Supporting Information

Highly Diastereo- and Enantioselective Direct Aldol Reactions Promoted by Simple Prolinamides in Water

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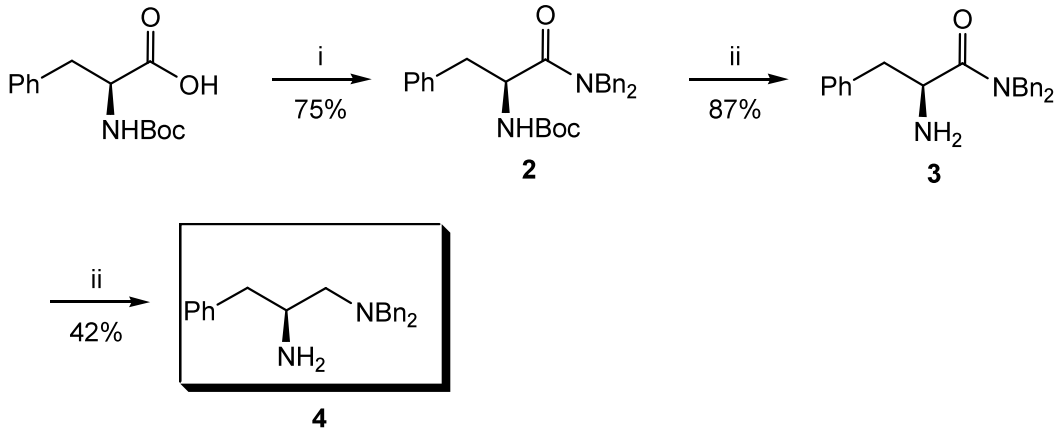
1. **Experimental section**

General information

^{1}H–NMR (300 MHz) and ^{13}C–NMR (75 MHz) spectra were recorded on a Bruker AC–300 spectrometer in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet m=multiplet, br=broad), coupling constants in Hertz, and integration. Specific rotations were measured on a Perkin–Elmer digital polarimeter using a 5–mL cell with a 1–dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Infrared spectra were recorded on a Perkin–Elmer FT–IR spectrometer and are reported in frequency of absorption. Melting points were obtained with open capillary tubes and are uncorrected. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass–backed plates coated with silica gel 60 and an F_{254} indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a Hewlett–Packard 1090 Series II instrument equipped with a quaternary pump, using a Daicel Chiralcel OD Column (250 × 4.6 mm) or Chiralpak AS–H, AD–H Column (250 × 4.6 mm). UV detection was monitored at 220 nm or at 254 nm. Racemic samples were prepared by using racemic proline as the catalyst in DMF[1] or DMSO.[2]

Organic compounds were purchased from Aldrich and used as received. Solvents were dried and stored over microwave–activated 4Å molecular sieves. All reactions were carried out under argon atmosphere.

Procedure for preparation of diamine 4



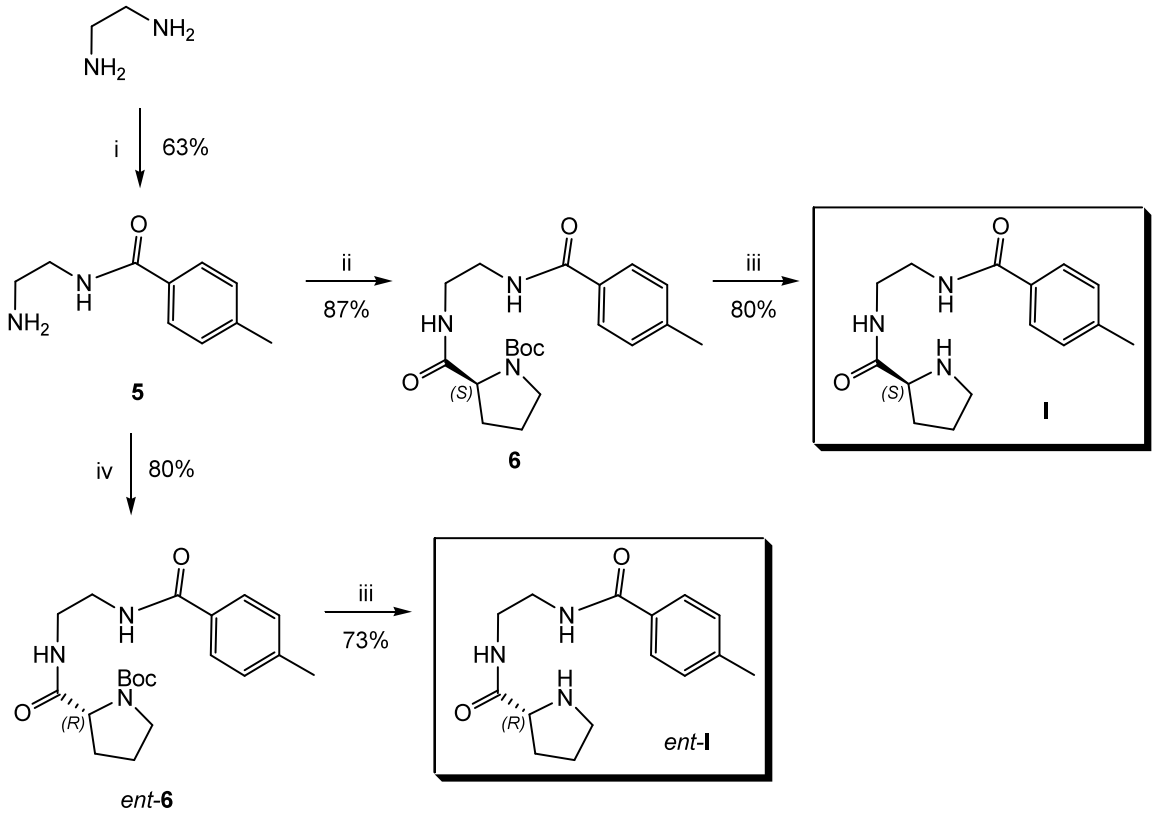
Scheme 1. *Reagents and conditions*: (i) $ClCO_2Et$, Bn_2NH, NMM (2 equiv), THF, -15 ºC to rt. (ii) TFA, CH_2Cl_2, rt. (iii) LAH (3 equiv), Et_2O, 0 ºC.

(*S*)-2-*tert*-Butoxycarbonylamino-*N*,*N*-dibenzyl-3-phenylpropanamide (2).[3] To a cold solution of Boc-*L*-phenylalanine (3.98 g, 15 mmol) and N-methylmorpholine (NMM) (1.66 mL, 15 mmol) in dry THF (45 mL) at -15 ºC, ethyl chloroformate (1.43 mL, 15 mmol) in THF (8 mL) was added dropwise in 15 min. After stirring for another 15 min, dibenzylamine (3 mL, 15 mmol) was added in one portion. Then the reaction mixture was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent *in vacuo*, the residue was diluted with EtOAc (60 mL) and the organic phase was washed with 10% Na_2CO_3 (50 mL), 0.1 M HCl (2 x 50 mL), brine (50 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave crude Boc-α-amino amide **2**, which was purified by recristallisation from hexane-ethyl acetate. Yield: 5.00 g (11.2 mmol, 75%). Colorless solid, mp 111-112 ºC.[Lit. mp 108-110 ºC.]; $[\alpha]_D^{25}$= -9.4 (*c* 1.0, $CHCl_3$) [Lit. $[\alpha]_D^{25}$= -10.3 (*c* 1.0, $CHCl_3$)] ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H); 3.00 (m, 2H); 4.29 (m, 3H); 4.70 (d, J = 14.5 Hz, 1H); 4.92 (m, 1H); 5.37 (d, J = 8.8 Hz, 1H); 7.15 (m, 15H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 28.4 ($\underline{C}H_3$); 40.1 ($\underline{C}H_2$); 48.4 ($\underline{C}H_2$); 49.9 ($\underline{C}H_2$); 51.8 ($\underline{C}H$); 79.9 ($\underline{C}$); 126.9, 127.1, 127.6, 127.8, 128.5, 128.6, 129.0, 129.7 ($\underline{C}$Har); 136.2, 136.7 ($\underline{C}$ar); 155.2 (N$\underline{C}O_2$); 172.8 ($\underline{C}$ON). IR (KBr): ν = 3343, 1684, 1635, 1527, 1170, 754, 701 cm^{-1}. HRMS calcd for $C_{28}H_{32}N_2O_3 + Na^+$, 467.2311; found, 467.2287.

(*S*)-2-Amino-*N*,*N*-dibenzyl-3-phenylpropanamide (3).[3] Boc-amino amide **2** (4.20 g, 9.45 mmol) was dissolved in mixture of TFA/CH_2Cl_2 (1:4) (18 mL), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC, basified with 2N ammonia solution and extracted with dichloromethane (3×20 mL). After the removal of the solvent at reduced pressure, the crude amino amide **3** was purified by recristallisation from hexane-ethyl acetate. Yield: 2.84 g (8.22 mmol, 87%). Colorless solid, mp 108-109 ºC. [Lit. mp 99-101 ºC]; $[\alpha]_D^{25}$= +33.2 (*c* 1, $CHCl_3$) [Lit. $[\alpha]_D^{25}$= +32.7 (*c* 1.14, $CHCl_3$)]; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.64 (br s, 2H); 2.83 (dd, J = 13.2 Hz, J = 7.5 Hz, 1H); 3.06 (dd, J = 13.2 Hz, J = 7.0 Hz, 1H); 3.91 (m, 1H); 4.26 (m, 3H); 4.95 (d, J = 14.9 Hz, 1H); 7.20 (m, 15H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 42.9 ($\underline{C}H_2$); 48.7 ($\underline{C}H_2$); 49.4 ($\underline{C}H_2$); 53.4 ($\underline{C}H$); 126.3, 126.6, 127.4, 127.7, 128.3, 128.5, 129.0, 129.4 ($\underline{C}$Har); 136.4, 136.9, 137.7 ($\underline{C}$ar); 175.6 ($\underline{C}$ON). IR (KBr): ν = 3363, 1624, 1451, 1077, 747, 700 cm^{-1}. HRMS calcd for $C_{23}H_{24}N_2O + Na^+$, 367.1786; found, 367.1761.

(*S*)-N^1, N^1-Dibenzyl-3-phenylpropane-1,2-diamine (4).[3] A solution of amino amide **3** (2.80 g, 8.13 mmol) in anhydrous ether (20 mL) was added dropwise to a suspension of $LiAlH_4$ (0.92 g, 24.4 mmol, 3 equiv) in 25 mL of the same solvent at 0 ºC, and the mixture was stirred at under nitrogen atmosphere for 4 h. Then, the suspension was sequentially treated at 0 ºC with water (0.9 mL), 15% NaOH solution (0.9 mL) and water (2.7 mL), and stirred for 2h. The white solids were removed by filtration, the solvent of the filtrate was evaporated on the rotavapor and the residue was purified by flash column chromatography on silica gel (ethyl acetate). Yield: 1.13 g (3.42 mmol, 42 %). Colorless oil. $[\alpha]_D^{25}$= +43.8 (*c* 1.2, $CHCl_3$) [Lit. $[\alpha]_D^{25}$= +54.3 (*c* 1.17, $CHCl_3$)] ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.58 (br s, 2H); 2.40 (m, 3H); 2.75 (m, 1H); 3.18 (m, 1H); 3.49 (d, J = 13.4 Hz, 2H); 3.70 (d, J = 13.4 Hz, 2H); 7.28 (m, 15H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 42.1 ($\underline{C}H_2$); 50.4 ($\underline{C}H$); 59.0 ($\underline{C}H_2$); 60.8 ($\underline{C}H_2$); 126.0, 126.9, 128.2, 128.3, 128.9, 129.1 ($\underline{C}$Har); 139.2, 139.5 ($\underline{C}$ar). IR (film): ν = 3360, 1601, 1493, 1452, 1068, 1027, 745, 699 cm^{-1}. HRMS calcd for $C_{23}H_{26}N_2 + H^+$, 331.2174; found, 331.2150.

Procedures for preparation of catalyst I, *ent*-I, II and III



Scheme 2. *Reagents and conditions*: (i) *p*-$CH_3C_6H_4COCl$, MeOH, 0 ^oC, 60s. (ii) Boc-*L*-proline, DCC, DCM, 0 ^oC to rt. (iii) TFA, DCM, rt. (iv) Boc-*D*-proline, DCC, DCM, 0 ^oC to rt .

***N*-(2-Aminoethyl)-4-methylbenzamide (5).**[4] Ethylenediamine (1.6 mL, 24 mmol, 1.2 equiv) was added all at once to a vigorously stirred solution of the *p*-toluoyl chloride (2.6 mL, 20 mmol) in methanol (100 mL) in an ice-water bath. Stirring was continued for 60 s, then the reaction was quenched with 10% NaOH solution (10 mL). The heterogeneous mixture was stirred at room temperature for 5 min and the methanol was eliminated under vacuum. The resulting aqueous phase was diluted with water and extracted with chloroform (3 x 25 mL). The combined organic layers were washed with water, dried with anhydrous $MgSO_4$ and the solvents were eliminated under vacuum. The residue was purified through flash column chromatography on silica gel (DCM/methanol: 3/2). to give **5** (2.24 g, 12.6 mmol, 63%) as a colorless oil. ^{1}H-NMR

(300 MHz, $CDCl_3$): δ = 2.33 (s, 5H); 2.87 (m, 2H); 3.45 (m, 2H); 7.15 (d, J = 8.3 Hz, 2H); 7.25 (br s, 1H), 7.68 (d, J = 8.3 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_3); 41.3 (CH_2); 42.2 (CH_2); 127.1, 129.2 (CHar); 131.7, 141.9 (Car); 168.0 (CON). IR (KBr): ν = 3293, 2924, 1636, 1544, 1505, 1305, 838, 752 cm^{-1}. HRMS calcd for $C_{10}H_{14}N_2O+ Na^+$, 201.1004; found, 201.0996.

(*S*)-*tert*-Butyl 2-(2-(4-methylbenzamido)ethylcarbamoyl)pyrrolidine-1-carboxylate (6). Boc-*L*-Proline (1.50 g, 6.96 mmol, 1.25 equiv) and N, N'-dicyclohexylcarbodiimide (DCC) (1.43 g, 6.96 mmol, 1.25 equiv) were dissolved in dichloromethane (15 mL) and cooled down to 0 ºC. After the solution was stirred for 30 min, a solution of **5** (0.99 g, 5.57 mmol, 1 equiv) in dichloromethane (15 mL) was added dropwise over 10 min. After the addition was complete, the mixture was warmed to room temperature and stirred for another 10 h. After filtration and removal of solvent at reduced pressure, the residue was purified through flash column chromatography on silica gel (eluent, ethyl acetate) to provide 1.82 g (4.85 mmol, 87%) of prolinamide **6** as a colorless oil. $[\alpha]_D^{23}$ = -21.9 (c 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$, 330K): δ = 1.39 (s, 9H); 1.83 (m, 2H); 2.00 (m, 2H); 2.34 (s, 3H); 3.50 (m, 6H); 4.17 (m, 1H); 6.97 (br s, 1H); 7.16 (d, J = 7.9 Hz, 2H); 7.23 (br s, 1H); 7.70 (d, J = 7.9 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$, 330K): δ = 21.4 (CH_3); 24.4 (CH_2); 28.5 (CH_3); 29.9 (CH_2); 39.9 (CH_2); 41.0 (CH_2); 47.3 (CH_2); 61.0 (CH); 127.3, 129.2 (CHar); 131.8, 141.7 (Car); 155.3 (NCO_2); 168.0 (CON); 174.2 (CON). IR (KBr): ν = 3313, 2976, 1651, 1538, 1393, 1162, 1123, 753.1 cm^{-1}. HRMS calcd for $C_{20}H_{29}N_3O_4+ Na^+$, 398.2056; found, 398.2054.

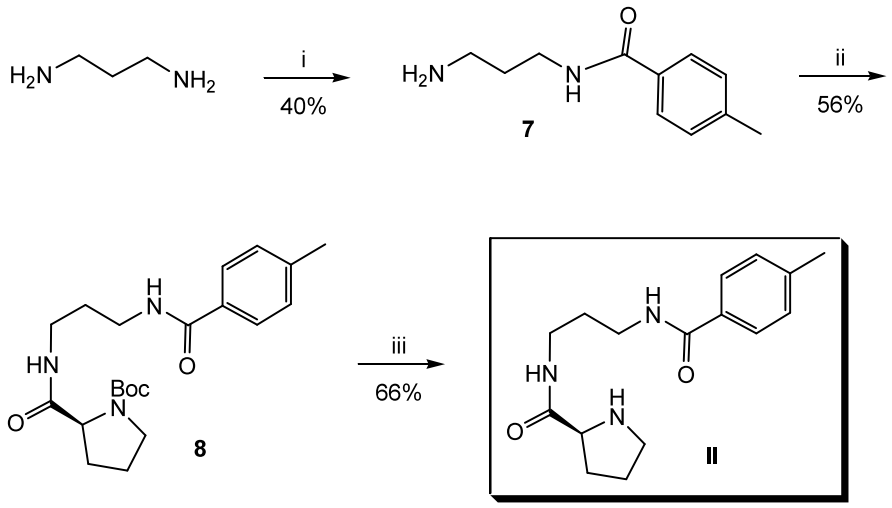
(*S*)-*N*-(2-(4-Methylbenzamido)ethyl)pyrrolidine-2-carboxamide (I). This compound was obtained by reaction of compound **6** (1.31 g, 3.5 mmol) with TFA/DCM (1:4) by the procedure described for the preparation of **3** and was purified by flash column

chromatography on silica gel (EtOAc/methanol: 5/1). Yield: 0.77 g (2.8 mmol, 80%). Colorless solid, mp 142-143 ºC (from EtOAc). $[\alpha]_D^{23}$ = -65.4 (c 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 2H); 1.81 (m, 1H); 2.09 (m, 2H); 2.36 (s, 3H); 2.86 (dt, J = 10.1 Hz, J = 6.1 Hz, 1H); 2.97 (dt, J = 10.1 Hz, J = 6.6 Hz, 1H); 3.52 (m, 4H); 3.72 (dd, J = 9.2 Hz, J = 5.3 Hz, 1H); 7.20 (d, J = 8.2 Hz, 2H); 7.57 (br s, 1H); 7.72 (d, J = 8.2 Hz, 2H); 8.13 (br s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3); 26.1 (CH_2); 30.8 (CH_2); 38.7 (CH_2); 41.7 (CH_2); 47.2 (CH_2); 60.4 (CH); 127.1, 129.1 (CHar); 131.3, 141.6 (Car); 167.7 (CON); 177.5 (CON). IR (KBr): ν = 3328, 3290, 2939, 1637, 1540, 1216, 835 cm^{-1}. HRMS calcd for $C_{15}H_{21}N_3O_2$+ H^+, 276.1712; found, 276.1702.

(*R*)-*tert*-Butyl 2-(2-(4-methylbenzamido)ethylcarbamoyl)pyrrolidine-1-carboxylate (*ent*-6). This compound was obtained by reaction of *p*-toluoylethylenediamine (0.66 g, 3.71 mmol) with Boc-*D*-proline (1.00 g, 4.64 mmol, 1.25 equiv) in the presence of DCC (0.95 g, 4.64 mmol, 1.25 equiv) by the procedure described for the preparation of **6** and was purified by flash column chromatography on silica gel (EtOAc). Yield: 1.12 g (2.97 mmol, 80%). Colorless oil. $[\alpha]_D^{23}$ = +21.7 (c 1.0, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$, 330K): δ = 1.39 (s, 9H); 1.83 (m, 2H); 2.00 (m, 2H); 2.34 (s, 3H); 3.50 (m, 6H); 4.17 (m, 1H); 6.97 (br s, 1H); 7.16 (d, J = 7.9 Hz, 2H); 7.23 (br s, 1H); 7.70 (d, J = 7.9 Hz, 2H).

(*R*)-*N*-(2-(4-Methylbenzamido)ethyl)pyrrolidine-2-carboxamide (*ent*-I). This compound was obtained by reaction of compound *ent*-**6** (0.94 g, 2.50 mmol) with TFA/DCM (1:4) by the procedure described for the preparation of **3** and was purified by flash column chromatography on silica gel (EtOAc/methanol: 5/1). Yield: 0.50 g (1.83 mmol, 73%). Colorless solid, mp 142-143 ºC (from EtOAc). $[\alpha]_D^{23}$ = +65.1 (c 1.0, $CHCl_3$). HRMS calcd for $C_{15}H_{21}N_3O_2$+ H^+, 276.1712; found, 276.1715. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 2H); 1.81 (m, 1H); 2.09 (m, 2H); 2.36 (s, 3H); 2.86 (dt, J = 10.1 Hz, J = 6.1 Hz, 1H); 2.97 (dt, J = 10.1 Hz, J = 6.6 Hz, 1H); 3.52 (m, 4H); 3.72 (dd,

J = 9.2 Hz, J = 5.3 Hz, 1H); 7.20 (d, J = 8.2 Hz, 2H); 7.57 (br s, 1H); 7.72 (d, J = 8.2 Hz, 2H); 8.13 (br s, 1H).

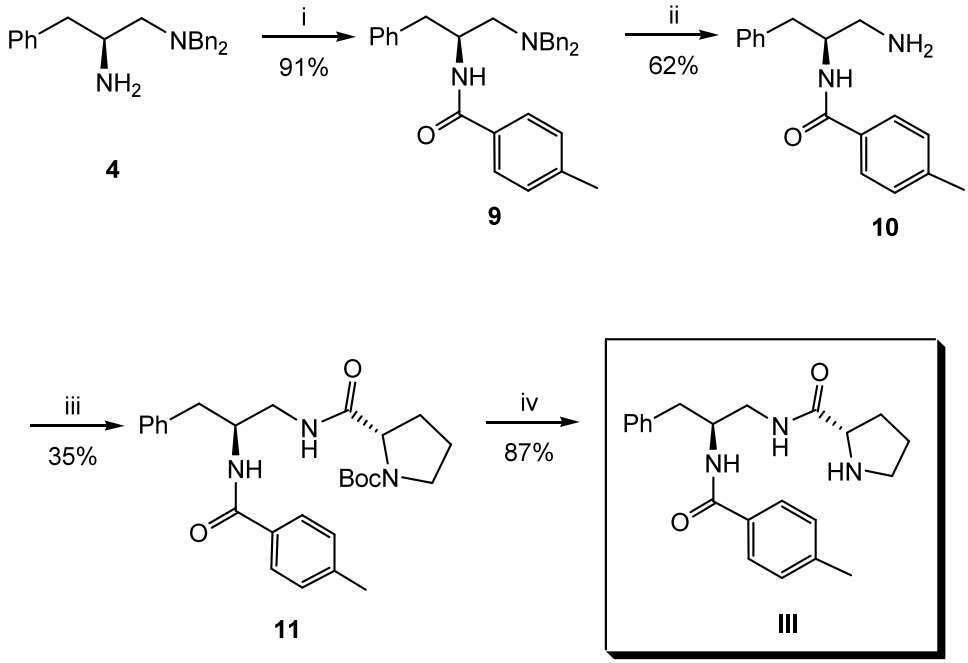


Scheme 3. *Reagents and conditions*: (i) *p*-$CH_3C_6H_4COCl$, MeOH, 0 ºC, 60 s. (ii) Boc-*L*-proline, DCC, DCM, 0 ºC to rt. (iii) TFA, DCM, rt.

N-(3-Aminopropyl)-4-methylbenzamide (7).[5] Propane-1,3-diamine (2 mL, 24 mmol, 1.2 equiv) was added all at once to a vigorously stirred solution of the *p*-toluoyl chloride (2.6 mL, 20 mmol) in methanol (100 mL) in an ice-water bath. Stirring was continued for 60 s, then the reaction was quenched with 10% NaOH solution (10 mL). The heterogeneous mixture was stirred at room temperature for 5 min and the methanol was eliminated under vacuum. The resulting aqueous phase was diluted with water and extracted with chloroform (3 x 25 mL). The combined organic layers were washed with water, dried with anhydrous $MgSO_4$ and the solvents were eliminated under vacuum. The residue was purified through flash column chromatography on silica gel (DCM/methanol: 3/2) to give **7** (1.52 g, 7.9 mmol, 40%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (br s, 2H); 1.68 (m, 2H); 2.34 (s, 3H); 2.83 (t, J = 6.1 Hz, 2H); 3.51 (m, 2H); 7.16 (d, J = 8.2 Hz, 2H); 7.67 (d, J = 8.2 Hz, 2H); 7.83 (br s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.5 ($\underline{C}H_3$); 31.7 ($\underline{C}H_2$); 39.1 ($\underline{C}H_2$); 40.7 ($\underline{C}H_2$); 127.0, 129.1 ($\underline{C}$Har); 131.9, 141.6 ($\underline{C}$ar); 167.5 ($\underline{C}$ON).

(*S*)-*tert*-Butyl 2-(3-(4-methylbenzamido)propylcarbamoyl)pyrrolidine-1-carboxylate (8). This compound was obtained by reaction of compound **7** (1.46 g, 7.6 mmol) with Boc-*L*-proline in the presence of DCC by the procedure described for the preparation of **6** and was purified by flash column chromatography on silica gel (EtOAc). Yield: 1.66 g (4.3 mmol, 56%). Colorless solid, mp. 131-132 ºC. $[\alpha]_D$ = -43.4 (*c* 0.7, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$, 330K): δ = 1.44 (s, 9H); 1.71 (m, 3H); 1.88 (m, 3H); 2.37 (s, 3H); 3.40 (m, 6H); 4.25 (m, 1H); 6.95 (br s, 1H); 7.20 (d, J = 8.3 Hz, 2H); 7.31 (br s, 1H); 7.75 (d, J = 8.3 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$, 330K): δ = 21.5 ($\underline{C}H_3$); 24.4 ($\underline{C}H_2$); 28.6 ($\underline{C}H_3$); 30.0 ($\underline{C}H_2$); 36.1 ($\underline{C}H_2$); 47.3 ($\underline{C}H_2$); 60.9 ($\underline{C}H$); 80.6 ($\underline{C}$); 127.2, 129.3 ($\underline{C}$Har); 132.0, 141.7 ($\underline{C}$ar); 155.0 (N$\underline{C}O_2$); 167.6 ($\underline{C}$ON); 173.8 ($\underline{C}$ON). IR (KBr): ν = 3328, 3274, 1707, 1634, 1543, 1385, 1167, 838, 754, 701 cm^{-1}. HRMS calcd for $C_{21}H_{31}N_3O_4$+ Na^+, 412.2212; found, 412.2195.

