Tetrahedron Vol. 48, No. 1, pp. 117-122, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00
Pergamon Press plc

Asymmetric Synthesis of Enantiomerically Pure Phosphonic Analogues of Glutamic Acid and Proline

Ulrich Groth, Lutz Richter, and Ulrich Schöllkopf*

Institut für Organische Chemie der Universität Göttingen, Tammannstr. 2,

D-3400 Göttingen, Federal Republic of Germany

(*Received in Germany* 10 *June* 1991)

Abstract - Michael addition of the metallated camphor derivatives **2** to vinylogous esters and subsequential hydrolysis afforded phosphonic analogues of glutamic acid. The enantiomerically pure lactam **6** was reduced by $LiBH_4/BF_3{\cdot}OEt_2$ to phosphoproline **7**.

I. Introduction

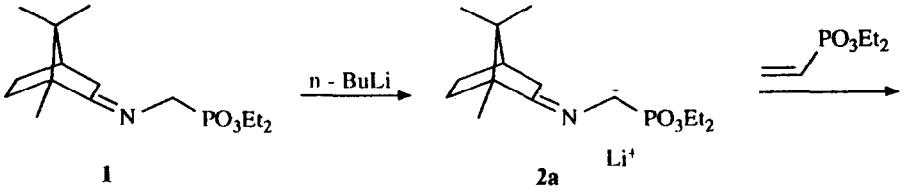
α-Aminophosphonic acids[1,2] as phosphonic analogues of naturally occurring α-amino acids are of great pharmacological interest.[3] They mimic tetrahedric intermediates of hydrolyzed esters, amides and peptides due to the tetrahedric structure of the phosphonic moiety. Thus they often act as inhibitors for esterases, peptidases and related enzymes. Many of these substances have been reported to show biological activity.[4]

Recently we described[1] the base-induced alkylation of the chiral (+)-camphor derivative **1**.[5] After hydrolysis of the corresponding alkylated products with citric acid, the diethyl esters of α-aminoalkanephosphonic acids were isolated in optical yields up to 95%.

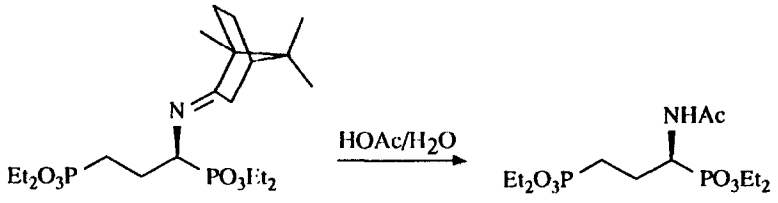
At this point we would like to report on the asymmetric synthesis of phosphonic derivatives of glutamic acid and proline esters which, to our knowledge, have not been prepared in enantiomerically pure form yet.

II. Results and Discussion

The lithium derivative **2a** reacts with diethylethenephosphonate[6] to yield the adduct **3** in 74% with 79% d.e.. Due to the significant upfield shift of the C-8' methyl group of the (*1R*)-diastereomer,[7] the (*1S*)-configuration was assigned to the major diastereomer.

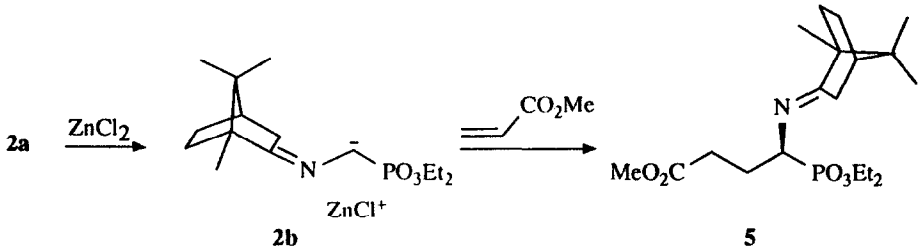


1 **2a**

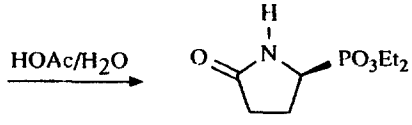


3 **4**

After hydrolysis with 90% aqueous acetic acid, the tetraethylester of the N-acetylated diphosphonic acid **4** was isolated in 73% yield. As will be shown below, no racemization occurs under the conditions of hydrolysis. (+)-Camphor was recovered in 68% yield without any decrease of optical purity.



