-1), 62.34 and 63.44 (2 d, J = 5 Hz; OCH_2), 188.60 (d, J = 10 Hz; C=N). Further signals of (1*S*,2*S*)-**4g** were covered by the signals of (1*S*,2*S*)-**4g**. – ^{31}P NMR ($CDCl_3$): δ = 22.48 [49%, (1*S*,2*R*)-**4g**], 22.73 [100%, (1*S*,2*S*)-**4g**]. – MS (70 eV): m/z (%) = 445 (29) [M^+], 386 (24) [$M^+ - CO_2CH_3$], 372 (31) [$M^+ - CH_2CO_2CH_3$], 308 (100) [$M^+ - PO_3Et_2$], 276 (39) [$M^+ - PO_3Et_2 - OCH_3 - H$], 248 (27) [$M^+ - PO_3Et_2 - H$].

$C_{21}H_{36}NO_7P$ (445.5) Calcd. C 56.62 H 8.14
Found C 56.42 H 8.10

Hydrolysis of the 1,4-Adducts **4**. – *Diethyl 5-Oxo-2-pyrrolidinylphosphonates* **5**. – *General Procedure:* The adducts **4** (ca. 2.5 mmol) were dissolved in 90% aqueous acetic acid (25 ml), and the solution was stirred for 6 d at 60°C. The acetic acid was removed at 40°C under reduced pressure, and ethyl acetate (30 ml) and saturated aqueous Na_2CO_3 solution (20 ml) were added. The layers were separated, and the aqueous layer was reextracted with ethyl acetate (3 portions of 20 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo and the residue purified by flash chromatography on silica gel.

Diethyl (2S,3S)- and (2S,3R)-5-Oxo-3-phenyl-2-pyrrolidinylphosphonate [(2*S*,3*S*)- and (2*S*,3*R*)-**5a**]: From 1.52 g (3.28 mmol) of **4a** (obtained from **2** and **6a**), 630 mg (65%) of (2*S*,3*S*)-**5a** and 95 mg (10%) of (2*S*,3*R*)-**5a** were obtained after flash chromatography on silica gel (80 g, diethyl ether/methanol, 10:1).

(2*S*,3*S*)-**5a**: R_f = 0.35. – $[\alpha]_D^{20}$ = +3.5 (c = 0.9, $CHCl_3$). – M.p. 127°C. – IR (KBr): $\tilde{\nu}$ = 3240 (N–H), 1710 (C=O), 1225 (P=O), 1040 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.27 and 1.31 (2 t, J = 7 Hz; 6H, CH_3), 2.50 and 2.95 (ABX system, J_{AB} = 17 Hz, J_{AX} = 9.5 Hz, J_{BX} = 5 Hz; 2H, 4-H_2), 3.75–3.96 (m; 2H, 2-H and 3-H), 4.03–4.27 (m; 4H, OCH_2), 6.69 (broad; 1H, NH), 7.27–7.44 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 15.91 and 16.18 (2 d, J = 1.5 Hz; CH_3), 37.87 (d, J = 3 Hz; C-4), 40.28 (d, J = 2 Hz; C-3), 57.72 (d, J = 161 Hz; C-1), 62.39 and 62.73 (2 d, J = 6 Hz; OCH_2), 126.24, 126.94, and 128.58 (arom. C), 142.75 (d, J = 8.5 Hz; C-1′), 177.05 (d, J = 5 Hz; C=O). – ^{31}P NMR: ($CDCl_3$): δ = 22.84.