(*S*)-*N*-(3-(4-Methylbenzamido)propyl)pyrrolidine-2-carboxamide (II). This compound was prepared by reaction of compound **8** (1.36 g, 3.5 mmol) with TFA in DCM by the procedure described for the preparation of **3** and was purified by flash column chromatography on silica gel (EtOAc/methanol: 5/1).Yield: 0.67 g (2.3 mmol, 66%). Colorless oil. $[\alpha]_D$ = -65.9 (*c* 0.8, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.66 (m, 4H); 1.84 (m, 1H); 2.11 (m, 1H); 2.32 (s, 3H); 2.89 (m, 1H); 2.97 (m, 1H); 3.35 (m, 4H); 3.75 (m, 1H); 7.16 (d, J = 7.9 Hz, 2H); 7.75 (d, J = 7.9 Hz, $\underline{3H}$); 8.00 (br s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.5 ($\underline{C}H_3$); 26.1 ($\underline{C}H_2$); 29.7 ($\underline{C}H_2$); 30.9 ($\underline{C}H_2$); 35.6 ($\underline{C}H_2$); 35.9 ($\underline{C}H_2$); 47.2 ($\underline{C}H_2$); 60.5 ($\underline{C}H$); 127.1, 129.1 ($\underline{C}$Har); 131.7, 141.6 ($\underline{C}$ar); 167.4 ($\underline{C}$ON); 176.2 ($\underline{C}$ON). IR (KBr): ν = 3312, 1643, 1548, 1439, 1305, 1119, 838, 753 cm^{-1}. HRMS calcd for $C_{16}H_{23}N_3O_2 + H^+$, 290.1869; found, 290.1880.



Scheme 4. *Reagents and conditions*: (i) *p*-$CH_3C_6H_4COCl$, Et_3N, DCM, 0 ºC to rt. (ii) H_2, $Pd(OH)_2$-C, MeOH. (iii) Boc-*L*-proline, DCC, DCM, 0 ºC to rt. (iv) TFA, DCM, rt.

(*S*)-*N*-(1-Dibenzylamino)-3-phenylpropan-2-yl)-4-methylbenzamide (9). Diamine **4** (1.16 g, 3.5 mmol) was added to dichloromethane (15 mL). The mixture was cooled down to 0 ºC and *p*-toluoyl chloride (0.56 mL, 4.2 mmol, 1.2 equiv) was added dropwise. After the addition was complete, the mixture was allowed to warm to room temperature and stirred for 5h. The resulting solution was basified with 2M ammonia solution (10 mL) and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water, dried with anhydrous $MgSO_4$ and the solvents were eliminated under vacuum. The residue was purified through flash column chromatography on silica gel (hexane/EtOAc: 8:1). to give **9** (1.71 g, 3.82 mmol, 91%) as a colorless solid. Mp 108-110 ºC. $[\alpha]_D^{25}$= -17.8 (*c* 1.2, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H); 2.51 (m, 2H); 2.80 (dd, J = 13.6 Hz, J = 7.5 Hz, 1H); 3.07 (dd, J = 13.6 Hz, J = 5.3 Hz, 1H); 3.48 (d, J = 13.4 Hz, 2H); 3.69 (d, J = 13.4 Hz, 2H); 4.48 (m, 1H); 6.03 (d, J = 6.2 Hz, 1H); 7.25 (m, 17H); 7.58 (d, J = 7.9 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4 ($\underline{C}H_3$); 38.5 ($\underline{C}H_2$); 48.6 ($\underline{C}H$); 55.4 ($\underline{C}H_2$); 58.4 ($\underline{C}H_2$); 126.2, 126.7, 126.8, 127.0, 128.2, 128.7, 129.1, 129.4 ($\underline{C}$Har); 131.8, 137.9, 138.0, 141.6 ($\underline{C}$ar); 167.1 ($\underline{C}$ON). IR (KBr): ν = 3335, 1635, 1533, 1076, 834, 755, 742, 700 cm^{-1}. HRMS calcd for $C_{31}H_{32}N_2O + H^+$, 449.2593; found, 449.2579.

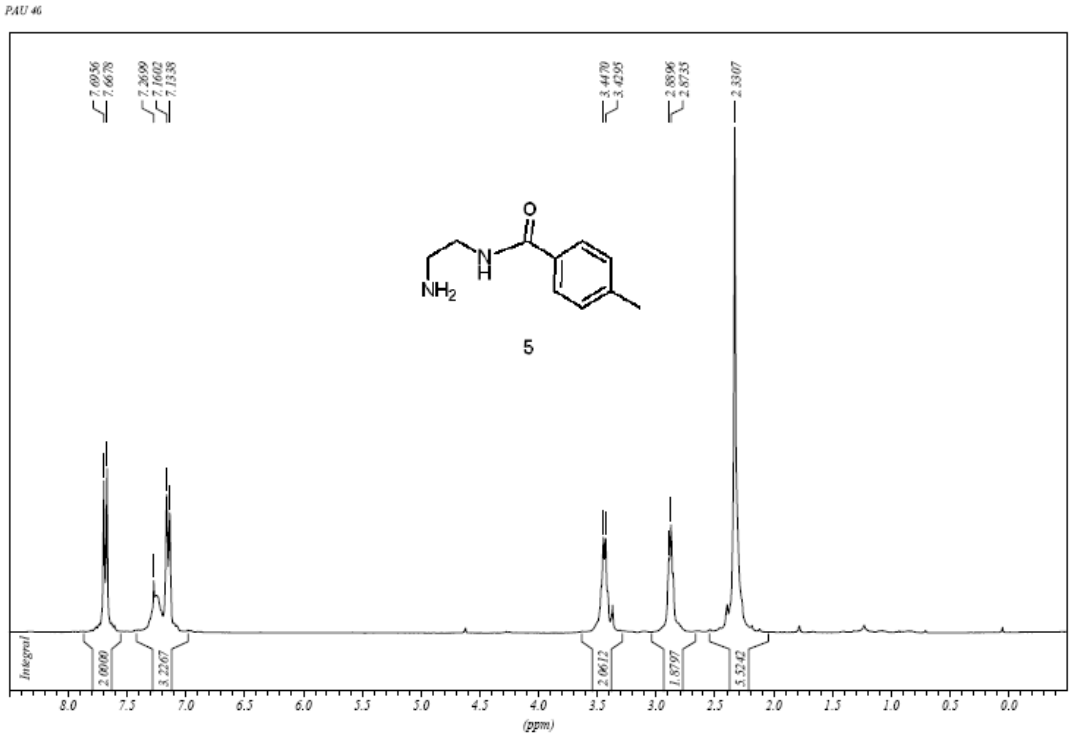
(*S*)-*N*-(1-Amino)-3-phenylpropan-2-yl)-4-methylbenzamide (10). To a solution of *p*-toluamide **9** (1.25 g, 2.80 mmol) in MeOH (30 mL) was added $Pd(OH)_2$-C (310 mg) in one portion. The mixture was stirred under hydrogen for 24 h and the catalyst was removed by filtration and washed with methanol. The solvent was evaporated under reduced pressure and the residue was washed with ethyl acetate to give **10** as a colorless solid: 465 mg (1.73 mmol, 62%). Mp 237-239 ºC (dec). $[\alpha]_D^{25}$= -64.3 (*c* 0.8, MeOH); ^{1}H-NMR (300 MHz, CD_3OD): δ = 2.38 (s, 3H); 3.00 (d, J = 7.5 Hz, 2H); 3.16 (m, 2H); 3.30 (br s, 2H); 4.56 (m, 1H); 7.27 (m, 7H); 7.67 (d, J = 7.9 Hz, 2H). ^{13}C-NMR (75 MHz, CD_3OD): δ = 21.6 ($\underline{C}H_3$); 39.3 ($\underline{C}H_2$); 44.5 ($\underline{C}H_2$); 51.6 ($\underline{C}H$); 128.0, 128.8, 129.8, 130.2, 130.5 ($\underline{C}$Har); 132.4, 138.8, 143.8 ($\underline{C}$ar); 171.1 ($\underline{C}$ON). IR (KBr): ν = 3323, 1640, 1540, 1048, 746, 701 cm^{-1}. HRMS calcd for $C_{17}H_{20}N_2O + H^+$, 269.1654; found, 269.1660.

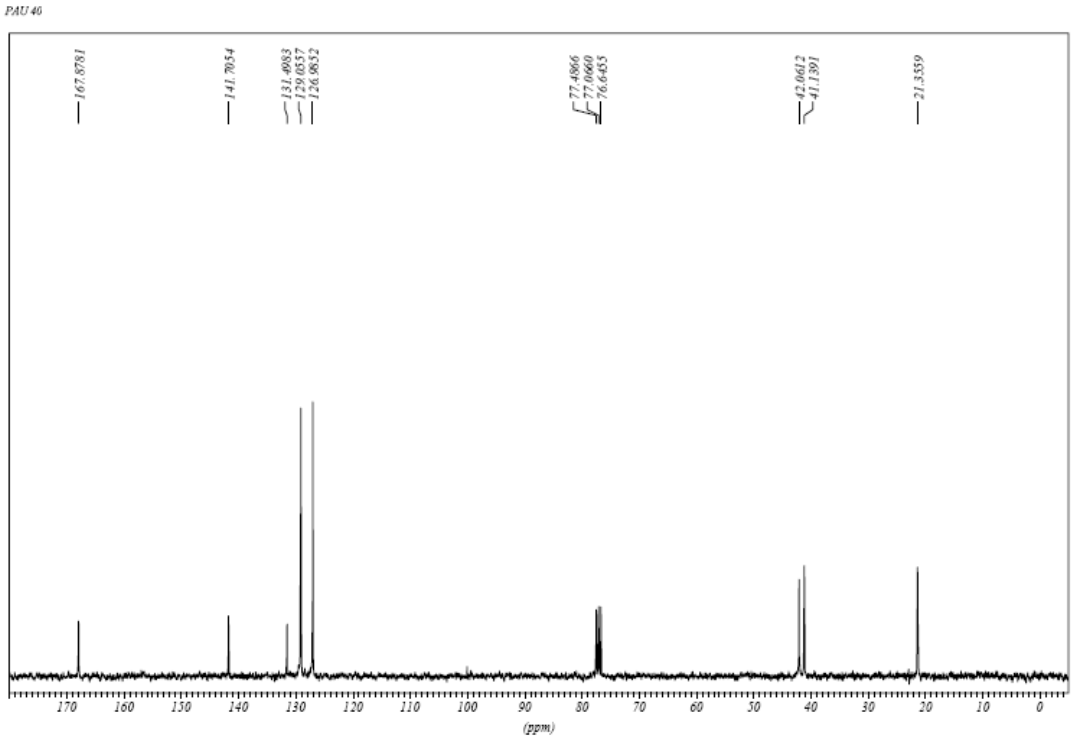
(*S*)-*tert*-Butyl 2-((*S*)-2-(4-methylbenzamido)-3 phenylpropylcarbamoyl)pyrrolidine -1-carboxylate (11). This compound was obtained by reaction of compound **10** (295 mg, 1.10 mmol, 1 equiv) with Boc-*L*-proline (296 mg, 1.37 mmoles, 1.25 equiv) in the presence of DCC (284 mg, 1.37 mmoles, 1.25 equiv) by the procedure described for the preparation of **6** and was purified by flash column chromatography on silica gel (hexane/EtOAc: 1/1). Yield: 179 mg (0.38 mmol, 88%). Colorless solid, mp 104-105 ºC. $[\alpha]_D^{25}$= -60.0 (*c* 0.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H); 1.91 (m, 3H); 2.18 (m, 1H); 2.37 (s, 3H); 2.83 (dd, 1H, J = 13.6 Hz, J = 7.9 Hz, 1H); 3.13 (dd, 1H, J = 13.6 Hz, J = 5.7 Hz, 1H); 3.44 (m, 4H); 4.23 (m, 1H); 4.38 (m, 1H); 6.90 (br s, 2H); 7.19 (d, J = 8.3 Hz, 2H); 7.27 (m, 5H); 7.65 (d, J = 8.3 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.0 ($\underline{C}H_3$); 24.1 ($\underline{C}H_2$); 28.2 ($\underline{C}H_3$); 33.8 ($\underline{C}H_2$); 38.4 ($\underline{C}H_2$); 42.5 ($\underline{C}H_2$); 47.0 ($\underline{C}H_2$); 52.8 ($\underline{C}H$); 60.5 ($\underline{C}H$); 80.3 ($\underline{C}$); 126.5, 126.9, 128.5, 128.9, 129.1 ($\underline{C}$Har); 131.8, 137.7, 141.4 ($\underline{C}$ar); 155.4 (N$\underline{C}O_2$); 167.2 (CON); 174.0 ($\underline{C}$ON). IR (KBr): ν = 3325, 1638, 1543, 1400, 1163, 751, 701 cm^{-1}. HRMS calcd for $C_{27}H_{35}N_3O_4 + Na^+$, 488.2525; found, 488.2503.

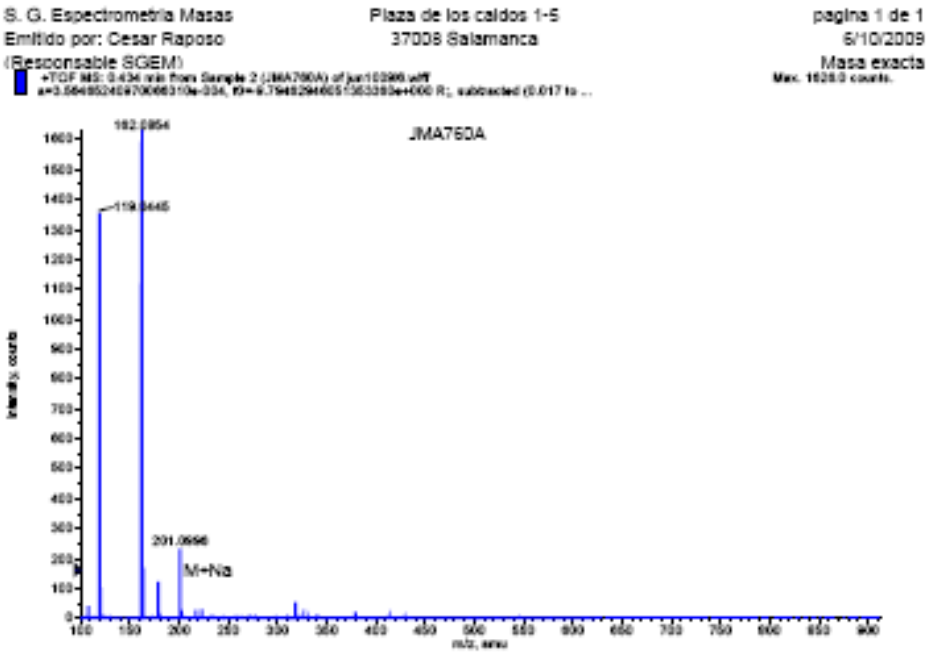
(*S*)-*N*-((*S*)-2-(4-methylbenzamido)-3-phenylpropyl)pyrrolidine-2-carboxamide (III). This compound was prepared by reaction of compound **11** (150 mg, 0.32 mmol) with TFA in DCM by the procedure described for the preparation of **3** and was purified by flash column chromatography on silica gel (EtOAc/methanol: 5/1). Yield: 102 mg

(0.28 mmol, 87%). Colorless solid, mp. 181-182 ºC (from EtOAc). $[\alpha]_D^{25}$= -34.3 (*c* 0.8, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.70 (m, 2H); 1.90 (m, 1H); 2.11 (m, 1H); 2.38 (s, 3H); 2.68 (m, 2H); 2.95 (m, 2H); 3.25 (m, 2H); 3.40 (m, 1H); 3.70 (dd, J = 9.0 Hz, J = 5.0 Hz, 1H); 4.34 (m, 1H); 7.22 (d, J = 7.9 Hz, 2H); 7.29 (m, 5H); 7.66 (d, J = 6.6 Hz, 1H); 7.72 (d, J = 7.9 Hz, 2H); 8.09 (br s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4 ($\underline{C}H_3$); 26.1 ($\underline{C}H_2$); 30.6 ($\underline{C}H_2$); 38.5 ($\underline{C}H_2$); 41.6 ($\underline{C}H_2$); 47.1 ($\underline{C}H_2$); 53.4 ($\underline{C}H$); 60.2 ($\underline{C}H$); 126.5, 127.0, 128.6, 129.1, 129.2 ($\underline{C}$Har); 131.3, 137.8, 141.6 ($\underline{C}$ar); 167.2 (CON); 177.2 ($\underline{C}$ON). IR (KBr): ν = 3322, 1660, 1633, 1544, 1509, 1111, 699 cm^{-1}. HRMS calcd for $C_{22}H_{27}N_3O_2 + H^+$, 366.2182; found, 366.2180.

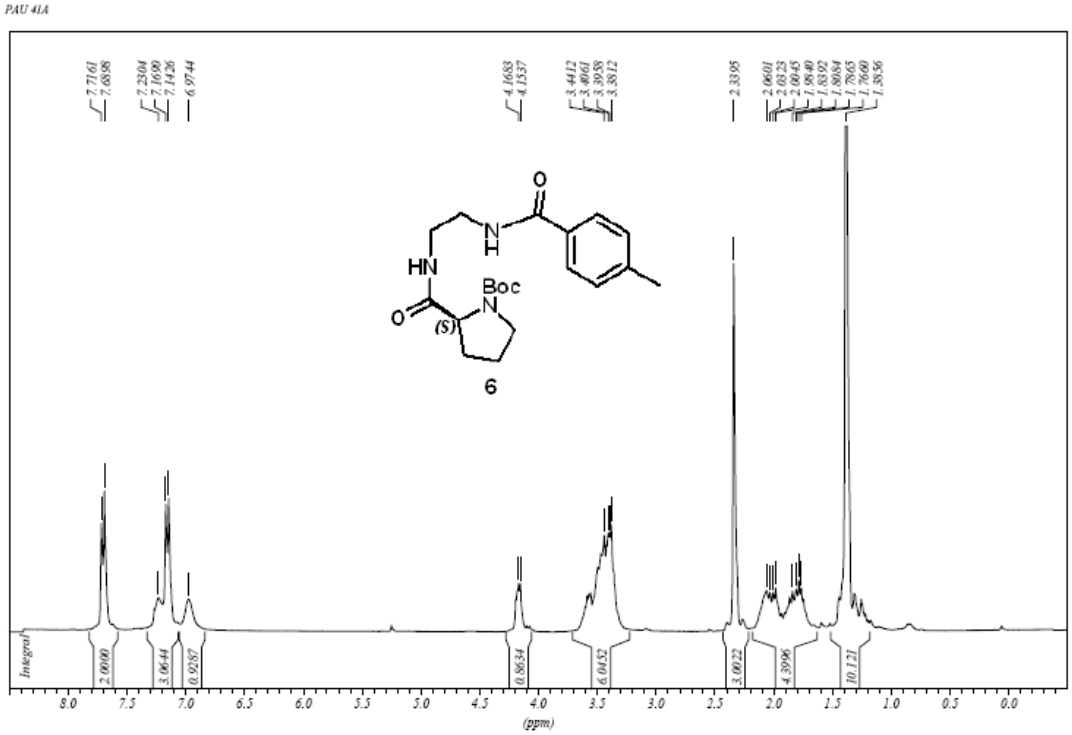
2. NMR Spectra and High resolution MS for New Compounds

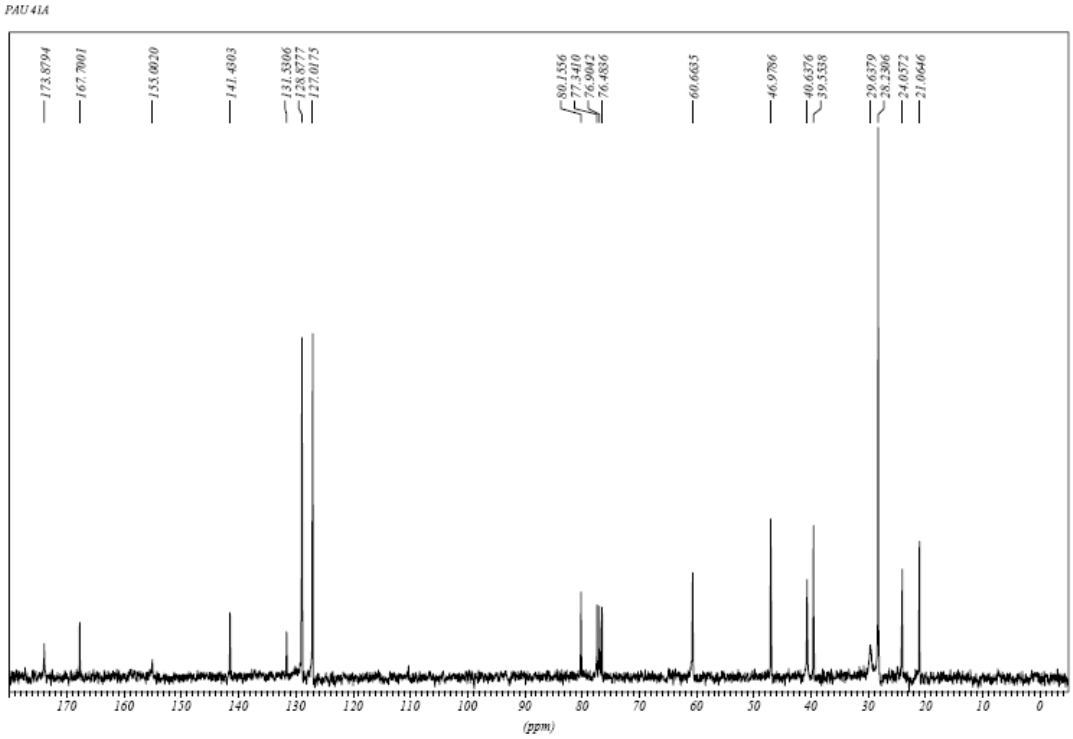


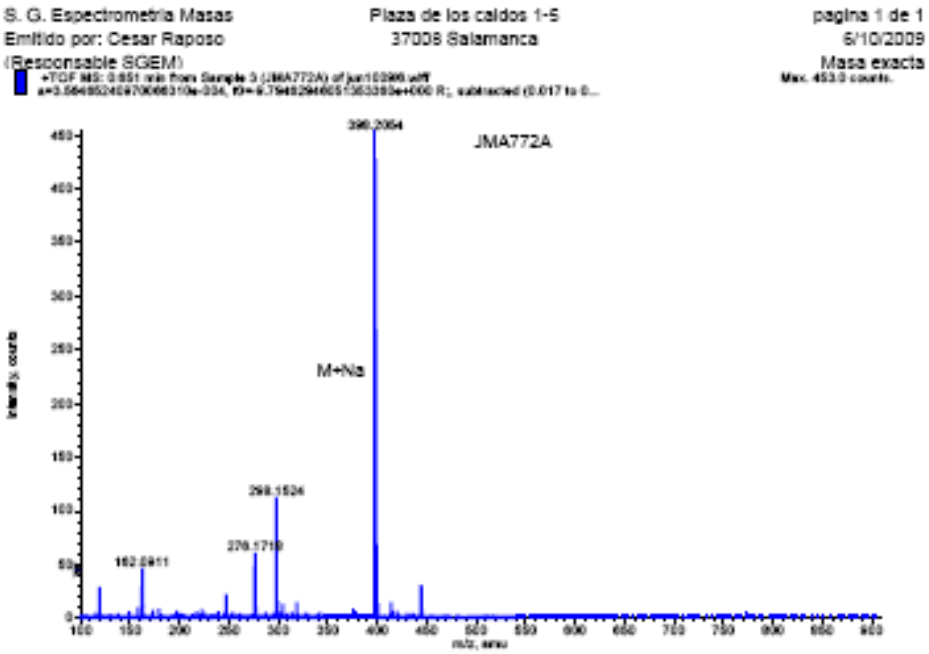




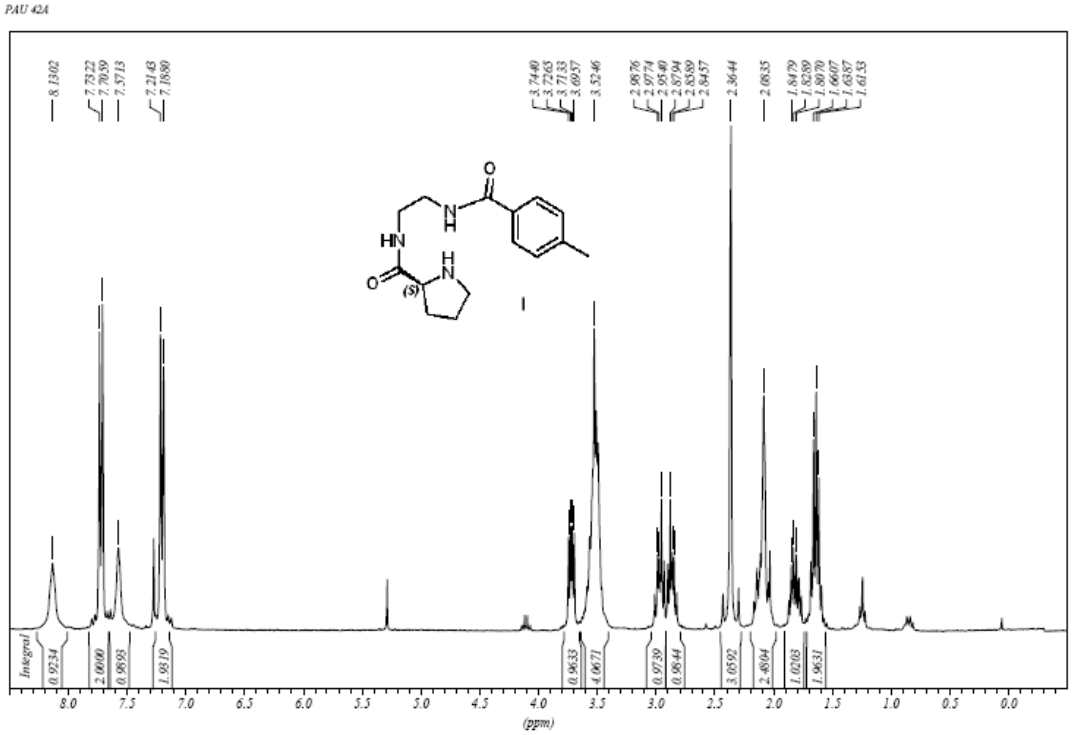
Formula	CalculatedMass	mDaError	ppmError	RDB
C10 H14 N2 O Na	201.099834	-0.234336	-1.16527	4.5
C7 H13 N4 O3	201.098217	1.383108	6.877707	3.5