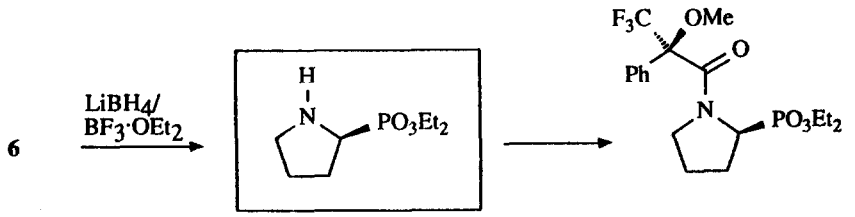
2b **5**



6

In contrast to the reaction of **2a** with diethylethenephosphonate, the lithium derivative **2a** gave upon treatment with methyl acrylate only unchanged starting material **1** and polymeric products. Thus the lithium compound **2a** was converted into its magnesium-, copper- and zinc derivatives, respectively. Only the reaction of the zinc compound

2b with methyl acrylate afforded the desired product **5** in 66% with 71% d.e.; unchanged starting material **1** was recovered in 25% yield. The (*1S*)-configuration for the major diastereomer was once more assigned due to the absorption of the C-8' methylprotons in the ^{1}H NMR spectra. The minor diastereomer was easily removed by flash chromatography on silica gel. After hydrolysis of diastereomerically pure (*1S*)-**5**, the pyroglutamic acid derivative **6** was isolated in 64% yield. The optical purity of **6** will be shown below to be ≥95% e.e.. (+)-Camphor - the chiral auxiliary in this synthesis - was recovered in 60% yield.



7 8

The pyroglutamic acid analogue **6** was reduced with $LiBH_4/BF_3{\cdot}OEt_2$[8] to the phosphoproline diethylester **7**. Under these reduction conditions, no evolution of phosphines as the result of a reduction of the phosphonic ester function was observed. The greatest obstacle proved to be the removal of persisting, boron-containing impurities. Pure phoshoproline diethylester was obtained in 61% yield after workup of the crude product with ammonia/methanol, column filtration and flash chromatography.

The phosphoproline ester **7** was not obtainable by alkylation of **2a** with diiodopropane and subsequential hydrolysis.[9]

The optical purities of the phosphoproline **7** and the glutamic acid analogue **6** were determined by conversion of the amine **7** into amide **8** with (*R*)-α–methoxy–α-(trifluoromethyl)phenylacetyl chloride (Mosher reagent).[10] According to ^{1}H NMR-, ^{13}C NMR- and ^{19}F NMR-data, the amine **7** and thus the lactam **6** were obtained in an optical purity ≥ 95% e.e..

Since camphor is available in both enantiomeric forms, both (*R*)- and (*S*)-enantiomers of **4**, **6** and **7** are accessible.

EXPERIMENTAL

Infrared (IR) spectra were obtained using a Perkin-Elmer 298 spectrometer. NMR spectra were recorded on Varian XL 200 and a VXR 200 spectrometer for ^{1}H 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 parts per million (δ) using tetramethylsilane as an internal standard for ^{1}H- 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 on Varian MAT 731 or 311 A spectrometers. Optical rotations were measured on a Perkin Elmer Mod. 141 polarimeter. 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. All reactions were carried out under a nitrogen or argon atmosphere except those involving hydrolysis. All reagents were purified and dried if necessary before use. The (+)-camphor derivative **1** was prepared as described previously.[1]