$C_{14}H_{20}NO_4P$ (297.3) Calcd. C 56.56 H 6.78
Found C 56.37 H 6.78

(2*S*,3*R*)-**5a**: R_f = 0.28, colorless oil. – $[\alpha]_D^{20}$ = –110.0 (c = 1.2, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3240 (N–H), 1710 (C=O), 1225 (P=O), 1040 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.04 und 1.15 (2 t, J = 7.5 Hz; 6H, CH_3), 2.51 (ddd, $^2J_1$ = 16.5 Hz, J_2 = 8 Hz, J_{PH} = 1.5 Hz; 1H, 4-H), 3.19 (ddd, J_1 = 16.5 Hz, J_2 = 12 Hz, J_{PH} = 2 Hz; 1H, 4-H), 3.37–3.58 (m; 1H, 3-H), 3.62–3.88 (m; 4H, OCH_2), 4.00–4.22 (m; 1H, 2-H), 6.80 (broad; 1H, NH), 7.22–7.43 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$); δ = 16.24 (d, J = 4 Hz; CH_3), 16.33 (d, J = 6 Hz; CH_3), 33.85 (C-4), 42.99 (C-3), 55.79 (d, J = 161 Hz; C-2), 127.64, 128.26, and 128.71 (arom. C). 136.05 (d, J = 4 Hz; C-1′), 177.34 (C=O). – ^{31}P NMR: ($CDCl_3$): δ = 21.70.

$C_{14}H_{20}NO_4P$ (297.3) Calcd. C 56.56 H 6.78
Found C 56.42 H 6.83

Diethyl (2S,3SS)-5-Oxo-3-phenyl-2-pyrrolidinylphosphonate [(2*S*,3*S*)-**5a**]: From 1.00 g (2.2 mmol) of diastereomerically pure **4a** (obtained from **2** and **3a**), 0.48 g (74%) of (2*S*,3*S*)-**5a** was obtained after column filtration on silica gel (60 g) and recrystallization from ethyl acetate. – R_f (ethyl acetate/methanol, 5:1) = 0.40. – $[\alpha]_D^{20}$ = +3.0 (c = 0.9, $CHCl_3$). – M.p. 127°C. – For spectroscopical data, see above.

Diethyl (2S,3R)-5-Oxo-3-methyl-2-pyrrolidinylphosphonate [(2*S*,3*R*)-**5b**]: From 1.50 g (3.7 mmol) of diastereomerically pure (1*S*,1′*R*,2*R*,4′*R*)-**4b**, 0.71 g (81%) of (2*S*,3*R*)-**5b** was obtained after flash chromatography on silica gel (80 g). – R_f (ethyl acetate/methanol, 10:1) = 0.25. – $[\alpha]_D^{20}$ = +1.5 (c = 1.1, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3200 (N–H), 1700 (C=O), 1225 (P=O), 1020 cm^{-1} (P–O) – ^{1}H NMR ($CDCl_3$): δ = 1.26 (dd, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 3H, CH_3), 1.44 and 1.45 (2 dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, OCH_2CH_3), 1.99 (dd, $^2J_1$ = 17 Hz, J_2 = 5.5 Hz; 1H, 4-H), 2.56– 2.98 (m; 2H, 3-H and 4-H), 3.41 (d, J = 4.5 Hz; 1H, 2-H), 4.18 (dq, J_1 = J_{PH} = 7 Hz; 4H, OCH_2), 6.44 (broad; 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 16.38 and 16.65 (OCH_2CH_3), 20.93 (d, J = 9 Hz; CH_3), 30.34 (d, J = 2.5 Hz; C-3), 38.23 (d, J = 3.5 Hz; C-4), 57.56 (d, J = 162 Hz; C-2), 62.72 and 62.88 (2 d, J = 7 Hz; OCH_2), 177.89 (d, J = 5.5 Hz; C=O). – ^{31}P NMR ($CDCl_3$): δ = 23.48. – MS (70 eV): m/z (%) = 235 (12) [M^+], 98 (100) [$M^+ - PO_3Et_2$].