Formula	CalculatedMass	mDaError	ppmError	RDB
C5 H25 N15 O5 Na	398.20553	-0.13044	-0.327569	0.5
C20 H29 N3 O4 Na	398.205028	0.372136	0.934631	7.5
C18 H24 N9 O2	398.204748	0.652268	1.638017	11.5
C21 H25 N7 Na	398.206365	-0.965176	-2.423811	12.5
C6 H21 N19 O Na	398.206868	-1.467752	-3.685912	5.5
C2 H24 N17 O7	398.203913	1.487004	3.734259	-0.5
C17 H28 N5 O6	398.20341	1.98958	4.996359	6.5
C22 H28 N3 O4	398.207433	-2.033124	-5.10571	10.5
C7 H24 N15 O5	398.207936	-2.5357	-6.36781	3.5
C9 H29 N9 O7 Na	398.208216	-2.815832	-7.071296	-0.5
C16 H25 N9 O2 Na	398.202342	3.057528	7.678258	8.5
C16 H32 N O10	398.202073	3.326892	8.354702	1.5
C14 H20 N15	398.202062	3.33766	8.381743	12.5
C23 H24 N7	398.20877	-3.370436	-8.464052	15.5
C25 H29 N O2 Na	398.209051	-3.650568	-9.167538	11.5
C8 H20 N19 O	398.209273	-3.873012	-9.726153	8.5



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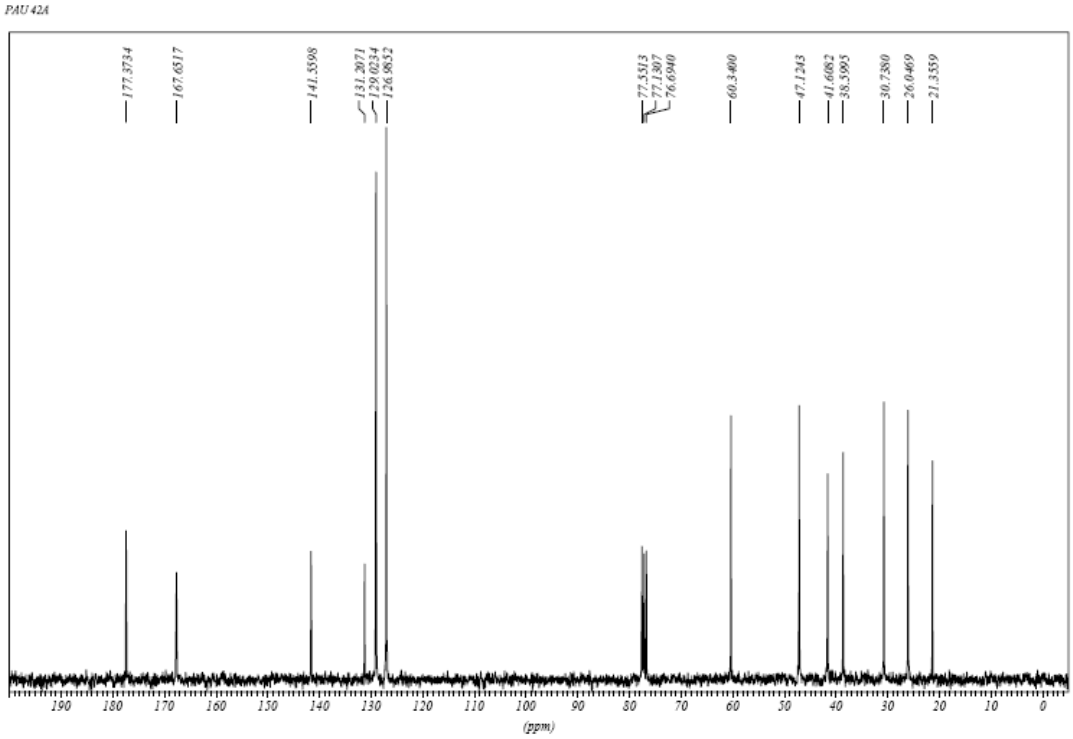
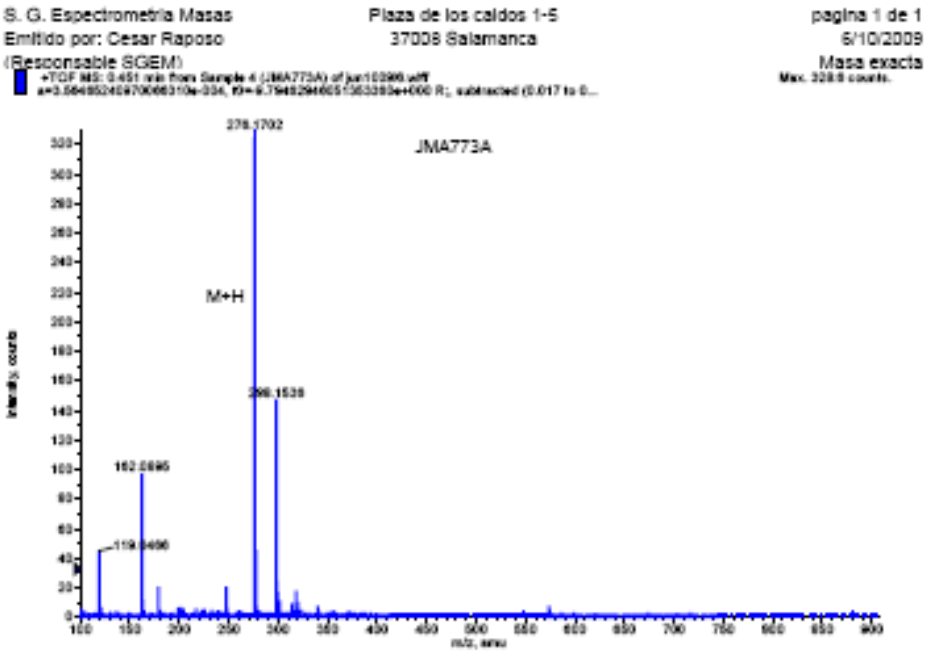
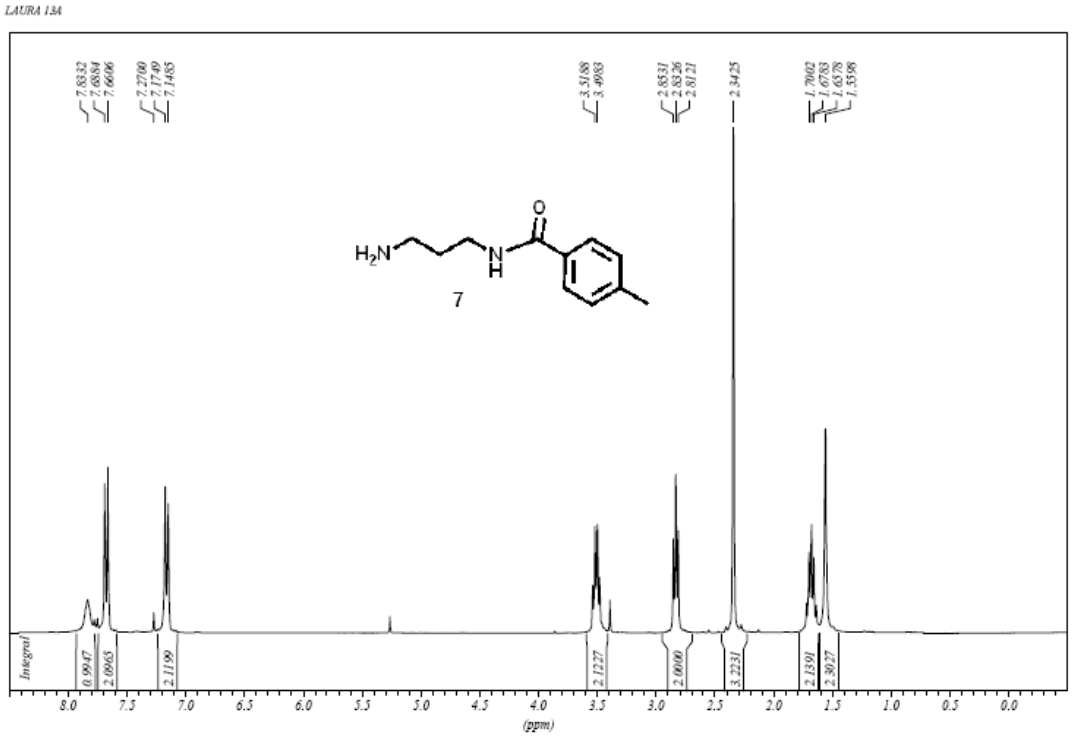
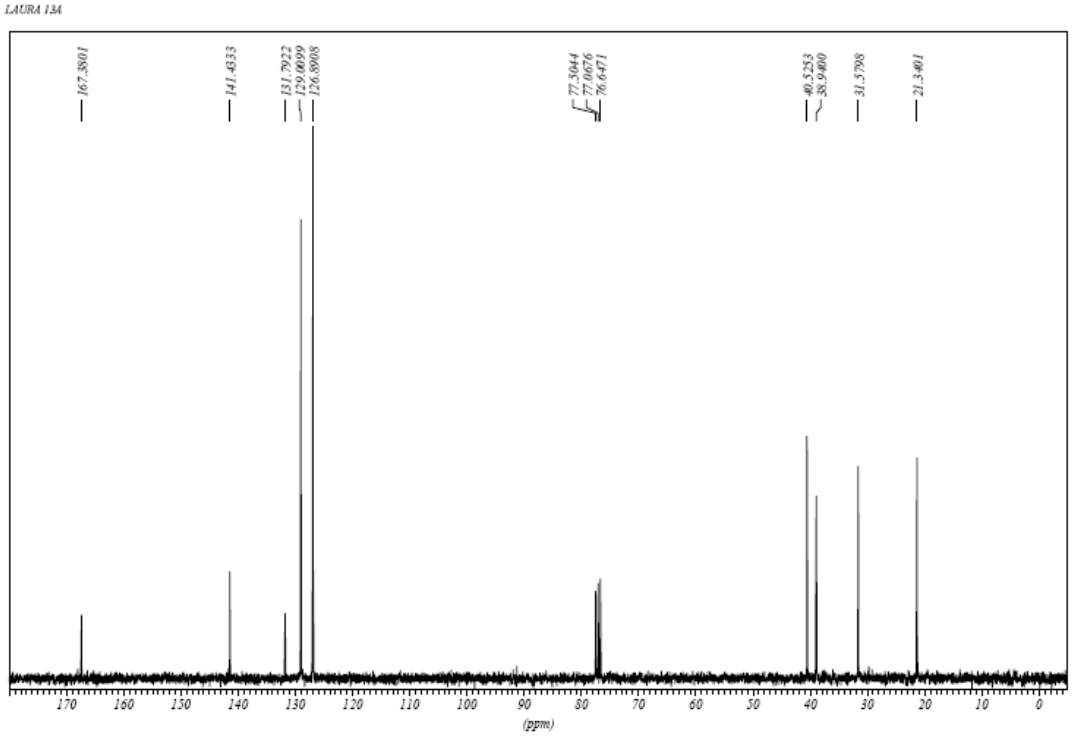
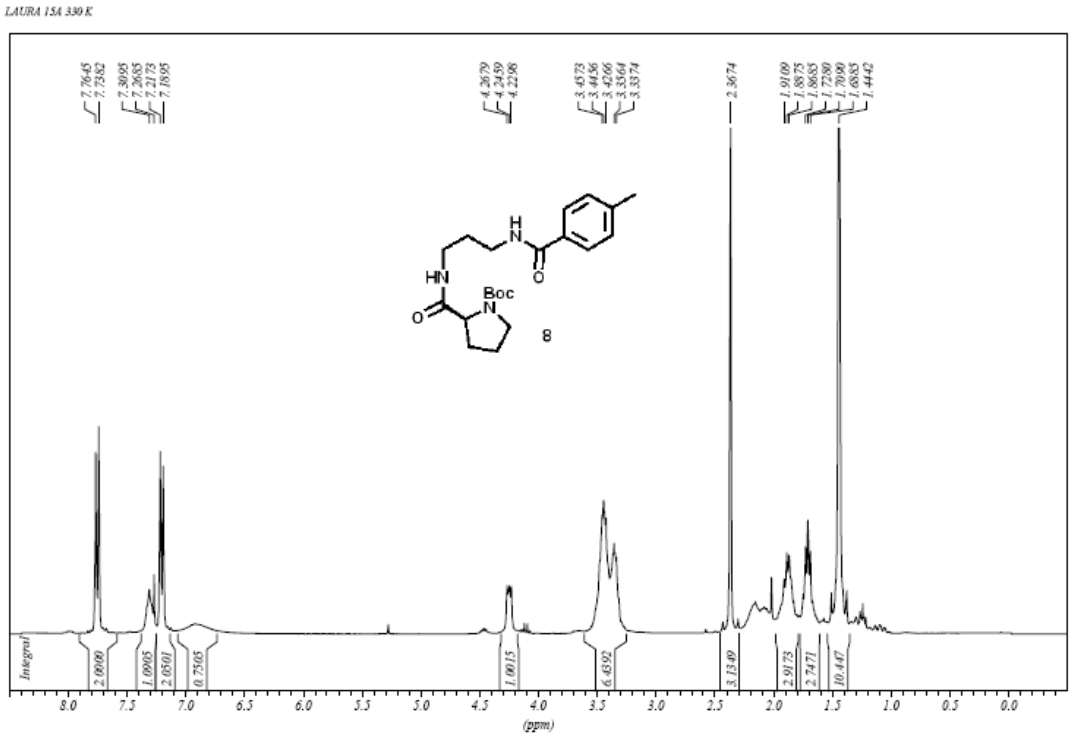


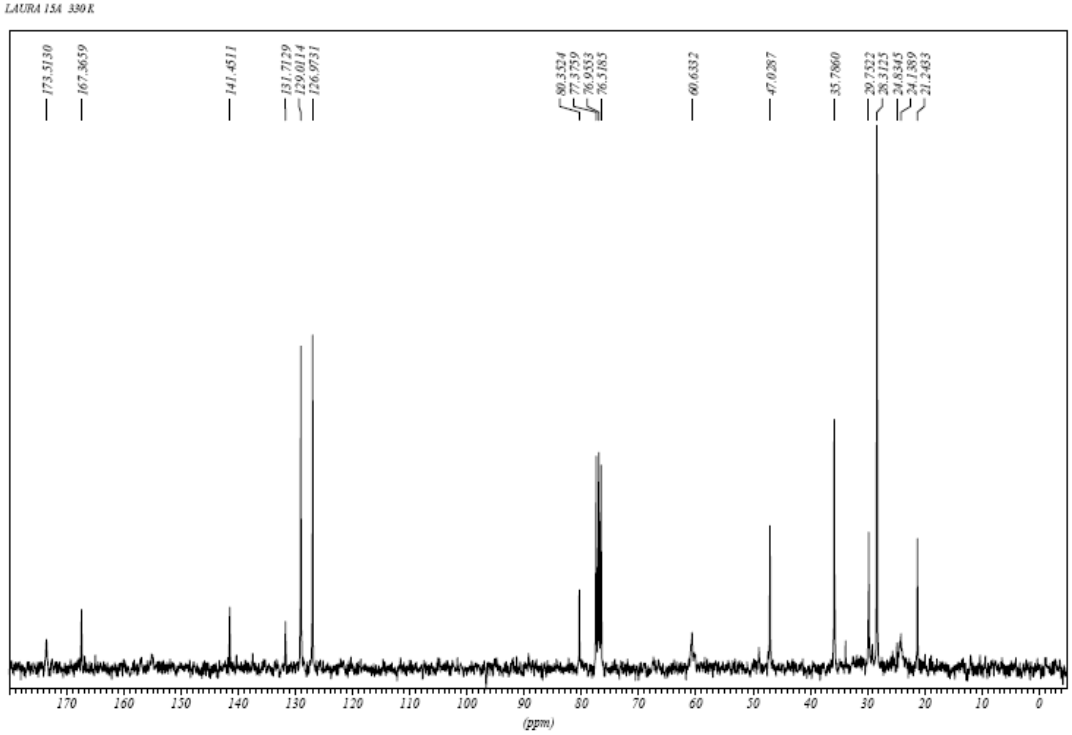


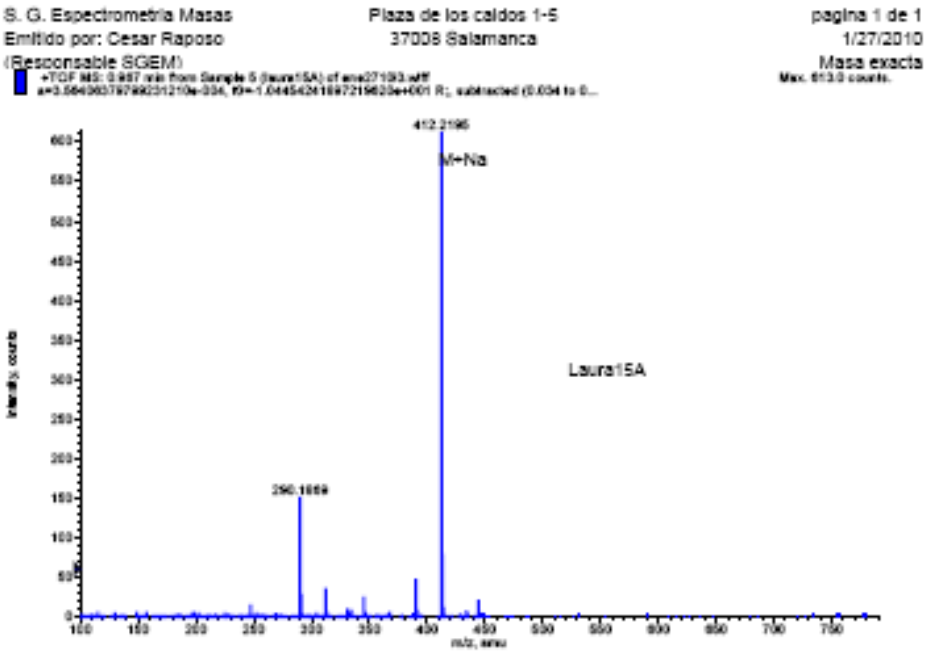
Formula	CalculatedMass	mDaError	ppmError	RDB
C15 H22 N3 O2	276.170654	-0.453604	-1.642477	6.5
H18 N15 O3	276.171156	-0.95618	-3.462278	-0.5
C13 H23 N3 O2 Na	276.168248	1.951656	7.066845	3.5
C18 H23 N Na	276.172271	-2.071048	-7.499158	7.5
C11 H18 N9	276.167968	2.231788	8.081189	7.5
C3 H19 N13 O Na	276.172774	-2.573624	-9.318959	0.5











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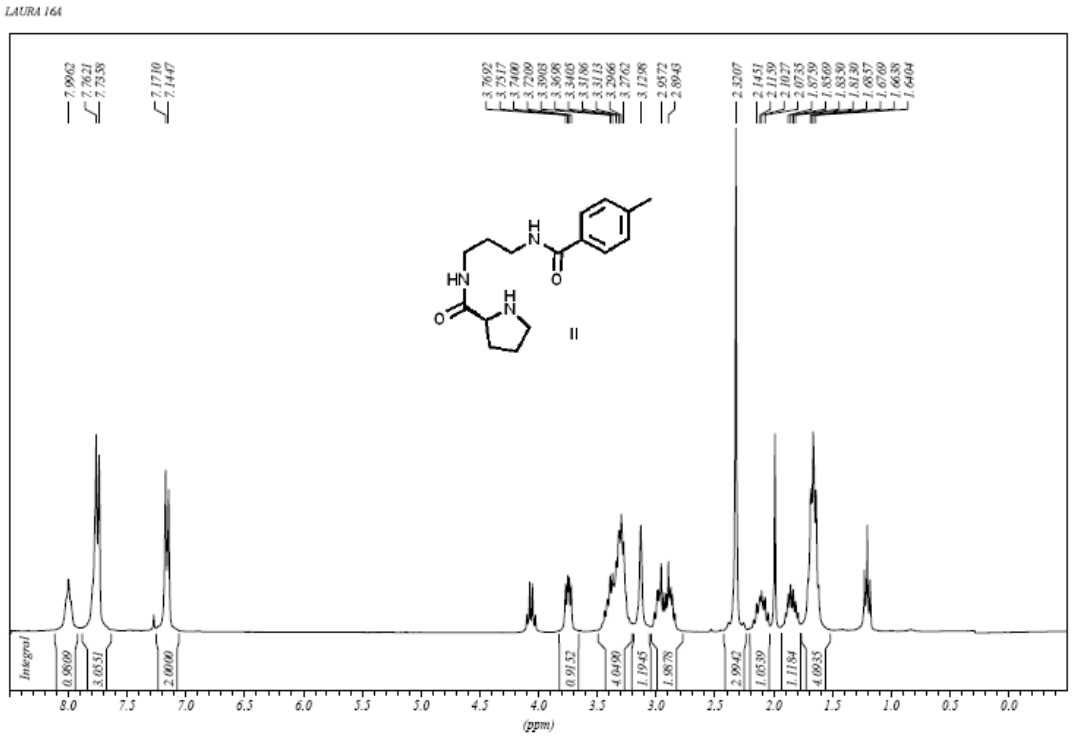
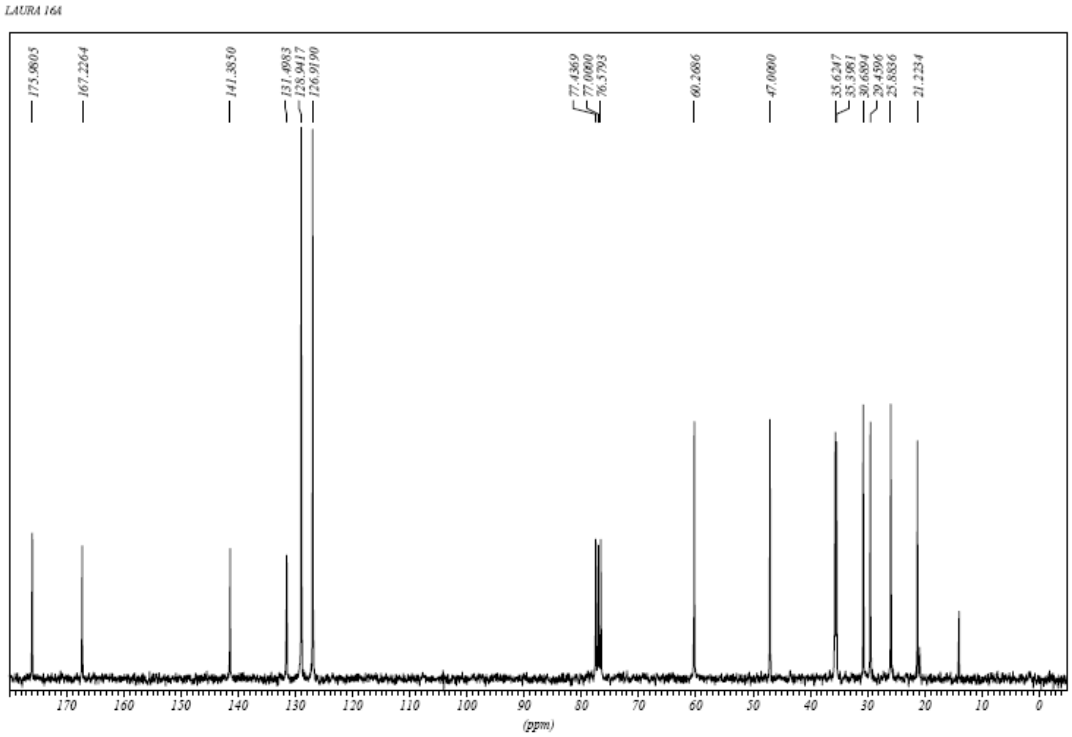
C3 H26 N17 O7	412.219563	-0.063076	-0.153015	-0.5
C18 H30 N5 O6	412.219061	0.4395	1.066178	6.5
C19 H26 N9 O2	412.220398	-0.897812	-2.177992	11.5
C21 H31 N3 O4 Na	412.220678	-1.177944	-2.857561	7.5
C17 H27 N9 O2 Na	412.217993	1.507448	3.656901	8.5
C6 H27 N15 O5 Na	412.221181	-1.68052	-4.076755	0.5
C17 H34 N O10	412.217723	1.776812	4.310348	1.5
C15 H22 N15	412.217712	1.78758	4.33647	12.5
C22 H27 N7 Na	412.222015	-2.515256	-6.101731	12.5
C16 H31 N5 O6 Na	412.216655	2.84476	6.901071	3.5
C7 H23 N19 O Na	412.222518	-3.017832	-7.320925	5.5
C14 H26 N11 O4	412.216375	3.124892	7.580641	7.5
C23 H30 N3 O4	412.223083	-3.583204	-8.692454	10.5
C8 H26 N15 O5	412.223586	-4.08578	-9.911648	3.5





S. G. Espectrometría Masas
Emitido por: Cesar Raposo
(Responsable SGEM)

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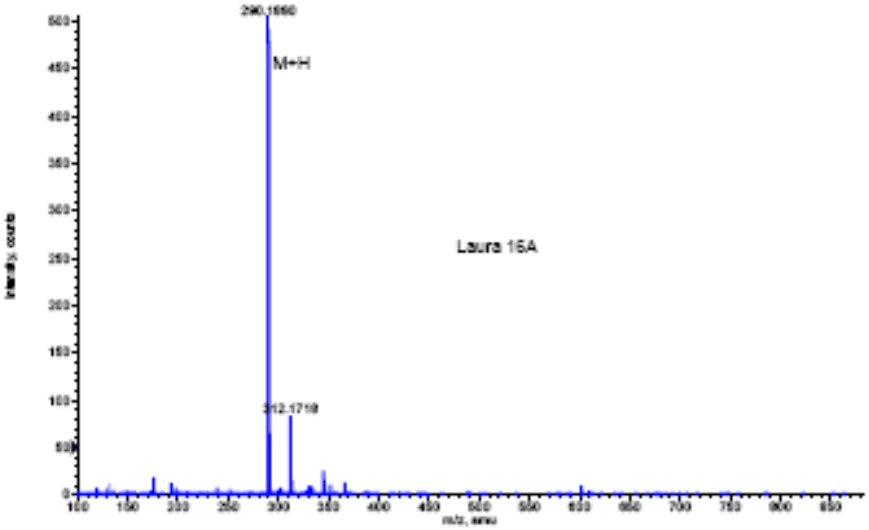
Masa exacta