(1'R,4'R,1S)-1-(1',7',7'-Trimethylbicyclo[2.2.1]hept-2'-ylidenamino)-1,3-tetraethylpropane-1,3-phosphonate (3): To a stirred solution of **1** (0.90 g, 3.0 mmol) in THF (15 ml), a solution of n-butyllithium in hexane (1.6 N, 2.1 ml, 3.3 mmol) was added at -70°C. After stirring at -70°C for 15 min, the formation of **2a** was completed and a cooled solution of diethylethenephosphonate[6] (0.54 g, 3.3 mmol) in THF (5 ml) was added dropwise; stirring was continued for 16 h at 70°C. Then acetic acid (0.21 g, 3.5 mmol) was added, and the solvent was removed in vacuo at room temp.. The residue was dissolved in ether (30 ml) and washed with aqueous 5% $NaHCO_3$ (30 ml) and saturated NaCl (30 ml). Aqueous layers were reextracted twice with ether (20 ml), and the combined organic layers were dried over $MgSO_4$. Ether was removed in vacuo and crude **3** was purified by bulb to bulb distillation to yield 1.03 g (2.2 mmol, 74%) **3** as a colorless oil; b.p. 140°C/0.01 Torr. - d.e.: 79%. - **IR (neat):** 1675 (C=N), 1240 (P=O), 1025 cm^{-1} (P-O). - **^{1}H NMR ($CDCl_3$):** δ = 0.74 (s; 3H, 8'-CH_3, minor diastereomer), 0.86 (s; 3H, 8'-CH_3, major diastereomer), 0.92 and 0.96 (2s; 6H, 9'- and 10'-CH_3), 1.12-1.26 (m; 2H, aliph. H), 1.28-1,32 (m; 12H, $OCH_2\underline{CH_3}$), 1.15-2.30 (m; 8H, aliph. H), 2.48-2.67 (m; 1H, 4'-H), 3.72 (ddd, J_1 = 12 Hz, J_2 = 8 Hz, J_3 = 4 Hz; 1H, 1-H), 4.00-4.24 (m; 8H, OCH_2). - **^{13}C NMR (50.3 MHz, $CDCl_3$):** a) (*1S*)-diastereomer: δ = 11.31 (C-10'), 16.41 and 16.52 (CH_3), 19.05 and 19.49 (C-8' and C-9'), 22.45 (dd, $^{1}J_{PC}$ = 140 Hz, $^{3}J_{PC}$ = 15 Hz; C-3), 24.25 (dd, $J_1 = J_2$ = 3.5 Hz; C-2), 27.44 (C-5'), 32.76 (d, J = 2 Hz; C-6'), 36.53 (d, J = 2 Hz; C-3'), 43.86 (C-4'), 47.49 (C-7'), 54.53 (d, J = 2 Hz; C-1'), 60.19 (dd, $^{1}J_{PC}$ = 155 Hz, $^{3}J_{PC}$ = 16 Hz; C-1), 61.44 (d, J = 6.5 Hz; OCH_2), 62.05 and 62.74 (2d, J = 7 Hz; OCH_2), 187.28 (d, J = 13.5 Hz; C=N). b) (*1R*)-diastereomer: δ = 11.46 (C-10'), 18.78 and 19.60 (C-8' and C-9'), 27.27 (C-5'), 31.79 (d, J = 4.5 Hz; C-6'), 35.80 (C-3'), 46.49 (C-7'), 59.69 (dd, $^{1}J_{PC}$ = 154 Hz, $^{3}J_{PC}$ = 15 Hz; C-1), 186.75 (d, J = 12.5 Hz; C=N); the other signals were not detectable. - **^{31}P NMR ($CDCl_3$):** δ = 24.24 and 31.93 [2d, J = 9 Hz; (*1R*)-diastereomer], 24.47 and 32.00 (2d, J = 9 Hz; (*1S*)-diastereomer). - **MS (70eV):** 465 (18%, M^+), 328 (42%, M^+-PO_3Et_2), 314 (100%, M^+-PO_3Et_2-CH_2). - **HRMS (70eV):** calc. for $C_{21}H_{41}NO_6P_2$ 465.2409, found 465.2409.- **$C_{21}H_{41}NO_6P_2$ (465.5)** calc. C,54.18;H,8.88, found C,54.16;H,8.74%.

