Azetidine-Derived Amino Acids *versus* Proline Derivatives. Alternative Trends in Reverse Turn Induction

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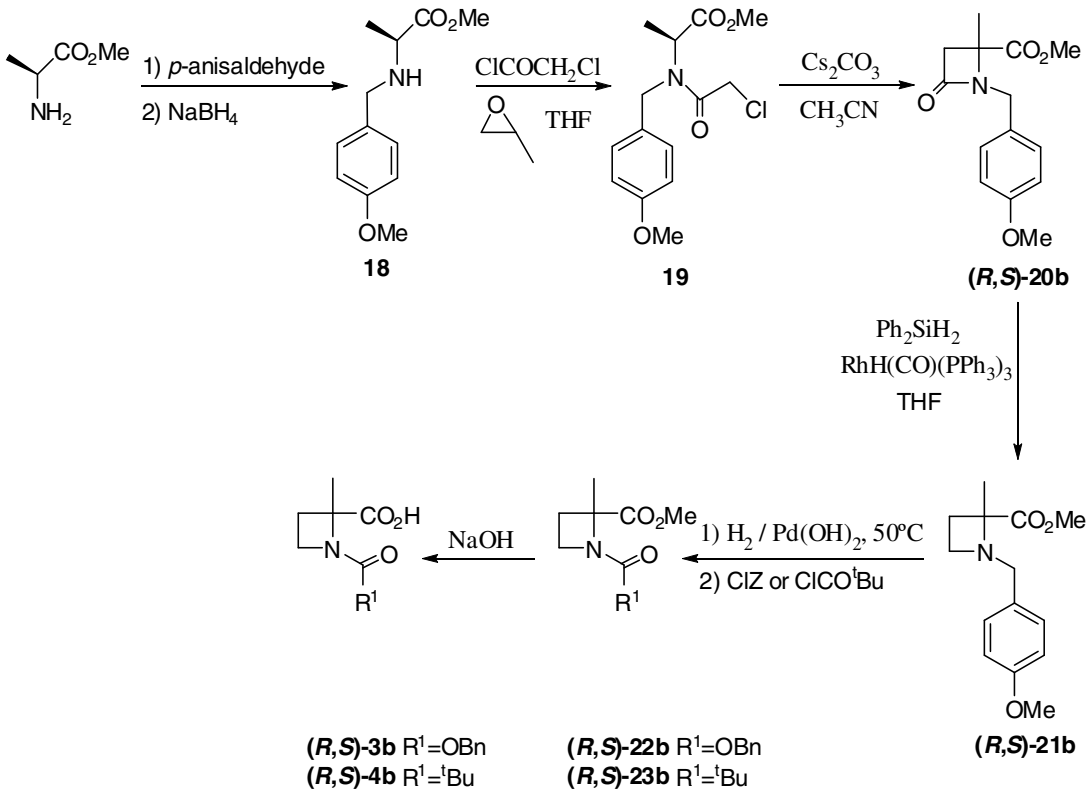
General Methods. All reagents were of commercial quality. Solvents were dried and purified by standard methods. Analytical TLC was performed on aluminum sheets coated with a 0.2 mm layer of silica gel 60 F254. Silica gel 60 (230-400 mesh) was used for flash chromatography. Preparative radial chromatography was performed on 20 cm diameter glass plates coated with a 1 mm layer of silica gel PF254. Analytical RP-HPLC was performed on a Novapak C18 (3.9 x 150 mm, 4μm) column, with a flow rate of 1 mL/min, and using a tunable UV detector set at 214 nm. Mixtures of CH_3CN (solvent A) and 0.05% TFA in H_2O (solvent B) were used as mobile phase. Melting points were taken on a micro hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz, unless other specifications are made. The NMR spectra assignment was based on COSY, HSQC and HMBC spectra. Electrospray mass spectra (ES-MS) were performed, in positive mode, using MeOH as solvent.

Synthetic Procedures for the Preparation of the Starting Pro and Azetidine Derivatives

Z-L-α-MePro-OH (1b).[1] To a solution of α-MePro-OH (150 mg, 1.16 mmol) in H_2O (13 mL) at 0 ºC was successively added Na_2CO_3 (283 mg, 2.67 mmol) and benzyl chloroformate (210 µl, 1.51 mmol). After stirring for 9 days at 50 ºC it was added ice/H_2O, and washed with CH_2Cl_2. The aqueous layer was acidified with HCl 1M to pH=2, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and evaporated to dryness, yielding the title compound without further purification in 72 %, syrup. HPLC: t_R= 4.08 min. (A:B=30:70). $[\alpha]_D$= -27.18 (c=1.51, $CHCl_3$). ^{1}H NMR ($CDCl_3$): *cis/trans* isomers ratio: 1.9:1. *Trans* isomer: δ 7.30 (m, 5H, Ph), 5.12 (s, 2H, CH_2-Z), 3.50 (m, 2H, δ-H, Pro), 2.30 (m, 1H, β-H, Pro), 1.95-1.70 (m, 3H, β-H, Pro, γ-H, Pro), 1.62 (s, 3H, CH_3-Pro), *cis* isomer: δ 7.30 (m, 5H, Ph), 5.10 (s, 2H, CH_2-Z), 3.70-3.51 (m, 2H, δ-H, Pro), 2.25 (m, 1H, β-H, Pro), 1.95-1.70 (m, 3H, β-H, Pro, γ-H, Pro), 1.52 (s, 3H, CH_3-αPro). ^{13}C NMR ($CDCl_3$): *Trans* isomer: δ 178.9 (COOH), 154.7 (CO-Z), 136.4 (C-Ph), 128.3, 127.7, 126.9 (CH-Ph), 66.9 (CH_2-Z), 65.7 (α-C, Pro), 47.9 (δ-C, Pro), 39.1 (β-C, Pro), 23.1 (γ-C, Pro), 21.1 (CH_3-αPro), *cis* isomer: δ 180.0 (COOH), 154.3 (CO-Z), 136.2 (C-Ph), 128.3, 127.7, 126.9 (CH-Ph), 67.1 (CH_2-Z), 64.8 (α-C, Pro), 48.5 (δ-C,

Pro), 40.5 (β-C, Pro), 22.6 (γ-C, Pro), 22.8 (CH_3-αPro). ES-MS: 264.0 $[M+1]^+$, 286.0 $[M+Na]^+$, 549.3 $[2M+Na]^+$. Anal. Calcd. for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32, Found: C 64.01, H 6.61, N 5.36.

Scheme 1



***N*-(*p*-Methoxybenzyl)-L-Ala-OMe (18).** To a solution of H-L-Ala-OMe·HCl (7.50 g, 53.74 mmol) in MeOH (50 mL) was added TEA (7.47 mL, 53.74 mmol) and *p*-anisaldehyde (7.82 mL, 64.44 mmol). After 1.5 h of stirring at room temperature $NaBH_4$ (4.06 g, 107.48 mmol) was added at 0 ºC. After stirring for 30 min. the solvent was evaporated, and the resulting residue was dissolved in EtOAc and was successively washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and evaporated, leaving a residue which was purified on a silica gel column, using as eluent a gradient from 6 to 10% of EtOAc in hexane. This led to compound **18** (10.09 g, oil) in 84% yield. HPLC: t_R= 2.60 min. (A:B=40:60). $[\alpha]_D$= -8.07 (c=0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.27 (d, 2H, *J*=8.3, 2-H and 6-H Pmb), 6.88 (d, 2H, *J*=8.3, 3-H and 5-H Pmb), 3.82 (s, 3H, *p*-OMe), 3.75 (s, 3H, OMe), 3.76 (d, 1H, *J*=12.6, *N*-CH_2), 3.63 (d, 1H, *J*=12.6, *N*-CH_2), 3.41 (q, 1H, *J*=6.9, α-H, Ala), 1.72 (br s, 1H, NH), 1.34 (d, 3H, *J*=6.9, β-H, Ala). ^{13}C NMR ($CDCl_3$): δ 176.1 (CO), 158.7 (4-C Pmb), 131.8 (1-C Pmb), 129.3 (2-C and 6-C Pmb), 113.7 (3-C and 5-C Pmb), 55.7 (*p*-OMe), 55.1 (α-C, Ala), 51.6 (OMe), 51.3 (*N*-CH_2), 19.0

(β-C, Ala). ES-MS: 224.0 $[M+1]^+$. Anal. Calcd. for $C_{12}H_{17}NO_3$: C 64.55, H 7.67, N 6.27, Found: C 64.47, H 7.61, N 6.19.

***N*-(*p*-Methoxybenzyl)-*N*-chloroacetyl-L-Ala-OMe (19).** A solution of the *N*-(*p*-methoxybenzyl)-L-Ala-OMe (**18**) (6.05 g, 27.11 mmol) in THF (30 mL) was treated with propylene oxide (28.49 mL, 406.65 mmol), and then at 0 ºC with chloroacetyl chloride (2.59 mL, 32.53 mmol). After stirring at room temperature for 2 h the solvent was evaporated, and the resulting residue was purified on a silica gel column, using as eluent a gradient from 14 to 20% of EtOAc in hexane. The title compound (7.76 g, 96%) was obtained as a syrup. HPLC: t_R= 3.36 min. (A:B=35:65). $[\alpha]_D$= -49.43 (c=1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.21 (d, 2H, *J*=8.5, 2-H and 6-H Pmb), 6.90 (d, 2H, *J*=8.5, 3-H and 5-H Pmb), 4.63 (d, 1H, *J*=16.7, *N*-CH_2), 4.53 (m, 1H, α-H, Ala), 4.52 (d, 1H, *J*=16.7, *N*-CH_2), 4.09 (d, 1H, *J*=12.7, CH_2-Cl), 4.01 (d, 1H, *J*=12.7, CH_2-Cl), 3.81 (s, 3H, *p*-OMe), 3.69 (s, 3H, OMe), 1.39 (d, 3H, *J*=7.2, β-H, Ala). ^{13}C NMR ($CDCl_3$): δ 171.4 (CO-Ala), 167.0 (CO-N), 159.3 (4-C Pmb), 128.9 (1-C Pmb), 127.8 (2-C and 6-C Pmb), 114.3 (3-C and 5-C Pmb), 55.2 (α-C, Ala), 54.7 (*p*-OMe), 52.2 (OMe), 50.3 (*N*-CH_2), 41.6 (CH_2-Cl), 14.4 (β-C, Ala). ES-MS: 322.0 $[M+Na]^+$, 621.3 $[2M+Na]^+$. Anal. Calcd. for $C_{14}H_{18}ClNO_4$: C 56.10, H 6.05, Cl 11.83, N 4.67, Found: C 55.93, H 6.11, Cl 11.94, N 4.60.

4(*R*,*S*)-1-(*p*-Methoxybenzyl)-4-methoxycarbonyl-4-methyl-2-azetidinone ((*R*,*S*)-20b). To a solution of compound **19** (11.52 g, 38.52 mmol) in dry CH_3CN (50 mL), under argon atmosphere, it was added Cs_2CO_3 (25.10 g, 77.04 mmol). After 5 days of reaction the solvent was evaporated to dryness, the crude was dissolved in EtOAc:H_2O (1:1) and the organic layer was successively washed with HCl (0.1 N), H_2O and brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified on a silica gel column, using as eluent a gradient from 17 to 33% of EtOAc in hexane, leading to the title product (5.83 g, 57%) as a syrup. HPLC: t_R= 3.12 min. (A:B=30:70). ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H, *J*=8.6, 2-H and 6-H Pmb), 6.84 (d, 2H, *J*=8.6, 3-H and 5-H Pmb), 4.46 (d, 1H, *J*=15.0, 1-CH_2), 4.27 (d, 1H, *J*=15.0, 1-CH_2), 3.79 (s, 3H, *p*-OMe), 3.60 (s, 3H, OMe), 3.25 (d, 1H, *J*=14.4, H-3), 2.81 (d, 1H, *J*=14.4, H-3), 1.37 (s, 3H, 4-CH_3). ^{13}C NMR ($CDCl_3$): δ 172.4 (COO), 165.5 (2-CO), 159.1 (4-C Pmb), 130.0 (2-C and 6-C Pmb), 127.7 (1-C Pmb), 113.8 (3-C and 5-C Pmb), 58.7 (4-C), 55.1 (*p*-OMe), 52.3 (OMe), 48.9 (3-C), 44.1 (1-CH_2), 20.6 (4-CH_3). ES-MS: 264.0 $[M+1]^+$, 286.0 $[M+Na]^+$, 549.3 $[2M+Na]^+$. Anal. Calcd. for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32, Found: C 64.01, H 6.42, N 5.36.

2(*R*,*S*)-1-(*p*-Methoxybenzyl)-2-MeAze-OMe ((*R*,*S*)-21b). Ph_2SiH_2 (8.37 mL, 45.37 mmol) was added to a solution of compound **(*R*,*S*)-20b** (4.77 g, 18.15 mmol) and $RhH(CO)(PPh_3)_3$ (166 mg, 0.18 mmol) in dry THF (23 mL), under argon atmosphere. After stirring for 24 h the solvent was evaporated to dryness, and the residue was dissolved in Et_2O and washed with HCl 1M. The aqueous phase was basified to pH=11 with NaOH 2N and extracted with EtOAc, following by purification by flash

chromatography using as eluent a gradient from 14 to 20% of EtOAc in hexane. This yield compound **(*R*,*S*)-21b** (4.52 g, oil) in 63% yield. HPLC: t_R= 3.25 min. (A:B=20:80). ^{1}H NMR ($CDCl_3$): δ 7.21 (d, 2H, *J*=8.7, 2-H and 6-H Pmb), 6.83 (d, 2H, *J*=8.7, 3-H and 5-H Pmb), 3.78 (s, 3H, *p*-OMe), 3.73 (s, 3H, OMe), 3.68 (d, 1H, *J*=12.5, 1-CH_2), 3.50 (d, 1H, *J*=12.5, 1-CH_2), 3.21 (ddd, 1H, *J*=8.3, 6.5, 4.5, H-4), 3.06 (dt, 1H, *J*=8.3, 6.8, H-4), 2.55 (m, 1H, H-3), 1.91 (m, 1H, H-3), 1.47 (s, 3H, 2-CH_3). ^{13}C NMR ($CDCl_3$): δ 175.1 (CO), 158.5 (4-C Pmb), 130.1 (1-C Pmb), 129.8 (2-C and 6-C Pmb), 113.6 (3-C and 5-C Pmb), 67.5 (1-C), 55.1 (*p*-OMe), 55.0 (1-CH_2), 51.6 (OMe), 48.9 (4-C), 28.5 (3-C), 18.7 (4-CH_3). ES-MS: 250.1 $[M+1]^+$. Anal. Calcd. for $C_{14}H_{19}NO_3$: C 67.45, H 7.68, N 5.62, Found: C 67.39, H 7.74, N 5.67.

2(*R*,*S*)-Z-2-MeAze-OMe ((*R*,*S*)-22b). To a solution of the *p*-methoxybenzyl protected azetidine **(*R*,*S*)-21b** (394 mg, 1.58 mmol) in MeOH (30 mL) was added concentrated HCl (0.14 mL, 1.58 mmol) and $Pd(OH)_2$ (118 mg, 30% w/w) at 0 ºC, and the suspension was hydrogenated at 50 ºC and 45 psi of pressure for 12 h. After filtration of the catalyst, the solvent was evaporated. The resulting residue was dissolved in dry CH_2Cl_2 (4 mL), cooled to 0 ºC, and Et_3N (0.22 mL, 1.58 mmol), propylene oxide (1.66 mL, 23.7 mmol), and benzyl chloroformate (0.36 mL, 2.53 mmol) were successively added. After stirring for 2 h at room temperature it was successively washed with citric acid 10%, $NaHCO_3$ 10%, H_2O and brine. The organic layer was dried over Na_2SO_4, the solvent was evaporated to dryness and the residue was purified by flash chromatography using as eluent a gradient from 11 to 20% of EtOAc in hexane. This led to the title compound (330 mg, oil) in 79% yield. HPLC: t_R= 6.59 min. (A:B=30:70). ^{1}H NMR ($CDCl_3$): *cis*/*trans* isomers ratio: 1:1.7. *T*rans isomer: δ 7.28 (m, 5H, Ph), 5.05 (m, 2H, CH_2-Z), 3.98 (m, 1H, H-4), 3.82 (m, 1H, H-4), 3.51 (s, 3H, OMe), 2.29 (m, 1H, H-3), 2.12 (m, 1H, H-3), 1.60 (s, 3H, 2-CH_3). ^{13}C NMR ($CDCl_3$): *trans* isomer: δ 173.0 (2-CO), 155.7 (CO-Z), 136.5 (C-Ph), 128.4, 127.9, 127.8 (CH-Ph), 68.1 (2-C), 66.5 (CH_2-Z), 52.3 (OMe), 44.8 (4-C), 28.6 (3-C), 22.9 (2-CH_3), *cis* isomer: δ 173.0 (2-CO), 155.7 (CO-Z), 136.5 (C-Ph), 129.8, 128.4, 126.9 (CH-Ph), 67.8 (2-C), 66.5 (CH_2-Z), 52.3 (OMe), 45.9 (4-C), 28.8 (3-C), 22.3 (2-CH_3). ES-MS: 264.0 $[M+1]^+$, 286.0 $[M+Na]^+$, 549.3 $[2M+Na]^+$. Anal. Calcd. for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32, Found: C 63.69, H 6.50, N 5.37.

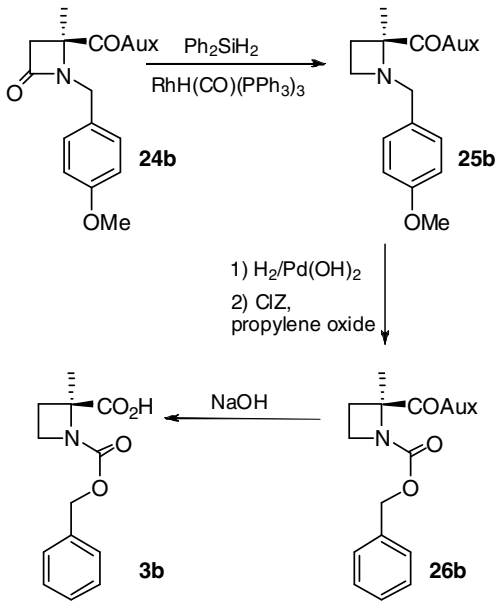
2(*R*,*S*)-Piv-2-MeAze-OMe ((*R*,*S*)-23b). Concentrate HCl (0.14 mL, 1.58 mmol) and $Pd(OH)_2$ (118 mg, 30% w/w) was added to a solution of **(*R*,*S*)-21b** (394 mg, 1.58 mmol) in MeOH (30 mL) at 0 ºC. The suspension was hydrogenated at 50 ºC and 45 psi of pressure for 12 h. After filtration of the catalyst and evaporation of the solvent, the resulting residue was dissolved in dry CH_2Cl_2 (4 mL), cooled to 0 ºC, and under argon atmosphere TEA (0.68 mL, 4.90 mmol) and pivaloyl chloride (0.31 mL, 2.53 mmol) were added. After stirring for 2 h at room temperature it was successively washed with citric acid 10%, $NaHCO_3$ 10%, H_2O and brine. The organic layer was dried over Na_2SO_4, the solvent was evaporated to

dryness and the residue was purified by flash chromatography using as eluent MeOH:CH_2Cl_2 (1:100). This yield compound **(*R*,*S*)-23b** (326 mg, syrup) in 95% yield. ^{1}H NMR ($CDCl_3$): δ 4.50-4.25 (m, 2H, H-4), 3.74 (s, 3H, OMe), 2.35 (ddd, 1H, *J*=11.1, 9.2, 5.3, H-3), 2.11 (ddd, 1H, *J*=11.1, 9.2, 7.0, H-3), 1.68 (s, 3H, 2-CH_3), 1.18 (s, 9H, CH_3-^{t}Bu). ^{13}C NMR ($CDCl_3$): δ 177.7 (CO-^{t}Bu), 173.2 (2-CO), 68.0 (2-C), 52.3 (OMe), 50.1 (4-C), 38.3 (C-^{t}Bu), 28.3 (3-C), 26.6 (CH_3-^{t}Bu), 22.2 (2-CH_3). ES-MS: 214.1 $[M+1]^+$, 449.2 $[2M+Na]^+$. Anal. Calcd. for $C_{11}H_{19}NO_3$: C 61.95, H 8.98, N 6.57, Found: C 61.92, H 8.87, N 6.57.