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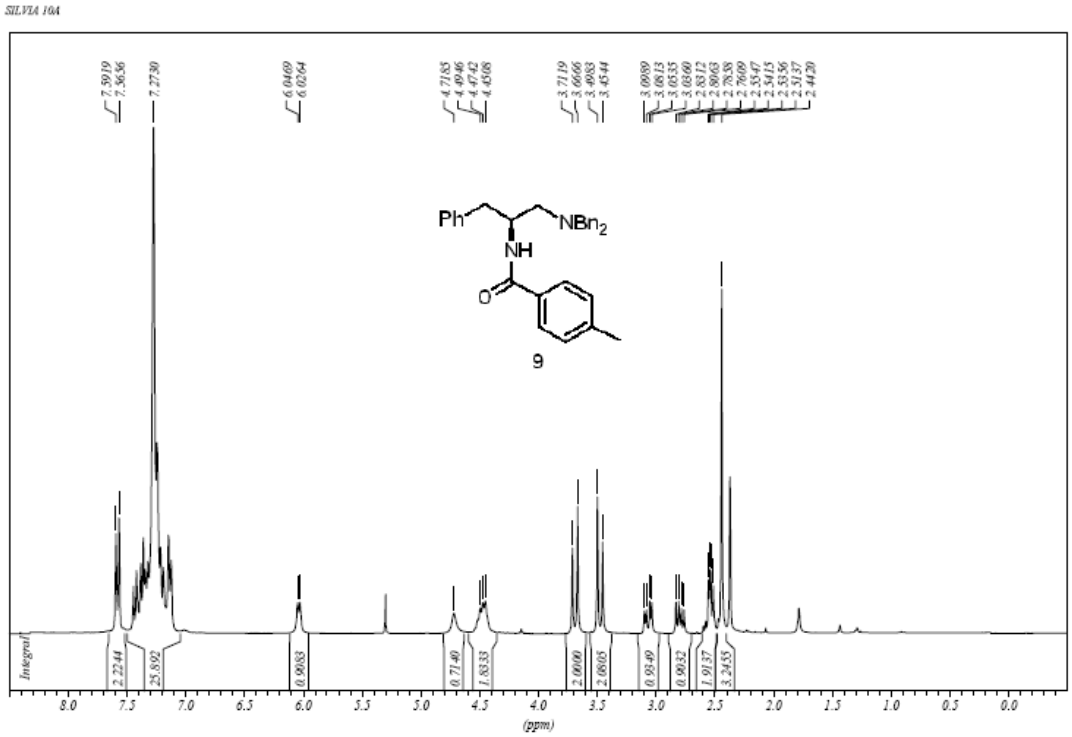
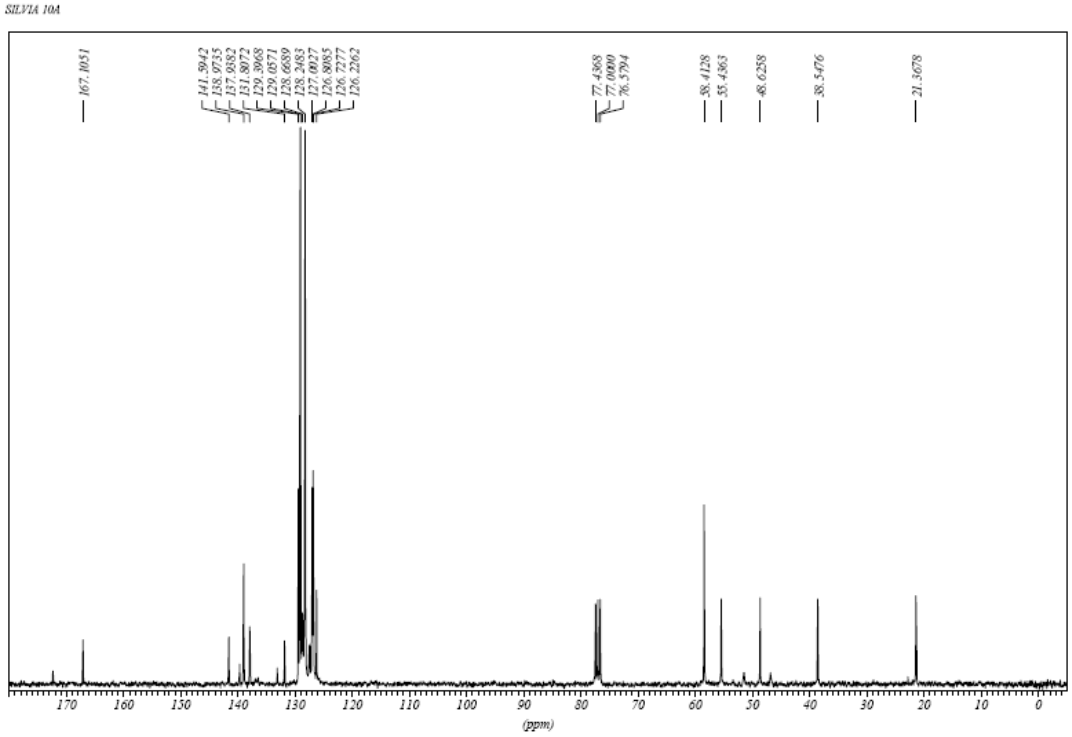
C4 H21 N13 O Na	290.188424	-0.423704	-1.460099	0.5
C H20 N15 O3	290.186805	1.19374	4.11367	-0.5
C16 H24 N3 O2	290.186304	1.696315	5.845565	6.5
C21 H24 N	290.190326	-2.326388	-8.016815	10.5
C6 H20 N13 O	290.190829	-2.828964	-9.74871	3.5





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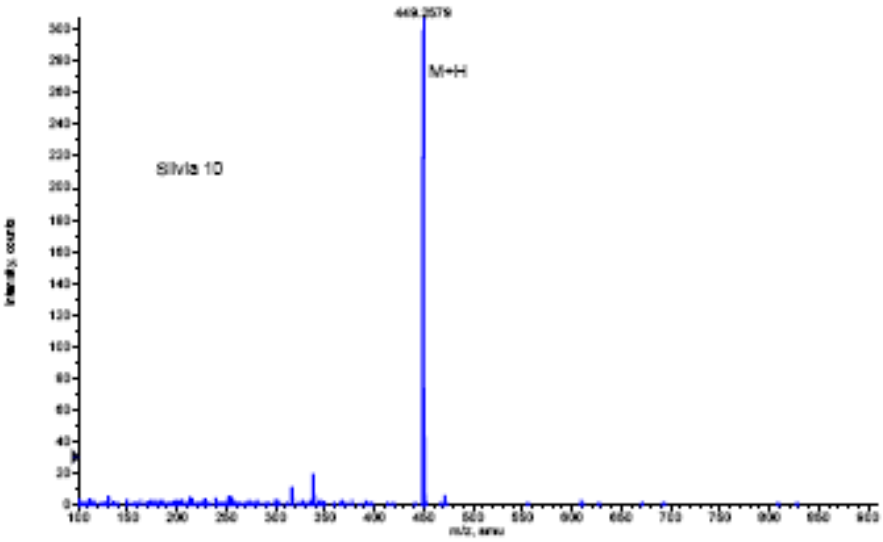
Masa exacta



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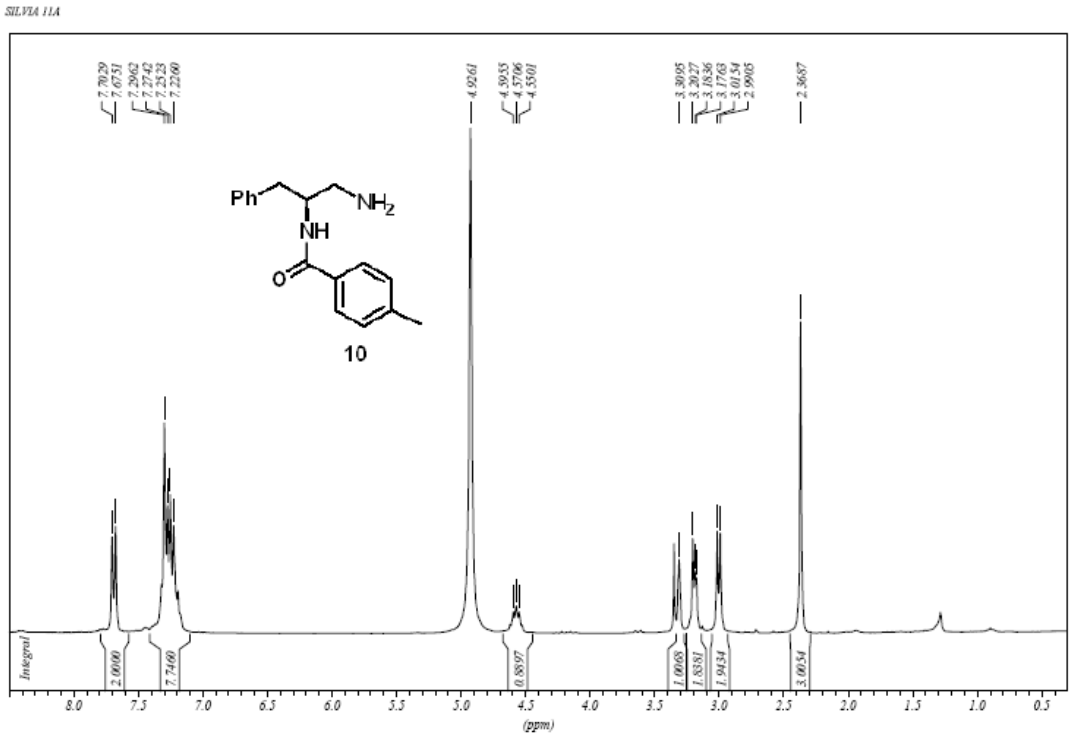
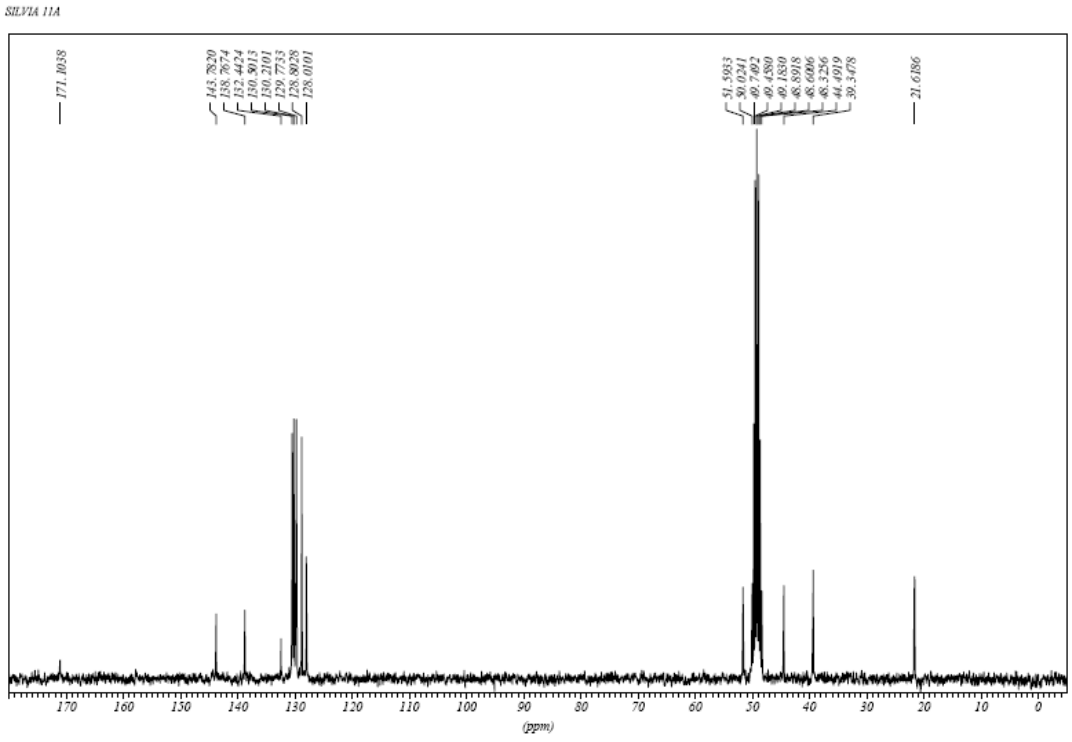
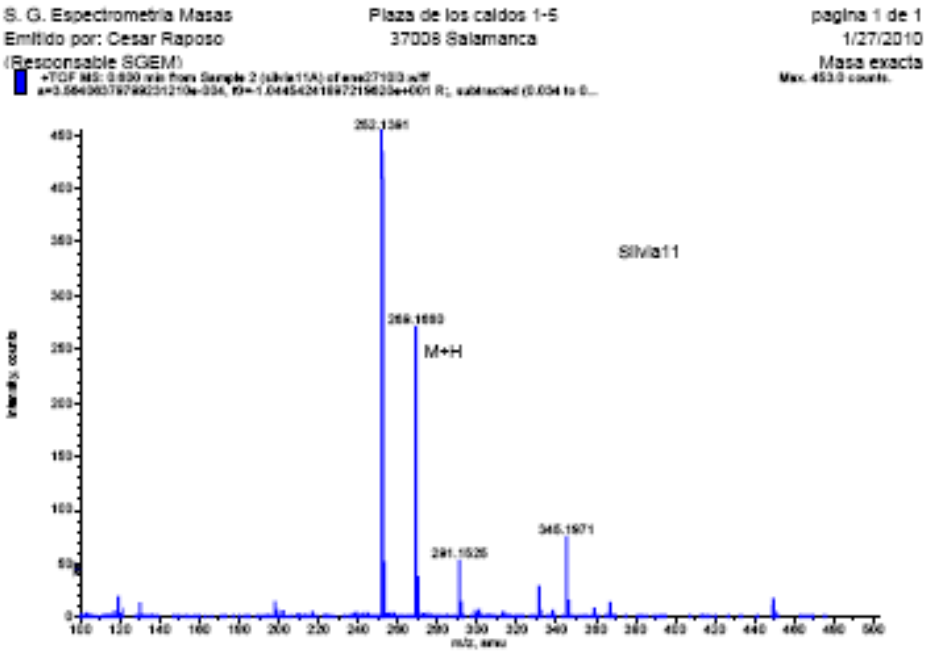
C15 H33 N10 O5	449.257906	-0.00566	-0.012599	4.5
C17 H38 N4 O8 Na	449.258186	-0.285792	-0.636142	0.5
C31 H33 N2 O	449.25874	-0.840396	-1.870629	16.5
C14 H30 N14 O2 Na	449.256838	1.062288	2.364537	6.5
C14 H37 N6 O10	449.256568	1.331652	2.964111	-0.5
C12 H25 N20	449.256558	1.34242	2.98808	10.5
C16 H29 N14 O2	449.259243	-1.342972	-2.989308	9.5
C29 H34 N2 O Na	449.256335	1.564864	3.483216	13.5
C18 H34 N8 O4 Na	449.259523	-1.623104	-3.612851	5.5
C13 H34 N10 O6 Na	449.2555	2.3996	5.341246	1.5
C11 H29 N16 O4	449.25522	2.679732	5.964789	5.5
C19 H37 N4 O8	449.260591	-2.691052	-5.989986	3.5
C19 H30 N12 Na	449.26086	-2.960416	-6.589561	10.5
C26 H33 N4 O3	449.254718	3.182308	7.083468	12.5
C10 H26 N20 Na	449.254152	3.74768	8.341924	7.5
C10 H33 N12 O8	449.253883	4.017044	8.941499	0.5
C20 H33 N8 O4	449.261928	-4.028364	-8.966696	8.5
C22 H38 N2 O6 Na	449.262208	-4.308496	-9.590239	4.5







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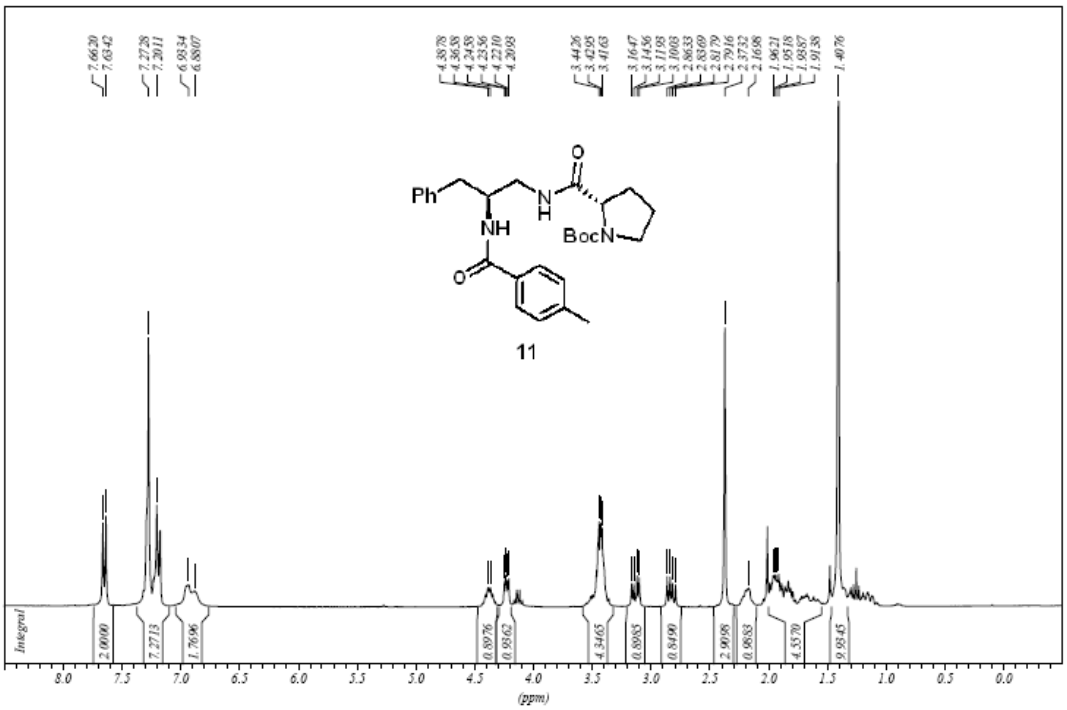
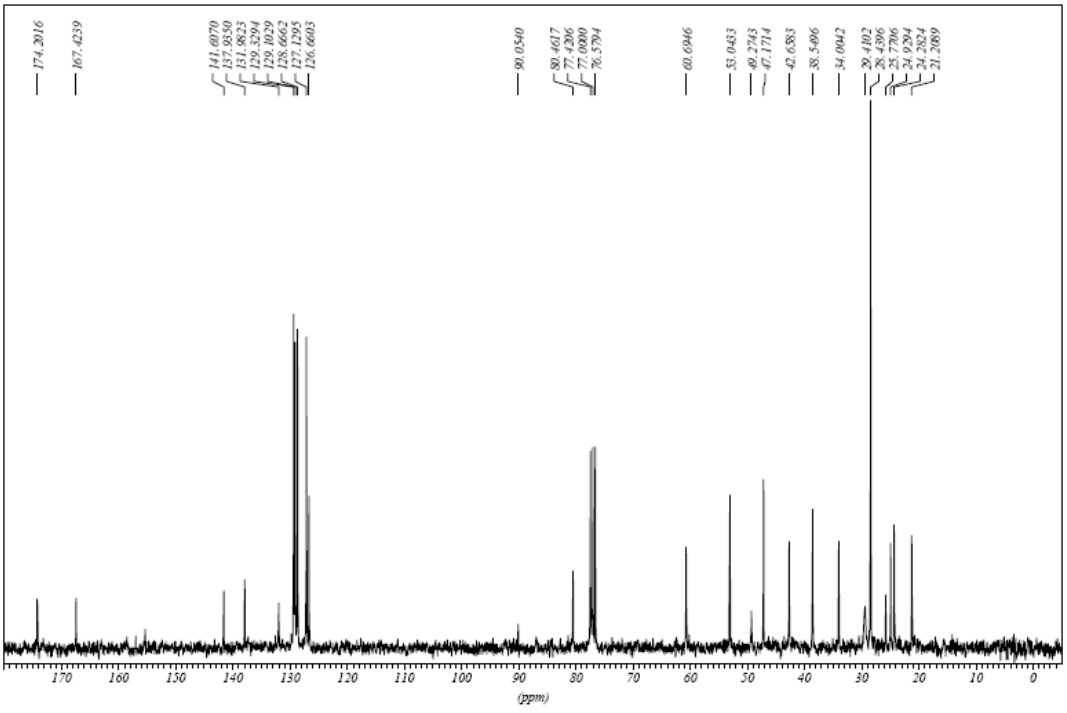
C5 H18 N12 Na	269.16696	-0.959936	-3.566327	2.5
C17 H21 N2 O	269.16484	1.160084	4.309911	8.5
C6 H21 N8 O4	269.168028	-2.027884	-7.533938	0.5