$C_9H_{18}NO_4P$ (235.2) Calcd. C 45.96 H 7.71
Found C 45.84 H 7.67

Diethyl 3-(4-Bromophenyl)-2-oxo-2-pyrrolidinylphosphonate [(2*S*,3*S*)-**5c**]: From 1.19 g (2.2 mmol) (1*S*,1′*R*,2*S*,4′*R*)-**4c**, 0.60 g (72%) of diastereomerically pure (2*S*,3*S*′)-**5c** was obtained after column filtration on silica gel (40 g) and recrystallization from ethyl acetate. – R_f (ethyl acetate/methanol, 20:1) = 0.20. – $[\alpha]_D^{20}$ = –5.9 (c = 1.9, $CHCl_3$). – M.p. 143°C. – IR (neat): $\tilde{\nu}$ = 3200 (N–H), 1710 (C=O), 1230 (P=O), 1010 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.29 and 1.32 (2 t, J = 7 Hz; 6H, CH_3), 2.45 and 2.95 (ABX system, J_{AB} = 17.5 Hz, J_{AX} = 9.5 Hz, J_{BX} = 5.5 Hz, J_{AP} = 1 Hz; 2H, 4-CH_2), 3.73–3.92 (m; 2H, 3-H and 2-H), 4.07–4.27 (m; 4H, OCH_2), 6.60 (broad; 1H, NH), 7.37 (AA′BB′ system, J_{AB} = 9 Hz, 4H, C_6H_4). – ^{13}C NMR ($CDCl_3$): δ = 16.45 (d, J = 5.5 Hz; CH_3), 37.95 (d, J = 3 Hz; C-4), 40.21 (d, J = 2 Hz; C-3), 57.81 (d, J = 161 Hz; C-2), 62.89 and 63.26 (2 d, J = 7 Hz; OCH_2), 121.28 (C-4′), 128.41 and 131.11 (arom. C), 141.86 (d, J = 8.5 Hz; C-1′), 176.80 (d, J = 4.5 Hz; C=O). – ^{31}P NMR ($CDCl_3$): δ = 22.36. – MS (70 eV): m/z (%) = 377 and 375 (2 and 2) [M^+], 240 and 238 (85 and 88) [$M^+ - PO_3Et_2$], 239 and 237 (90 and 90) [$M^+ - PO_3Et_2 - H$].

$C_{14}H_{19}BrNO_4P$ (376.2) Calcd. C 44.70 H 5.09
Found C 44.73 H 5.10

Diethyl (2S,3S,4S)-4-Methoxycarbonyl-5-oxo-3-phenyl-2-pyrrolidinylphosphonate [(2S,3S,4S)-5d]: From 1.66 g (3.18 mmol) of (1*S*,1′*R*,2*S*,4′*R*)-**4d**, 0.46 g (41%) of enantio- and diastereomerically pure (2*S*,3*S*,4*S*)-**5d** was obtained after column filtration on silica gel (60 g) and recrystallization from diethyl ether/chloroform (1:1). – R_f (ethyl acetate/methanol, 50:1) = 0.25. – $[\alpha]_D^{20}$ = +27.9 (c = 2.25, $CHCl_3$). – M.p. 75°C. – IR (KBr): $\tilde{\nu}$ = 3180 (N–H), 1730 (C=O), 1700 (C=O), 1220 (P=O), 1040 cm^{-1} (P–O). – ^{1}H NMR ($CDCl_3$): δ = 1.12 and 1.28 (2 t, J = 7 Hz; 6H, CH_3), 3.66 (d, J = 10 Hz; 1H, 2-H), 3.77 (s; 3H, OCH_3), 3.93 (dd, J_1 = 9 Hz, J_{PH} = 2 Hz; 1H, 4-H), 3.95–4.19 (m; 4H, OCH_2), 4.30 (ddd, $^3J_{PH}$ = 18.5 Hz, J_2 = 10 Hz, J_3 = 9 Hz; 1H, 3-H), 6.40 (broad; 1H, NH), 7.27–7.38 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 16.06 (d, J = 6 Hz; CH_3), 16.36 (d, J = 5.5 Hz; CH_3), 45.38 (d, J = 3.5 Hz; C-3), 52.72 (OCH_3), 55.67 (d, J = 164 Hz; C-1), 56.38 (d, J = 7.5 Hz; C-4), 62.82 (d, J = 7 Hz; OCH_2), 63.50 (d, J = 6.5 Hz; OCH_2), 127.73, 127.81, and 128.91 (arom. C), 139.08 (d, J = 2 Hz; C-1′), 168.73 (C=O), 171.26 (d, J = 10.5 Hz; C=O). – ^{31}P NMR