2(*R*,*S*)-Z-2-MeAze-OH ((*R*,*S*)-3b). NaOH 2N (1.40 mL, 2.78 mmol) was added to a solution of the methyl ester **(*R*,*S*)-22b** (366 mg, 1.39 mmol) in MeOH (5 mL). After stirring 24 h at room temperature, the solvent was evaporated, and the crude product was dissolved in water and washed with EtOAc. Subsequently, the aqueous phase was acidified with HCl 1M to pH=2, and the mixture was extracted with EtOAc. The organic extracts were dried over Na_2SO_4 and evaporated to dryness, yielding the free carboxylic acids **(*R*,*S*)-3b** (317 mg, syrup) in 92% yield. HPLC: t_R= 3.42 min. (A:B=30:70). ^{1}H NMR ($CDCl_3$): *cis*/*trans* isomers ratio: 1:4. *T*rans isomer: δ 8.65 (m, 1H, COOH), 7.30 (m, 5H, Ph), 5.16 (s, 2H, CH_2-Z), 3.91 (m, 2H, H-4), 2.76 (m, 1H, H-3), 2.14 (m, 1H, H-3), 1.74 (s, 3H, 2-CH_3). ^{13}C NMR ($CDCl_3$): δ 174.6 (2-CO), 157.1 (CO-Z), 135.5 (C-Ph), 128.6, 128.2, 127.7 (CH-Ph), 69.1 (2-C), 67.7 and 66.8 (CH_2-Z), 44.7 (4-C), 28.8 and 28.0 (3-C), 22.3 (2-CH_3). ES-MS: 250.1 $[M+1]^+$, 272.0 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{15}NO_4$: C 62.64, H 6.07, N 5.62, Found: C 62.62, H 6.15, N 5.57.

2(*R*,*S*)-Piv-2-MeAze-OH ((*R*,*S*)-4b): Following the same procedure as for compound **(*R*,*S*)-3b**, but starting from **(*R*,*S*)-23b**. This yielded the title compound (syrup) in 75% yield. ^{1}H NMR ($CDCl_3$): δ 13.38 (br s, 1H, COOH), 4.23 (m, 1H, H-4), 4.11 (ddd, 1H, *J*=9.9, 9.0, 5.4, H-4), 2.81 (ddd, 1H, *J*=12.1, 9.9, 7.3, H-3), 2.01 (ddd, 1H, *J*=12.1, 9.1, 5.4, H-3), 1.66 (s, 3H, 2-CH_3), 1.10 (s, 9H, CH_3-^{t}Bu). ES-MS: 200.1 $[M+1]^+$, 222.0 $[M+Na]^+$, 421.2 $[2M+Na]^+$. Anal. Calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03, Found: C 60.22, H 8.53, N 7.12.

Scheme 2



Aux= (+)-10(*N,N*-dicyclohexyl-sulfamoyl)isoborneol

Analytical and spectroscopic data of compounds **24b** and **3b** have been described previously.[2,3]

2(*S*)-1-(*p*-Methoxybenzyl)-2-(10'-*N*,*N*-dicyclohexylsulfamoyl)isobornylcarbonyl)-2-methyl-azetidine (25b). Ph_2SiH_2 (8.37 mL, 45.37 mmol) was added to a solution of the β-lactam **24b** (11.34 g, 18.15 mmol) and $RhH(CO)(PPh_3)_3$ (166 mg, 0.18 mmol) in dry THF (23 mL), under argon atmosphere. After stirring for 24 h the solvent was evaporated to dryness, and the residue was dissolved in Et_2O and washed with HCl 1M. The aqueous phase was basified to pH=11 and extracted with EtOAc, following by purification by flash chromatography using as eluent a gradient from 9 to 14% of EtOAc in hexane. The title compound was obtained as a syrup in 42% yield. HPLC: t_R= 4.77 min. (A:B=30:70). $[\alpha]_D$= +5.73 (c=1.09, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H, *J*=8.5, 2-H and 6-H Pmb), 6.79 (d, 2H, *J*=8.5, 3-H and 5-H Pmb), 4.91 (dd, 1H, *J*=7.8, 2.7, H-1'), 3.76 (s, 3H, OMe), 3.74 (d, 1H, *J*=12.9, 1-CH_2), 3.55 (d, 1H, *J*=12.9, 1-CH_2), 3.25 (m, 2H, H-4, H-1"), 3.16 (d, 1H, *J*=13.4, H-10'), 3.00 (m, 1H, H-4), 2.59 (d, 1H, *J*=13.4, H-10'), 2.56 (m, 1H, H-3), 2.00 (m, 1H, H-3), 1.81 (m, 2H, H-3', H-6'), 1.73 (m, 16H, H-2", H-3', H-3", H-4', H-5', H-6'), 1.56 (m, 2H, H-4"), 1.45 (s, 3H, 4-CH_3), 1.24 (m, 5H, H-3", H-4'), 0.98 (m, 2H, H-4"), 0.93 (s, 3H, H-8' or H-9'), 0.83 (s, 3H, H-8' or H-9'). ^{13}C NMR ($CDCl_3$): δ 173.2 (2-CO), 158.2 (4-C Pmb), 134.6 (1-C Pmb), 129.8 (2-C and 6-C Pmb), 113.6 (3-C and 5-C Pmb), 78.7 (1'-C), 67.5 (2-C), 57.4 (1"-C), 55.2 (OMe), 54.6 (1-CH_2), 54.0 (10'-C), 49.5 and 49.2 (2'-C and 7'-C), 48.8 (4-C), 44.4 (5'-C), 39.9 (6'-C), 33.3 and 32.3 (2"-C), 30.6 (3'-C), 28.9 (3-C), 27.1 (4'-C),

26.4 (3”-C), 25.2 (4”-C), 20.4 (2-CH_3), 20.2 and 19.6 (8’-C and 9’-C). ES-MS: 615.3 $[M+1]^+$. Anal. Calcd. for $C_{35}H_{54}N_2O_5S$: C 68.37, H 8.85, N 4.56, S 5.21, Found: C 68.54, H 8.73, N 4.41, S 5.33.

2(*S*)-1-Benzyloxycarbonyl-2-(10’-*N*,*N*-dicyclohexylsulfamoyl)isobornylcarbonyl)-2-methyl-azetidine (26b). To a solution of the *p*-methoxybenzyl protected azetidine **25b** (972 mg, 1.58 mmol) in MeOH (30 mL) was added concentrated HCl (0.14 mL, 1.58 mmol) and $Pd(OH)_2$ (30% w/w) at 0 ºC, and the suspension was hydrogenated at 50 ºC and 45 psi of pressure for 12 h. After filtration of the catalyst, the solvent was evaporated. The resulting residue was dissolved in dry CH_2Cl_2 (4 mL), cooled to 0 ºC, and Et_3N (0.22 mL, 1.58 mmol), propylene oxide (1.66 mL, 23.7 mmol), and benzyl chloroformate (0.36 mL, 2.53 mmol) were successively added. After stirring for 2 h at room temperature it was successively washed with citric acid 10%, $NaHCO_3$ 10%, H_2O and brine. The organic layer was dried over Na_2SO_4, the solvent was evaporated to dryness and the residue was purified by flash chromatography using as a gradient from 5 to 11% of EtOAc in hexane. Compound **26b** was obtained as a syrup in 49% yield. ^{1}H NMR ($CDCl_3$): *cis*/*trans* isomers ratio: 1:1. δ 7.30 (m, 5H, Ph), 5.06 (s, 2H, CH_2-Z), 4.96 (m, 1H, H-1’), 4.11 (m, 1H, H-4), 3.86 (m, 1H, H-4), 3.31 (d, 1H, *J*=13.4, H-10’), 3.22 (m, 1H, H-1”), 3.09 (d, 1H, *J*=13.4, H-10’), 2.57 (m, 2H, H-3), 2.05 (m, 2H, H-3’, H-6’), 1.70 (m, 18H, H-2”, H-3’, H-3”, H-4’, H-4”, H-5’, H-6’), 1.60 (s, 3H, 4-CH_3), 1.26 (m, 7H, H-3”, H-4’, H-4”), 0.98 and 0,87 (s, 3H, H-8’ or H-9’), 0.82 and 0.78 (s, 3H, H-8’ or H-9’). ^{13}C NMR ($CDCl_3$): Isomer A: δ 170.9 (2-CO), 156.4 (CO-Z), 136.6 (C-Ph), 128.3, 127.9, 127.6 (CH-Ph), 79.7 (1’-C), 68.3 (2-C), 66.7 (CH_2-Z), 57.4 (1”-C), 53.9 (10’-C), 49.3 and 49.0 (2’-C and 7’-C), 45.1 (4-C), 44.3 (5’-C), 39.4 (6’-C), 32.9 and 32.6 (2”-C), 30.5 (3’-C), 28.9 (3-C), 26.9 (4’-C), 26.4 (3”-C), 25.1 (4”-C), 22.8 (2-CH_3), 20.3 and 19.8 (8’-C and 9’-C), Isomer B: δ 171.4 (2-CO), 156.4 (CO-Z), 136.4 (C-Ph), 128.3, 127.8, 127.6 (CH-Ph), 79.7 (1’-C), 68.1 (2-C), 66.2 (CH_2-Z), 57.3 (1”-C), 53.9 (10’-C), 49.5 and 49.2 (2’-C and 7’-C), 46.0 (4-C), 44.3 (5’-C), 39.7 (6’-C), 33.1 and 32.4 (2”-C), 30.5 (3’-C), 29.0 (3-C), 27.1 (4’-C), 26.4 (3”-C), 25.1 (4”-C), 22.3 (2-CH_3), 20.4 and 19.9 (8’-C and 9’-C). ES-MS: 629.3 $[M+1]^+$, 651.3 $[M+Na]^+$, 1279.7 $[2M+Na]^+$. Anal. Calcd. for $C_{35}H_{52}N_2O_6S$: C 66.85, H 8.33, N 4.45, S 5.10, Found: C 66.78, H 8.51, N 4.27, S 4.99.

By-products obtained in the aminolysis of compounds 5b and (*R*,*S*)-7b.

2(*R*) and 2(*S*)-1-(*N*-methyl)carbamoyl-2-MeAze-L-Ala-NHMe ((*R*,*S*)-16): Syrup, 58% yield (obtained from **(*R*,*S*)-7b**, along with **9b**). Eluent: ^{i}PrOH:CH_2Cl_2 (1:5). ^{1}H NMR ($CDCl_3$): Diastereoisomer A: *cis/trans* isomers ratio: 1:3.5. *Trans* isomer: δ 8.10 (m, 1H, NH-Ala), 6.61 (br s, 1H, NH-CH_3), 5.10 (br s, 1H, NH-CON), 4.36 (q, 1H, *J*=7.3, α-H, Ala), 3.74 (m, 2H, H-4), 2.82 (d, 3H, *J*=4.7, CH_3-NHCON), 2.78 (d, 3H, *J*=4.7, CH_3-NH), 2.70 (m, 1H, H-3), 2.02 (m, 1H, H-3), 1.67 (s, 3H,

2-CH_3), 1.41 (d, 3H, *J*=7.3, β-H, Ala), *cis* isomer: δ 8.10 (m, 1H, NH-Ala), 6.61 (br s, 1H, NH-CH_3), 5.10 (br s, 1H, NH-CON), 4.28 (q, 1H, *J*=7.5, α-H, Ala), 3.74 (m, 2H, H-4), 2.82 (m, 3H, CH_3-NHCON), 2.78 (m, 3H, CH_3-NH), 2.70 (m, 1H, H-3), 2.02 (m, 1H, H-3), 1.67 (s, 3H, 2-CH_3), 1.41 (m, 3H, β-H, Ala). ^{13}C NMR ($CDCl_3$): *trans* isomer: δ 174.5 and 172.9 (CON), 159.3 (NCO), 69.5 (2-C), 48.9 (α-C, Ala), 43.6 (4-C), 27.4 (3-C), 26.6 (CH_3-NH or CH_3-NHCON), 26.1 (CH_3-NH or CH_3-NHCON), 20.9 (2-CH_3), 17.7 (β-H, Ala), *cis* isomer: δ 175.4 and 173.5 (CON), 157.8 (NCO), 70.2 (2-C), 49.3 (α-C, Ala), 43.6 (4-C), 27.2 (3-C), 26.6 (CH_3-NH or CH_3-NHCON), 26.1 (CH_3-NH or CH_3-NHCON), 21.8 (2-CH_3), 19.1 (β-C, Ala). ^{1}H NMR ($CDCl_3$): Diastereoisomer B: *cis/trans* isomers ratio: 1:3.5. *Trans* isomer: δ 8.42 (m, 1H, NH-Ala), 6.51 (br s, 1H, NH-CH_3), 5.00 (br s, 1H, NH-CON), 4.36 (q, 1H, *J*=7.2, α-H, Ala), 3.74 (m, 2H, H-4), 2.81 (d, 3H, *J*=4.5, CH_3-NHCON), 2.79 (d, 3H, *J*=4.9, CH_3-NH), 2.70 (m, 1H, H-3), 2.02 (m, 1H, H-3), 1.67 (s, 3H, 2-CH_3), 1.40 (d, 3H, *J*=7.2, β-H, Ala), *cis* isomer: δ 8.42 (m, 1H, NH-Ala), 6.51 (br s, 1H, NH-CH_3), 5.00 (br s, 1H, NH-CON), 4.28 (q, 1H, *J*=7.5, α-H, Ala), 3.74 (m, 2H, H-4), 2.81 (m, 3H, CH_3-NHCON), 2.79 (m, 3H, CH_3-NH), 2.70 (m, 1H, H-3), 2.02 (m, 1H, H-3), 1.67 (s, 3H, 2-CH_3), 1.40 (m, 3H, β-H, Ala). ^{13}C NMR ($CDCl_3$): *trans* isomer: δ 175.0 and 172.9 (CON), 159.2 (NCO), 69.7 (2-C), 48.9 (α-C, Ala), 43.6 (4-C), 26.6 (3-C), 26.2 (CH_3-NH or CH_3-NHCON), 25.9 (CH_3-NH or CH_3-NHCON), 22.2 (2-CH_3), 17.5 (β-C, Ala), *cis* isomer: δ 175.4 and 173.5 (CON), 157.8 (NCO), 70.2 (2-C), 49.3 (α-C, Ala), 43.6 (4-C), 27.2 (3-C), 26.2 (CH_3-NH or CH_3-NHCON), 25.9 (CH_3-NH or CH_3-NHCON), 22.3 (2-CH_3), 18.7 (β-C, Ala). ES-MS: 257.0 $[M+1]^+$, 279.0 $[M+Na]^+$, 535.1 $[2M+Na]^+$. Anal. Calcd. for $C_{11}H_{20}N_4O_3$: C 51.55, H 7.87, N 21.86, Found: C 51.33, H 7.99, N 21.69.

(*S*)-*N*-methyl-2-((*S*)-7a-methyl-1,3-dioxo-1*H*-pyrrolo[1,2-*c*]imidazol-2(3*H*,5*H*,6*H*,7*H*,7a*H*)-yl)propanamide (17): Syrup, 14% yield (obtained from **5b**, along with **8b**). Eluent: Acetone:EtOAc (1:5). ^{1}H NMR ($CDCl_3$): δ 6.02 (br s, 1H, NH-CH_3), 4.57 (c, 1H, *J*=7.5, α-H, Ala), 3.69 (m, 1H, δ-H, Pro), 3.21 (m, 1H, δ-H, Pro), 2.76 (d, 3H, *J*=4.7, CH_3-NH), 2.05 (m, 2H, γ-H, Pro), 1.83 (m, 2H, β-H, Pro), 1.57 (d, 3H, *J*=7.5, β-H, Ala), 1.37 (s, 3H, α-CH_3, Pro). ^{13}C NMR ($CDCl_3$): δ 176.7 and 169.6 (CON), 159.6 (CO-N), 68.7 (α-C, Pro), 50.5 (α-C, Ala), 44.7 (δ-C, Pro), 33.5 (β-C, Pro), 26.6 (CH_3-NH), 25.9 (γ-C, Pro), 21.5 (α-CH_3, Pro), 15.0 (β-C, Ala). ES-MS: 240.1 $[M+1]^+$, 501.2 $[2M+Na]^+$. Anal. Calcd. for $C_{11}H_{17}N_3O_3$: C 55.22, H 7.16, N 17.56, Found: C 54.93, H 7.22, N 17.40.

Relevant Conformational Parameters of Dipeptide Derivatives

Table 1. More relevant topographical parameters of the minimum energy families (within a 3 Kcal/mol window of the global minimum) of conformers for Ac-L-Pro-Ala-NHMe (**12a**)

CONF.	ΔE (Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	d(CO^i-NH^{i+3})	d(CO^i-NH^{i+2})	d(CO^{i+1}-NH^{i+2})	d(αC^i-αC^{i+3})
12a-1	0	-49.4	-50.7	-70.5	-55.5	3.22	3.53	4.14	5.12
12a-2	0.19	-67.1	-49.5	-84.1	-71.4	3.84	3.91	2.23	5.94
12a-3	0.46	-77.5	77.4	-71.9	-60.5	4.79	2.17	4.29	8.88
12a-4	0.49	-77.2	78.5	-82.1	75.1	5.84	2.19	2.25	9.01
12a-5	0.54	-77.5	75.2	-159.0	-60.7	3.14	2.12	4.88	6.76
12a-6	0.69	-69.3	-46.8	-155.0	-61.6	6.08	3.89	4.91	6.54
12a-7	0.70	-73.9	159.3	-69.9	-59.3	6.74	4.31	4.21	9.12
12a-8	0.77	-68.4	-46.1	-150.0	71.7	3.90	3.86	4.07	5.49
12a-9	0.78	-74.8	86.1	58.9	63.4	3.31	2.31	4.07	5.48
12a-10	0.89	-77.5	76.8	-155.0	77.2	5.28	2.15	4.22	8.26
12a-11	0.92	-51.3	-50.1	-154.0	-62.2	5.68	3.57	4.93	6.41
12a-12	1.03	-77.6	75.8	-159.0	150.3	6.32	2.14	4.95	8.67
12a-13	1.19	-53.7	142.9	-82.0	74.8	5.32	3.95	2.24	8.62
12a-14	1.21	-68.7	-47.6	71.6	-69.8	5.46	3.89	2.08	8.95
12a-15	1.32	-51.7	119.7	57.5	61.2	2.95	3.32	3.98	5.62
12a-16	1.77	-76.1	82.5	67.4	170.4	6.12	2.24	4.91	7.50
12a-17	2.09	-51.2	-51.5	66.4	170.9	6.73	3.59	4.90	9.48

Table 2. More relevant topographical parameters of the minimum energy families (within a 3 Kcal/mol window of the global minimum) of conformers for Ac-L-αMePro-Ala-NHMe (**12b**)

CONF.	ΔE (Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	d(CO^i-NH^{i+3})	d(CO^i-NH^{i+2})	d(CO^{i+1}-NH^{i+2})	d(αC^i-αC^{i+3})
12b-1	0	-49.3	-39.7	-60.8	36.1	2.18	3.20	3.40	5.57
12b-2	0.05	-74.4	64.7	-78.9	68.8	5.65	1.98	2.08	8.89
12b-3	0.48	-74.5	65.5	71.0	-64.7	5.29	1.98	1.99	6.69
12b-4	0.49	-74.5	64.0	-70.0	-55.4	4.43	1.97	4.12	8.65
12b-5	0.63	-73.7	65.6	-158	-57.2	2.95	1.96	4.86	6.46
12b-6	0.63	-61.4	-39.8	-65.2	-47.7	2.93	3.50	3.82	5.43
12b-7	0.70	-51.4	-46.5	70.3	-65.8	5.16	3.43	1.99	8.85
12b-8	1.06	-69.2	173.9	-79.0	68.8	5.19	4.65	2.07	7.92
12b-9	1.12	-73.6	67.3	57.7	57.8	3.60	1.99	3.90	5.78
12b-10	1.17	-74.5	64.2	-152.0	70.2	4.84	1.97	4.13	7.86
12b-11	1.27	-51.5	-44.7	-154.0	-61.9	5.50	3.40	4.93	6.18
12b-12	1.53	-52.2	135.8	71.7	-63.4	3.56	3.75	1.97	5.82

12b-13	1.53	-68.2	171.4	70.6	-64.5	3.96	4.58	1.98	6.74
12b-14	1.66	-50.7	108.5	57.2	38.3	2.12	2.98	3.34	5.04
12b-15	1.68	-69.4	174.1	-67.4	-54.6	6.73	4.65	4.04	8.67
12b-16	1.94	-63.3	-40.7	56.3	58.8	6.19	3.56	3.89	8.80
12b-17	2.36	-68.1	168.6	54.7	56.7	4.37	4.54	3.81	7.01
12b-18	2.45	-69.0	173.4	-149.0	72.9	6.91	4.63	4.06	9.94

Table 3. More relevant topographical parameters of the minimum energy families (within a 3 Kcal/mol window of the global minimum) of conformers for Ac-L-Aze-Ala-NHMe (**14a**)

CONF.	ΔE (Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	d(CO^i-NH^{i+3})	d(CO^i-NH^{i+2})	d(CO^{i+1}-NH^{i+2})	d(αC^i-αC^{i+3})
14a-1	0	-69.6	58.0	-78.8	69.0	5.71	2.00	2.08	8.98
14a-2	0.37	-57.8	-48.4	-80.0	67.2	3.94	3.77	2.09	6.36
14a-3	0.42	-69.7	59.4	70.4	-64.9	5.36	2.01	1.99	7.00
14a-4	0.45	-69.9	56.5	-70.6	-56.4	4.41	1.99	4.16	8.68
14a-5	0.48	-67.5	59.0	-158.0	-56.5	2.85	1.98	4.85	6.53
14a-6	0.71	-54.1	-43.3	-65.6	-48.0	2.96	3.56	3.84	5.68
14a-7	1.06	-67.8	62.7	57.7	58.6	3.54	2.03	3.94	6.05
14a-8	1.15	-60.8	-46.1	70.1	-65.8	5.61	3.74	1.99	9.00
14a-9	1.22	-67.2	179.6	-78.4	69.2	5.29	4.97	2.08	7.86
14a-10	1.27	-69.8	58.1	-157.0	156.5	6.20	2.01	4.97	8.57
14a-11	1.66	-60.9	-44.4	-155.0	-62.0	5.86	3.71	4.93	6.37
14a-12	1.73	-59.9	-44.5	-155.0	157.4	6.28	3.70	4.97	7.38
14a-13	1.84	-67.3	178.8	-67.6	-55.3	6.92	4.95	4.07	8.60
14a-14	2.00	-60.8	-45.3	56.1	60.1	6.47	3.73	3.93	8.90