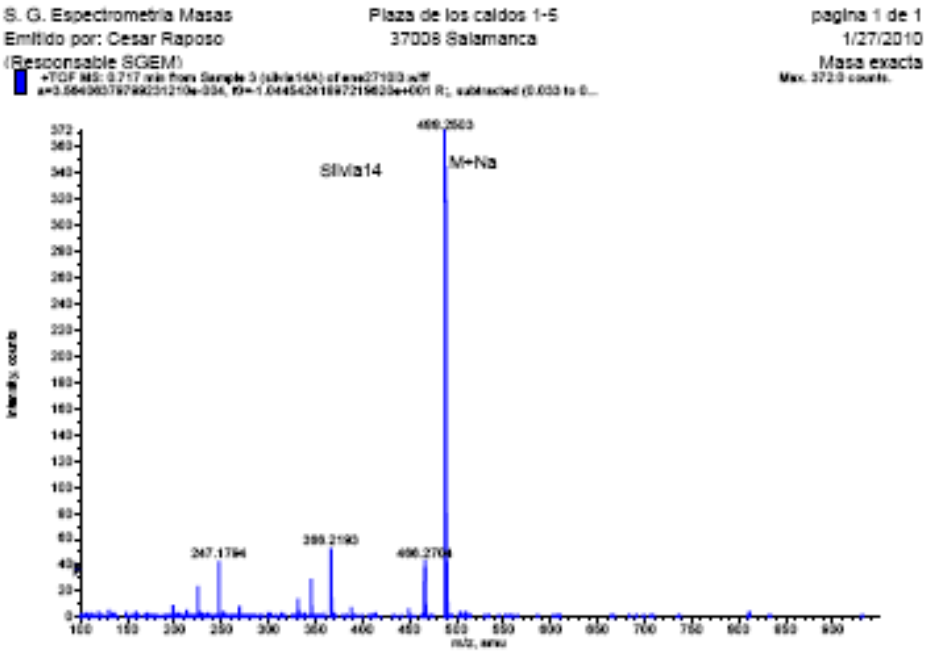
SILVIA 14A; 1H 330K



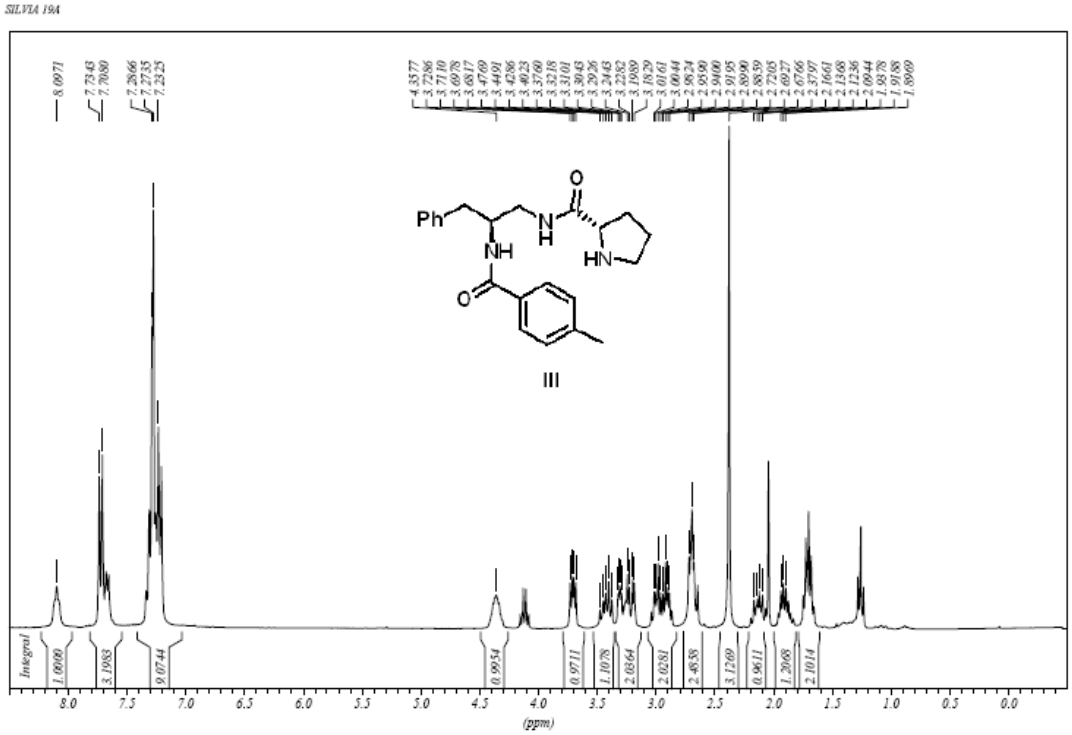
11

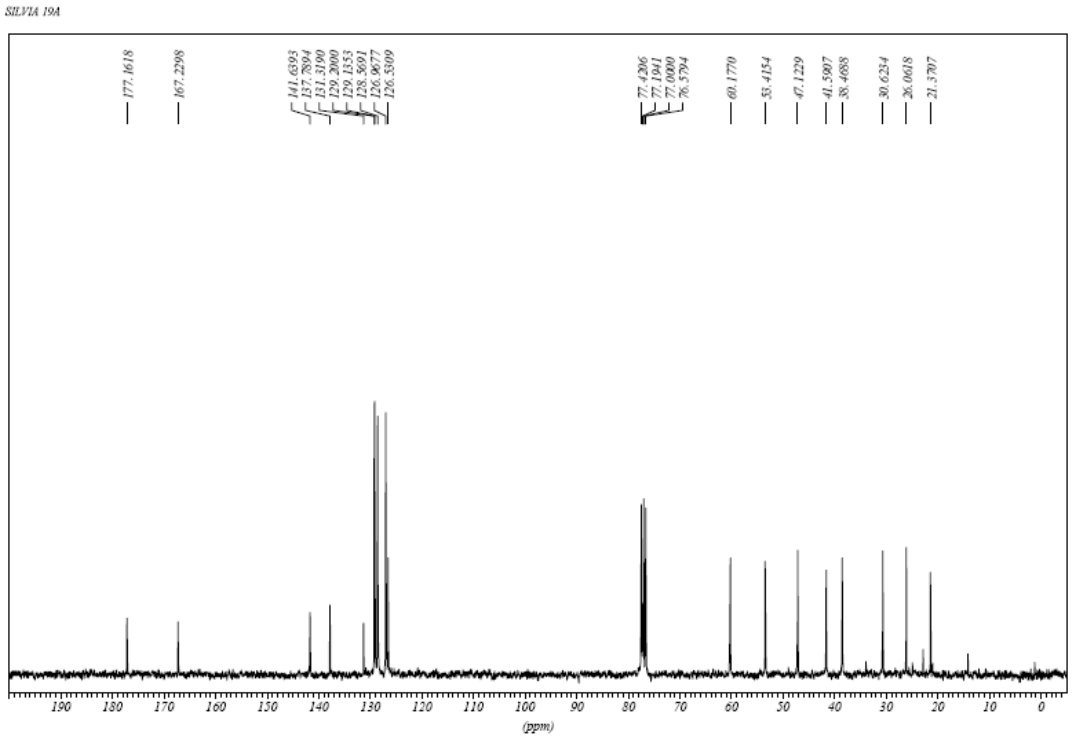
SILVIA 14A; 13C DEPT 330K

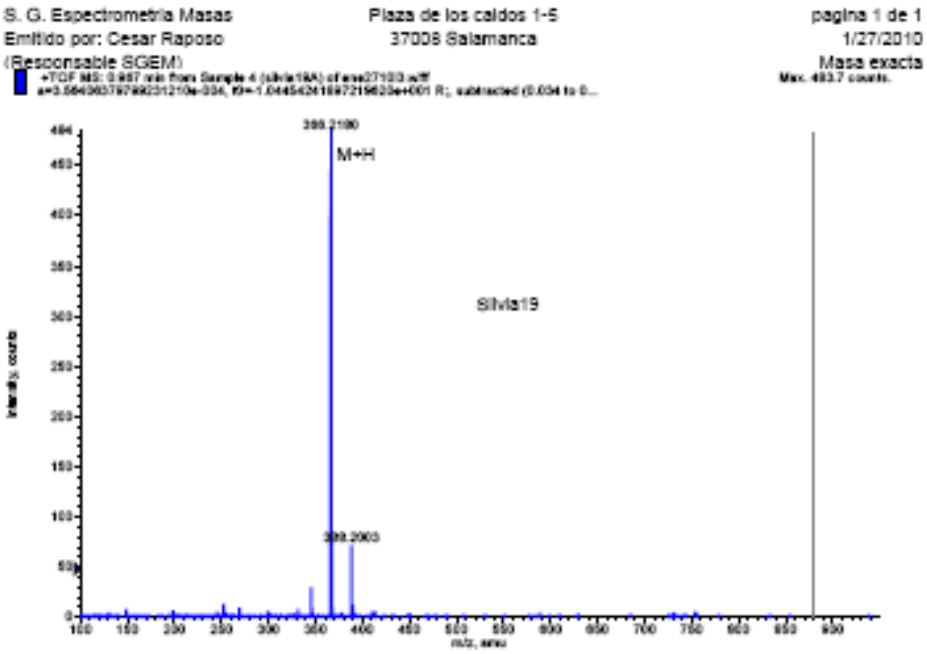




Formula	CalculatedMass	mDaError	ppmError	RDB
C24 H34 N5 O6	488.250361	-0.06066	-0.124239	10.5
C9 H30 N17 O7	488.250863	-0.563236	-1.153579	3.5
C11 H35 N11 O9 Na	488.251143	-0.843368	-1.727325	-0.5
C23 H31 N9 O2 Na	488.249293	1.007288	2.063054	12.5
C23 H38 N O10	488.249023	1.276652	2.614746	5.5
C21 H26 N15	488.249013	1.28742	2.6368	16.5
C25 H30 N9 O2	488.251698	-1.397972	-2.863225	15.5
C27 H35 N3 O4 Na	488.251978	-1.678104	-3.436971	11.5
C7 H31 N17 O7 Na	488.248458	1.842024	3.7727	0.5
C12 H31 N15 O5 Na	488.252481	-2.18068	-4.466311	4.5
C22 H35 N5 O6 Na	488.247955	2.3446	4.80204	7.5
C20 H30 N11 O4	488.247675	2.624732	5.375786	11.5
C28 H31 N7 Na	488.253315	-3.015416	-6.175956	16.5
C13 H34 N11 O9	488.253549	-3.248628	-6.653604	2.5
C4 H30 N19 O9	488.246841	3.459468	7.085432	-0.5
C13 H27 N19 O Na	488.253818	-3.517992	-7.205296	9.5
C21 H39 N O10 Na	488.246618	3.681912	7.541025	2.5
C19 H27 N15 Na	488.246607	3.69268	7.56308	13.5
C19 H34 N7 O8	488.246338	3.962044	8.114771	6.5
C29 H34 N3 O4	488.254383	-4.083364	-8.36325	14.5
C14 H30 N15 O5	488.254886	-4.58594	-9.39259	7.5
C16 H35 N9 O7 Na	488.255166	-4.866072	-9.966336	3.5

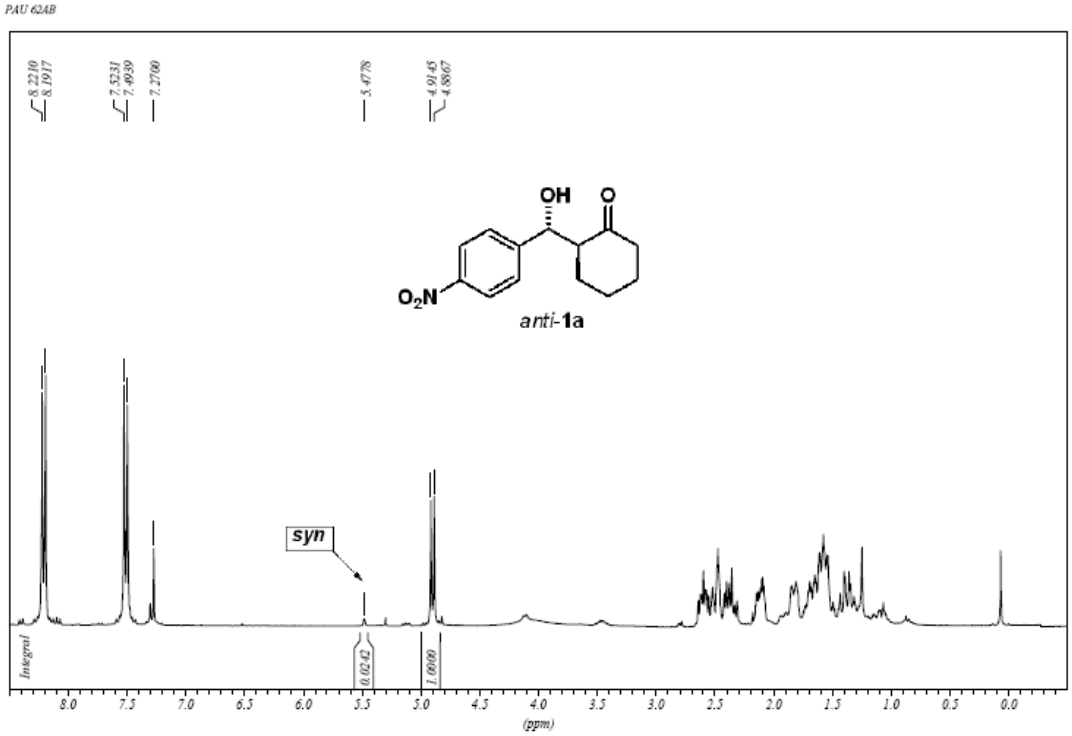


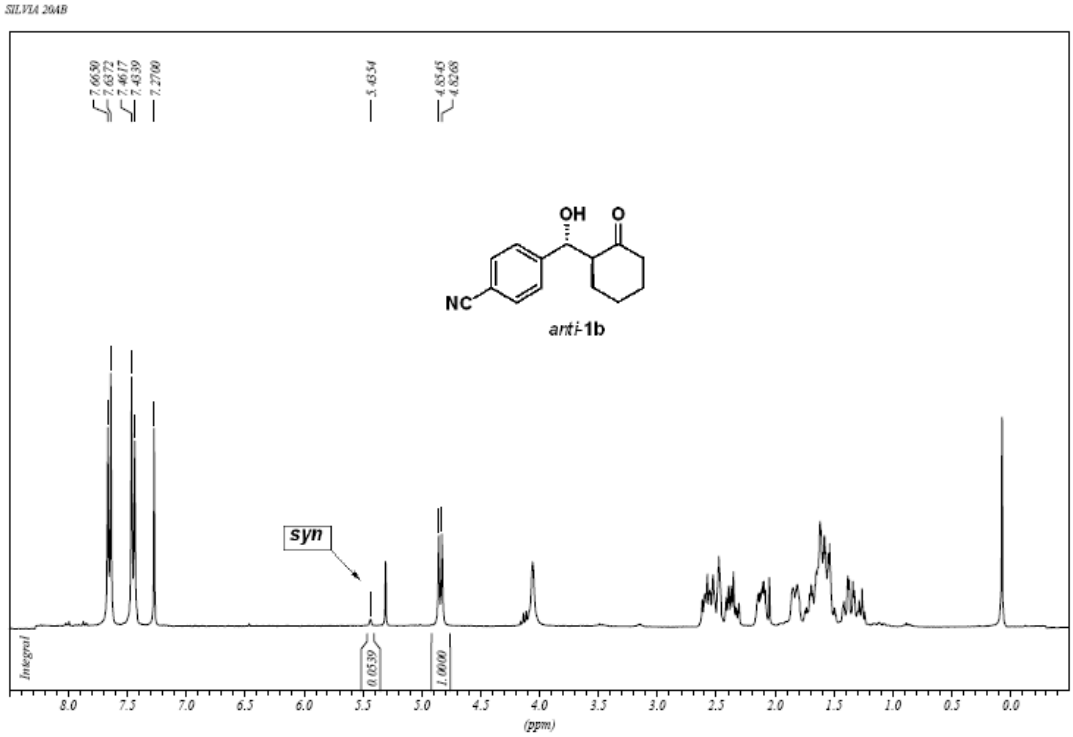


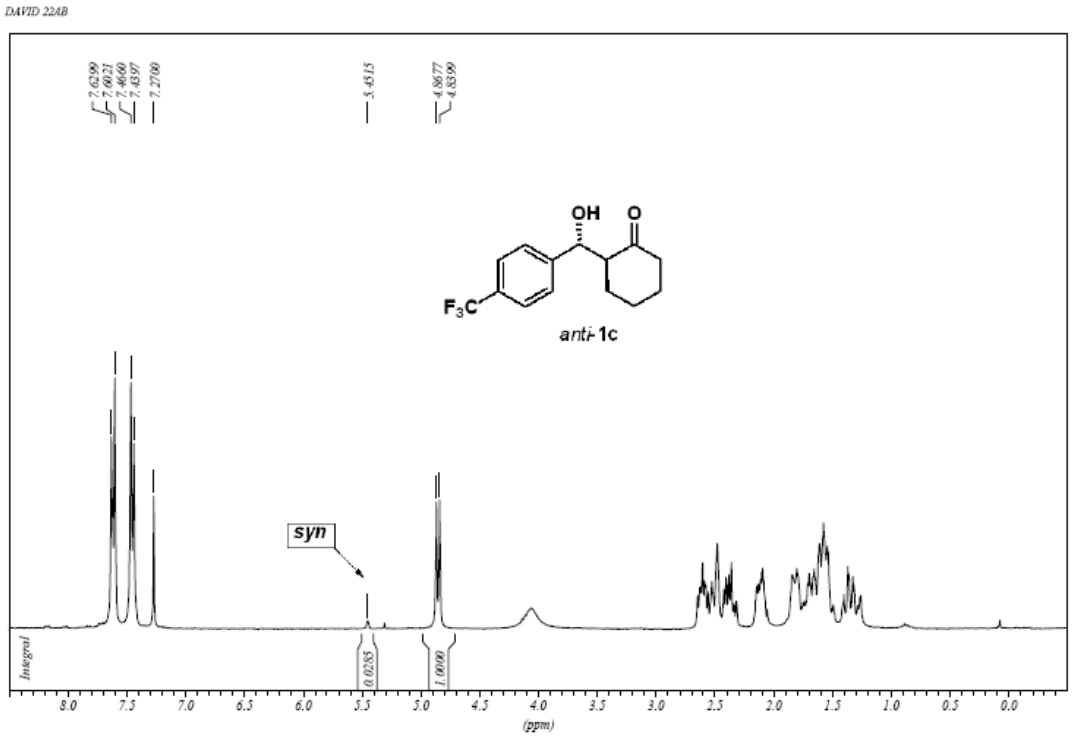


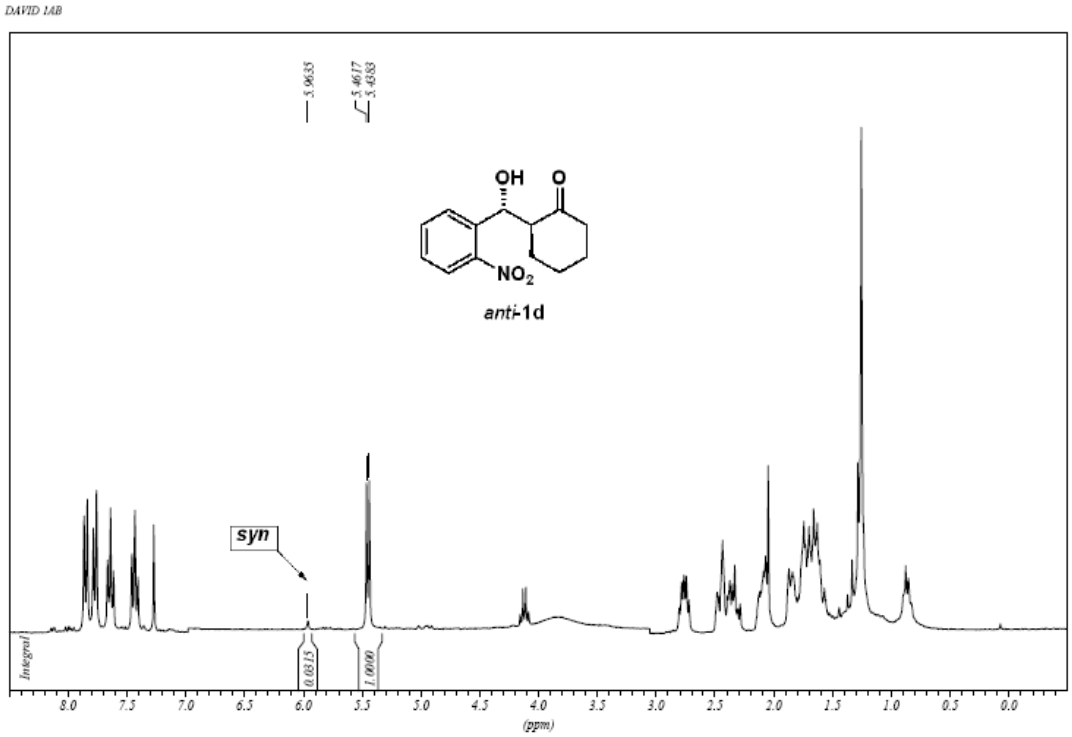
Formula	CalculatedMass	mDaError	ppmError	RDB
C7 H24 N15 O3	366.218106	-0.10642	-0.290592	3.5
C9 H29 N9 O6 Na	366.218387	-0.386552	-1.055523	-0.5
C22 H28 N3 O2	366.217604	0.396156	1.081748	10.5
C25 H29 N Na	366.219221	-1.221288	-3.334861	11.5
C10 H25 N13 O Na	366.219724	-1.723864	-4.7072	4.5
C5 H25 N15 O3 Na	366.215701	2.29884	6.277235	0.5
C11 H28 N9 O5	366.220792	-2.791812	-7.62335	2.5
C20 H29 N3 O2 Na	366.215199	2.801416	7.649574	7.5
C18 H24 N9	366.214918	3.081548	8.414506	11.5
C27 H28 N	366.221627	-3.626548	-9.902688	14.5

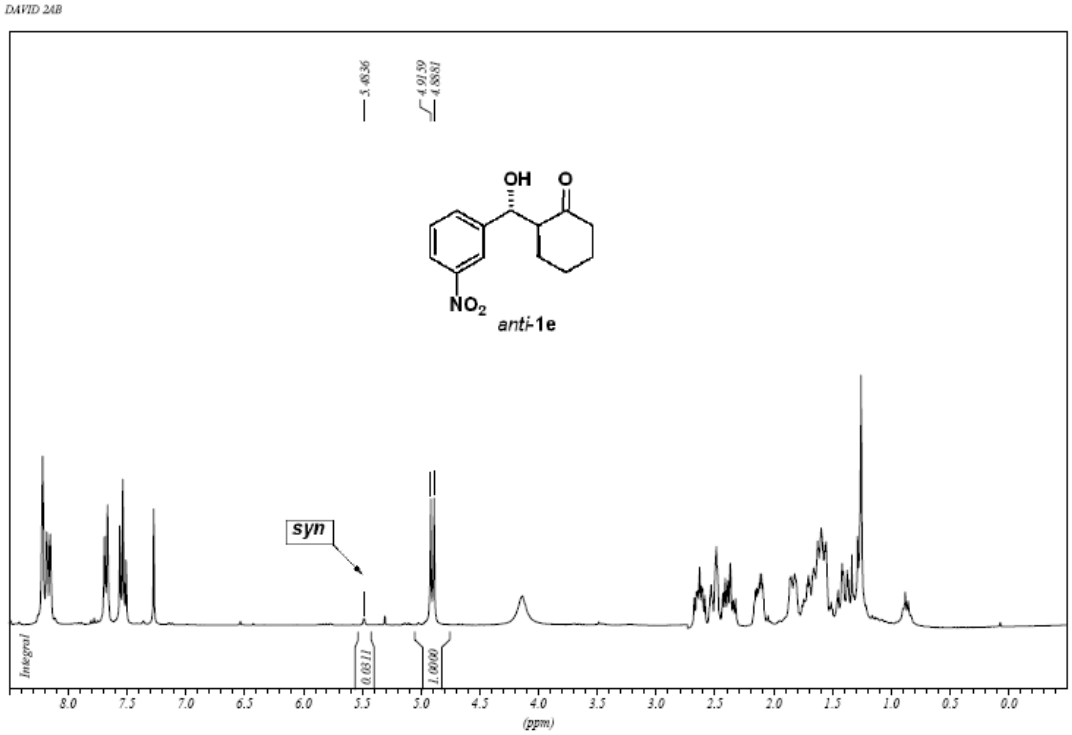
3. NMR Spectra of the aldol reaction mixtures