(1S)-1-Acetamido-tetraethyl-propane-1,3-diphosphonate (4): The Michael adduct **3** (1.01 g, 2.16 mmol) was dissolved in 90% aqueous acetic acid (20 ml). After stirring at 60°C for 6 d, the acetic acid was removed at 40°C under reduced pressure and ethyl acetate (30 ml) and saturated aqueous Na_2CO_3 (20 ml) were added. The layers were separated and the aqueous layer was reextracted twice with ethyl acetate (20 ml). The combined organic layers were dried over $MgSO_4$, the solvent removed in vacuo and the residue purified by flash chromatography on silica gel (ethyl acetate/methanol 5:1) to yield **4** (0.59 g, 1.61 mmol, 73%, R_f = 0.25) as a colorless oil. - **$[\alpha]_D^{20}$** = + 12.2° (c = 2.5, $CHCl_3$). - **IR (neat):** ν = 3250 (N-H), 1675 (C=O), 1225 (P=O), 1020 cm^{-1} (P-O). - **^{1}H NMR ($CDCl_3$):** δ = 1.23, 1.24, 1.25 and 1.27 (4dt, J_1 = 7 Hz; J_{PH} = 0.5 Hz; 12H, $4CH_3$), 1.76-2.40 (m; 4H, 2- and 3-H), 2.07 (s; 3H, $COCH_3$), 4.10 (m; 8H, OCH_2), 4.50 (m; 1H, 1-H), 6.74 and 6.93 (2d, J = 8 Hz; 1H, NH; E/Z-isomers). - **^{13}C NMR ($CDCl_3$):** δ = 16.32, 16.38, 16.44 and 16.50 (CH_3), 22.10 (dd, $^{1}J_{PC}$ = 121 Hz, $^{3}J_{PC}$ = 21 Hz; C-3), 22.79 ($CO\underline{C}H_3$), 22.88 (d, J = 4 Hz; C-2), 45.39 (dd, $^{1}J_{PC}$ = 157 Hz, $^{3}J_{PC}$ = 18 Hz; C-1), 61.74, 62.51, 62.54 and 62.99 (4d, J = 7 Hz; OCH_2), 170.38 (d, J = 5 Hz; C=O). - **^{31}P NMR ($CDCl_3$):** δ = 24.43 and 31.85 (2d, J = 6.5 Hz). - **MS (70eV):** 373 (4%, M^+), 236 (86%, M^+-PO_3Et_2), 194 (100%, M^+-PO_3Et_2-$NHCOCH_3$). - **$C_{13}H_{29}NO_7P_2$ (373.3)** calc. C,41.83;H,7.83, found C,41.83;H,7.91%.

(1'R,4'R,1S)-3-Methoxycarbonyl-1-(1',7'-7'-trimethylbicyclo[2.2.1]hept-2'-ylidenaminodiethyl propanephospho nate (5): To a stirred solution of **2a** (3.0 mmol, see above) in THF (15 ml), a suspension of $ZnCl_2$·OEt_2 in ether