Table 4. More relevant topographical parameters of the minimum energy families (within a 3 Kcal/mol window of the global minimum) of conformers for Ac-2(*S*)-2-MeAze-Ala-NHMe (**14b**)

CONF.	ΔE (Kcal/mol)	ϕ_2	ψ_2	ϕ_3	ψ_3	d(CO^i-NH^{i+3})	d(CO^i-NH^{i+2})	d(CO^{i+1}-NH^{i+2})	d(αC^i-αC^{i+3})
24a-1	0	-68.4	54.7	-79.1	68.6	5.69	1.98	2.08	8.94
24a-2	0.41	-68.7	53.6	-70.3	-55.6	4.31	1.97	4.13	8.60
24a-3	0.50	-68.6	55.8	70.3	-65.0	5.41	1.98	1.99	7.06
24a-4	0.52	-66.7	56.4	-158.0	-56.1	2.82	1.96	4.85	6.45
24a-5	0.84	-56.9	-46.6	-79.2	67.2	3.84	3.71	2.09	6.20
24a-6	1.08	-51.8	-35.0	-60.6	-38.8	2.19	3.29	3.53	5.62
24a-7	1.11	-68.6	54.0	-153.0	70.2	4.75	1.97	4.13	7.79
24a-8	1.15	-67.3	57.9	57.2	58.7	3.66	1.99	3.93	6.10
24a-9	1.32	-68.6	55.1	-157.0	156.7	6.18	1.99	4.97	8.48
24a-10	1.36	-67.8	-166.0	-78.5	69.1	5.08	5.15	2.08	7.46

24a-11	1.67	-60.0	-44.0	70.7	-65.7	5.60	3.68	1.99	8.95
24a-12	1.83	-67.4	-167.0	70.5	-64.9	4.31	5.12	1.98	7.65
24a-13	1.98	-67.9	-166.0	-67.7	-55.2	6.86	5.15	4.08	8.17
24a-14	2.66	-67.9	-166.0	-157.0	158.0	8.01	5.15	4.97	10.65

Atomic Coordinates for Figure 2 conformers

Atomic coordinates in pdb format for the conformer of derivative Ac-Pro-Ala-NHMe (**12a**) depicted in Figure 2:

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REMARK   4
REMARK   4 PROA COMPLIES WITH FORMAT V. 2.0,  4-OCT-2007
ATOM      1  N   PROn    1       1.958   1.738  -0.073  1.00  0.00           N
ATOM      2  CA  PROn    1       2.313   0.388  -0.513  1.00  0.00           C
ATOM      3  HA  PROn    1       3.401   0.302  -0.459  1.00  0.00           H
ATOM      4  C   PROn    1       1.842   0.065  -1.939  1.00  0.00           C
ATOM      5  O   PROn    1       2.637  -0.390  -2.762  1.00  0.00           O
ATOM      6  CB  PROn    1       1.702  -0.561   0.529  1.00  0.00           C
ATOM      7  HB1 PROn    1       0.671  -0.815   0.271  1.00  0.00           H
ATOM      8  HB2 PROn    1       2.286  -1.475   0.651  1.00  0.00           H
ATOM      9  CG  PROn    1       1.691   0.292   1.797  1.00  0.00           C
ATOM     10  HG1 PROn    1       0.956  -0.054   2.526  1.00  0.00           H
ATOM     11  HG2 PROn    1       2.687   0.290   2.244  1.00  0.00           H
ATOM     12  CD  PROn    1       1.369   1.687   1.258  1.00  0.00           C
ATOM     13  HD1 PROn    1       0.288   1.812   1.175  1.00  0.00           H
ATOM     14  HD2 PROn    1       1.779   2.447   1.926  1.00  0.00           H
ATOM     15  N1  PROn    1       0.554   0.309  -2.225  1.00  0.00           N
ATOM     16  HN1 PROn    1      -0.033   0.689  -1.496  1.00  0.00           H
ATOM     17  C1  PROn    1      -0.070   0.068  -3.523  1.00  0.00           C
ATOM     18  H1  PROn    1       0.186  -0.943  -3.850  1.00  0.00           H
ATOM     19  C2  PROn    1       0.443   1.077  -4.562  1.00  0.00           C
ATOM     20  O1  PROn    1       0.954   0.678  -5.608  1.00  0.00           O
ATOM     21  C3  PROn    1      -1.598   0.129  -3.383  1.00  0.00           C
ATOM     22  H31 PROn    1      -2.067  -0.067  -4.348  1.00  0.00           H
ATOM     23  H32 PROn    1      -1.937  -0.627  -2.672  1.00  0.00           H
ATOM     24  H33 PROn    1      -1.915   1.111  -3.028  1.00  0.00           H
ATOM     25  C4  PROn    1       2.178   2.868  -0.776  1.00  0.00           C
ATOM     26  O2  PROn    1       2.723   2.869  -1.880  1.00  0.00           O
ATOM     27  C5  PROn    1       1.722   4.197  -0.167  1.00  0.00           C
ATOM     28  H51 PROn    1       1.844   5.005  -0.889  1.00  0.00           H
ATOM     29  H52 PROn    1       0.669   4.142   0.112  1.00  0.00           H
ATOM     30  H53 PROn    1       2.321   4.427   0.714  1.00  0.00           H
ATOM     31  N2  PROn    1       0.308   2.380  -4.268  1.00  0.00           N
ATOM     32  H2  PROn    1      -0.116   2.634  -3.387  1.00  0.00           H
ATOM     33  C6  PROn    1       0.739   3.464  -5.138  1.00  0.00           C
ATOM     34  H61 PROn    1       1.815   3.401  -5.307  1.00  0.00           H
ATOM     35  H62 PROn    1       0.215   3.409  -6.093  1.00  0.00           H
ATOM     36  H63 PROn    1       0.510   4.417  -4.661  1.00  0.00           H
END
```

Atomic coordinates in pdb format for the conformer of derivative Ac-α-MePro-Ala-NHMe (**12b**) depicted in Figure 2:

```
REMARK   4
REMARK   4 MEPR COMPLIES WITH FORMAT V. 2.0,  4-OCT-2007
ATOM      1  N   PROn    1       1.641   2.811  -1.081  1.00  0.00           N
ATOM      2  CA  PROn    1       1.257   3.053  -2.481  1.00  0.00           C
ATOM      3  C   PROn    1       0.572   1.832  -3.145  1.00  0.00           C
ATOM      4  O   PROn    1      -0.383   1.985  -3.906  1.00  0.00           O
ATOM      5  CB  PROn    1       2.584   3.372  -3.196  1.00  0.00           C
ATOM      6  HB1 PROn    1       3.075   2.454  -3.528  1.00  0.00           H
ATOM      7  HB2 PROn    1       2.461   4.040  -4.050  1.00  0.00           H
ATOM      8  CG  PROn    1       3.446   3.995  -2.098  1.00  0.00           C
ATOM      9  HG1 PROn    1       4.514   3.903  -2.305  1.00  0.00           H
ATOM     10  HG2 PROn    1       3.186   5.048  -1.976  1.00  0.00           H
```

```
ATOM     11  CD  PROn    1       3.026   3.207  -0.856  1.00  0.00           C
ATOM     12  HD1 PROn    1       3.644   2.312  -0.765  1.00  0.00           H
ATOM     13  HD2 PROn    1       3.143   3.828   0.034  1.00  0.00           H
ATOM     14  N1  PROn    1       1.070   0.619  -2.857  1.00  0.00           N
ATOM     15  HN1 PROn    1       1.860   0.573  -2.230  1.00  0.00           H
ATOM     16  C1  PROn    1       0.559  -0.648  -3.383  1.00  0.00           C
ATOM     17  H1  PROn    1       0.619  -0.610  -4.474  1.00  0.00           H
ATOM     18  C2  PROn    1      -0.909  -0.918  -2.991  1.00  0.00           C
ATOM     19  O1  PROn    1      -1.659  -1.483  -3.787  1.00  0.00           O
ATOM     20  C3  PROn    1       1.472  -1.789  -2.912  1.00  0.00           C
ATOM     21  H31 PROn    1       1.458  -1.864  -1.823  1.00  0.00           H
ATOM     22  H32 PROn    1       1.134  -2.736  -3.335  1.00  0.00           H
ATOM     23  H33 PROn    1       2.497  -1.609  -3.241  1.00  0.00           H
ATOM     24  C4  PROn    1       0.835   2.297  -0.128  1.00  0.00           C
ATOM     25  O2  PROn    1      -0.327   1.959  -0.351  1.00  0.00           O
ATOM     26  C5  PROn    1       1.406   2.118   1.280  1.00  0.00           C
ATOM     27  H51 PROn    1       2.316   1.518   1.243  1.00  0.00           H
ATOM     28  H52 PROn    1       1.625   3.092   1.718  1.00  0.00           H
ATOM     29  H53 PROn    1       0.681   1.607   1.916  1.00  0.00           H
ATOM     30  C7  PROn    1       0.351   4.304  -2.527  1.00  0.00           C
ATOM     31  H71 PROn    1       0.142   4.583  -3.560  1.00  0.00           H
ATOM     32  H72 PROn    1      -0.598   4.105  -2.026  1.00  0.00           H
ATOM     33  H73 PROn    1       0.828   5.151  -2.032  1.00  0.00           H
ATOM     34  N2  PROn    1      -1.314  -0.525  -1.772  1.00  0.00           N
ATOM     35  H2  PROn    1      -0.659  -0.028  -1.185  1.00  0.00           H
ATOM     36  C6  PROn    1      -2.664  -0.709  -1.259  1.00  0.00           C
ATOM     37  H61 PROn    1      -3.381  -0.191  -1.897  1.00  0.00           H
ATOM     38  H62 PROn    1      -2.911  -1.771  -1.222  1.00  0.00           H
ATOM     39  H63 PROn    1      -2.724  -0.295  -0.252  1.00  0.00           H
END
```

Atomic coordinates in pdb format for the conformer of derivative Ac-Aze-Ala-NHMe (**14a**) depicted in Figure 2:

```
REMARK   4
REMARK   4 SAZG COMPLIES WITH FORMAT V. 2.0,  4-OCT-2007
ATOM      1  N1  AZE     1       8.230   1.923  -5.990  1.00  0.00           N
ATOM      2  C2  AZE     1       9.502   2.595  -5.924  1.00  0.00           C
ATOM      3  C   AZE     1       8.806   0.671  -5.553  1.00  0.00           C
ATOM      4  HC  AZE     1       8.755  -0.084  -6.340  1.00  0.00           H
ATOM      5  C3  AZE     1      10.215   1.309  -5.458  1.00  0.00           C
ATOM      6  H21 AZE     1       9.512   3.384  -5.169  1.00  0.00           H
ATOM      7  H22 AZE     1       9.845   2.939  -6.901  1.00  0.00           H
ATOM      8  H31 AZE     1      10.630   1.399  -4.452  1.00  0.00           H
ATOM      9  H32 AZE     1      10.918   0.917  -6.195  1.00  0.00           H
ATOM     10  C9  AZE     1       7.023   2.275  -6.456  1.00  0.00           C
ATOM     11  O1  AZE     1       6.081   1.485  -6.504  1.00  0.00           O
ATOM     12  C10 AZE     1       6.848   3.715  -6.932  1.00  0.00           C
ATOM     13 H101 AZE     1       7.080   4.403  -6.118  1.00  0.00           H
ATOM     14 H102 AZE     1       7.517   3.909  -7.771  1.00  0.00           H
ATOM     15 H103 AZE     1       5.820   3.885  -7.254  1.00  0.00           H
ATOM     16  C4  AZE     1       8.227   0.147  -4.227  1.00  0.00           C
ATOM     17  O4  AZE     1       8.962  -0.089  -3.267  1.00  0.00           O
ATOM     18  N   ALA     1B      6.902  -0.059  -4.188  1.00  0.00           N
ATOM     19  HN  ALA     1B      6.369   0.171  -5.017  1.00  0.00           H
ATOM     20  C5  ALA     1B      6.158  -0.551  -3.028  1.00  0.00           C
ATOM     21  C6  ALA     1B      4.694  -0.101  -3.154  1.00  0.00           C
ATOM     22  C7  ALA     1B      6.304  -2.078  -2.877  1.00  0.00           C