($CDCl_3$): δ = 20.85. – MS (70 eV): *m/z* (%) = 355 (15) [M^+], 218 (64) [$M^+ - PO_3Et_2$], 217 (86) [$M^+ - PO_3Et_2 - H$], 186 (100) [$M^+ - PO_3Et_2 - OCH_3 - H$].

$C_{16}H_{22}NO_6P$ (355.3) Calcd. C 54.08 H 6.24
Found C 53.95 H 6.31

Diethyl (2S,3S)-3-(4-Bromophenyl)-1-(tert-butoxycarbonyl)-2-pyrrolidinylphosphonate: To a stirred suspension of sodium hydride (28 mg, 1.2 mmol) in THF (5 ml), a solution of (2*S*,3*S*)-**5c** (380 mg, 1.0 mmol) in THF (5 ml) was added at 0°C. After stirring for 15 min at 0°C, a solution of di-*tert*-butyl dicarbonate (262 mg, 1.44 mmol) in THF (5 ml) was added, and stirring was continued for 1 h at 0°C. Then aqueous 10% $NaHCO_3$ solution was added, and the solvent was removed in vacuo. The residue was dissolved in diethyl ether (40 ml) and water (30 ml), and the aqueous layer was reextracted with diethyl ether (2 portions of 30 ml each). The combined organic layers were dried with $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel (60 g) to yield 220 mg (46%) of the corresponding *N*-protected lactam as a colorless oil. – R_f (ethyl acetate/methanol, 20:1) = 0.57. – IR (neat): $\tilde{\nu}$ = 1780, 1750 and 1715 (C=O), 1250 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.35 and 1.35 (2 dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, CH_3), 2.53 (ddd, $^2J_1$ = 17.5 Hz, J_{PH} = 1 Hz, J_3 = 0.5 Hz; 1H, 4-H), 3.32 (dd, $^2J_1$ = 17.5 Hz, J_2 = 9 Hz; 1H, 4-H), 3.79 (dddd, J_{PH} = 13.5 Hz, J_2 = 9 Hz, J_3 = 1 Hz, J_4 = 0.5 Hz; 1H, 3-H), 4.17–4.24 (m; 4H, OCH_2), 4.41 (ddd, J_{PH} = 5.5 Hz, J_2 = 1 Hz, J_3 = 0.5 Hz; 1H, 2-H), 7.07 and 7.47 (AA'BB' system, J_{AB} = 8.5 Hz; 4H, C_6H_4). – ^{13}C NMR ($CDCl_3$): δ = 16.44 (d, *J* = 3.5 Hz; OCH_2CH_3), 16.55 (d, *J* = 3 Hz; OCH_2CH_3), 27.91 (tBu CH_3), 37.12 (C-3), 39.38 (C-4), 60.28 (d, *J* = 158 Hz; C-2), 63.01 (d, *J* = 4.5 Hz; OCH_2), 63.14 (d, *J* = 4 Hz; OCH_2), 84.02 ($OC(CH_3)_3$), 121.51 (C-4'), 127.76 and 132.37 (arom. C), 141.99 (d, *J* = 14 Hz; C-1'), 149.46 (C=O), 172.24 (C=O). – ^{31}P NMR ($CDCl_3$): δ = 21.98. – MS (70 eV): *m/z* (%) = 377 and 375 (11 and 11) [$M^+ - tBuCO_2 + H$], 240 and 238 (55 and 56) [$M^+ - tBuCO_2 - PO_3Et_2 + H$], 239 and 237 (53 and 51) [$M^+ - tBuCO_2 - PO_3Et_2$], 57 (100) [$(CH_3)_3C^+$].