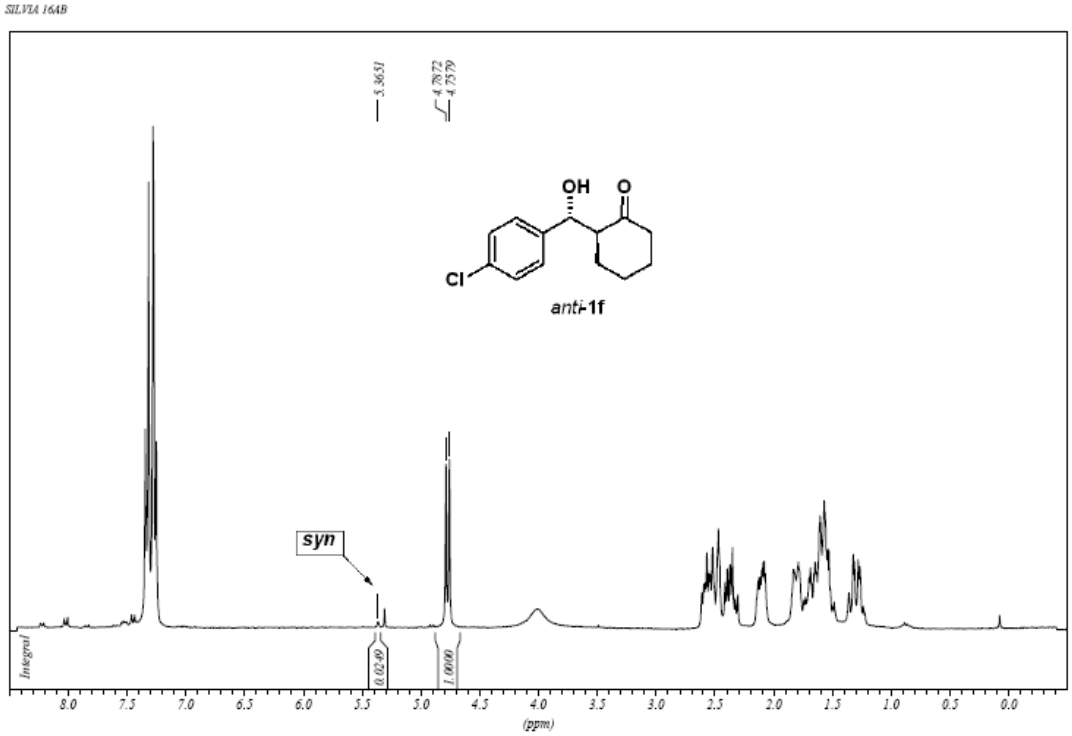


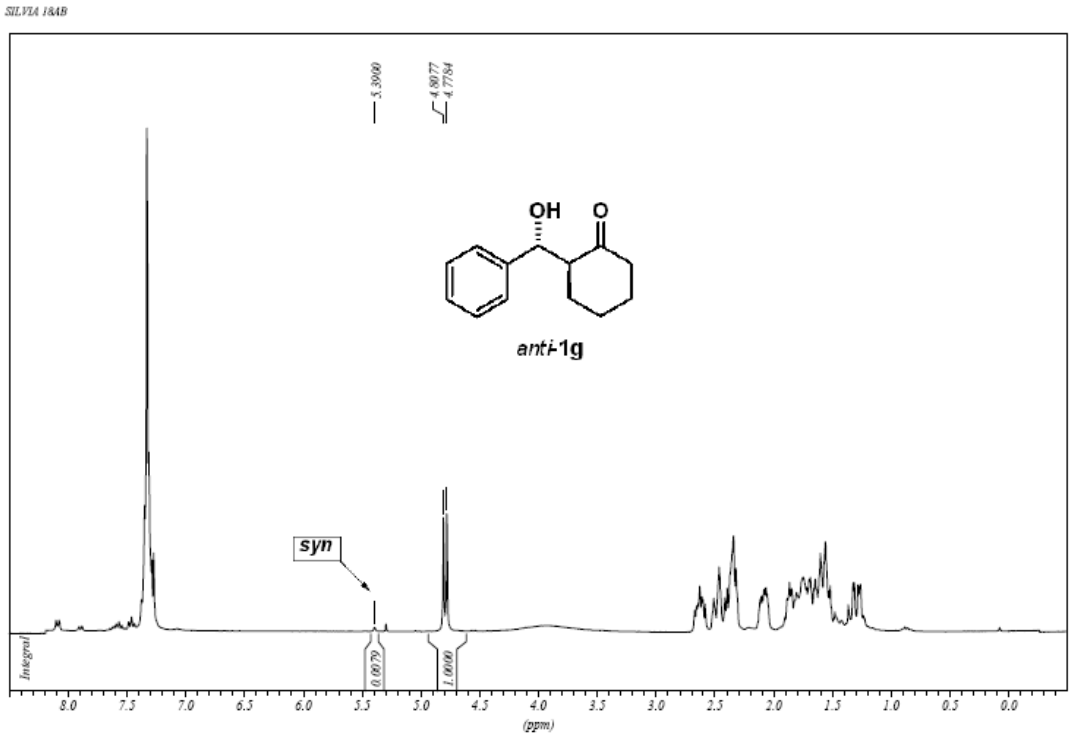


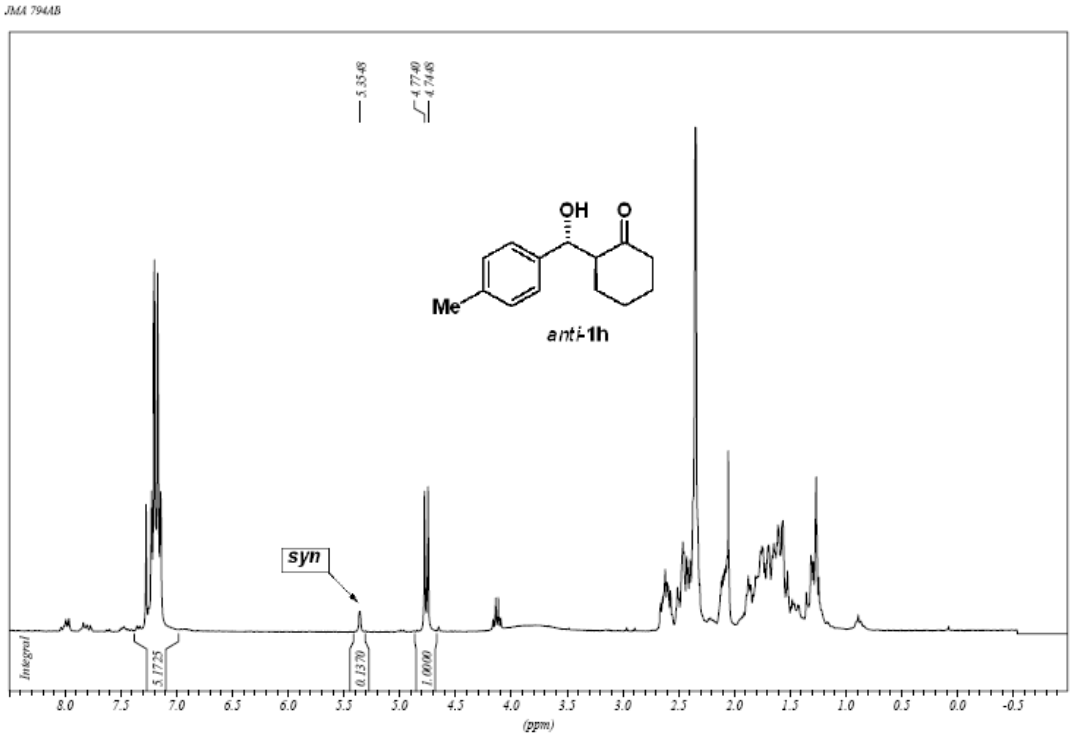


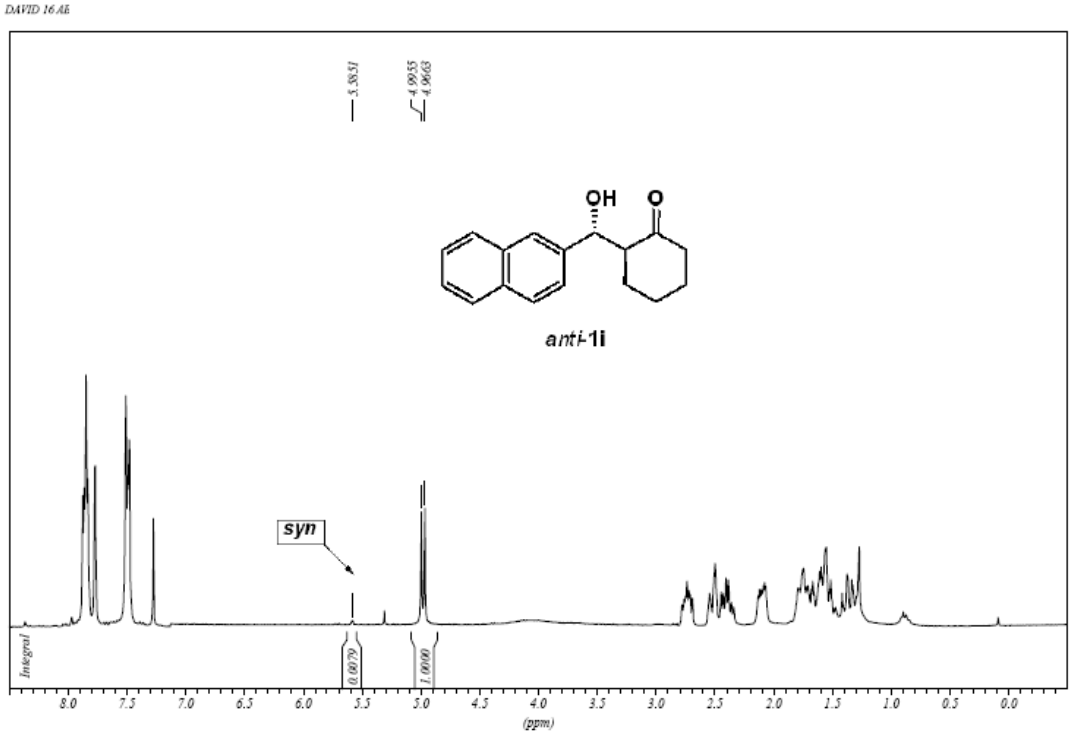


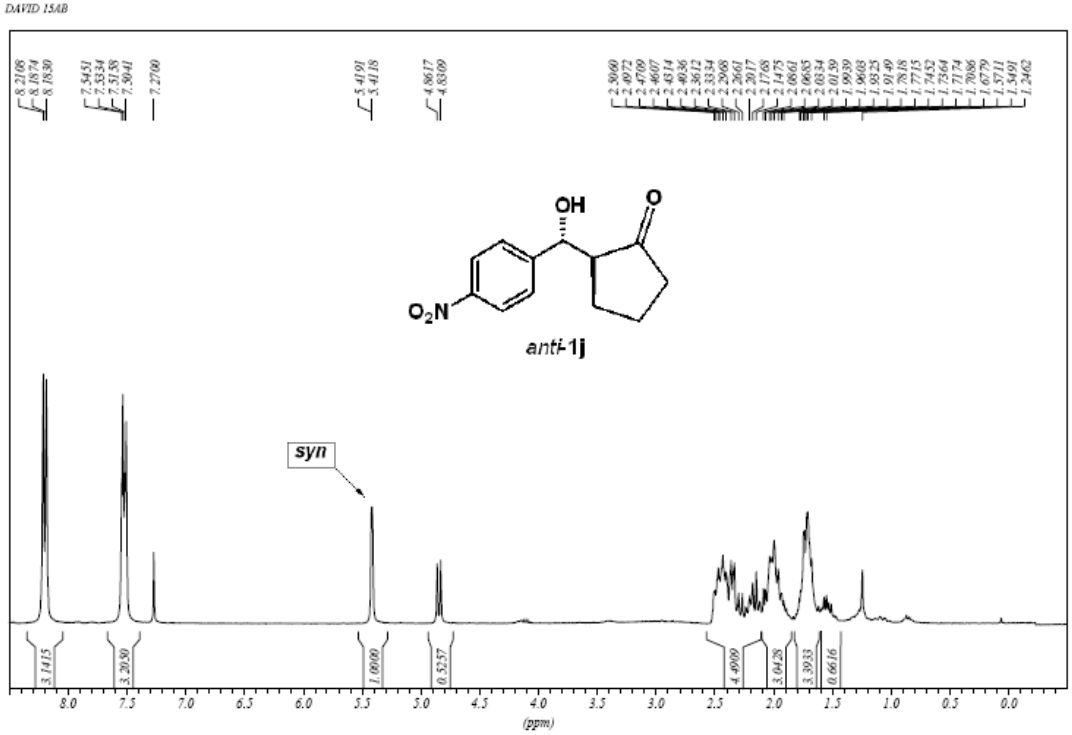


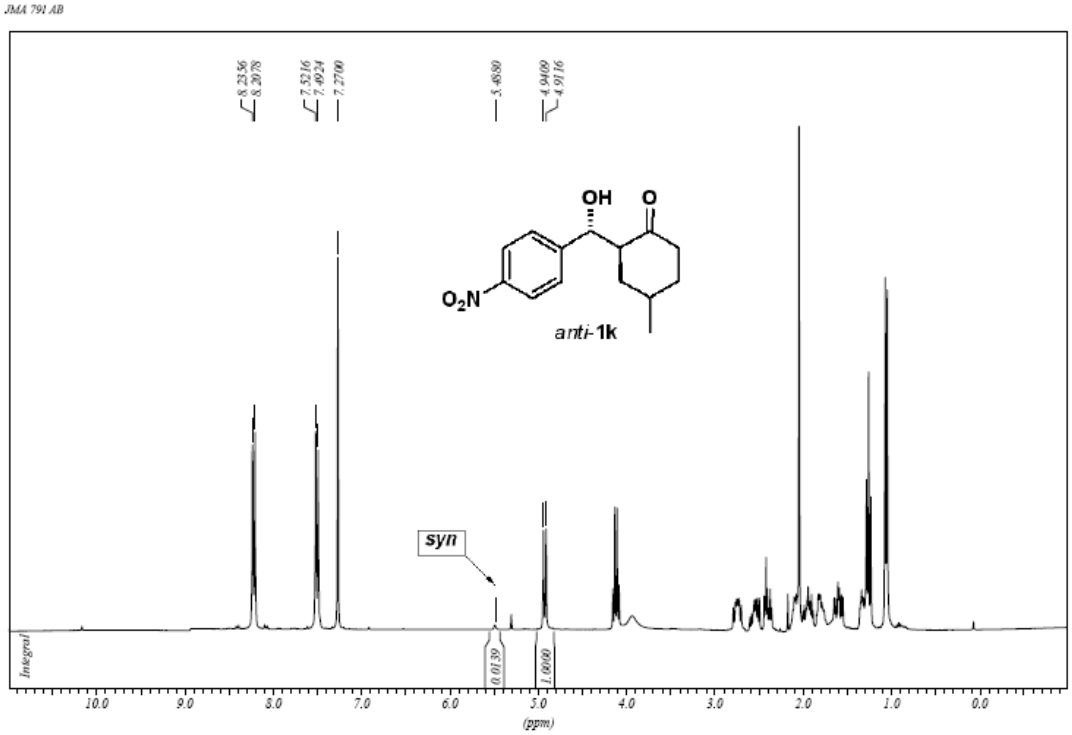


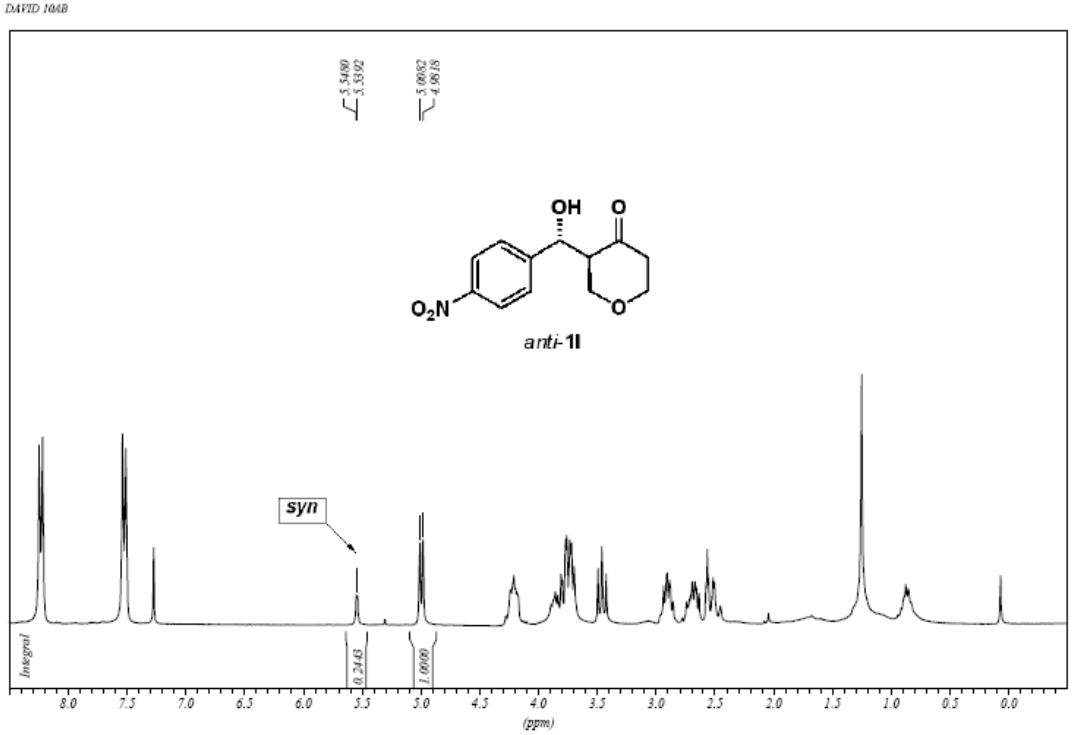


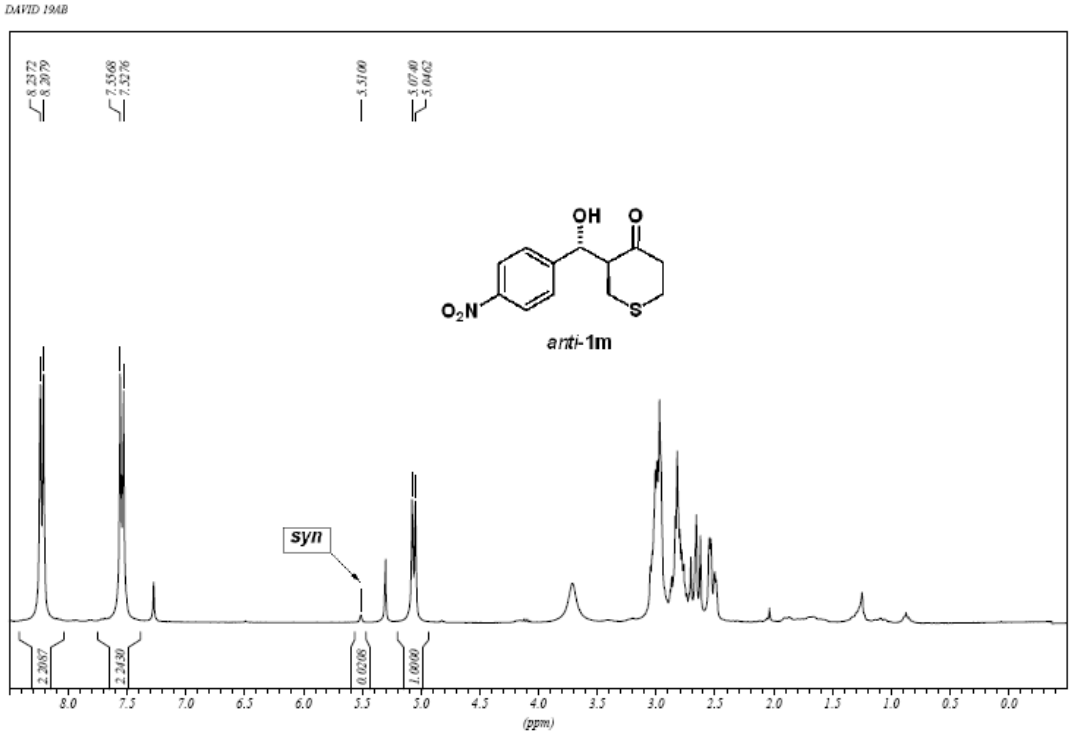


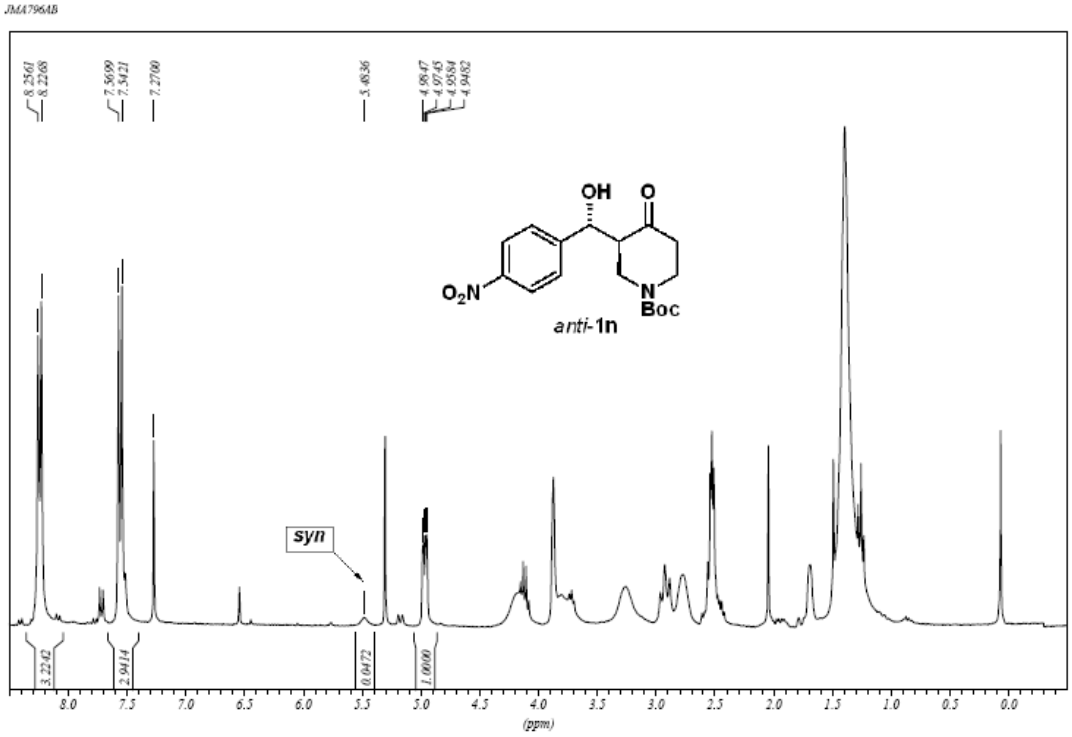




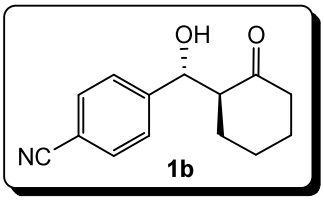




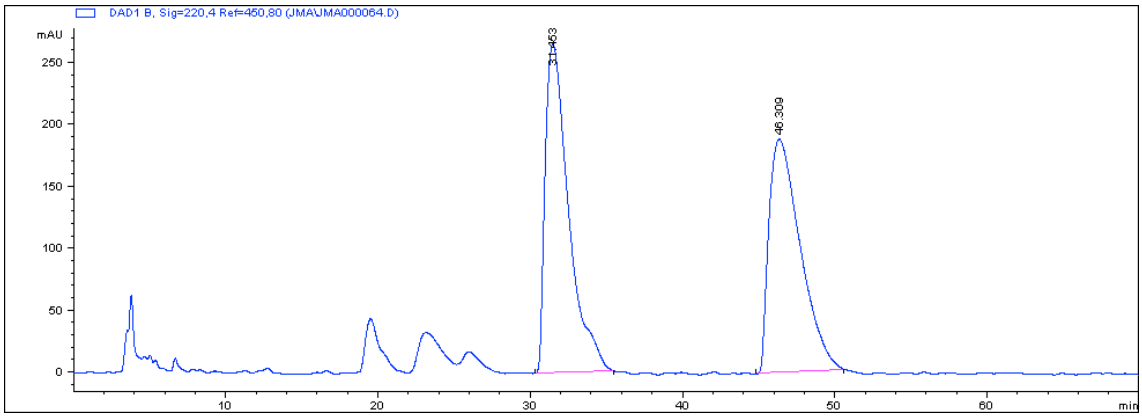




4. HPLC profiles of the Aldol Products (*anti*-1a-i, *Table 3*) catalyzed by catalyst I.

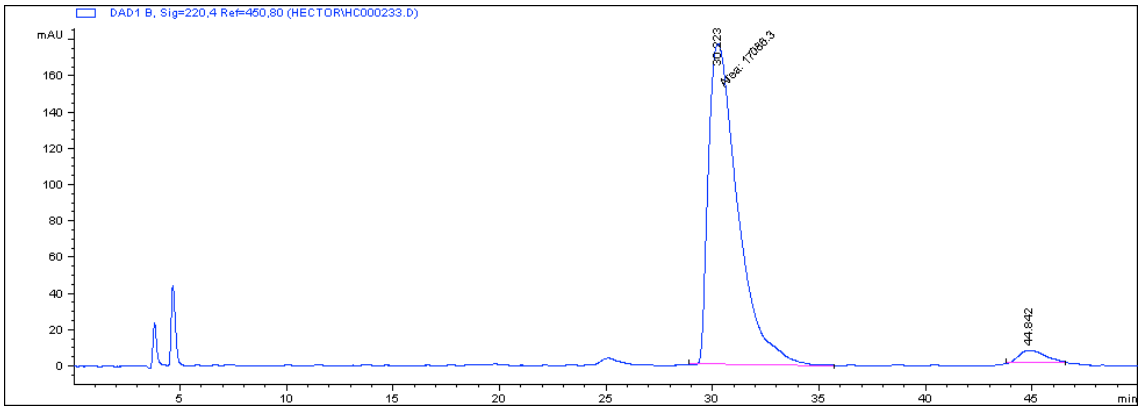


Racemic molecule

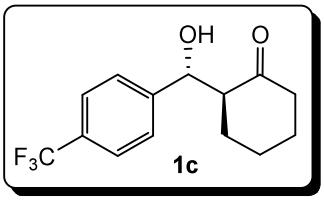


#	Time	Area	Height	Width	Area%
1	31.453	28441.6	265.5	1.4739	51.302
2	46.309	26998.2	188.5	1.6997	48.698

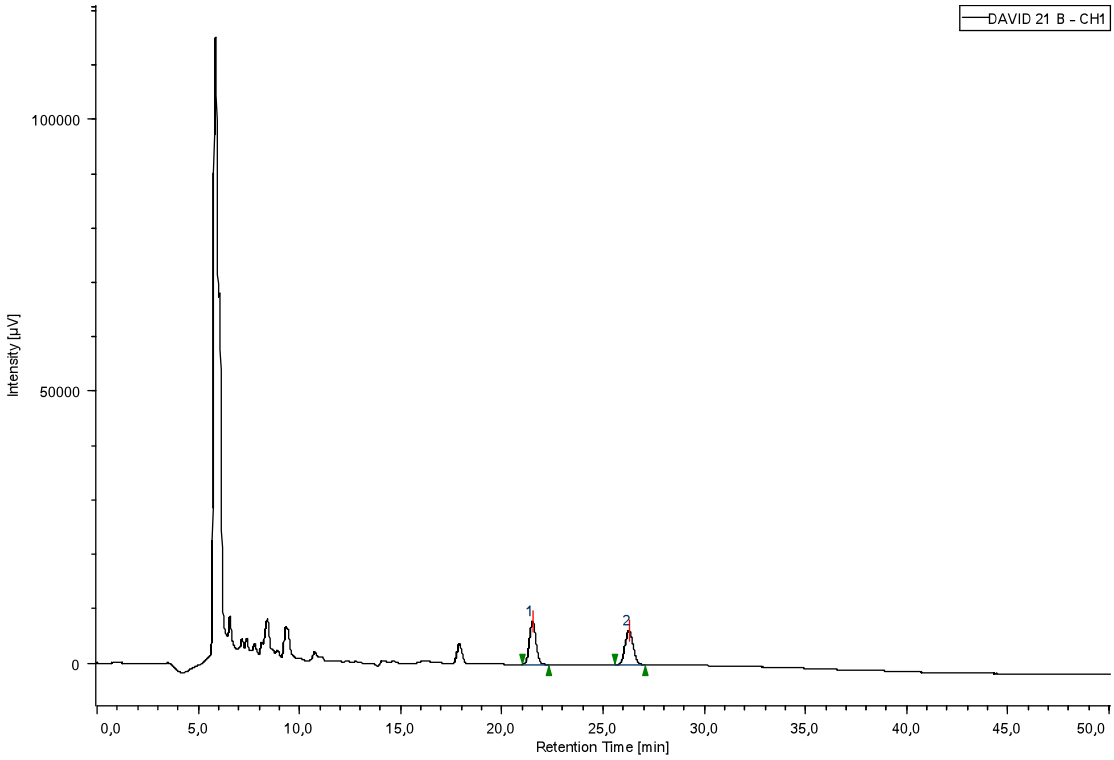
HPLC profile for Entry 1, Table 3. 97:3 er



#	Time	Area	Height	Width	Area%	Symmetry
1	30.223	17086.3	176.9	1.6094	96.452	0.448
2	44.842	628.4	7.2	1.0347	3.548	0.616

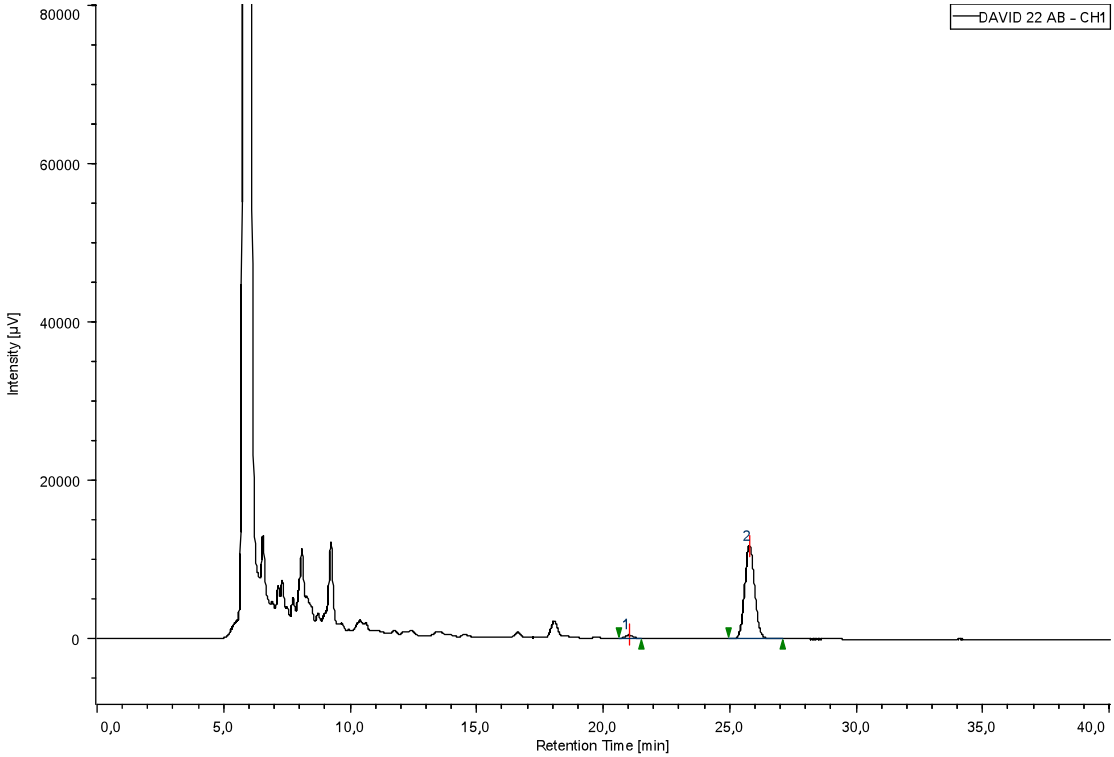


Racemic molecule

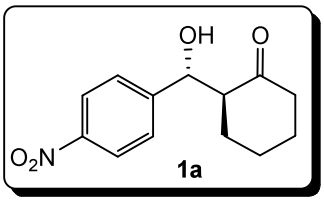


#	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution
1	21,492	179485	7981	50,209	55,678	N/A	21045	7,130
2	26,242	177990	6353	49,791	44,322	N/A	19942	N/A