ATOM     23  O   ALA     1B      5.346  -2.827  -3.070  1.00  0.00           O
ATOM     24  N2  ALA     1B      7.516  -2.533  -2.524  1.00  0.00           N
ATOM     25  C8  ALA     1B      7.845  -3.938  -2.334  1.00  0.00           C
ATOM     26  H5  ALA     1B      6.553  -0.084  -2.123  1.00  0.00           H
ATOM     27  H61 ALA     1B      4.126  -0.427  -2.281  1.00  0.00           H
ATOM     28  H62 ALA     1B      4.642   0.988  -3.213  1.00  0.00           H
ATOM     29  H63 ALA     1B      4.238  -0.523  -4.051  1.00  0.00           H
ATOM     30  H2  ALA     1B      8.257  -1.854  -2.408  1.00  0.00           H
ATOM     31  H81 ALA     1B      8.895  -4.026  -2.052  1.00  0.00           H
ATOM     32  H82 ALA     1B      7.228  -4.364  -1.542  1.00  0.00           H
ATOM     33  H83 ALA     1B      7.679  -4.490  -3.260  1.00  0.00           H
```

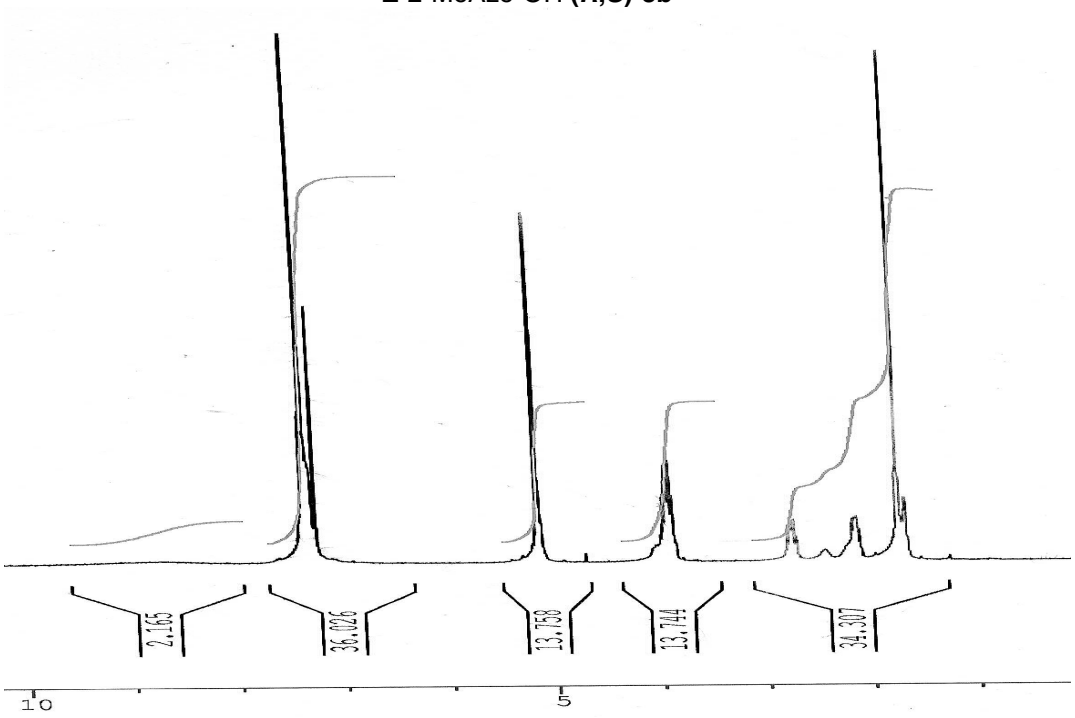
```
END
```

Atomic coordinates in pdb format for the conformer of derivative Ac-2-MeAze-Ala-NHMe (**14b**) depicted in Figure 2:

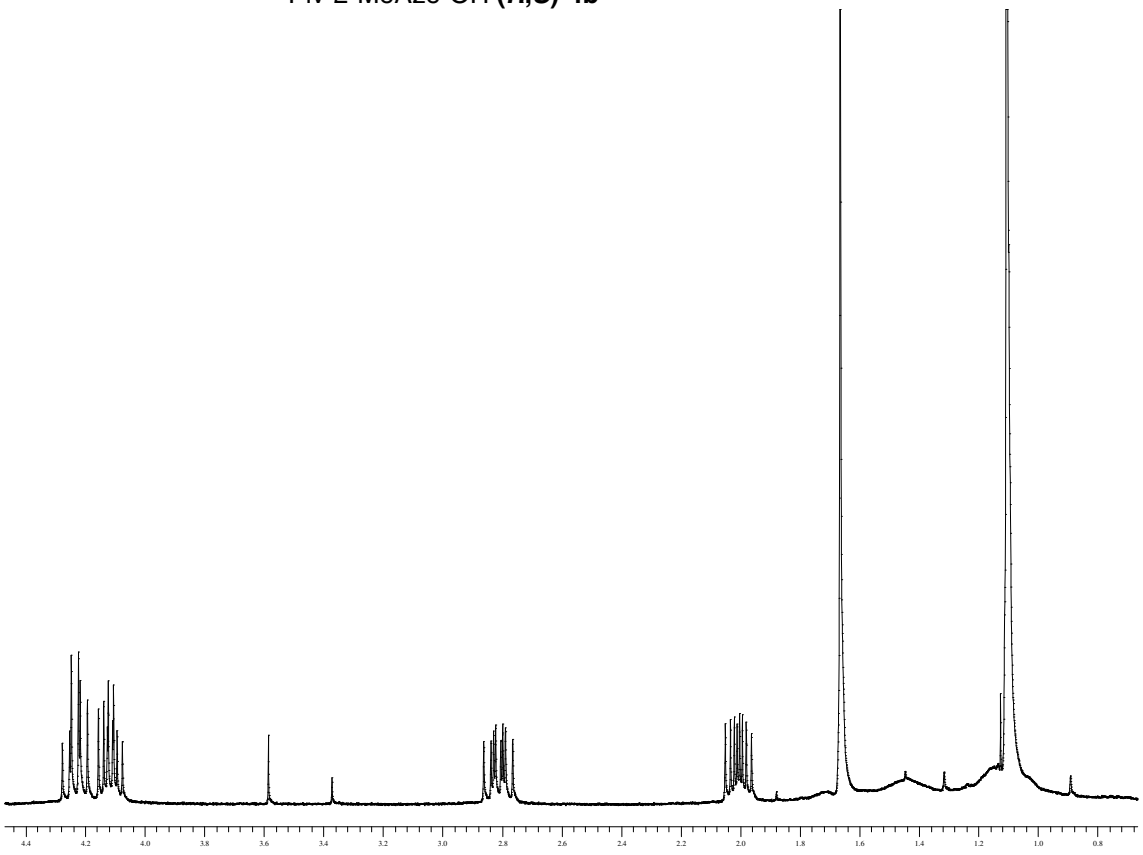
```
REMARK   4
REMARK   4   F7 COMPLIES WITH FORMAT V. 2.0,  4-OCT-2007
ATOM      1  C1  AZE     1       8.664  -1.860  -4.286  1.00  0.00           C
ATOM      2  H11 AZE     1       8.487  -2.922  -4.106  1.00  0.00           H
ATOM      3  H12 AZE     1       9.575  -1.754  -4.877  1.00  0.00           H
ATOM      4  H13 AZE     1       8.809  -1.364  -3.325  1.00  0.00           H
ATOM      5  N1  AZE     1       6.219  -1.564  -4.409  1.00  0.00           N
ATOM      6  C2  AZE     1       5.790  -2.345  -5.541  1.00  0.00           C
ATOM      7  C   AZE     1       7.482  -1.232  -5.043  1.00  0.00           C