$C_{19}H_{27}BrNO_6P$ (476.3) Calcd. C 47.91 H 5.71
Found C 48.08 H 5.62

Reduction of the Diethyl 5-Oxo-2-pyrrolidinylphosphonates **5a** *and* **b**. – *Diethyl 2-Pyrrolidinylphosphates* **7**. – *General Procedure:* $Et_2O \cdot BF_3$ (ca. 30 mmol, 10 eq.) was added dropwise to a stirred solution of lactam **5** (ca. 3 mmol) in THF (10 ml) at 0°C. This mixture was dropped through a Teflon tube to a stirred solution of $LiBH_4$ (ca. 4.5 mmol, 1.5 eq.) in THF (5 ml) at 0°C. The solution was kept at 0°C for 15 min, and stirring was continued for 36 h at 25°C. Then the solvent was removed in vacuo, the residue was cooled to 0°C, and 3-ml portions of methanol and ammonia were added. After stirring for 30 min at 25°C, diethyl ether (30 ml) was added, and the solution was decanted from the precipitate. The precipitate was washed three times with 20-ml portions of diethyl ether/methanol/ammonia (100:10:1), the solvents were removed in vacuo, and the crude product was first purified by column filtration on silica gel [60 g, diethyl ether/methanol/ammonia (100:10:1), $R_f \approx 0.4$) and then purified by column chromatography on silica gel.

Diethyl (2S,3S)-3-Phenyl-2-pyrrolidinylphosphonate [(2*S*,3*S*)-**7a**]: From 900 mg (3.02 mmol) of **5a** (obtained via **6a**), 4.28 g (30.2 mmol) of $Et_2O \cdot BF_3$ and 100 mg (4.60 mmol) of $LiBH_4$, 590 mg (69%) of (2*S*,3*S*)-**7a** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether/methanol, 10:1) = 0.16. – $[\alpha]_D^{20}$ = –15.0 (*c* = 0.89, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3300 (N–H), 1590 (C=C), 1240 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.18 and 1.24 (2 dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, CH_3), 1.84–2.05 (m; 1H, 4-H), 2.18 (broad; 1H, NH), 2.28–2.46 (m; 1H, 4-H), 3.21 and 3.25 (2 d, *J* = 6 Hz; 1H each, 5-CH_2) 3.40–3.65 (m; 2H, 2-H and 3-H) 3.95–4.19 (m; 4H, OCH_2), 7.19–7.42 (m; 5H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 16.29 and 16.41 (2 d, *J* = 1.5 Hz; CH_3), 36.82 (d, *J* = 9 Hz; C-4), 46.86 (C-3), 47.83 (d, *J* = 10 Hz; C-5) 62.06 and 62.20 (2 d, *J* = 2.5 Hz; OCH_2), 62.11 (d, *J* = 160 Hz; C-2, 126.53, 127.48 and 128.48 (arom. C), 143.40 (d, *J* = 4.5 Hz; arom. C-1'). – ^{31}P NMR ($CDCl_3$): δ = 27.92. – MS (70 eV): *m/z* (%) = 283 (3) [M^+], 146 (100) [$M^+ - PO_3Et_2$].

$C_{14}H_{22}NO_3P$ (283.1) Calcd. C 59.35 H 7.83
Found C 59.14 H 7.71

Diethyl (2S,3S)-3-Phenyl-2-pyrrolidinylphosphonate [(2*S*,3*S*)-**7a**]: From 890 mg (2.99 mmol) of **5a** (obtained via **3a**), 4.26 g (30.0 mmol) of $Et_2O \cdot BF_3$ and 98 mg (4.50 mmol) of $LiBH_4$, 605 mg (71%) of (2*S*,3*S*)-**7a** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether/methanol, 10:1) = 0.16. – $[\alpha]_D^{20}$ = –12.6 (*c* = 1.1, $CHCl_3$). – For spectroscopical data, see above.