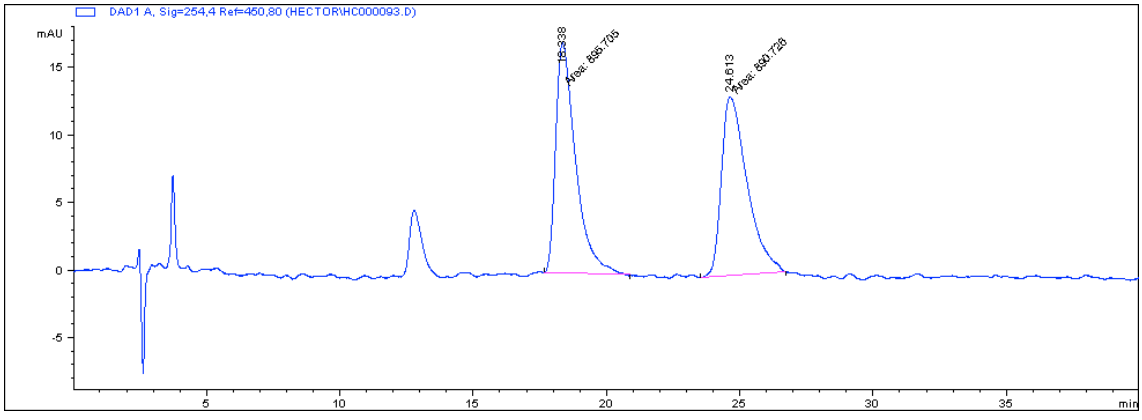
HPLC profile for Entry 2, Table 3. 97:3 er



#	tR	Area	Height	Area%	Height%	Quantity	NTP	Resolution
1	20,992	8414	403	2,580	3,334	N/A	22535	7,495
2	25,758	317761	11698	97,420	96,666	N/A	20703	N/A

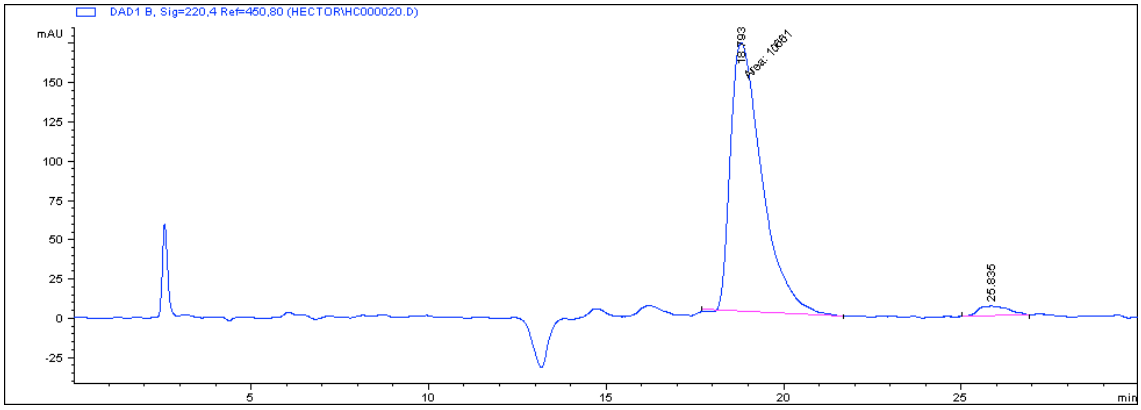


Racemic molecule

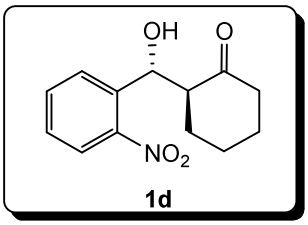


#	Time	Area	Height	Width	Area%
1	18.338	895.7	17.1	0.8741	50.139
2	24.613	890.7	13.2	1.1223	49.861

HPLC profile for Entry 3, Table 3. 97:3 er

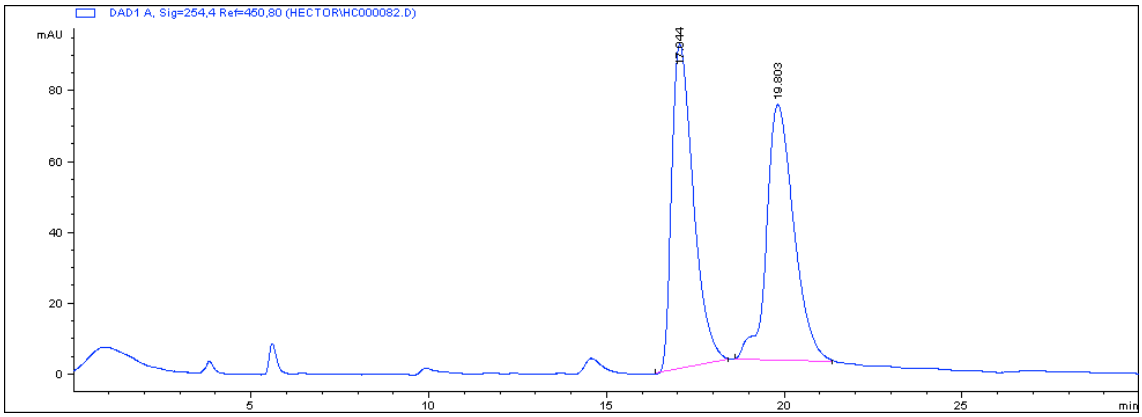


#	Time	Area	Height	Width	Area%	Symmetry
1	18.793	10661	171.3	1.0375	96.576	0.501
2	25.835	378	6.2	0.7285	3.424	0.71



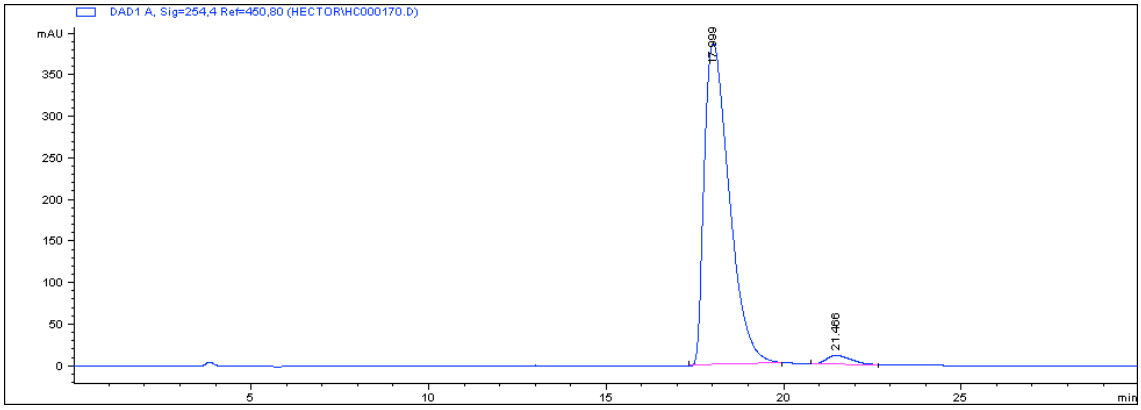
1d

Racemic molecule

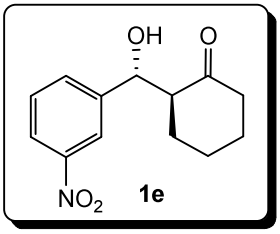


#	Time	Area	Height	Width	Area%
1	17.044	3900.1	91.9	0.6232	50.216
2	19.803	3866.5	72.2	0.7784	49.784

HPLC profile for Entry 4, Table 3. 97:3 er

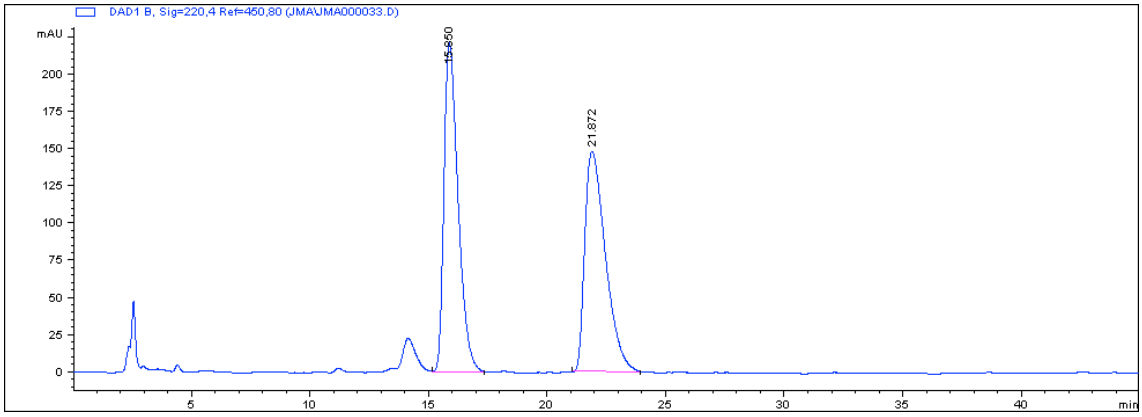


#	Time	Area	Height	Width	Area%	Symmetry
1	17.999	18980.6	387.9	0.7533	97.400	0.508
2	21.466	506.6	10.6	0.5681	2.600	0.613



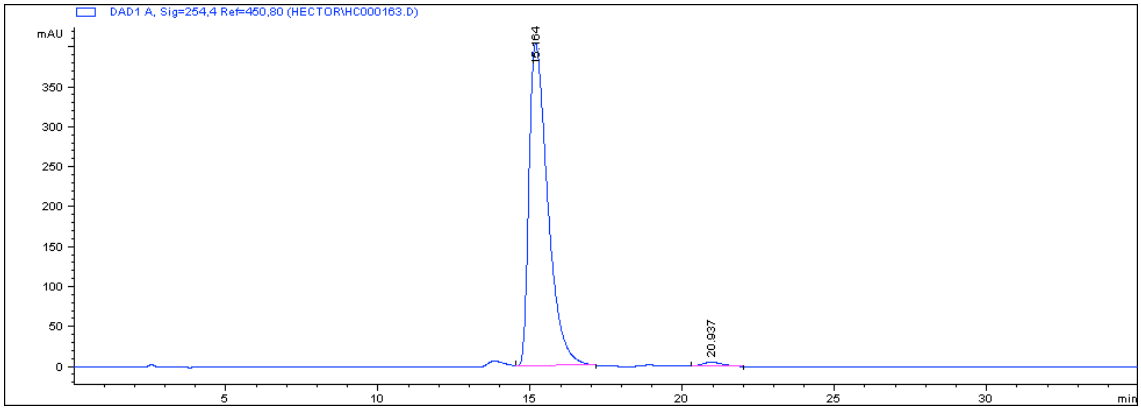
1e

Racemic molecule

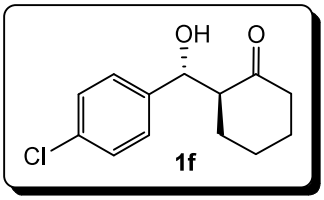


#	Time	Area	Height	Width	Area%
1	15.85	9188	221.2	0.6286	50.421
2	21.872	9034.6	148.2	0.8647	49.579

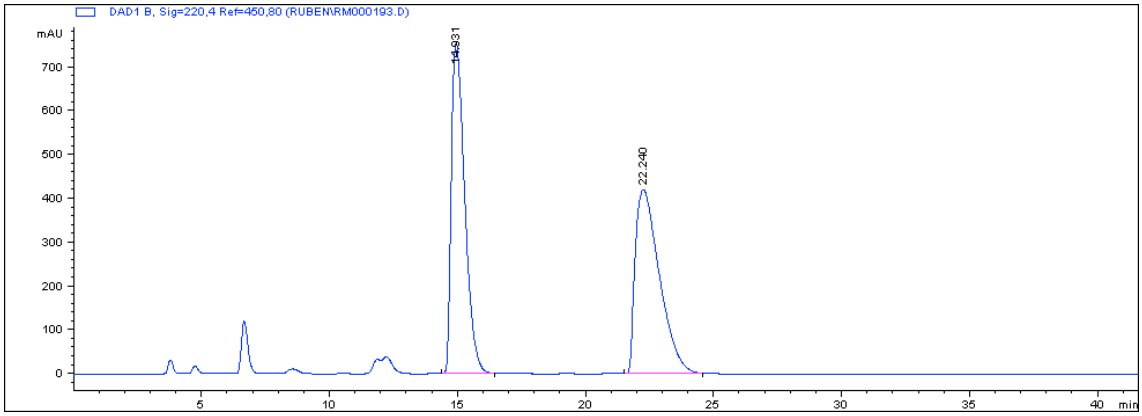
HPLC profile for Entry 5, Table 3. 99:1 er



#	Time	Area	Height	Width	Area%	Symmetry
1	15.164	17360.6	404.7	0.6476	98.763	0.499
2	20.937	217.5	4.9	0.5368	1.237	0.669

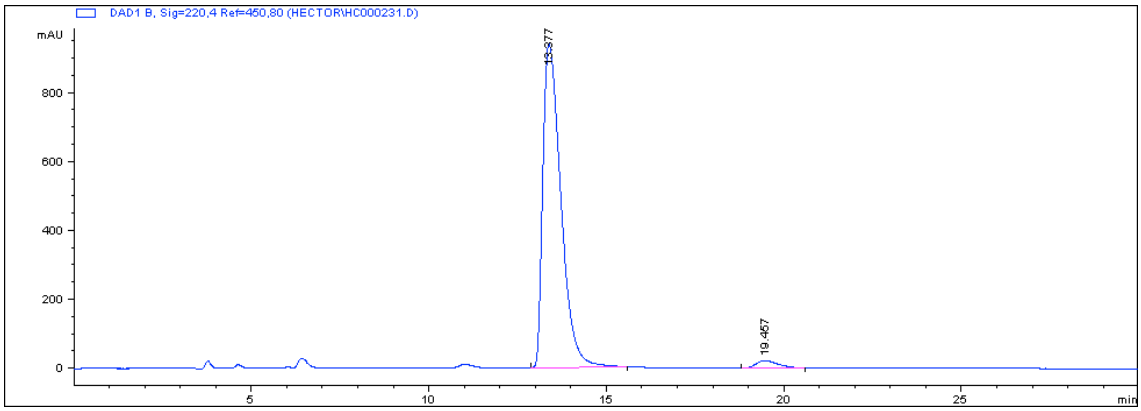


Racemic molecule

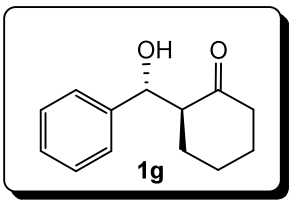


#	Time	Area	Height	Width	Area%
1	14.931	27504.8	753.9	0.5696	49.915
2	22.24	27598.7	419.6	0.9722	50.085

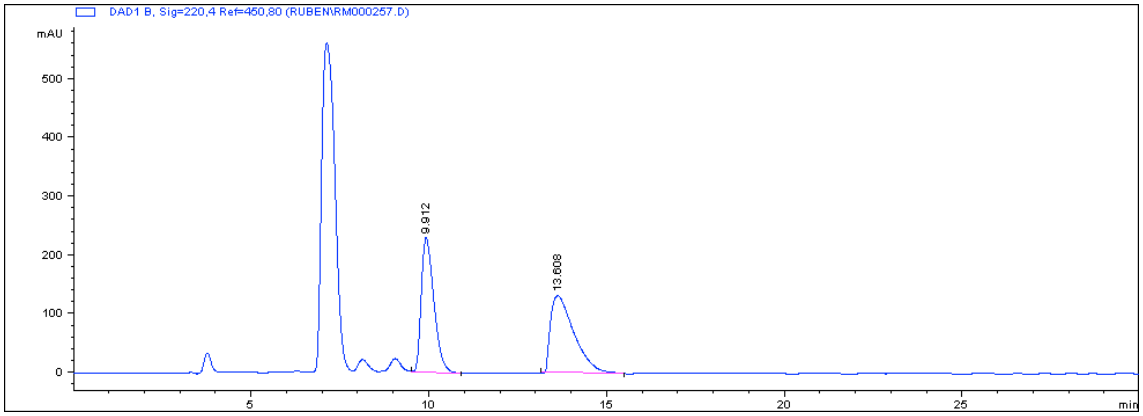
HPLC profile for Entry 6, Table 3. 97:3 er



#	Time	Area	Height	Width	Area%	Symmetry
1	13.377	33480.8	940.7	0.5528	97.248	0.5
2	19.457	947.4	21.9	0.5686	2.752	0.633

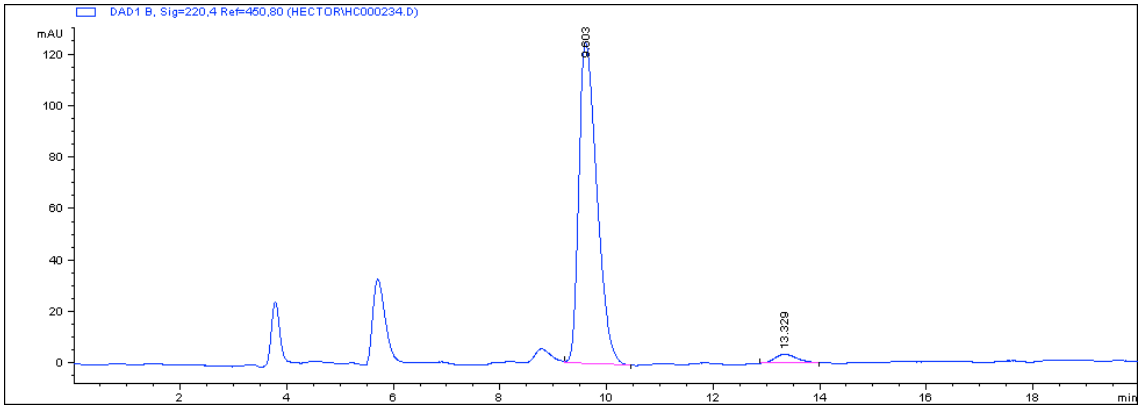


Racemic molecule

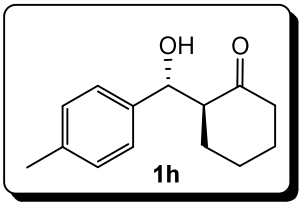


#	Time	Area	Height	Width	Area%
1	9.912	5798	230.3	0.3897	48.943
2	13.608	6048.3	131.6	0.6707	51.057

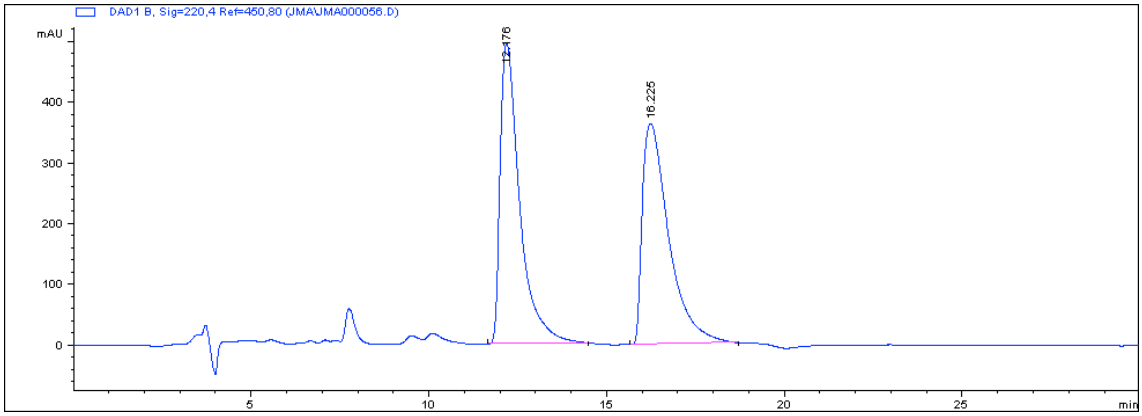
HPLC profile for Entry 7, Table 3. 97:3 er



#	Time	Area	Height	Width	Area%	Symmetry
1	9.603	2962	124.9	0.3696	96.851	0.606
2	13.329	96.3	3.4	0.3671	3.149	0.693

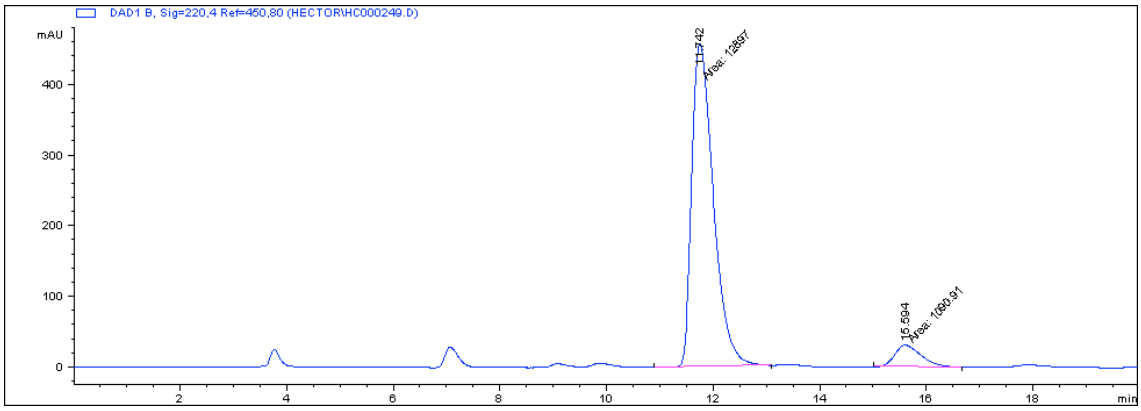


Racemic molecule

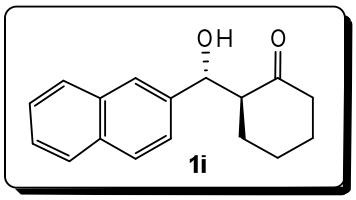


#	Time	Area	Height	Width	Area%
1	12.176	18945	495.3	0.571	50.090
2	16.225	18876.6	363.5	0.7722	49.910

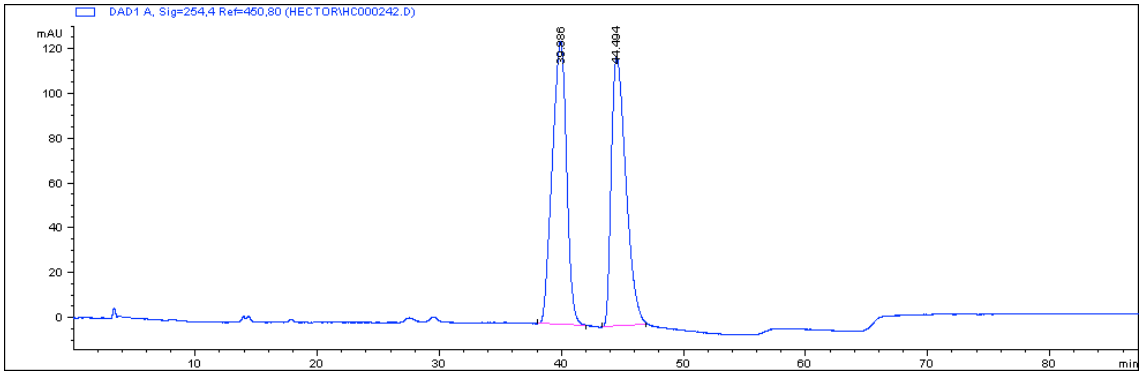
HPLC profile for Entry 9, Table 3. 92:8 er



#	Time	Area	Height	Width	Area%	Symmetry
1	11.742	12897	457.2	0.4701	92.201	0.569
2	15.594	1090.9	31	0.5861	7.799	0.649

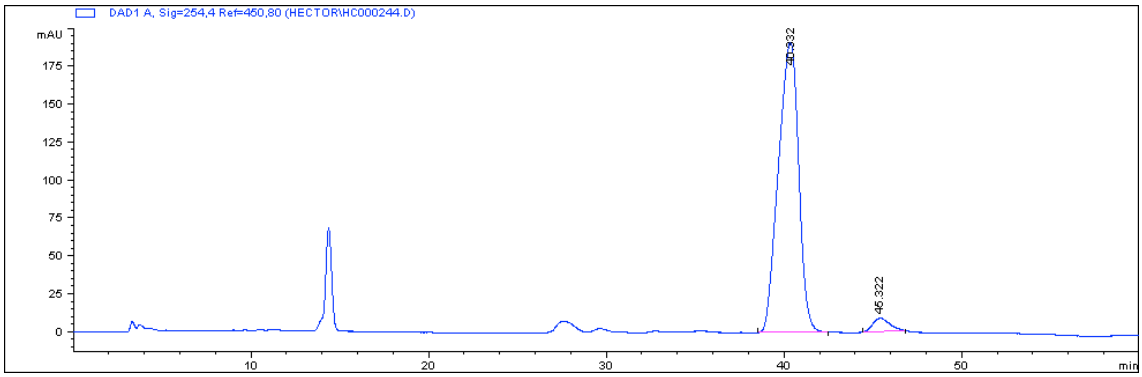


Racemic molecule



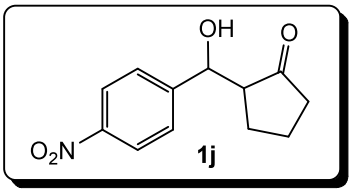
#	Time	Area	Height	Width	Area%	Symmetry
1	39.886	10282.2	126.4	1.1446	50.706	1.322
2	44.494	9995.7	120.3	1.1483	49.294	0.563

HPLC profile for Entry 10, Table 3. 96:4 er

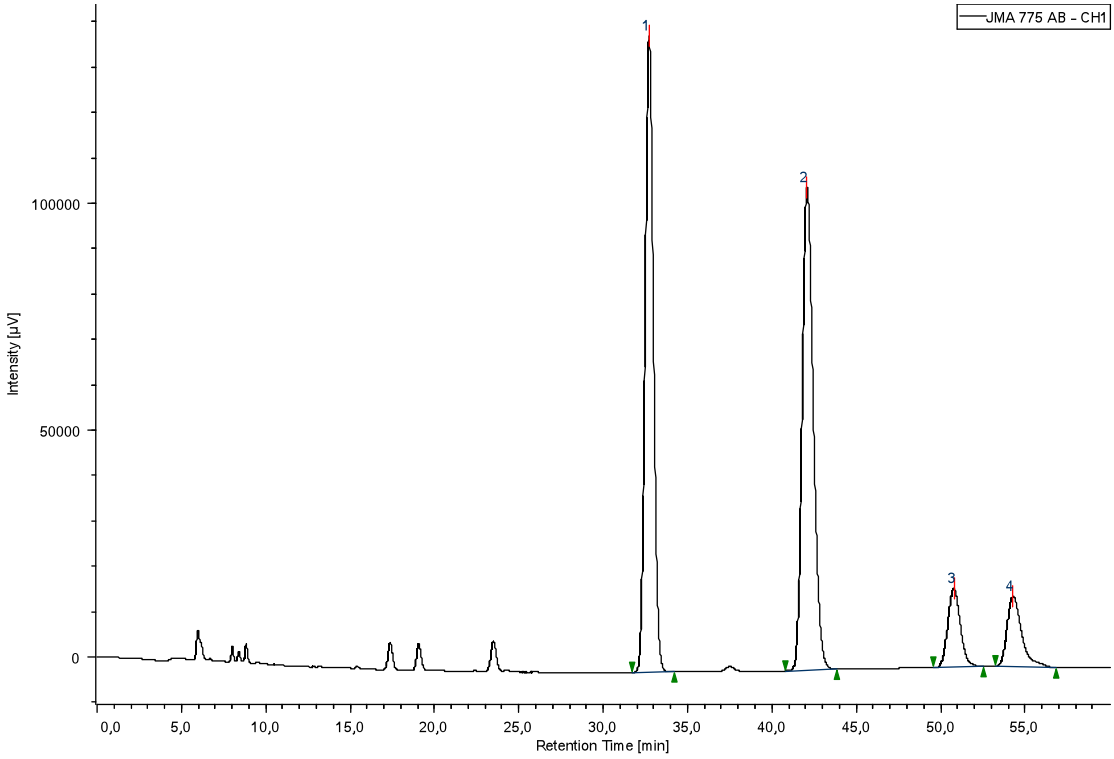


#	Time	Area	Height	Width	Area%	Symmetry
1	40.332	15152.3	191.4	1.1094	96.197	1.391
2	45.322	599.1	8.8	0.8113	3.803	0.586

HPLC profiles of the Aldol Products (*anti*-1j-n, *Table 4*) promoted by catalyst I.