ATOM      8  C3  AZE     1       7.096  -2.050  -6.304  1.00  0.00           C
ATOM      9  H21 AZE     1       4.910  -1.921  -6.029  1.00  0.00           H
ATOM     10  H22 AZE     1       5.663  -3.402  -5.304  1.00  0.00           H
ATOM     11  H31 AZE     1       6.937  -1.463  -7.210  1.00  0.00           H
ATOM     12  H32 AZE     1       7.717  -2.929  -6.483  1.00  0.00           H
ATOM     13  C9  AZE     1       5.699  -1.349  -3.192  1.00  0.00           C
ATOM     14  O1  AZE     1       6.280  -0.685  -2.334  1.00  0.00           O
ATOM     15  C10 AZE     1       4.332  -1.962  -2.897  1.00  0.00           C
ATOM     16 H101 AZE     1       4.392  -3.048  -2.974  1.00  0.00           H
ATOM     17 H102 AZE     1       4.009  -1.697  -1.890  1.00  0.00           H
ATOM     18 H103 AZE     1       3.599  -1.589  -3.612  1.00  0.00           H
ATOM     19  C4  AZE     1       7.669   0.281  -5.295  1.00  0.00           C
ATOM     20  O4  AZE     1       7.951   0.700  -6.418  1.00  0.00           O
ATOM     21  N   ALA     1B      7.538   1.096  -4.237  1.00  0.00           N
ATOM     22  HN  ALA     1B      7.304   0.674  -3.348  1.00  0.00           H
ATOM     23  C5  ALA     1B      7.676   2.552  -4.272  1.00  0.00           C
ATOM     24  C6  ALA     1B      6.896   3.150  -3.089  1.00  0.00           C
ATOM     25  C7  ALA     1B      9.159   2.971  -4.284  1.00  0.00           C
ATOM     26  O   ALA     1B      9.663   3.540  -3.315  1.00  0.00           O
ATOM     27  N2  ALA     1B      9.854   2.686  -5.396  1.00  0.00           N
ATOM     28  C8  ALA     1B     11.261   3.004  -5.592  1.00  0.00           C
ATOM     29  H5  ALA     1B      7.210   2.937  -5.182  1.00  0.00           H
ATOM     30  H61 ALA     1B      6.956   4.239  -3.114  1.00  0.00           H