Diethyl (2S,3R)-3-Methyl-2-pyrrolidinylphosphonate [(2*S*,3*R*)-**7b**]: From 710 mg (3.02 mmol) of (2*S*,3*R*)-**5b**, 4.34 g (30.6 mmol) of $Et_2O \cdot BF_3$ and 100 mg (4.60 mmol) of $LiBH_4$, 455 mg (68%) of (2*S*,3*R*)-**7b** was obtained after flash chromatography on silica gel (80 g). – R_f (diethyl ether/methanol, 10:1) = 0.15. – $[\alpha]_D^{20}$ = –3.6 (*c* = 1.1, $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3300 (N–H), 1220 (P=O), 1020 cm^{-1} (P–O). – ^1H NMR ($CDCl_3$): δ = 1.16 (d, *J* = 7 Hz; 3H, CH_3), 1.34 (t, *J* = 7 Hz; 6H, OCH_2CH_3), 1.42 (ddddd, J_1 = 12.5 Hz, J_2 = J_3 = 8 Hz, J_4 = 7.5 Hz, J_5 = 1 Hz; 1H, 4-H), 2.05 (ddddd, J_1 = 12.5 Hz, J_2 = 8 Hz, J_3 = 7.5 Hz, J_4 = 5.5 Hz, J_5 = 1 Hz; 1H, 4-H), 2.34 (broad; 1H, NH), 2.41 (ddddq, J_1 = 16.5 Hz, J_2 = J_3 = J_4 = 8 Hz, J_5 = 6.5 Hz; 1H, 3-H), 2.90 (dd, J_1 = 8 Hz, J_{PH} = 5.5 Hz; 1H, 2-H), 3.00 (dd, J_1 = 5.5 Hz, J_2 = 1 Hz; 1H, 5-H), 3.02 (dd, J_1 = 7.5 Hz, J_2 = 2.5 Hz; 1H, 5-H), 4.12–4.23 (m; 4H, OCH_2). – ^{13}C NMR ($CDCl_3$): δ = 16.51 and 16.63 (OCH_2CH_3), 19.68 (d, *J* = 5.5 Hz; CH_3), 35.50 (d, *J* = 9.5 Hz; C-4), 35.59 (C-3), 46.87 (d, *J* = 11 Hz; C-5), 61.36 (d, *J* = 161 Hz; C-2), 61.99 and 62.05 (2 d, *J* = 5 Hz; OCH_2). – ^{31}P NMR ($CDCl_3$): δ = 28.81. – MS (70 eV): *m/z* (%) = 221 (2) [M^+], 84 (100) [$M^+ - PO_3Et_2$].

$C_9H_{20}NO_3P$ (221.2) Calcd. C 48.86 H 9.11
Found C 48.83 H 8.98

Preparation of the Amides **8**. *General Procedure:* The pyrrolidines **7** (0.10 mmol) were treated with 30 µg (0.12 mmol) of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride under standard conditions. After usual workup, the product was examined by ^1H-NMR, ^{13}C-NMR and ^{19}F-NMR spectroscopy.