(0.8 N, 4.5 ml, 3.6 mmol) was added at -70°C. The solution was allowed to warm up to 0°C and stirred for 30 min at 0°C. Then, the solution was cooled to -70°C, and a cooled solution of methyl acrylate (0.3 ml, 3.3 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred for 2 h at -70°C and then allowed to warm up to 0°C within 16 h. Acetic acid (0.3 ml, 5.0 mmol) was added and the solvent was removed in vacuo. Ether (15 ml) and 10% aqueous NH_4Cl (15 ml) were added and the layers were separated. The organic layer was washed with 5% $NaHCO_3$ (10 ml) and saturated NaCl (10 ml), and the aqueous layers were reextracted twice with ether (15 ml). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate/cyclohexane 3:1) to afford diastereomerically pure (*1S*)-**5** (0.60 g, 51%, R_f = 0.30). Moreover, a mixture of both diastereomers of **5** [0.18 g, 15%, R_f = 0.23 for (*1R*)-**5**] and unchanged starting material **1** (0.22 g, 0.73 mmol, 25%) was isolated. - **IR (neat)** : ν = 1730 (C=O), 1670 (C=N), 1240 (P=O), 1020 cm^{-1} (P-O). - **^{1}H NMR ($CDCl_3$)**: a) (*1S*)-diastereomer: δ = 0.86 (s; 3H, 8'-CH_3), 0.92 and 0.96 (2s; 6H, 9'-and 10'-CH_3), 1.32 and 1.33 (2dt, J_1 = 7.5 Hz, J_{PC} = 0.5 Hz; 6H, CH_3), 1.10-1.38 (m; 2H, aliph. H), 1.60-2.48 (m; 8H, aliph. H), 2.48-2.64 (m; 1H, 4'-H), 3.68 (s; 3H, OCH_3), 3.70-3.85 (m; 1H, 1-H), 4.04-4.26 (m; 4H, OCH_2). b) (*1R*)-diastereomer: δ = 0.74 (s; 3H, 8'-CH_3), 0.93 and 0.96 (2s; 6H, 9'- and 10'-CH_3), 1.30 (m; 2H, aliph. H), 1.33 and 1.34 (2dt, J_1 = 7.5 Hz, J_{PH} = 0.5 Hz; 6H, CH_3), 1.58-2.50 (m; 9H, aliph. H), 3.66 (s; 3H, OCH_3), 3.72-3.84 (m; 1H, 1-H), 4.04-4.26 (m; 4H, OCH_2). - **^{13}C NMR ($CDCl_3$)**: a) (*1S*)-diastereomer: δ = 11.31 (C-8'), 16.44 and 16.55 (CH_3), 19.06 and 19.51 (C-9' and C-10'), 26.13 (d, J = 3.5 Hz; C-2), 27.50 (C-5'), 30.56 (d, J = 15.5 Hz; C-3), 32.58 (d, J = 3.5 Hz; C-6'), 36.43 (d, J = 2 Hz; C-3'), 43.90 (C-4'), 47.51 (d, J = 1.5 Hz; C-7'), 51.52 (OCH_3), 54.52 (d, J = 2 Hz; C-1'), 59.00 (d, J = 156 Hz; C-1), 62.06 (d, J = 7 Hz; OCH_2), 62.80 (d, J = 6.5 Hz; OCH_2), 173.48 (C=O), 187.16 (d, J = 13.5 Hz; C=N). b) (*1R*)-diastereomer: δ = 11.47 (C-8'), 16.46 and 16.57 (CH_3), 18.85 and 19.43 (C-9' and C-10'), 26.04 (d, J = 3 Hz; C-2), 27.30 (C-5'), 30.75 (d, J = 16 Hz; C-3), 31.86 (d, J = 4.5 Hz; C-6'), 35.72 (d, J = 1.5 Hz; C-3'), 43.96 (C-4'), 46.53 (C-7'), 51.48 (OCH_3), 54.58 (d, J = 2 Hz; C-1'), 58.89 (d, J = 154 Hz; C-1), 62.21 (d, J = 7 Hz; OCH_2), 62.53 (d, J = 6.5 Hz; OCH_2), 173.54 (C=O), 186.73 (d, J = 13 Hz; C=N). - **^{31}P NMR ($CDCl_3$)**: δ = 24.67 ((*1R*)-diastereomer), 24.89 ((*1S*)-diastereomer). - **MS (70eV)**: 387 (13%; M^+), 250 (100%, M^+-PO_3Et_2). - **HRMS (70eV)**: calc. for $C_{19}H_{34}NO_5P$ 387.2175, found 387.2175. - **$C_{19}H_{34}NO_5P$** (387.5) calc. C,58.90;H,8.84, found C,58.83;H,8.94%.

(S)-2-Diethoxyphosphoryl-pyrrolidin-5-one (6): The diastereomerically pure lactam (*1S*)-**5** (2.40 g, 6.19 mmol) was dissolved in 90% aqueous acetic acid (40 ml) and hydrolyzed as described above. After usual workup (see above) and flash chromatography on silica gel (ethyl acetate/methanol 5:1), the lactam **6** (880 mg, 64%, R_f = 0.28) was isolated as a colorless oil; $[\alpha]_D^{20}$ = +8.7° (c = 0.97, $CDCl_3$). - **IR (neat)**: ν = 3200 (N-H), 1690 (P=O), 1020 cm^{-1} (P-O). - **^{1}H NMR ($CDCl_3$)**: δ = 1.35 and 1.36 (2t, J = 7.5 Hz; 6H, CH_3), 2.24-2.59 (m; 4H, 3-H and 4-H), 3.86 (dd, J_1 = 6 Hz, J_2 = 7 Hz; 2-H), 4.08-4.30 (m; 8H, OCH_2), 6.50 (broad; 1H, NH). - **^{13}C NMR ($CDCl_3$)**: δ = 16.50 (d, J = 2.5 Hz; CH_3), 16.60 (d, J = 2 Hz; CH_3), 21.77 (d, J = 3.5 Hz; C-3), 29.45 (d, J = 2 Hz; C-4), 50.10 (d, J = 163.5 Hz; C-2), 62.73 (d, J = 7.5 Hz; OCH_2), 63.03 (d, J = 7 Hz; OCH_2), 178.56 (d, J = 5 Hz; C=O). - **^{31}P NMR ($CDCl_3$)**: δ = 24.19. - **MS (70eV)**: 221 (20%,M^+), 84 (100%, M^+-PO_3Et_2). - **HRMS (70eV)**: calc. for $C_8H_{16}NO_4P$ 221.0817, found 221.0817. - **$C_8H_{16}NO_4P$ (221.2)** calc. C,43.44;H,7.29, found C,43.37;H,7.34%.