ATOM     31  H62 ALA     1B      5.845   2.860  -3.151  1.00  0.00           H
ATOM     32  H63 ALA     1B      7.304   2.793  -2.142  1.00  0.00           H
ATOM     33  H2  ALA     1B      9.372   2.196  -6.138  1.00  0.00           H
ATOM     34  H81 ALA     1B     11.415   4.081  -5.524  1.00  0.00           H
ATOM     35  H82 ALA     1B     11.867   2.502  -4.836  1.00  0.00           H
ATOM     36  H83 ALA     1B     11.572   2.662  -6.579  1.00  0.00           H
END
```

^{1}H and ^{13}C NMR spectra of the final products

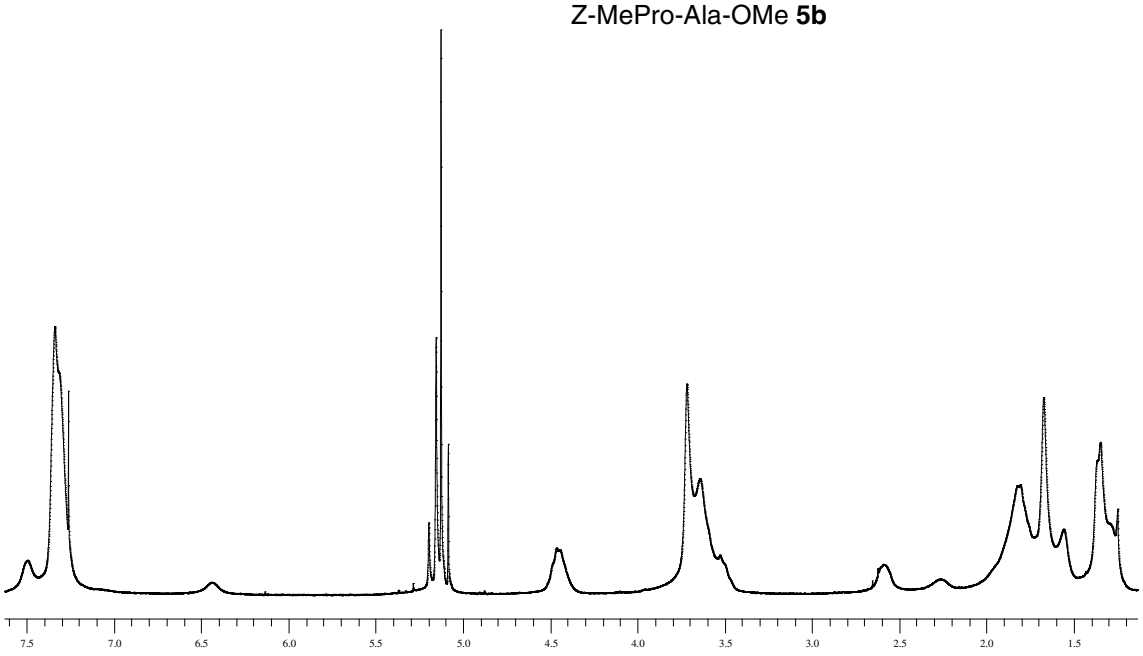
Z-2-MeAze-OH (***R,S***)-**3b**



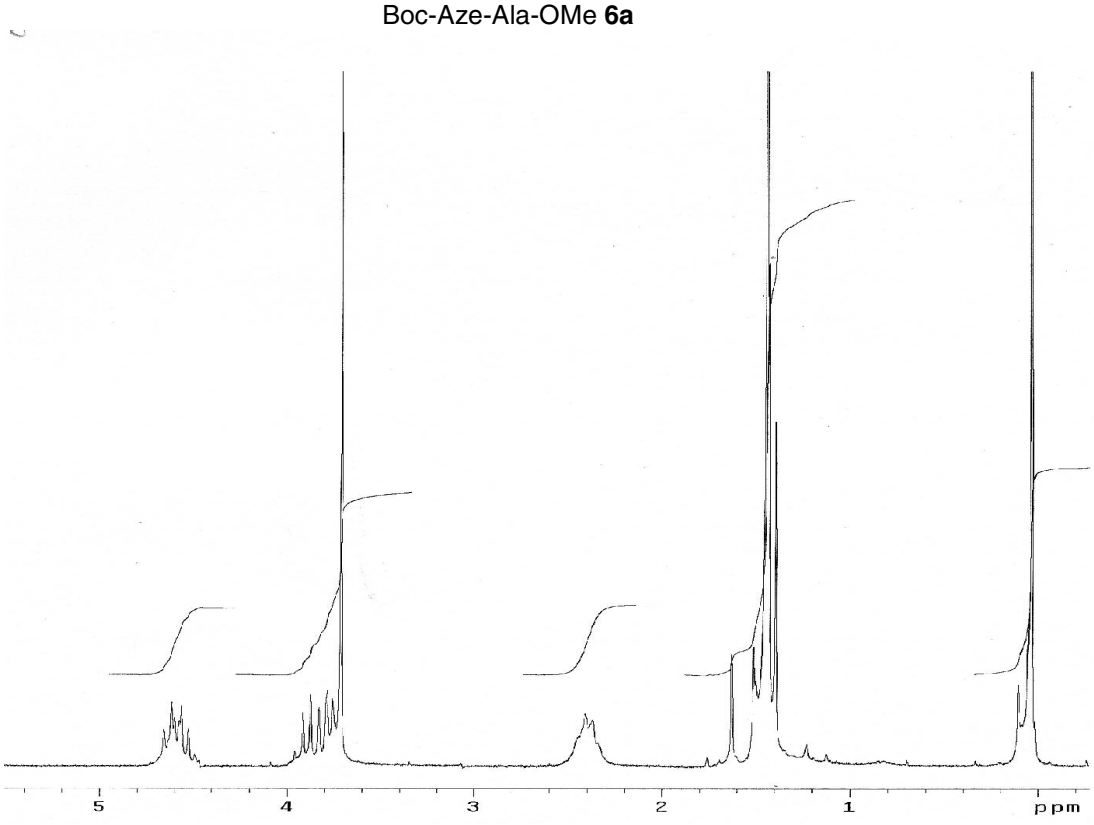
Piv-2-MeAze-OH (***R,S***)-**4b**



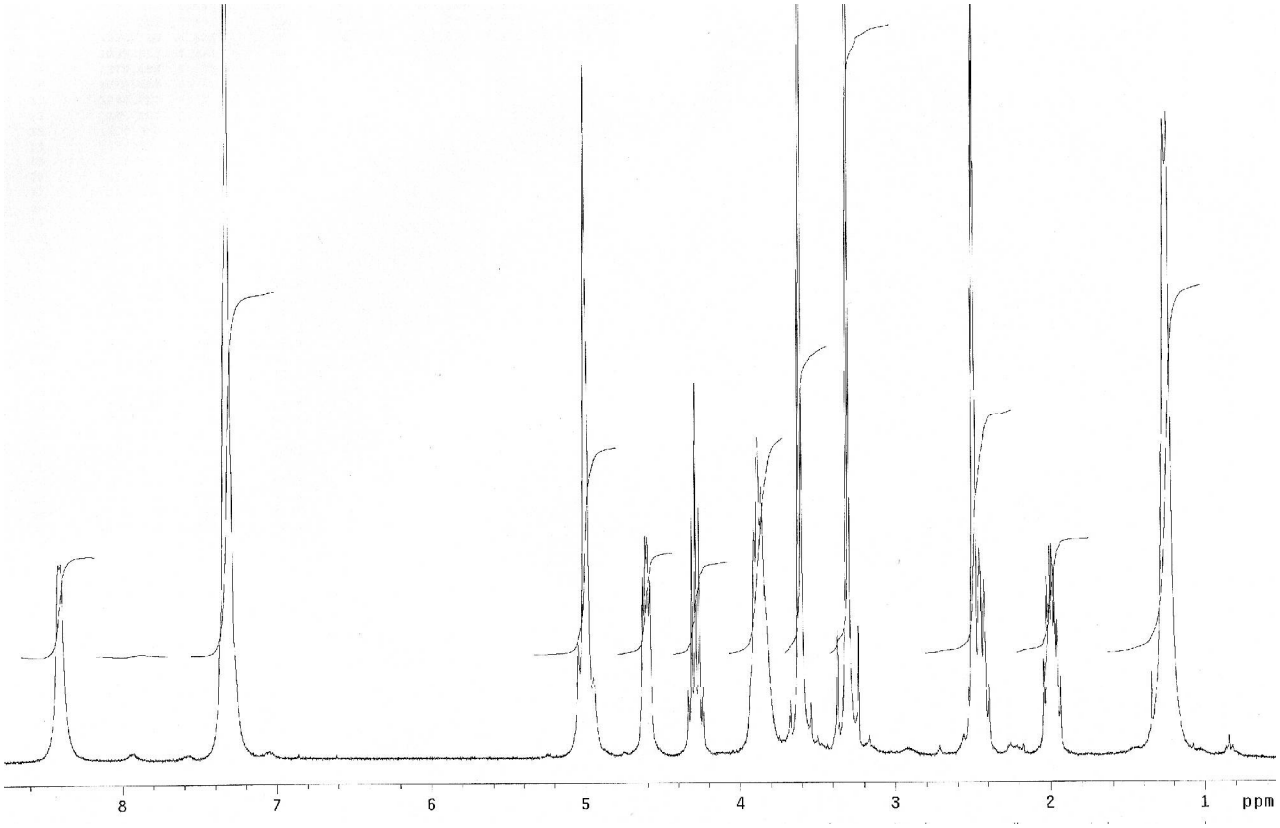
Z-MePro-Ala-OMe **5b**



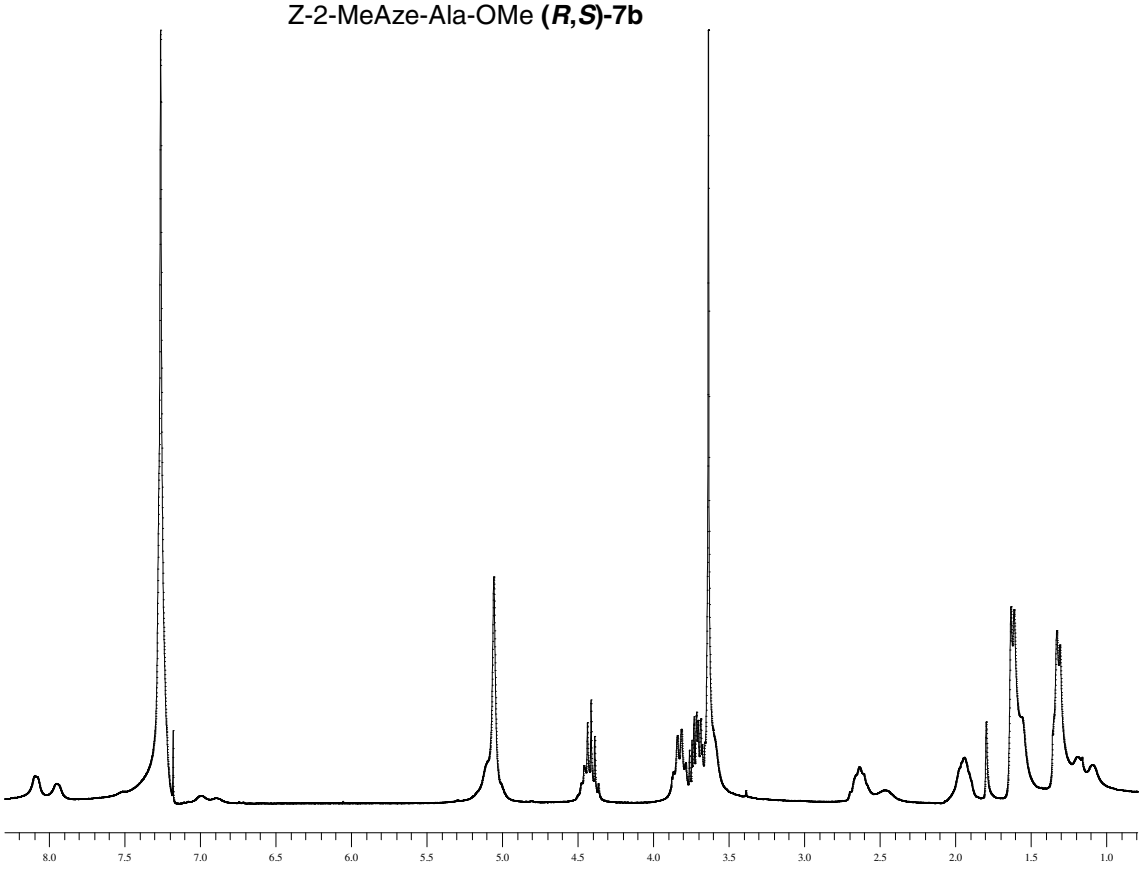
Boc-Aze-Ala-OMe **6a**

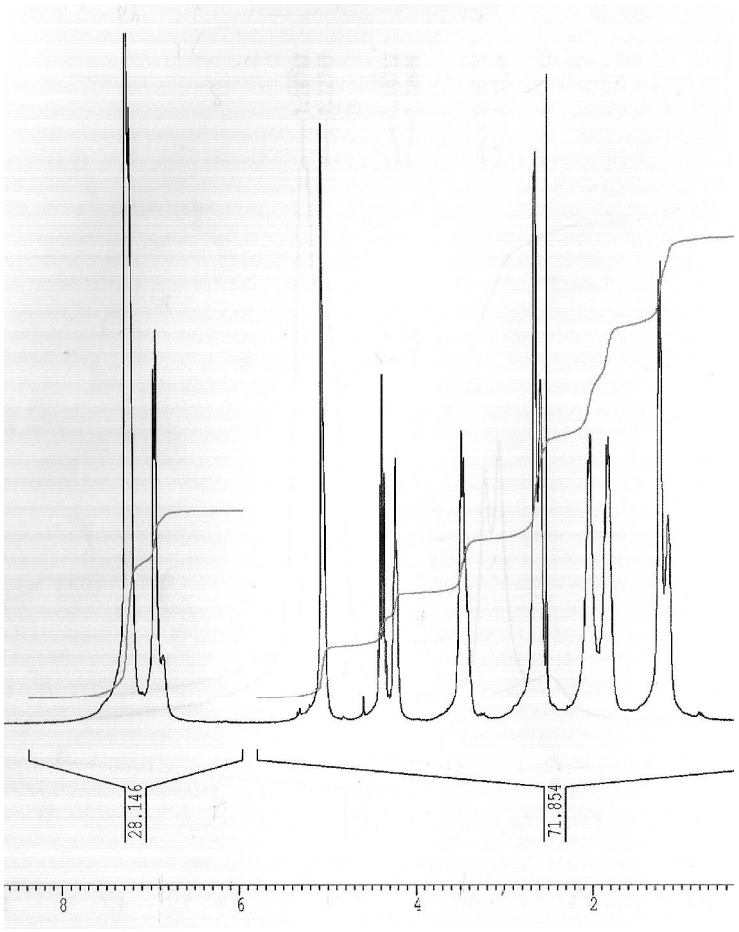


Z-Aze-Ala-OMe **7a**



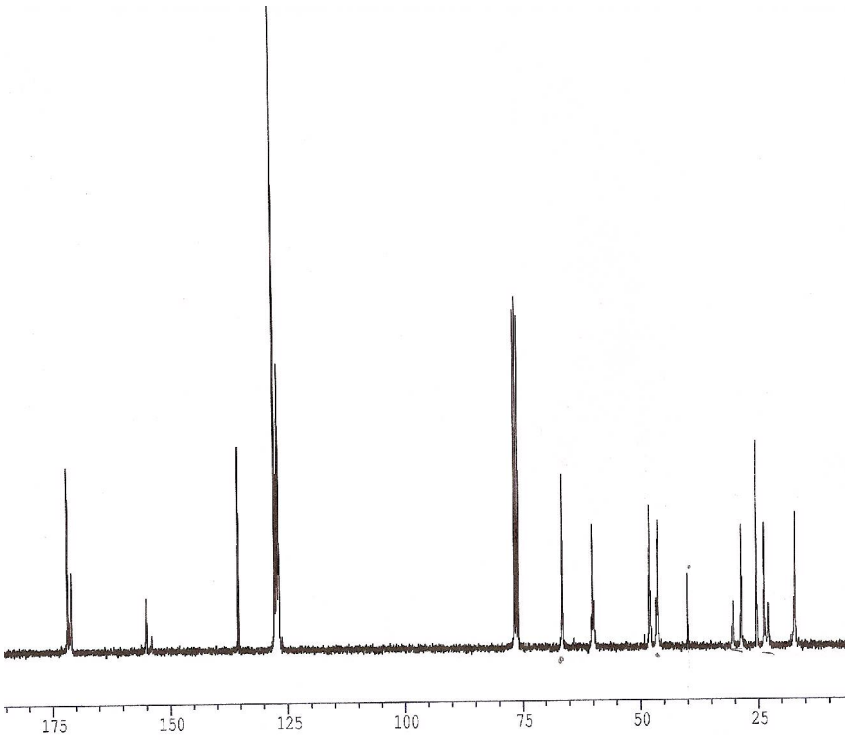
Z-2-MeAze-Ala-OMe **(*R*,*S*)-7b**



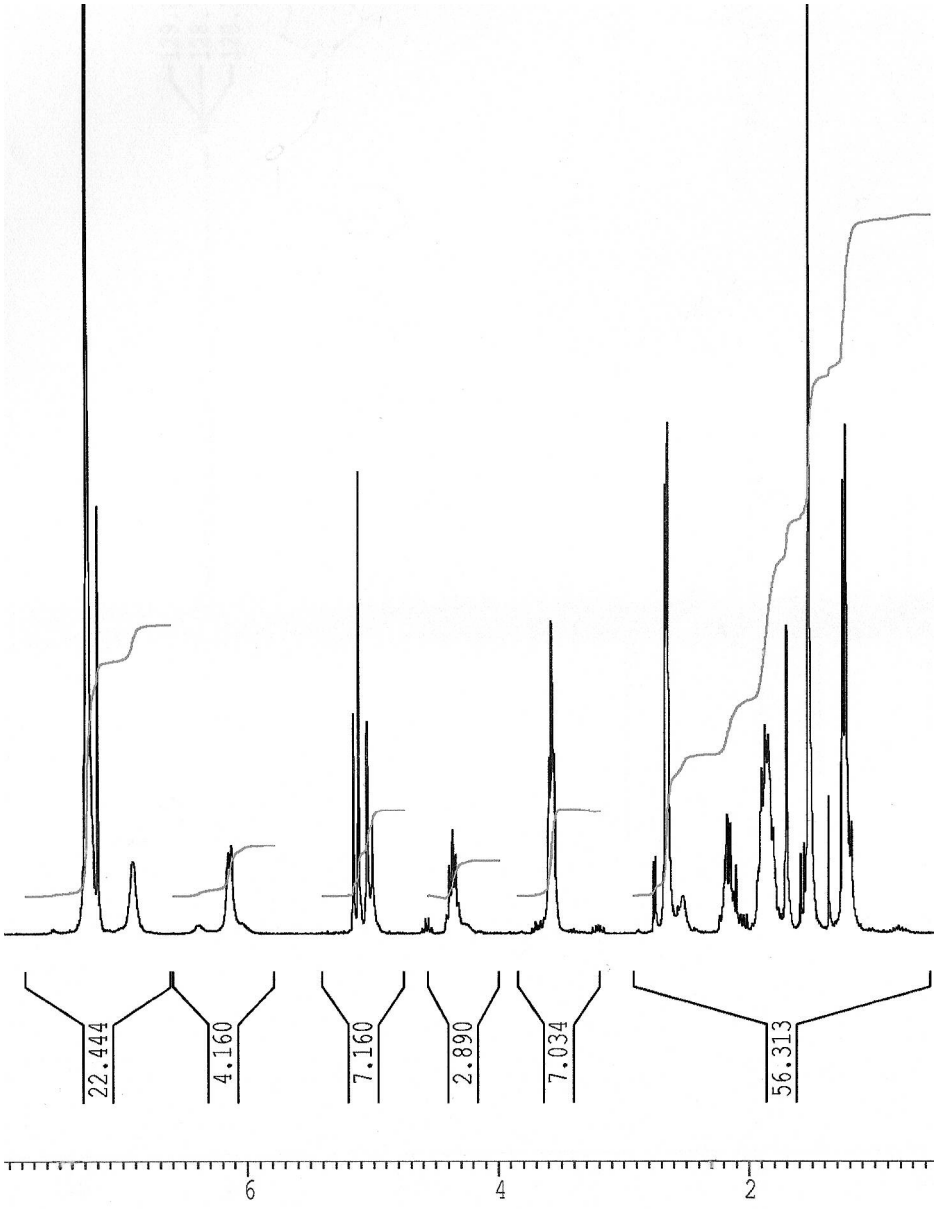


Z-Pro-Ala-NHMe **8a**

Cis/trans: 1:2.6

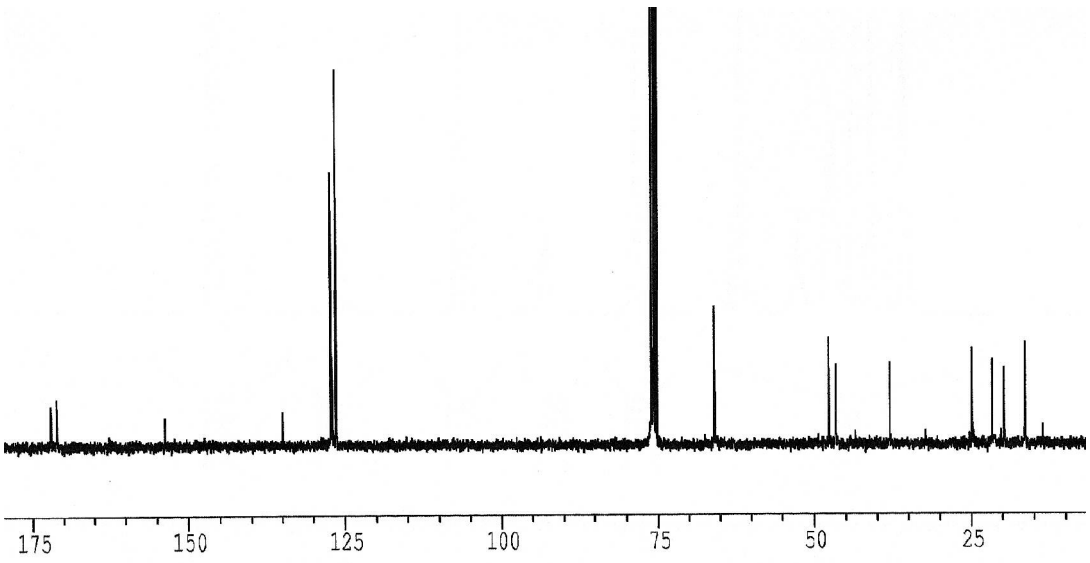


Z-Pro-Ala-NHMe **8a**

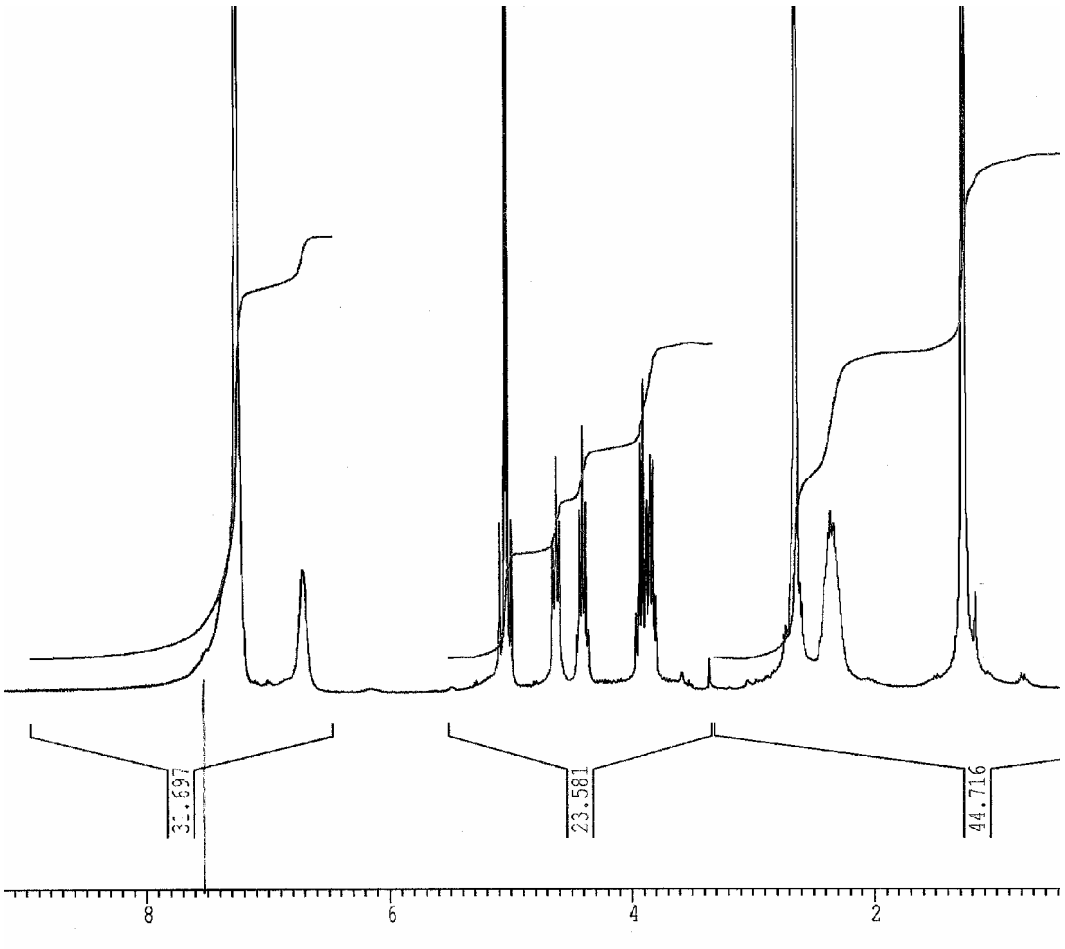


Z-α-MePro-Ala-NHMe **8b**

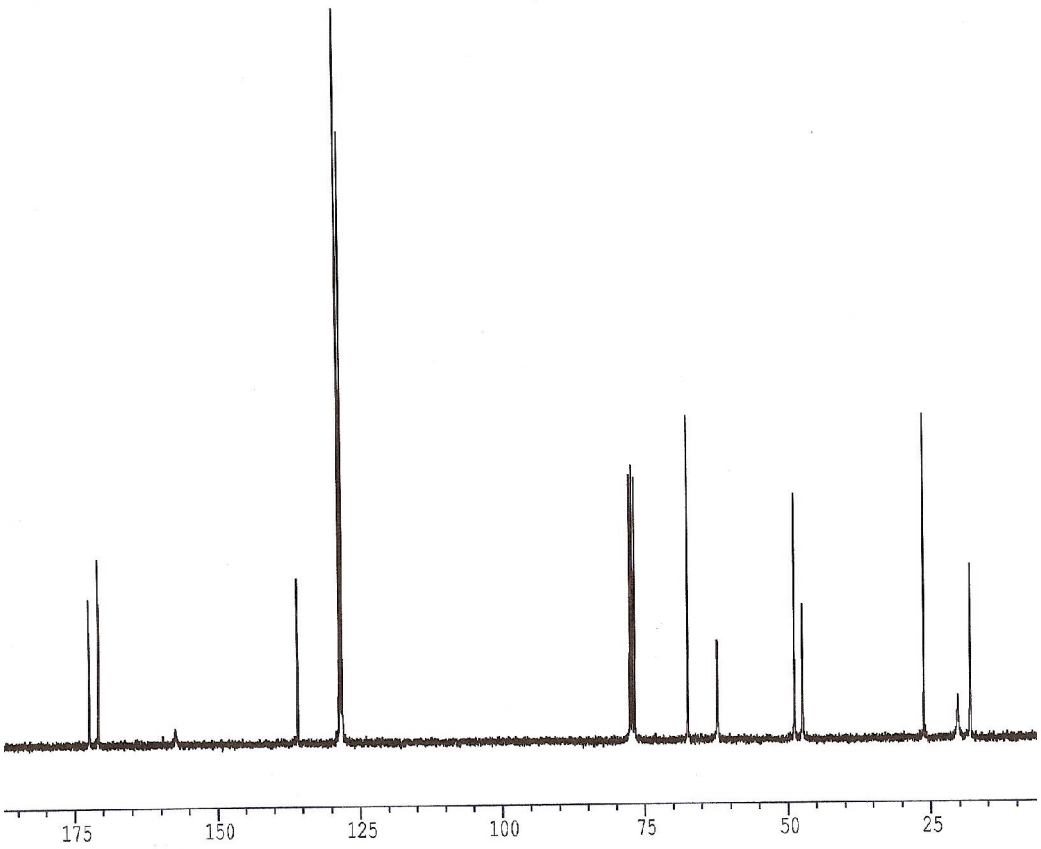
Cis/trans: 1:6



Z-α-MePro-Ala-NHMe **8b**



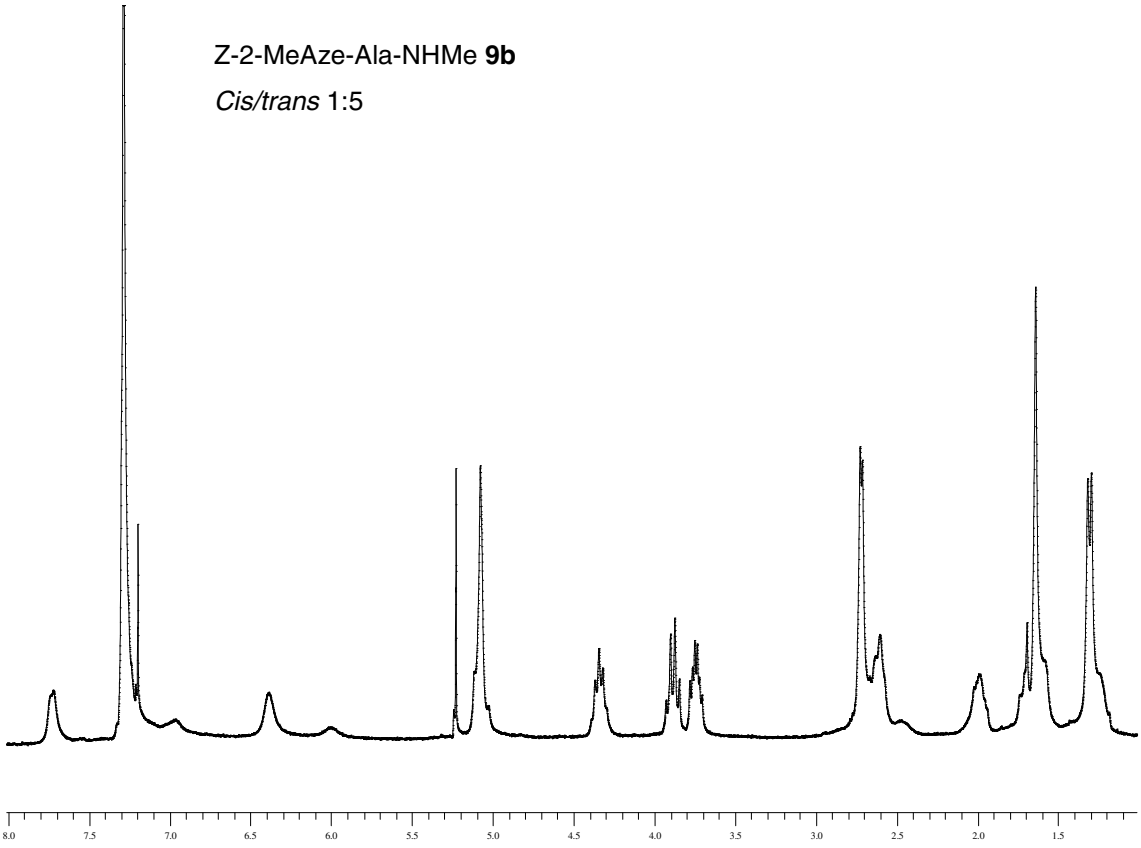
Z-Aze-Ala-NHMe **9a**



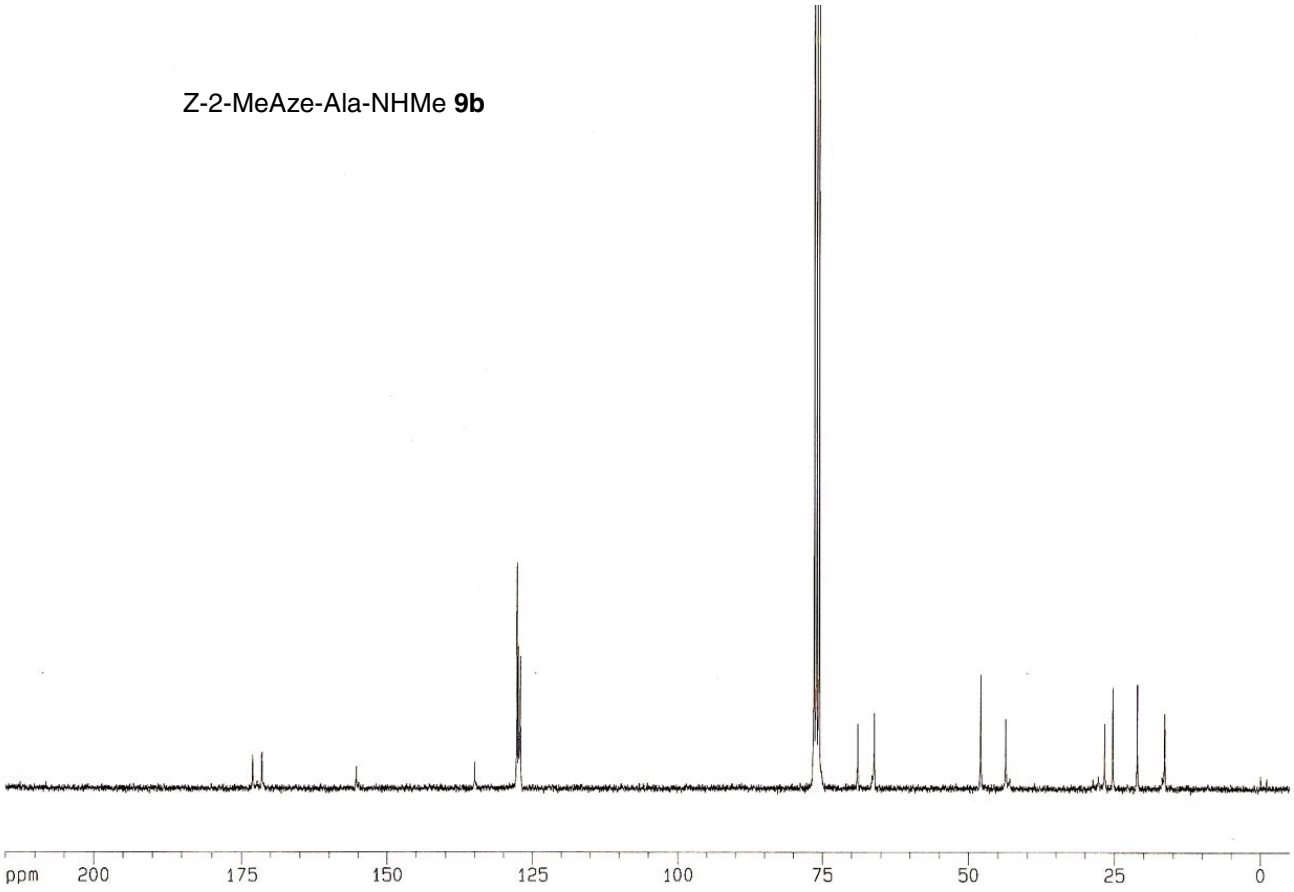
Z-Aze-Ala-NHMe **9a**

Z-2-MeAze-Ala-NHMe **9b**

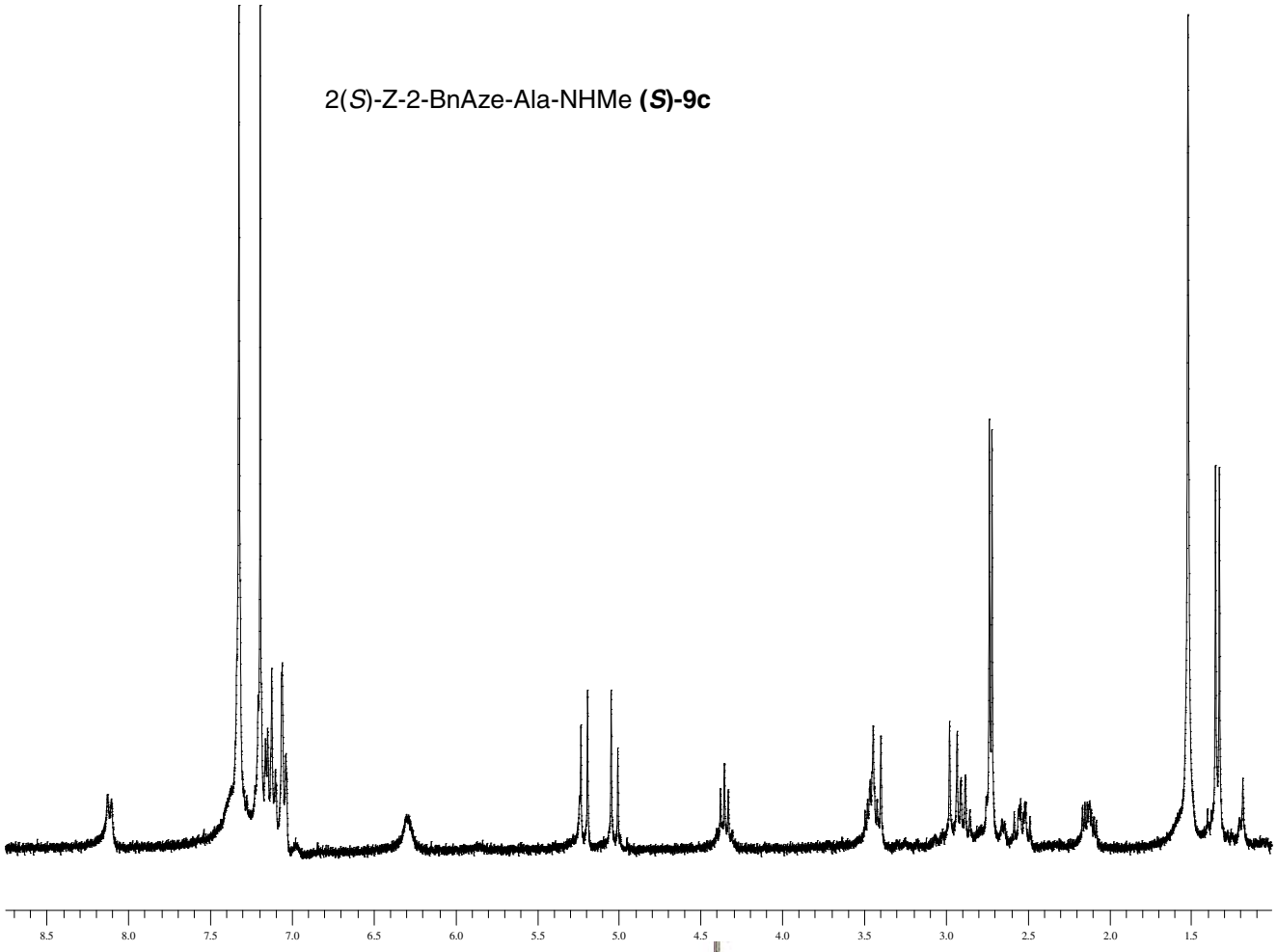
Cis/trans 1:5



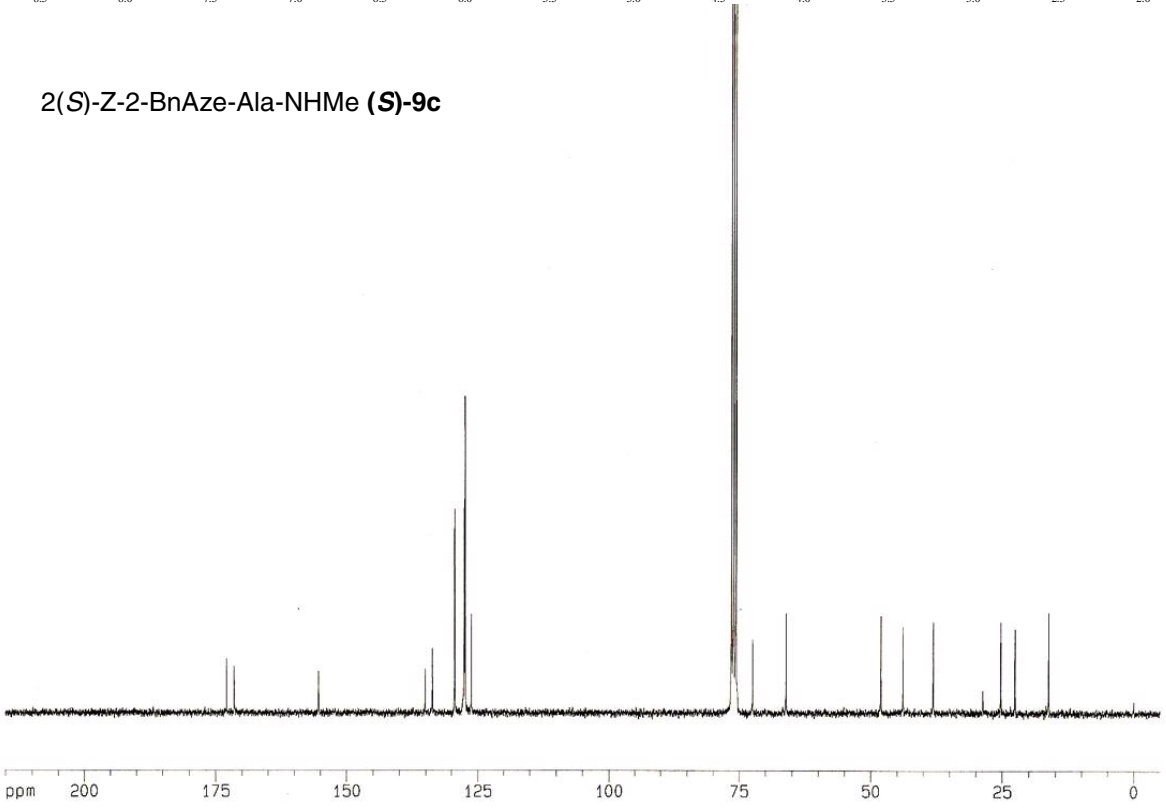
Z-2-MeAze-Ala-NHMe **9b**



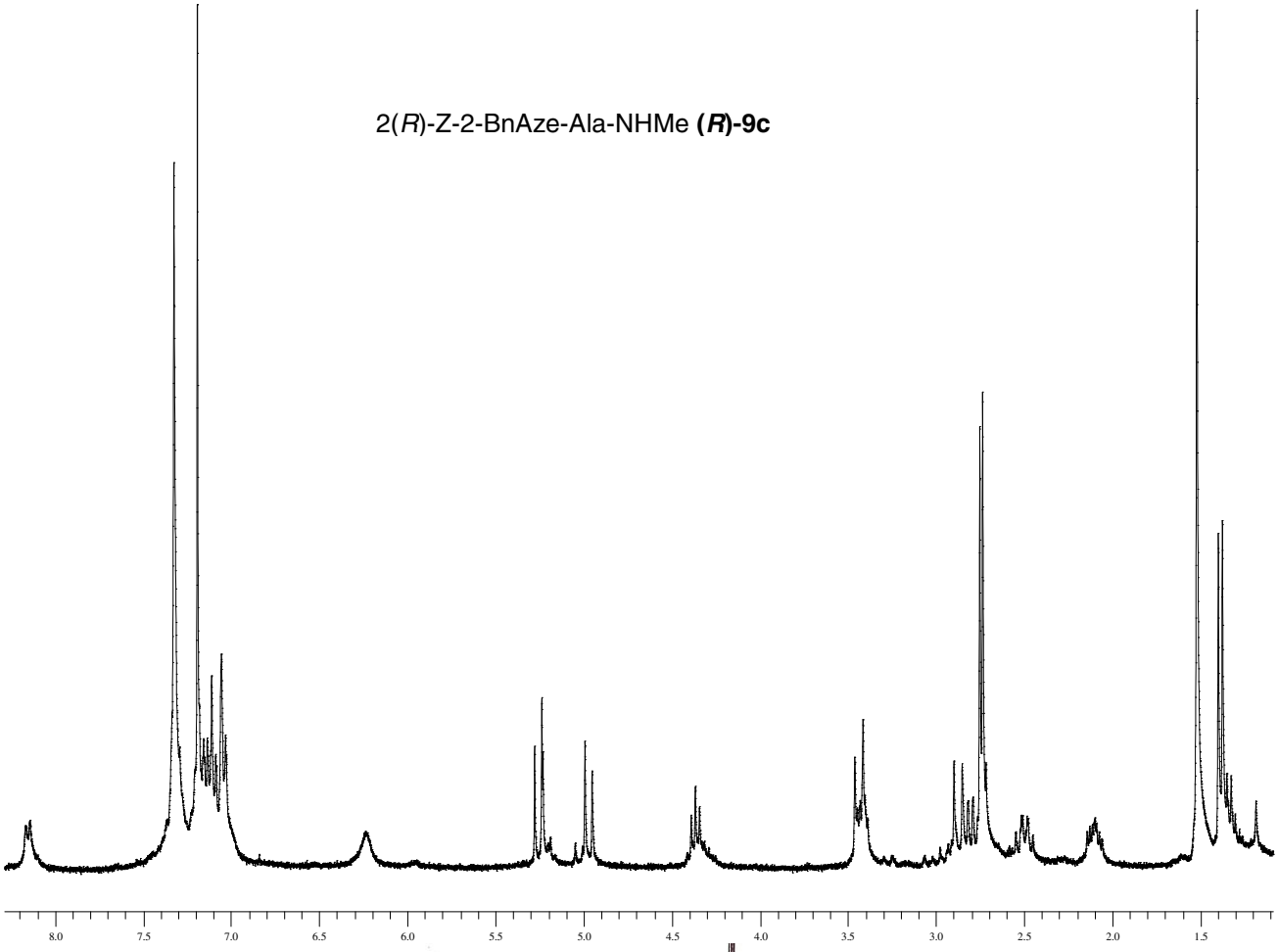
2(*S*)-Z-2-BnAze-Ala-NHMe **(*S*)-9c**



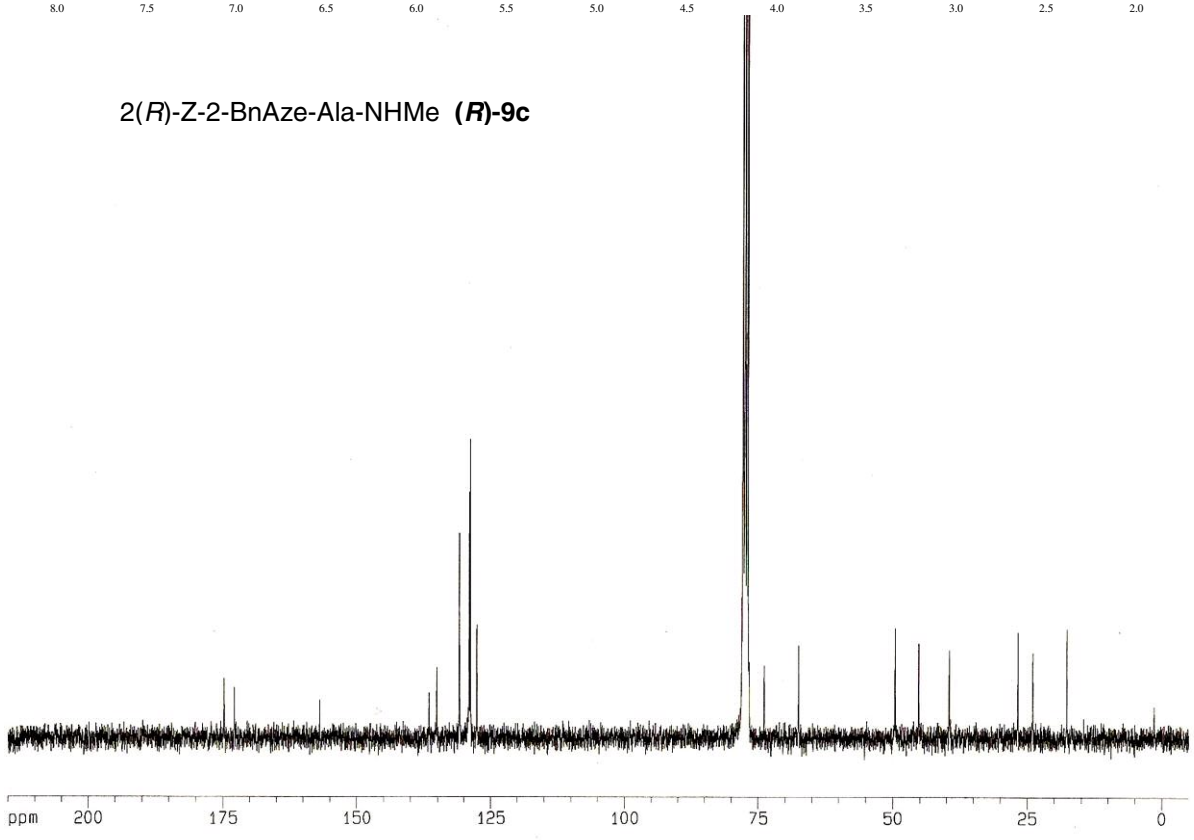
2(*S*)-Z-2-BnAze-Ala-NHMe **(*S*)-9c**



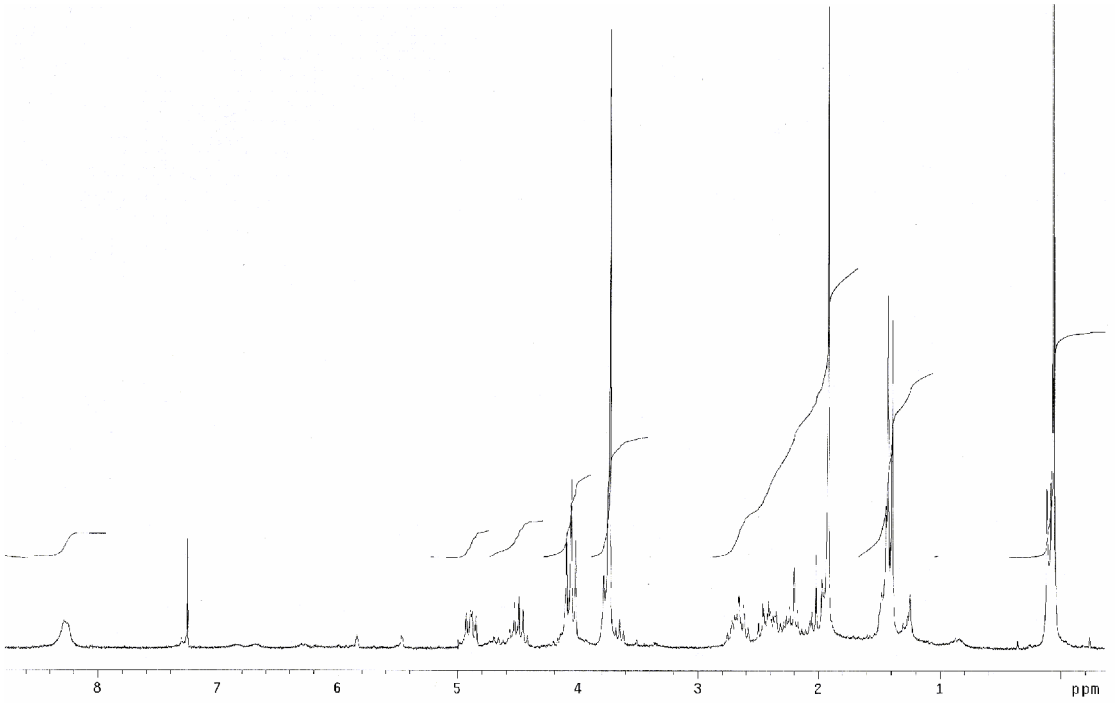