Diethyl (2S,2'R,3S)-1-[2'-Methoxy-2'-phenyl-2'-(trifluoromethyl)-acetyl]-3-phenyl-2-pyrrolidinylphosphonate [(2*S*,2'*R*,3*S*)-**8a**]: From 0.28 g (0.10 mmol) of **7a** (obtained via **6a**), 45 mg (90%) of (2*S*,2'*R*,3*S*)-**8a** was obtained; d.e. = 95%. – ^1H NMR: ($CDCl_3$): δ = 1.31 and 1.35 (2 t, *J* = 7 Hz; 6H, CH_3), 1.56 (dddd, $^2J_1$ = 13 Hz, J_2 = 12.5 Hz, J_3 = 6 Hz, J_4 = 1 Hz; 1H, 4-H), 2.39 (dddd, $^2J_1$ = 13 Hz, J_2 = 8 Hz, J_3 = J_4 = 6.5 Hz; 1H, 4-H), 3.26 (ddd, $^2J_1$ = 11.5 Hz, J_2 = 8 Hz, J_3 = 5.5 Hz; 1H, 5-H), 3.52 (dddd, $^2J_1$ = 11.5 Hz, J_2 = 8 Hz, J_3 = 6.5 Hz, J_4 = 1 Hz; 1H, 5-H), 3.60–3.80 (m; 1H, 3-H), 3.79 (q, J_{FH} = 2 Hz; 3H, OCH_3), 4.03–4.36 (m; 4H, OCH_2), 4.87 (dd, J_1 = 8.5 Hz, J_{PH} = 3.5 Hz; 1H, 2-H), 6.98–7.62 (m; 10H, C_6H_5). – ^{13}C NMR ($CDCl_3$): δ = 16.24 and 16.38 (2 d, *J* = 6.5 Hz; CH_3), 33.46 (C-4), 43.32 (C-3), 46.82 (C-5), 55.26 (q, J_{FC} = 2 Hz; OCH_3), 59.50 (d, *J* = 157 Hz; C-2), 62.48 (d, *J* = 7 Hz; OCH_2), 62.81 (d, *J* = 6 Hz; OCH_2), 84.51 (q, J_{FC} = 25.5 Hz; F_3CCOMe), 123.63 (q, J_{FC} = 290 Hz; CF_3), 126.67, 126.86, 126.99,

128.34, 128.73, and 129.57 (arom. C), 132.87 (C-1″), 142.97 (d, J = 10.5 Hz; C-1′), 164.67 (d, J = 2 Hz; C=O. – ^{19}F-NMR ($CDCl_3$): δ = −70.52 [(2*S*,3*S*)-**8a**, 100%], −71,58 [(2*R*,3*R*)-**8a**, 2.5%].

Diethyl (2SR,2′R,3SR)-1-[2′-Methoxy-2′-phenyl-2′-(trifluoromethyl)acetyl]-3-phenyl-2-pyrrolidinylphosphonate [(2*SR*,2′*R*,3*SR*)-**8a**]: From 0.28 g (0.10 mmol) of **7a** (obtained via **3a**), 43 mg (86%) of (2*SR*,2′*R*,3*SR*)-**8a** was obtained; d.e. = 84%. – ^{1}H NMR ($CDCl_3$): a) (2*S*,3*S*)-**8a**: See above. b) (2*R*,3*R*)-**8a**: δ = 3.67 (q, J_{FC} = 2 Hz; 3H, OCH_3). Further signals of (2*R*,3*R*)-**8a** were covered by the signals of (1*S*,2*S*)-**8a**. – ^{13}C NMR (125.7 MHz, $CDCl_3$): a) (2*S*,3*S*)-**8a**: See above. b) (2*R*,3*R*)-**8a**: δ = 46.25 (C-5), 59.68 (d, J = 156 Hz; C-2), 128.04, 128.79, 129.13 (arom. C). Further signals of (2*R*,3*R*)-**8a** were covered by the signals of (1*S*,2*S*)-**8a**. – ^{19}F NMR ($CDCl_3$): δ = −70.52 [(2*S*,3*S*)-**8a**, 100%], −71.58 [(2*R*,3*R*)-**8a**, 8%].