(S)-2-Diethoxyphosphorylpyrrolidine (7): $BF_3{\cdot}OEt_2$ (4.43 g, 31.2 mmol) was added dropwise at 0°C to a stirred solution of the lactam **6** (690 mg, 3.12 mmol) in THF (10 ml). This mixture was dropped through a teflon hose to a stirred solution of $LiBH_4$ (103 mg, 4.73 mmol) in THF (5 ml) at 0°C. The solution was kept at 0°C for 15 min and stirring was continued at 25°C for 36 h. Then the solvent was removed in vacuo, the residue was cooled to 0°C, and methanol (3 ml) and ammonia (3 ml) were added. After stirring for 30 min at 25°C, ether (30 ml) was added, and the solution was decantated from the precipitate. The residue was washed three times with ether/methanol/ammonia (100:10:1) (20 ml), the solvent was removed in vacuo, and the crude product was prepurified by column filtration on silica gel (ether/methanol/ammonia 100:10:1, R_f = 0.4). After flash chromatography on silica gel (ether/methanol 10:1), the pyrrolidine **7** (400 mg, 62%, R_f = 0.23) was isolated as a colorless liquid; $[\alpha]_D^{20}$ = + 16.4° (c = 1.0, $CHCl_3$). - **IR (neat)**: ν = 3300 (N-H), 1230 (P=O), 1025 cm^{-1} (P-O). - **^{1}H NMR ($CDCl_3$)**: δ = 1.34 (t, J = 7 Hz; 6H, CH_3), 1.64-2.12 (m; 4H, 3-H and 4-H), 2.12 (broad; 1H, NH), 2.93 and 3.08 (ABMN system, J_{AB} = 10 Hz, J_{AM} = 1 Hz, J_{AN} = 7.5 Hz, J_{BM} = 7.5 Hz, J_{BN} = 6 Hz; 2H, 5-H), 3.35 (ddd, J_1 = 8 Hz, J_2 = 7.5 Hz, J_3 = 5.5 Hz; 1H, 2-H), 4.10-4.28 (m; 4H, OCH_2). - **^{13}C NMR ($CDCl_3$)**: δ = 16.58 (d, J = 5.5 Hz; CH_3), 26.03 (d, J = 8 Hz; C-4), 26.81 (C-3), 47.65 (d, J = 11.5 Hz; C-5), 54.03 (d, J = 163 Hz; C-1), 62.14 (d, J = 7 Hz; OCH_2). - **^{31}P NMR ($CDCl_3$)**: δ = 28.90. - MS (70 eV): 70 (100%, M^+-PO_3Et_2), 207 (7%), M^+). - **HRMS (70eV)**: calc. for $C_8H_{18}NO_3P$ 207.1024, found 207.1024. - **$C_8H_{18}NO_3P$ (207.2)** calc. C,46.37;H,8.76 found C,46.02;H,8.96%.