2(*R*)-Z-2-BnAze-Ala-NHMe **(*R*)-9c**



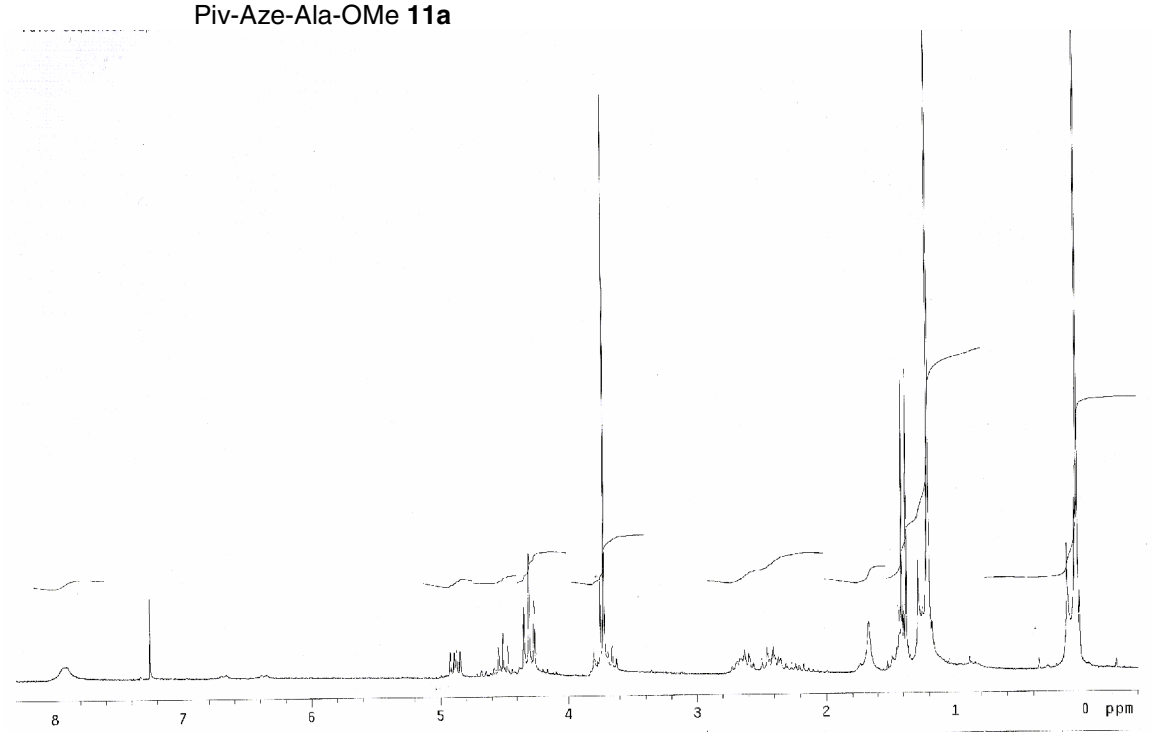
2(*R*)-Z-2-BnAze-Ala-NHMe **(*R*)-9c**

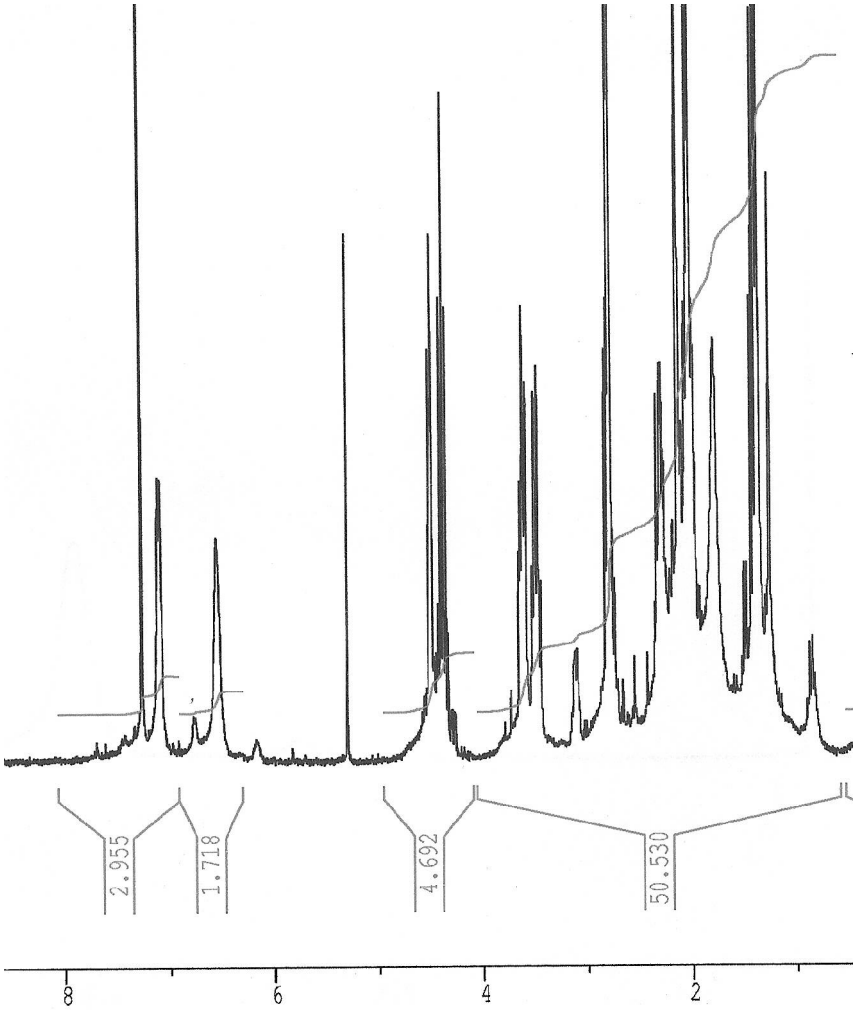


Ac-Aze-Ala-OMe **10a**



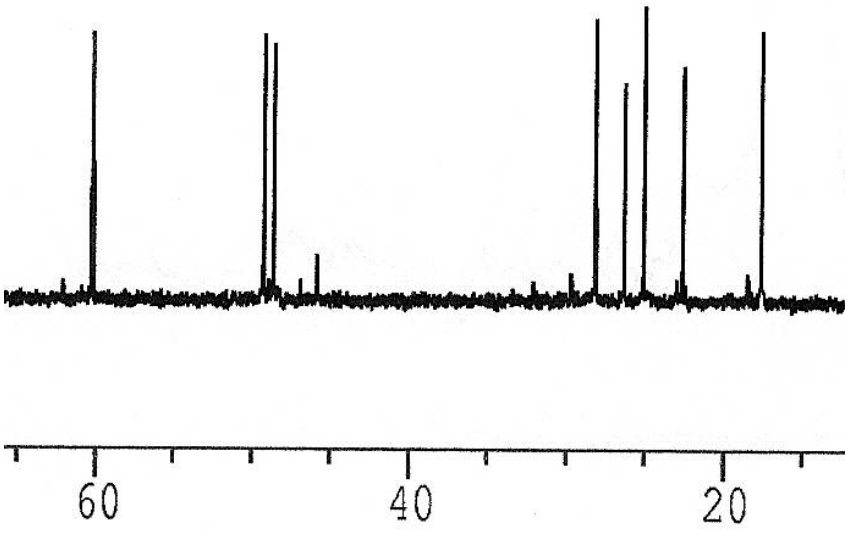
Piv-Aze-Ala-OMe **11a**





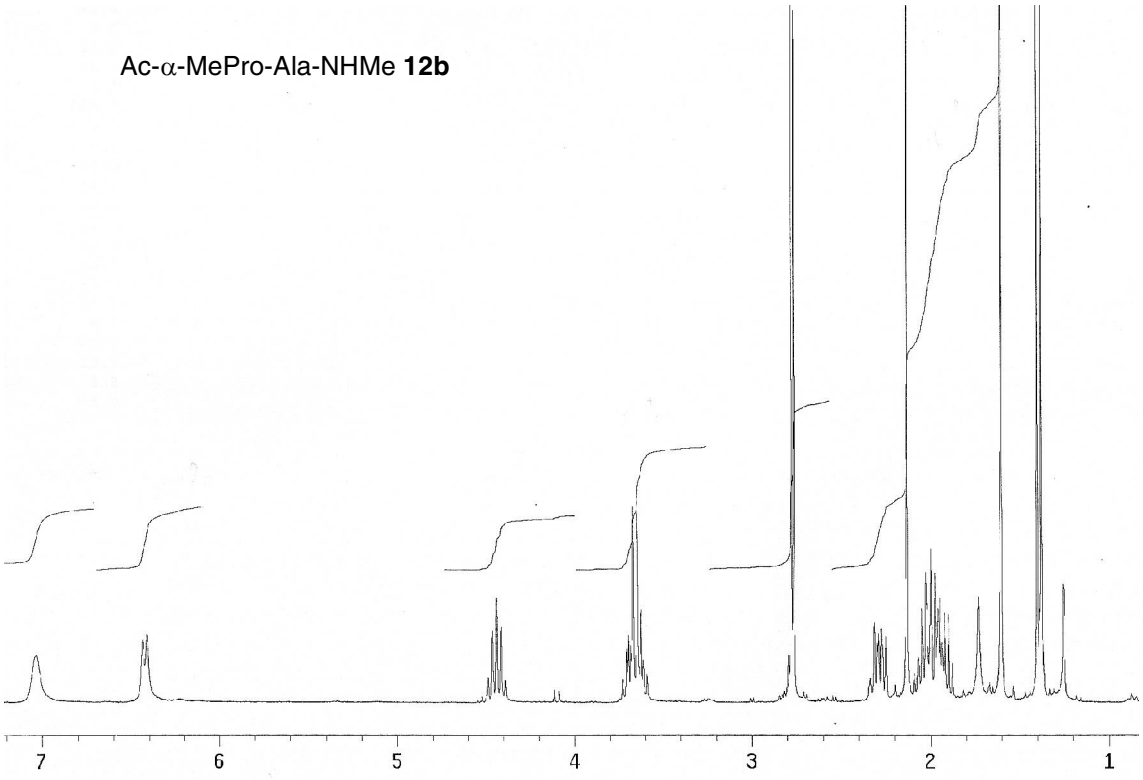
Ac-Pro-Ala-NHMe **12a**

Cis/trans: 1:6

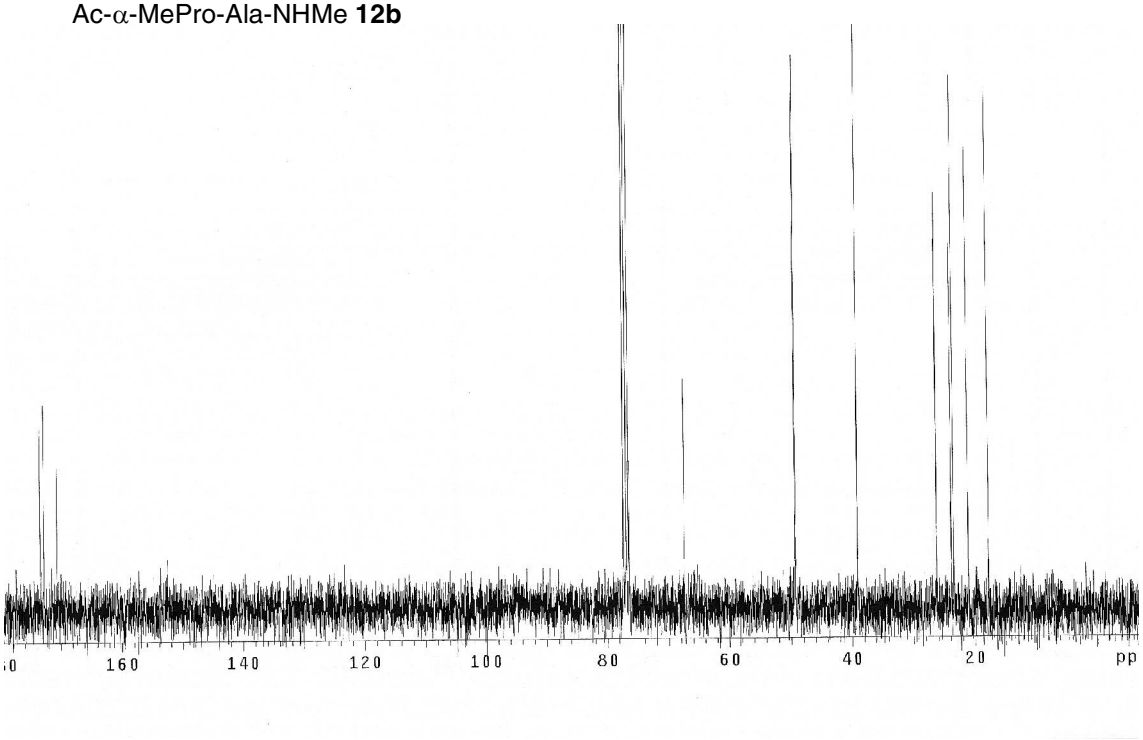


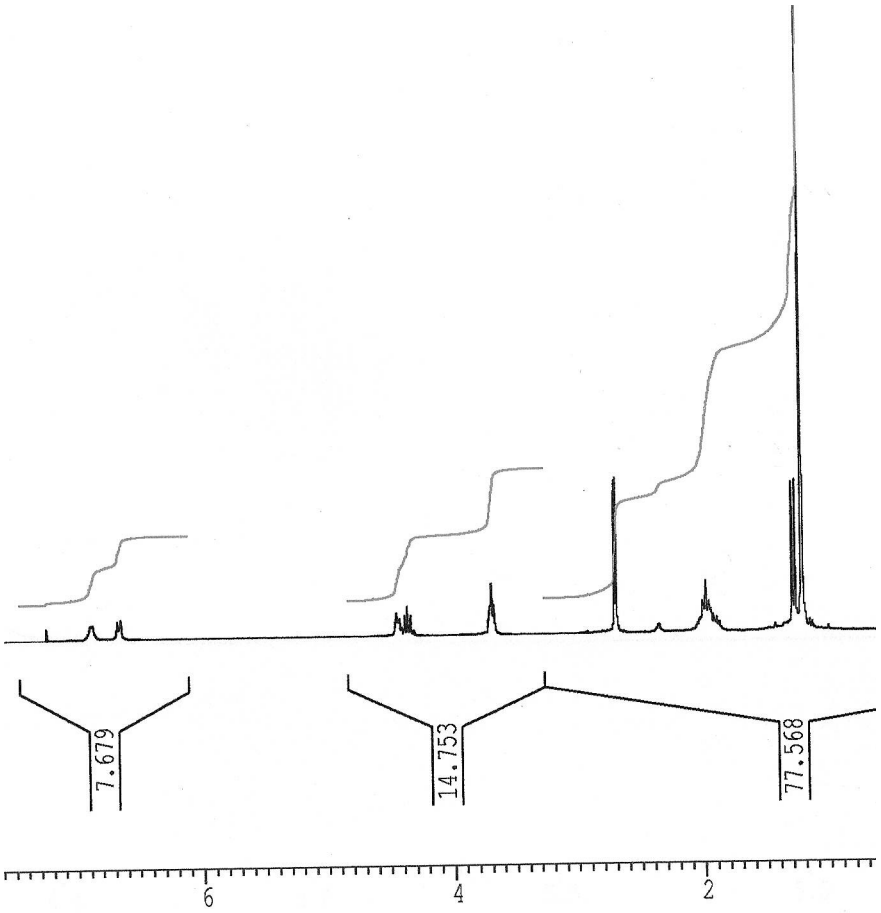
Ac-Pro-Ala-NHMe **12a**

Ac-α-MePro-Ala-NHMe **12b**

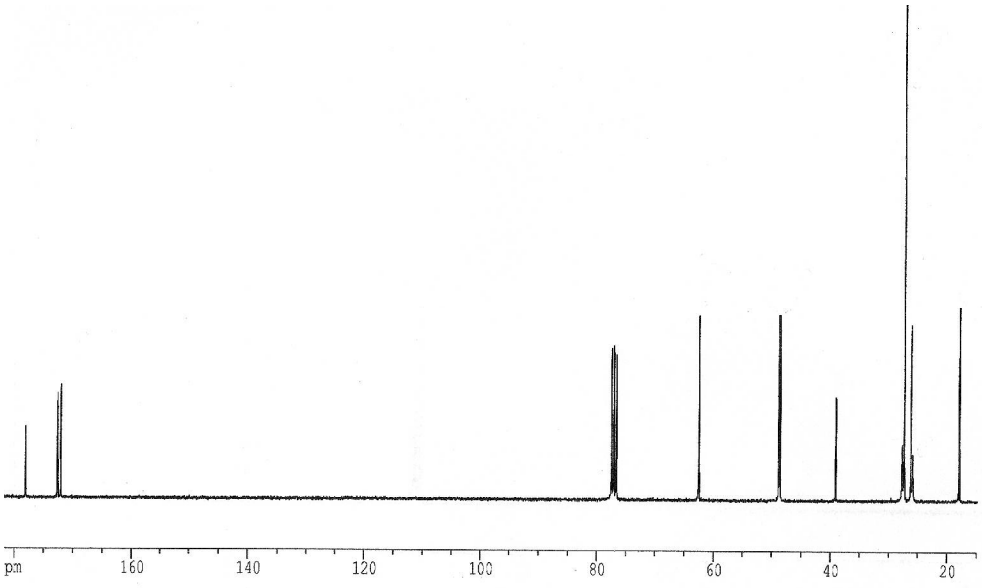


Ac-α-MePro-Ala-NHMe **12b**

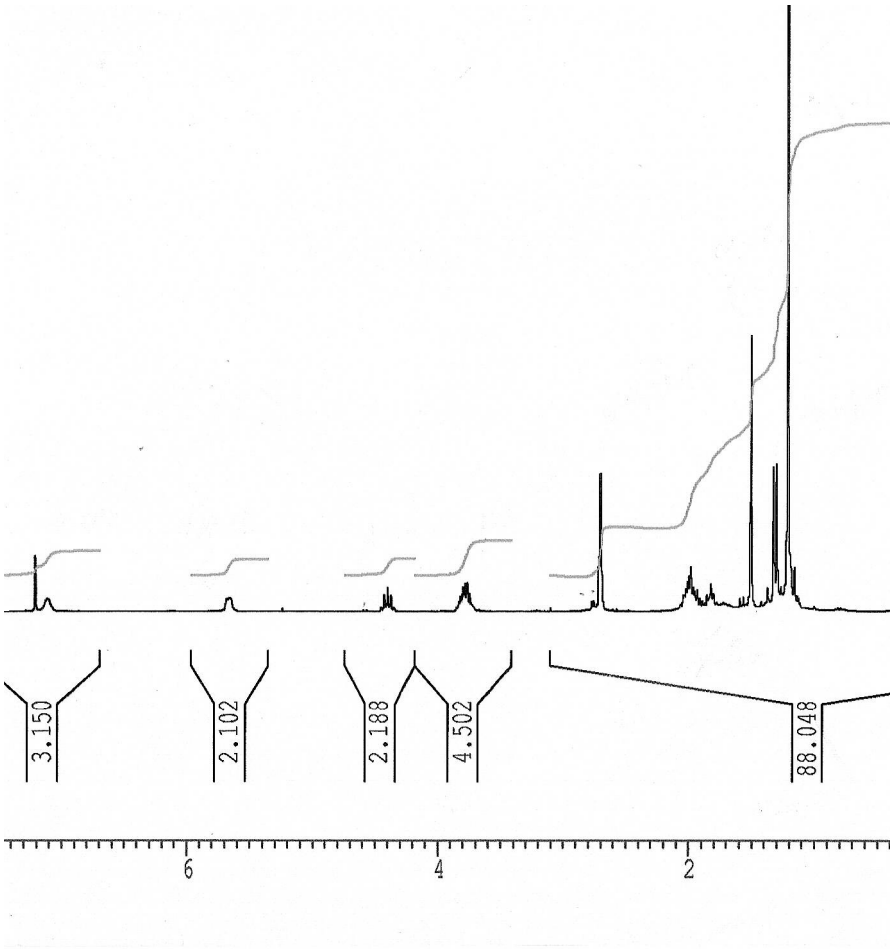




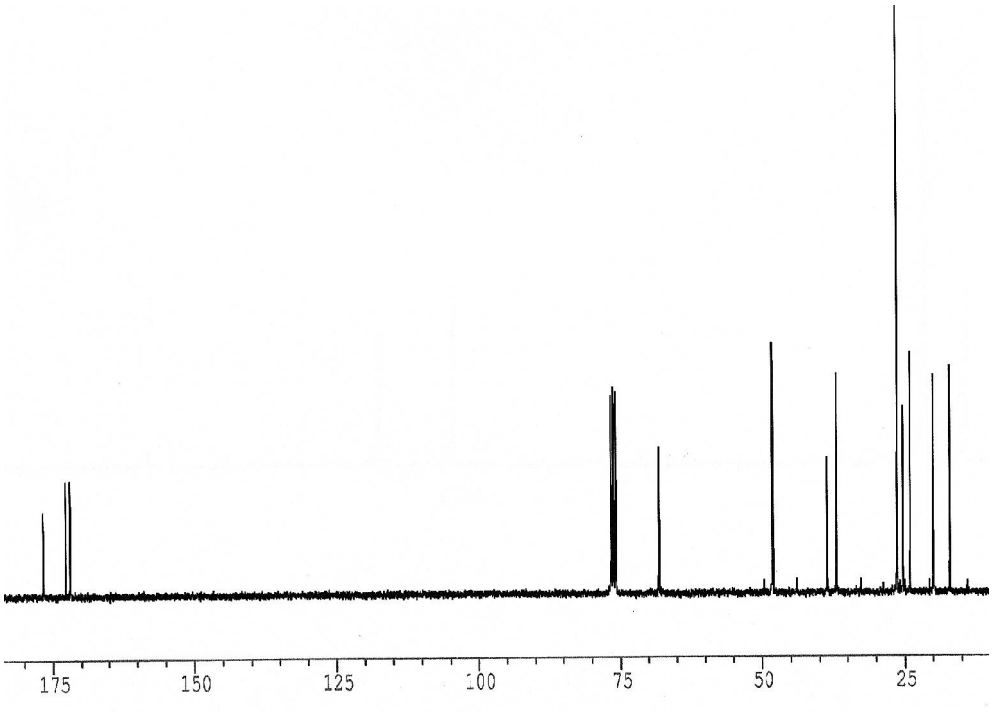
Piv-Pro-Ala-NHMe **13a**



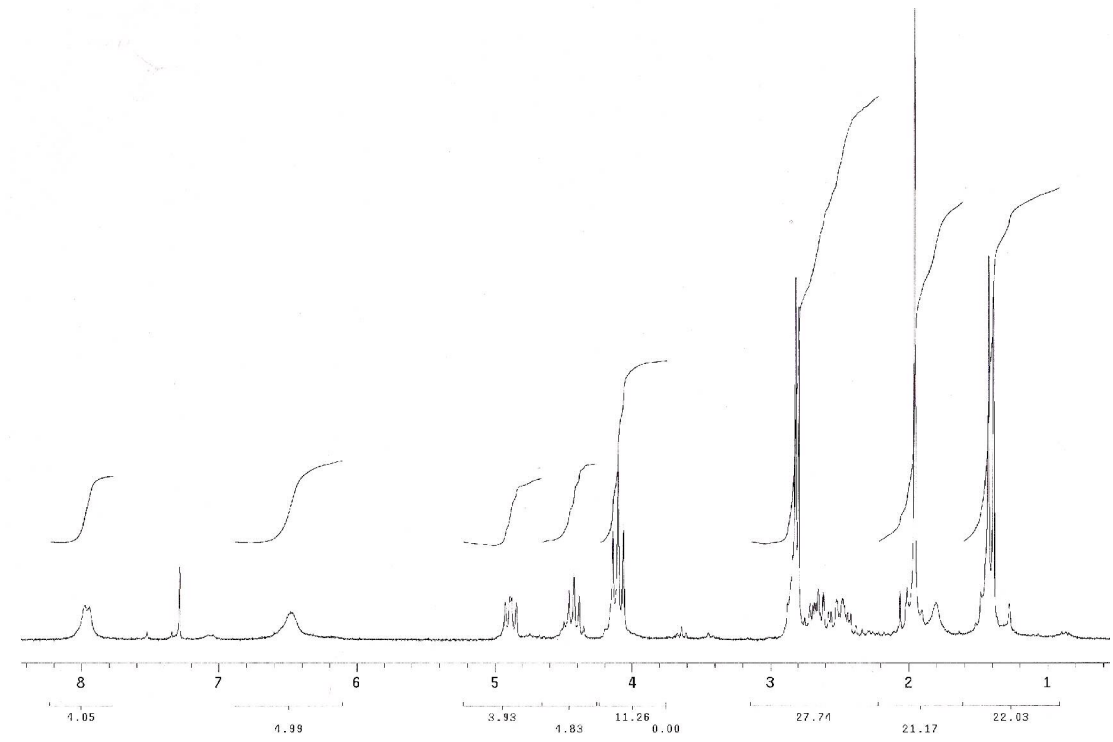
Piv-Pro-Ala-NHMe **13a**



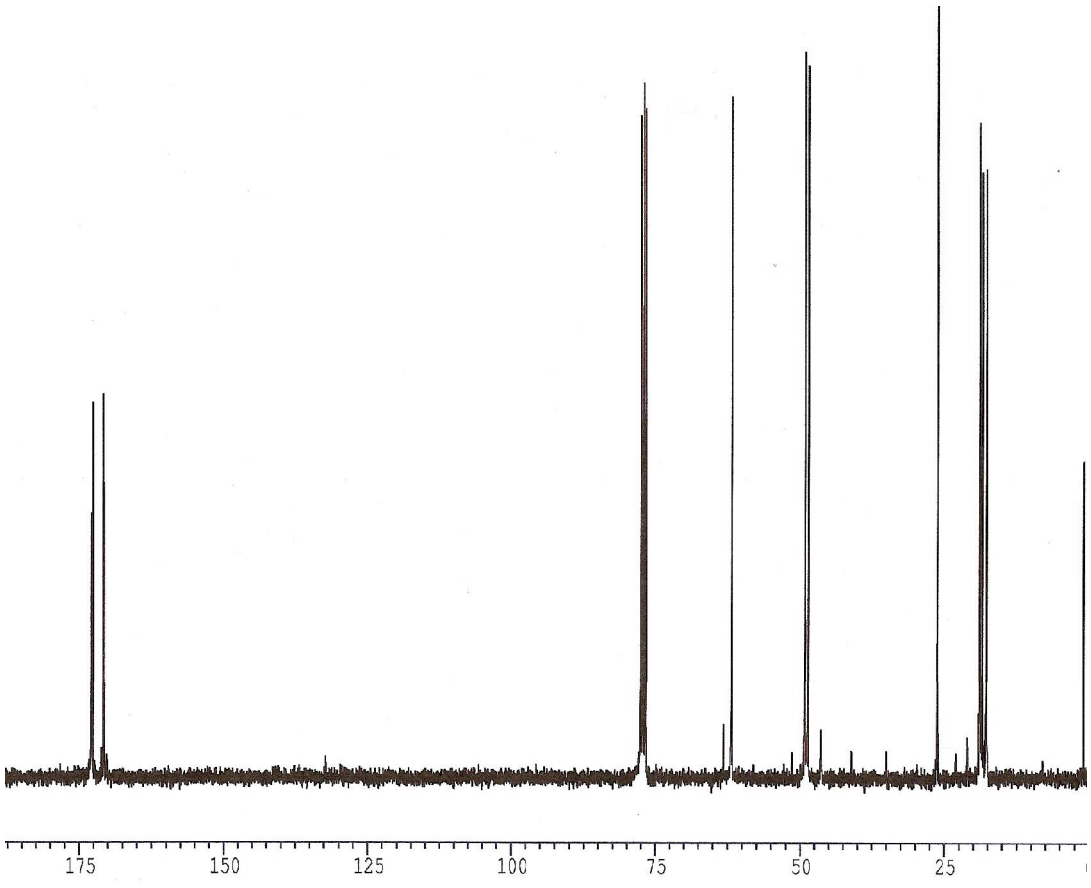
Piv-α-MePro-Ala-NHMe **13b**



Piv-α-MePro-Ala-NHMe **13b**

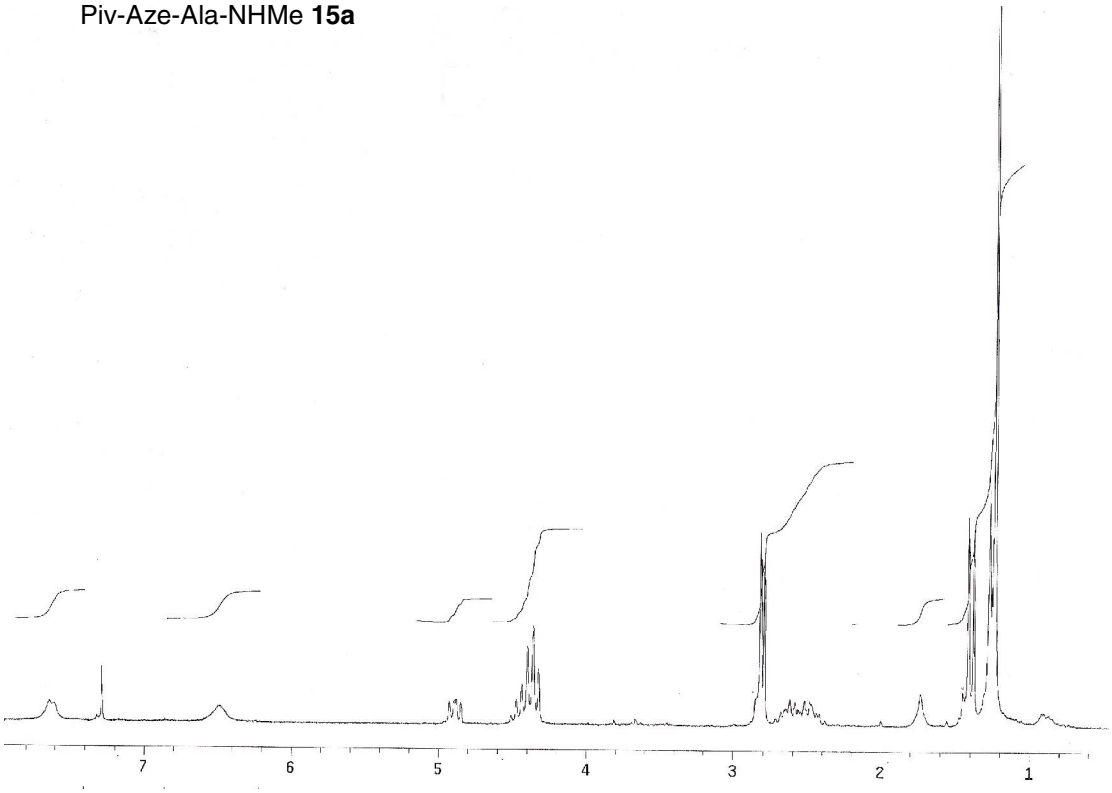


Ac-Aze-Ala-NHMe **14a**

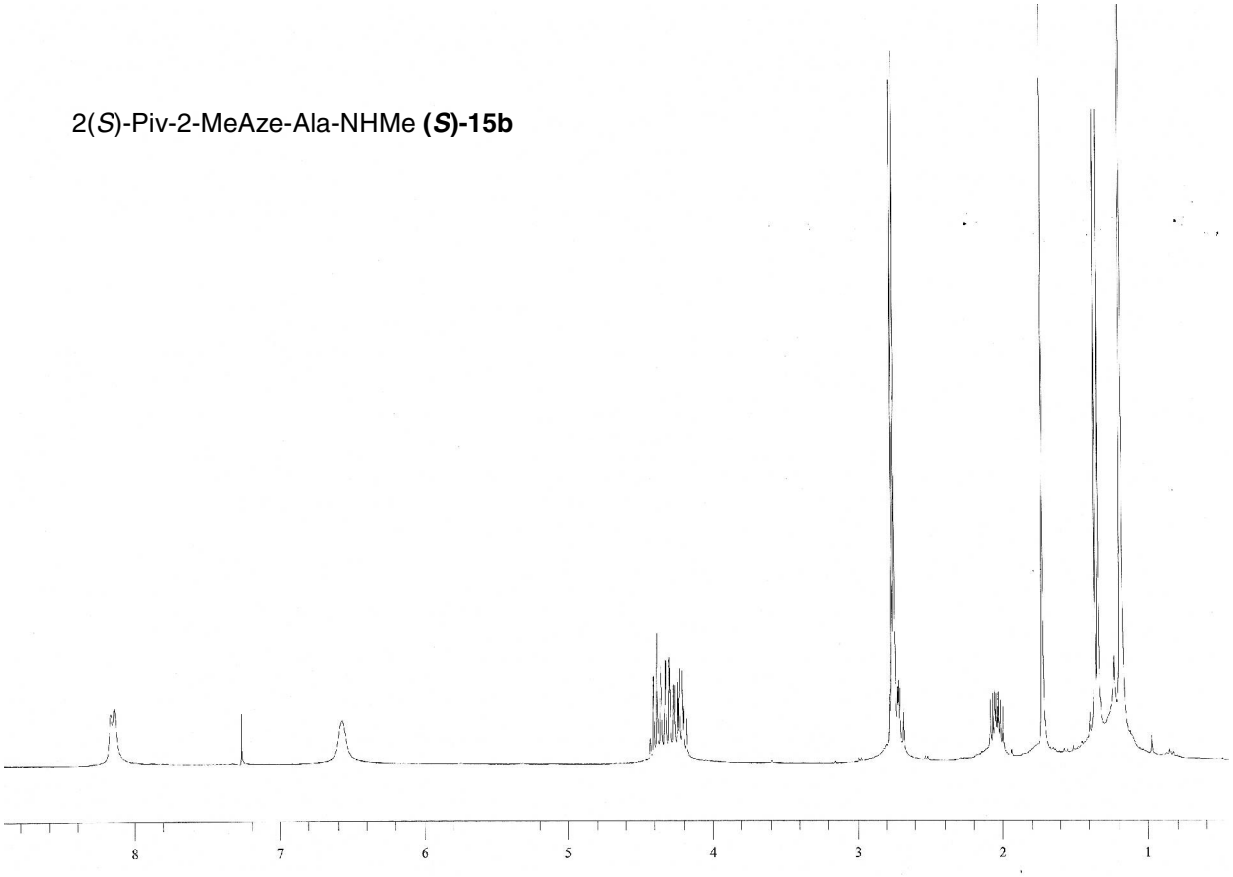


Ac-Aze-Ala-NHMe **14a**

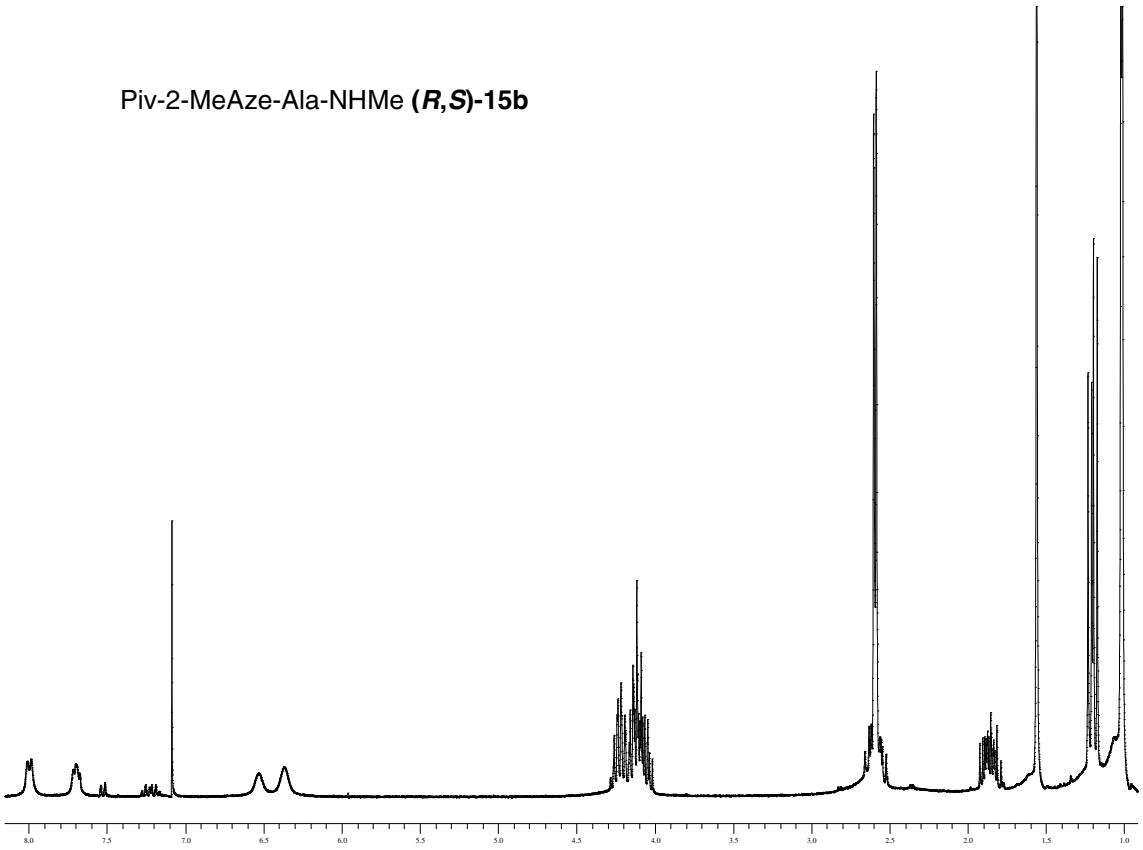
Piv-Aze-Ala-NHMe **15a**



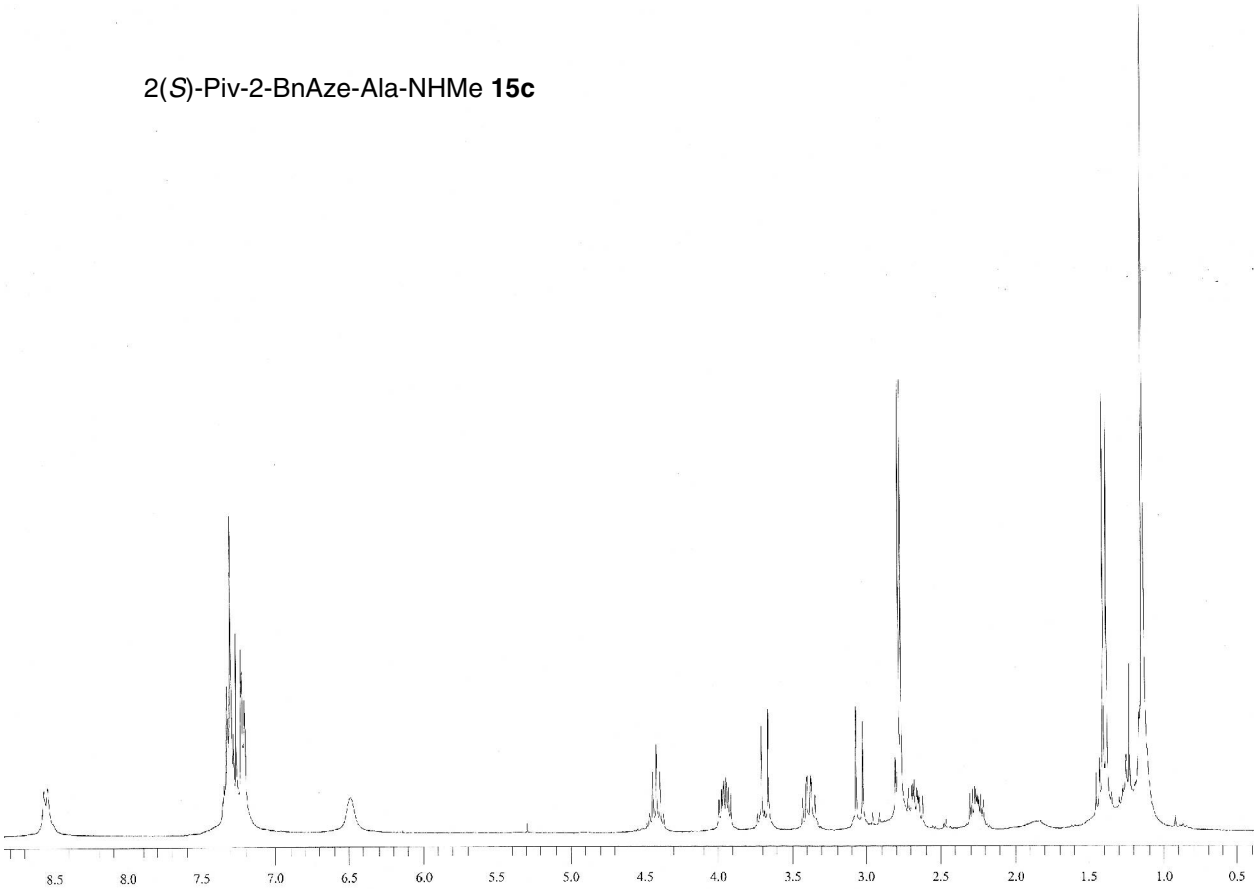
2(*S*)-Piv-2-MeAze-Ala-NHMe **(*S*)-15b**



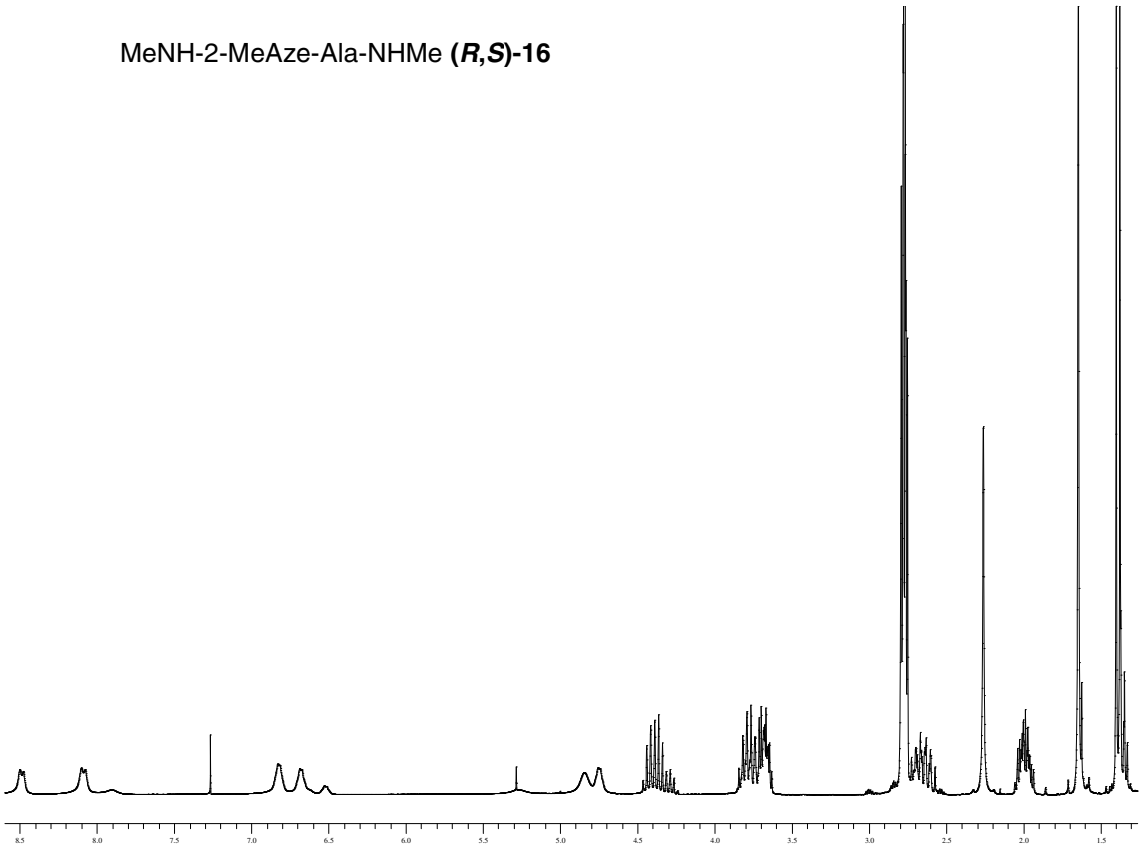
Piv-2-MeAze-Ala-NHMe ***(R,S)*-15b**



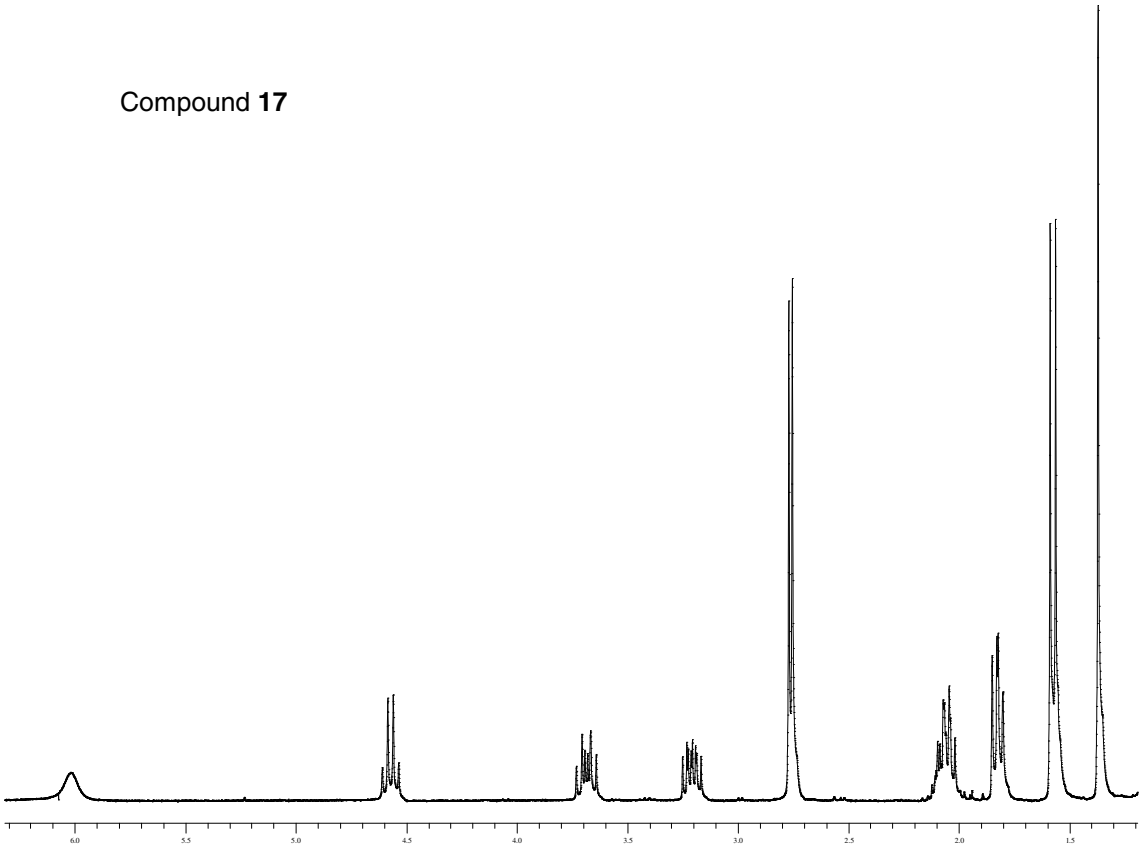
2(*S*)-Piv-2-BnAze-Ala-NHMe **15c**



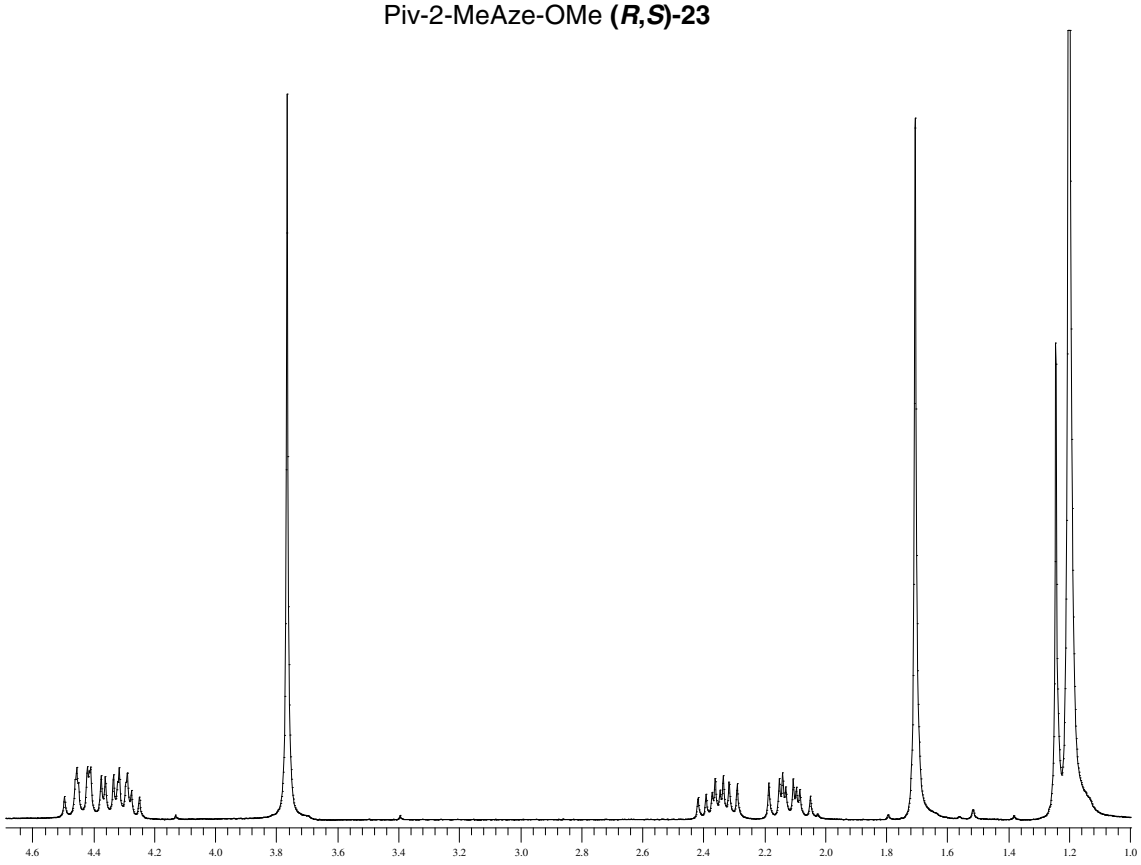
MeNH-2-MeAze-Ala-NHMe **(*R*,*S*)-16**



Compound **17**



Piv-2-MeAze-OMe **(*R,S*)-23**



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(2) Gerona-Navarro, G.; García-López, M. T.; González-Muñíz, R. *J. Org. Chem.* **2002**, *67*, 3953-3956.

(3) Baeza, J.L.; Gerona-Navarro, G.; Pérez de Vega, M. J.; García-López, M., T.; González-Muñiz, R. and Martín-Martínez, M. *Tetrahedron Lett.* **2007**, *48*, 3689-3693.