Diethyl (2SR,2′R,3SR)-1-[2′-Methoxy-2′-phenyl-2′-(trifluoromethyl)acetyl]-3-methyl-2-pyrrolidinylphosphonate [(2*SR*,2′*R*,3*SR*)-**8b**]: From 21 mg (0.10 mmol) of (2*S*,3*R*)-**5b**, 35 mg (83%) of (2*SR*,2′*R*,3*SR*)-**8b** was obtained; d.e. = 77%. – ^{1}H NMR ($CDCl_3$): a) (2*S*,3*R*)-**8b**: δ = 0.98 (dd, J_1 = 6 Hz, J_{PH} = 1 Hz; 3H, CH_3), 1.08 (ddd, J_{PH} = 14 Hz, J_2 = 7 Hz, J_3 = 1 Hz, 1H, 4-H), 1.32 and 1.36 (2 t, J = 7 Hz; 6H, OCH_2CH_3), 1.95–2.18 (m; 1H, 5-H), 2.46–2.75 (m; 1H, 5-H), 3.07 (dddd, $^2J_1$ = 11.5 Hz, J_2 = 8 Hz, J_3 = 5.5 Hz, J_4 = 1 Hz; 1H, 5-H), 3.32 (dddd, $^2J_1$ = 11.5 Hz, J_2 = 8 Hz, J_3 = 7 Hz, J_4 = 1.5 Hz; 1H, 5-H), 3.73 (q, J_{FH} = 2 Hz; 3H, OCH_3), 4.06–4.34 (m; 4H, OCH_2), 4.38 (dd, J_1 = 7.5 Hz, J_{PH} = 4 Hz; 1H, 2-H), 7.05–7.60 (m; 5H, C_6H_5). b) (2*R*,3*S*)-**8b**: δ = 3.67 (q, J_{FH} = 2 Hz; 3H, OCH_3). Further signals of (2*R*,3*S*)-**8b** were covered by the signals of (1*S*,2*R*)-**8b**. – ^{13}C NMR ($CDCl_3$) a) (2*S*,3*R*)-**8b**: δ = 16.27 and 16.42 (2d, J = 6.5 Hz; OCH_2CH_3), 20.52 (d, J = 11.5 Hz; CH_3), 32.71 (d, J = 2.5 Hz; C-4), 33.15 (C-3), 46.39 (C-5), 55.12 (OCH_3), 59.38 (d, J = 157 Hz; C-2), 62.13 (d, J = 7.5 Hz; OCH_2), 62.64 (d, J = 6.5 Hz; OCH_2), 84.59 (q, J_{FC} = 25 Hz; F_3CCOMe), 123.64 (q, J_{FC} = 290 Hz; CF_3), 126.71, 128.34 and 129.50 (arom. C), 133.26 (C-1′), 165.03 (C=O). b) (2*R*,3*S*)-**8b**: δ = 33.22 (C-3), 45.69 (C-5), 59.92 (d, J = 160 Hz; C-2), 127.30, 127.99 and 129.11 (arom. C). Further signals of (2*R*,3*S*)-**8b** were covered by the signals of (1*S*,2*R*)-**8b**. – ^{19}F NMR ($CDCl_3$): δ = −70.56 [(2*S*,3*R*)-**8b**, 100%], −71.77 [(2*R*,3*S*)-**8b**, 12.5%].

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[9] We use the *syn/anti* nomenclature for 1,2-disubstituted α-aminophosphonic acids where the carbon chain is understood to be extended by the diethoxyphosphoryl group. According to the conventional definition (see S. Masamune, Sk. A. Ali, D. L. Snitman, D. S. Garvey, *Angew. Chem.* **1980**, *92*, 573; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 557), the stereoisomer where the substituents at C-1 and C-2 are on different sides of the chain are called *anti*.

[10] Major stereoisomers of **4b** and **4f** are (1*S*,2*R*)-, minor stereoisomers (1*R*,2*S*)-configurated due to the change in the priority of the substituents by applying the CIP nomenclature.

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[13] No signals of minor stereoisomers were detected in the ^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR spectra.

[14] No epimerization is observed under the conditions of hydrolysis. Consequently, the diasteromerically pure adduct **4d** is converted into the enantiomerically pure lactam **5d**.

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[49/92]