(2S,2'R)-2-Diethoxyphosphoryl-1-(2'-methoxy-2'-trifluoromethyl)phenylacetylpyrrolidine (8): The pyrrolidine **7** (20 mg, 97 µmol) was treated with *R*-(+)-α-methoxy–α-(trifluoromethyl)phenyl-acetyl chloride (30 mg, 0.12 mmol) under standard conditions.[10] After usual workup, the product was examined by ^{1}H NMR-, ^{13}C NMR- and ^{19}F NMR spectroscopy. - **^{1}H NMR ($CDCl_3$):** δ = 1.43 and 1.45 (2dt, J_1 = 7 Hz, J_{PH} = 0.5 Hz; 6H, CH_3), 1.46 (m; 1H, aliph. H), 1.78-2.33 (m; 3H, aliph. H), 3.05 and 3.32 (m; 2H, 5-H), 3.75 (q, J_{FH} = 2 Hz; 3H, OCH_3), 4.10-4.38 (m; 4H, OCH_2), 4.81 (ddd, J_1 = 9 Hz, J_2 = 6.5 Hz, J_3 = 4.5 Hz; 1H, 2-H), 7.35-7.85 (m; 5H, phenyl). - **^{13}C NMR ($CDCl_3$) :** δ = 16.23 (d, J = 7 Hz; CH_3), 16.36 (d, J = 6.5 Hz; CH_3), 24.69 (d, J = 2 Hz; C-4), 24.76 (C-3), 46.93 (C-5), 52.20 (d, J = 159 Hz; C-2), 55.14 (OCH_3), 62.08 (d, J = 7 Hz; OCH_2), 62.67 (d, J = 6 Hz; OCH_2), 84.49 (q, J = 25.5 Hz; $F_3C\underline{C}OMe$), 123.60 (q, J_{FC} = 290 Hz; CF_3), 126.65 128.33 and 129.38 (arom. CH), 133.14 (arom. C_q), 164.82 (d, J = 2 Hz; C=O). - **^{19}F NMR (75.4 MHz, $CDCl_3$):** δ = -70.54; signals for (*1R*)-**8** were not detectable.

Acknowledgements - Financial support by the *Stiftung Volkswagenwerk* and the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

REFERENCES

1. Asymmetric Synthesis of α-Aminophosphonic Acids, Part 4; for Part 3 see: U. Schöllkopf, R. Schütze, *Liebigs Ann. Chem.* **1987**, 45.

2. Recent examples for asymmetric syntheses of optically active α-aminoalkanephosphonic acids: Review: B. Dhawan, D. Redmore, *Phosphorus and Sulfur* **1987**, *32*, 119; I. Hoppe, U. Schöllkopf, M. Nieger, E. Egert, *Angew. Chem.* **1985**, *97*, 1066; *Angew. Chem. Int. Ed. Engl.* **1985**, *14*, 1067; T. Schrader, R. Kober, W. Steglich, *Synthesis* **1986**, 372; R. Huber, A. Vasella, *Helv. Chim. Acta* **1987**, *70*, 1461; R. Jacquier, F Ouazzani, M.-L. Roumestant, P. Viallefont, *Phosphorus and Sulfur* **1988**, *36*, 73; M. Sawamura, Y.Ito, T. Hayashi, *Tetrahedron Lett.* **1989**, 2247; S. Hanessian, Y.L. Bennani, *Tetrahedron Lett.* **1990**, 6465; M. Sting, W. Steglich, *Synthesis* **1990**, 132.

3. K. Issleib, *Nachr. Chem. Tech.* **1987**, *35*, 1037; N.E. Jacobsen, P.A. Bartlett, *J. Am. Chem. Soc.* **1981**, *103*, 654.

4. E.W. Petrillo, E.R. Spitzmiller, *Tetrahedron Lett.* **1979**, 4929; E. Gruszecka, M. Soroka, P. Mastalerz, *Pol. J. Chem.* **1979**, *53*, 75.

5. For the base-induced alkylation of carboxylic ester analogues of **1** see: J.M. McIntosh, R.K. Leavitt, P. Mishra, K.C. Cassidy, J.E. Drake, R. Chadha, *J. Org. Chem.* **1988**, *53*, 1947 and references cited therein.

6. For the preparation of diethylethenephosphonate see G.M. Kosolapoff, *J. Am. Chem. Soc.* **1948**, *70*, 1971.

7. R. Schütze, *Ph.D.Thesis*, University of Göttingen **1986**.

8. G. Pettit, U.R. Ghatak, T.R. Kasturi, D.M. Piatak, *J. Org. Chem.* **1961**, *26*, 1685.

9. L. Richter, *Ph.D.Thesis*, University of Göttingen **1991**.

10. J.A. Dale, H.S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.