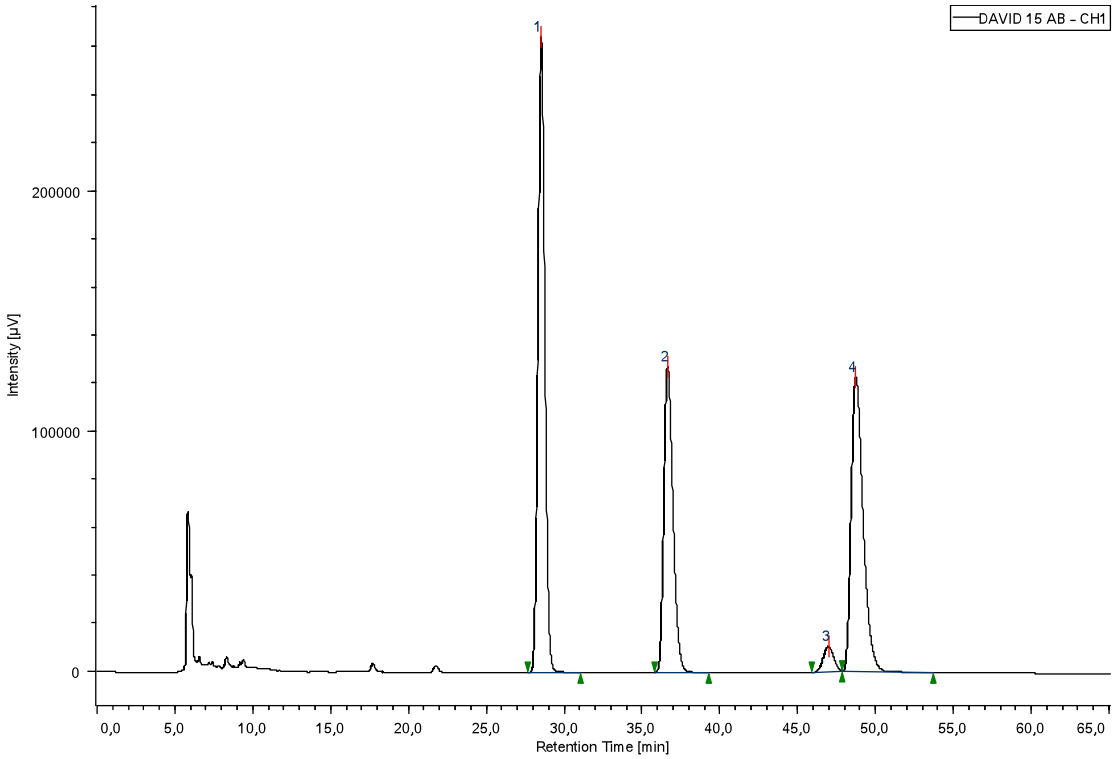


Racemic molecule

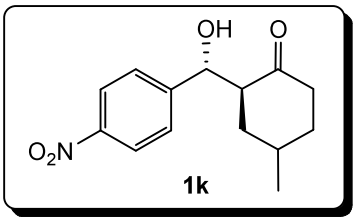


#	tR	Area	Height	Area%	Height %	NTP	Resolution	Symmetry Factor
1	32,683	4771058	139979	41,636	50,160	21131	8,929	1,067
2	42,033	4853074	106183	42,352	38,050	19610	6,821	1,217
3	50,717	905050	17404	7,898	6,236	22505	2,473	1,142
4	54,225	929682	15497	8,113	5,553	21118	N/A	1,628

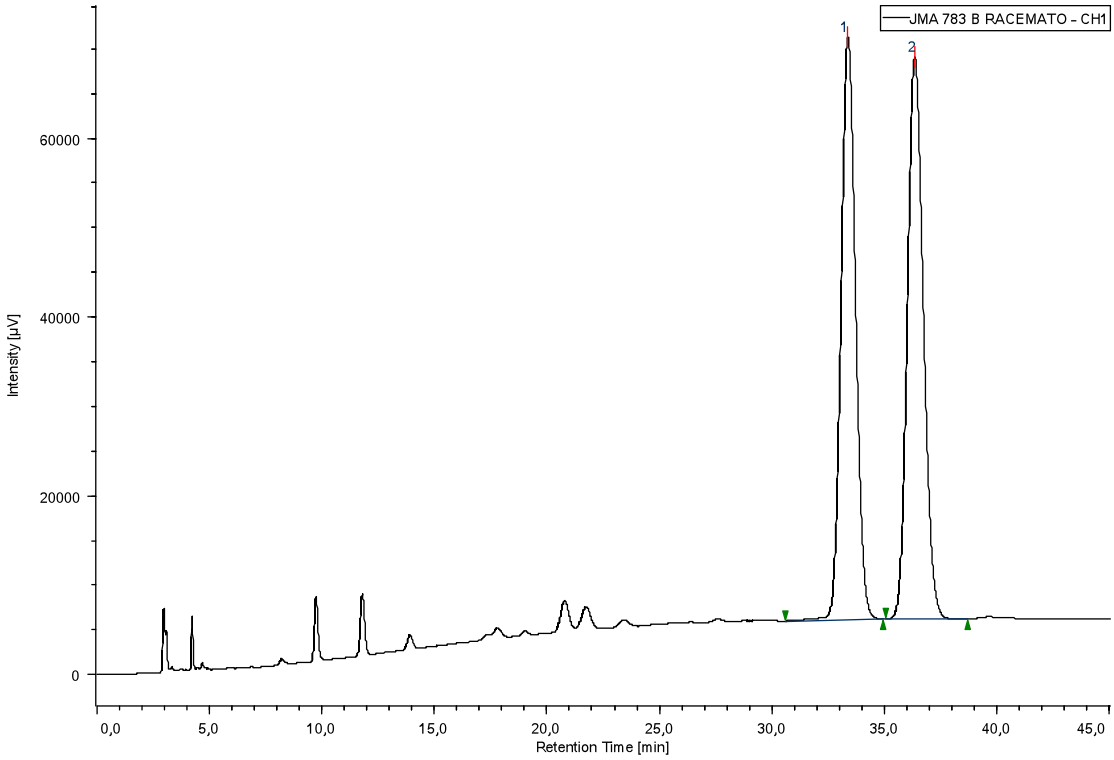
HPLC profile for Entry 1, Table 4. 93:7 er



#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	28,500	8078377	264159	39,839	50,355	20115	8,672
2	36,600	5193249	127388	25,611	24,283	18747	8,947
3	46,917	485448	10552	2,394	2,012	22786	1,349
4	48,683	6520497	122491	32,156	23,350	19827	N/A

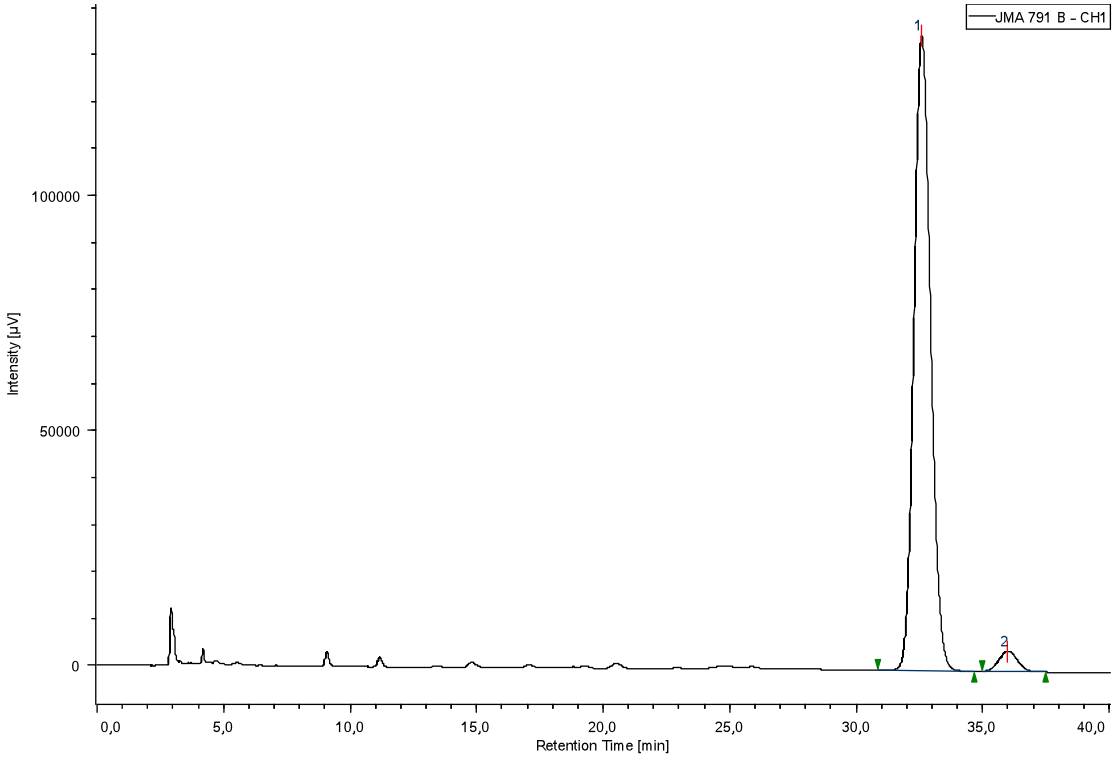


Racemic molecule

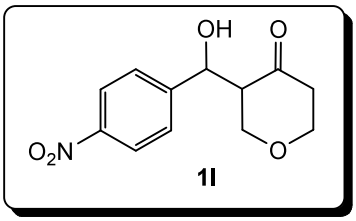


#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	33,350	2909053	65001	48,572	50,891	12880	2,409
2	36,317	3080088	62725	51,428	49,109	12592	N/A

HPLC profile for Entry 3, Table 4. 96:4 er

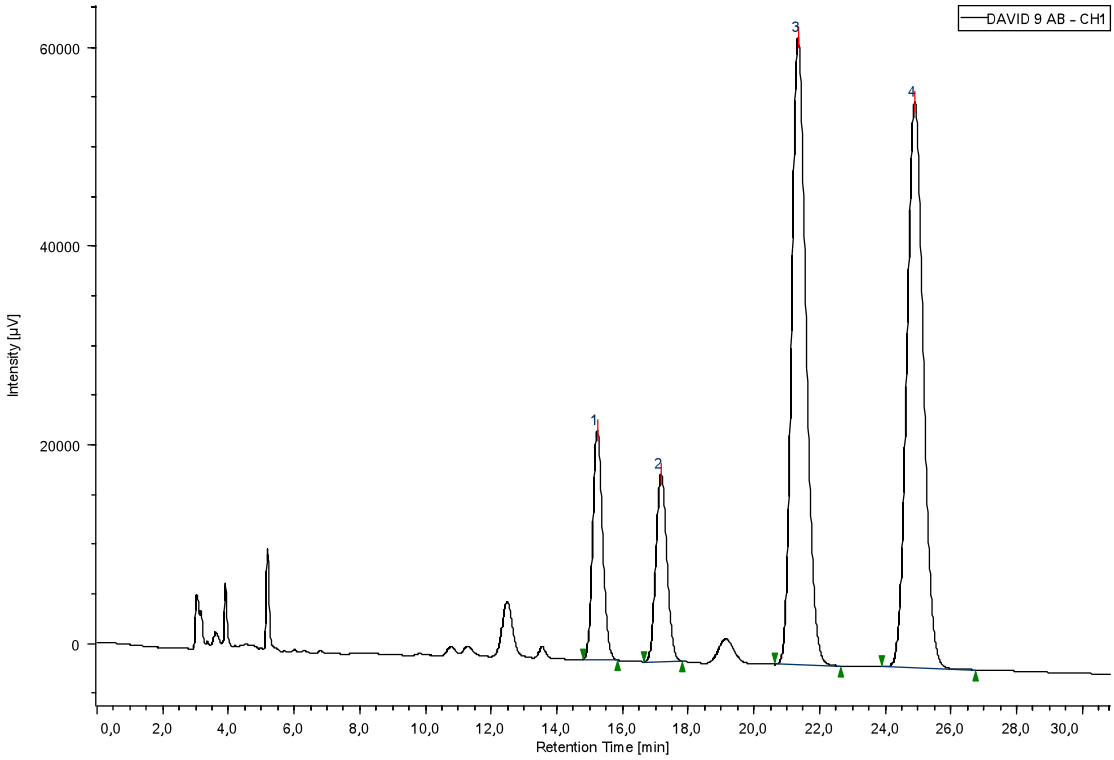


#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	32,558	6158191	134793	96,481	96,861	11663	2,643
2	35,942	224632	4368	3,519	3,139	11156	N/A



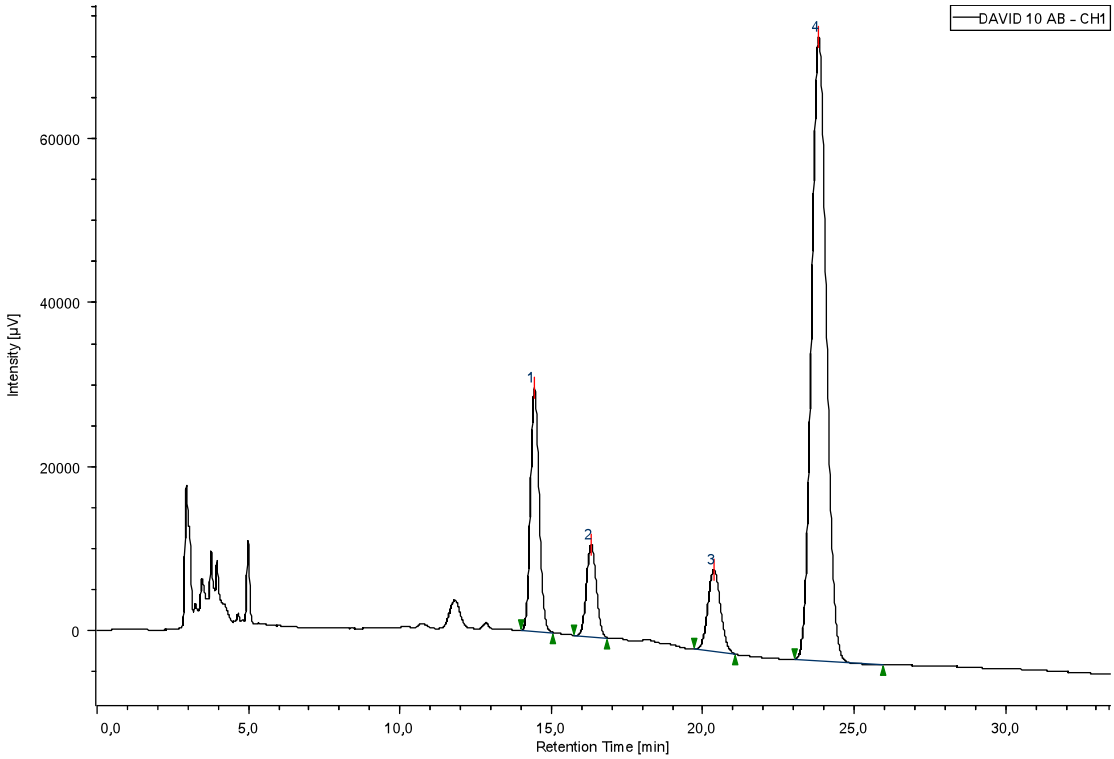
1l

Racemic molecule

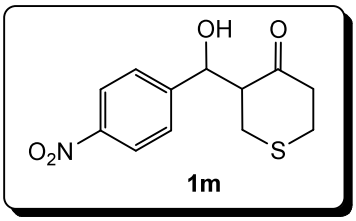


#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	15,217	481950	23056	9,987	14,251	12206	3,331
2	17,158	440709	18896	9,132	11,679	12329	5,875
3	21,325	1924293	63022	39,875	38,952	11253	4,122
4	24,867	1978889	56819	41,006	35,118	11718	N/A

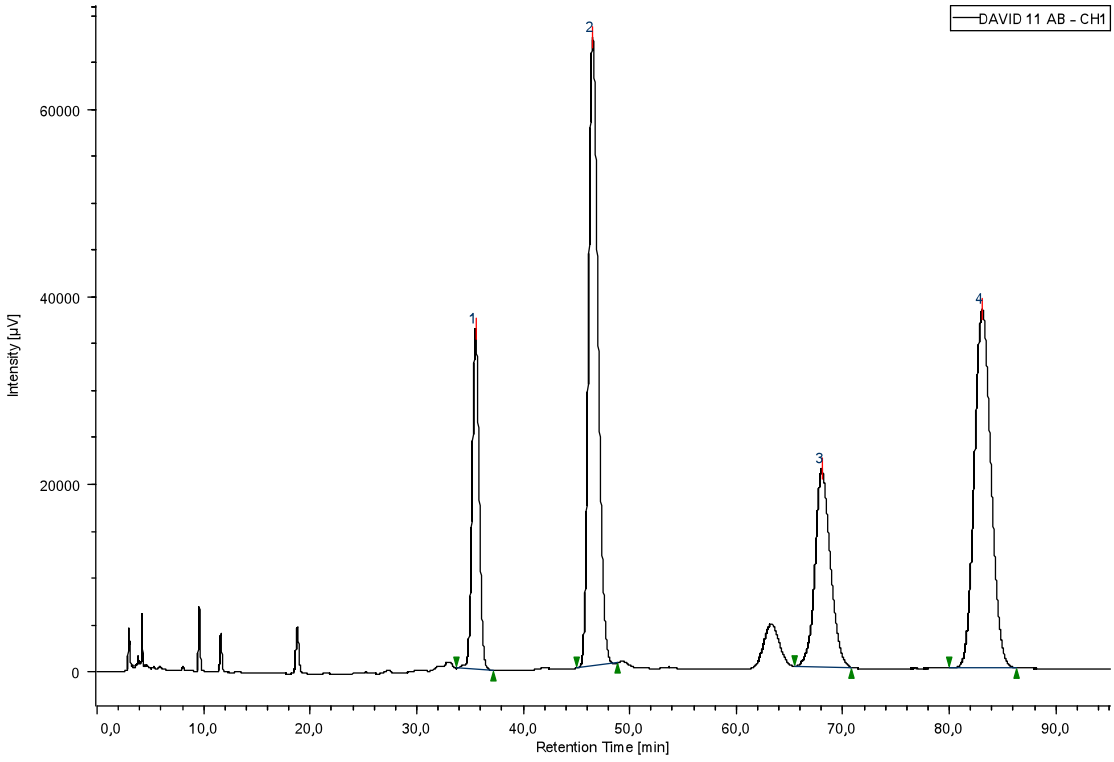
HPLC profile for Entry 4, Table 4. 90:10 er



#	tR	Area	Height	Area%	Height%	.NTP	Resolution
1	14,425	586742	29561	15,785	23,316	12120	3,353
2	16,300	253235	11280	6,813	8,897	11914	5,928
3	20,342	290595	9998	7,818	7,886	11167	4,150
4	23,800	2586478	75948	69,584	59,902	11160	N/A

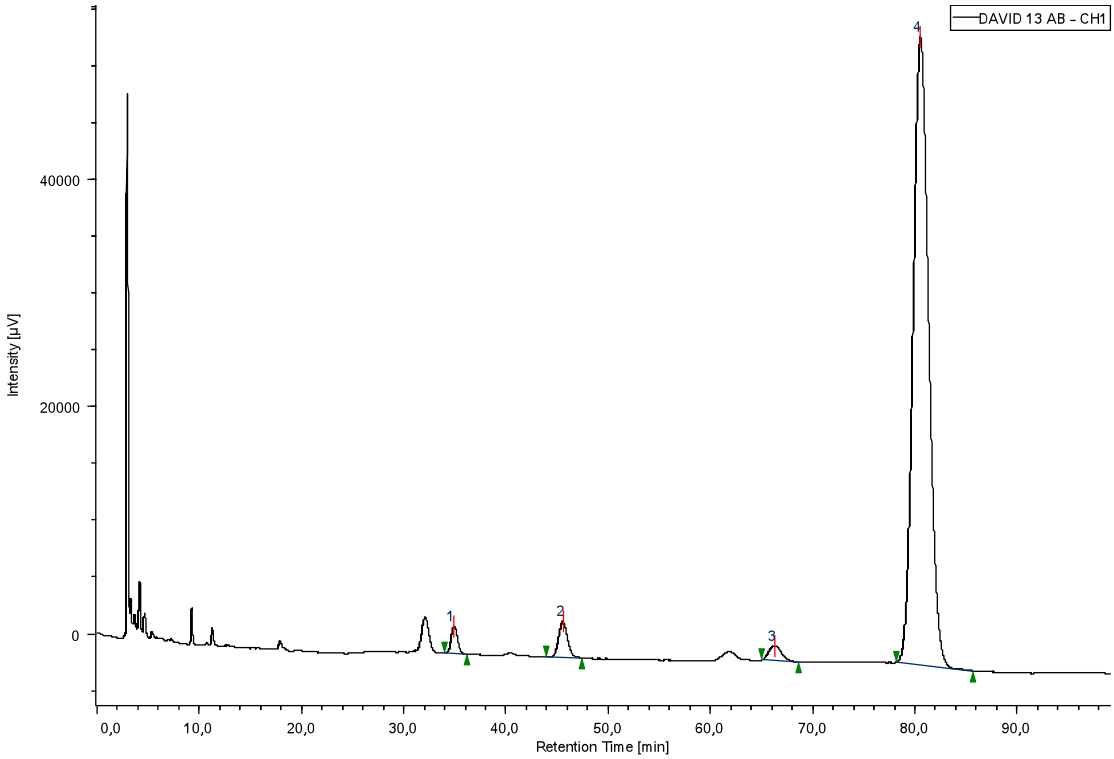


Racemic molecule

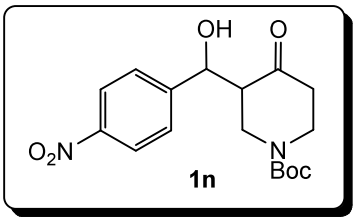


#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	35,492	1644872	36227	13,632	22,305	14293	7,801
2	46,475	4153949	66928	34,427	41,208	12914	10,311
3	67,942	2105686	21041	17,451	12,955	11455	5,568
4	82,992	4161502	38220	34,489	23,532	13272	N/A

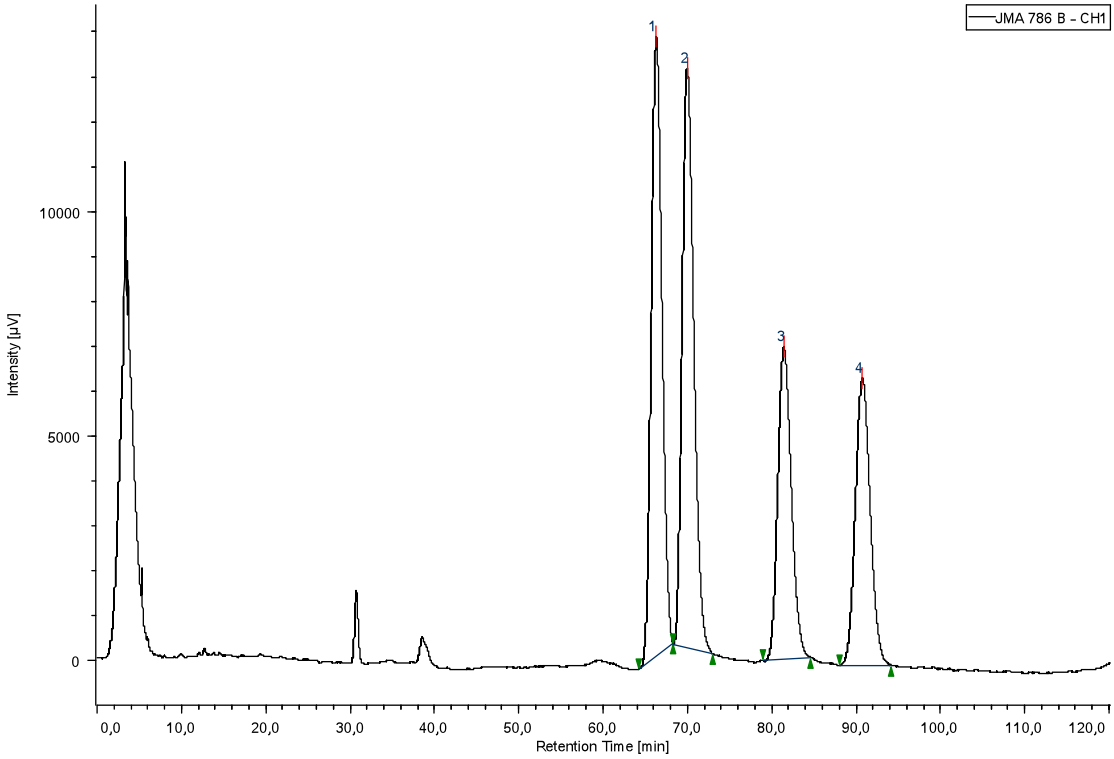
HPLC profile for Entry 6, Table 4. 97:3 er



#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	34,892	105272	2455	1,685	3,947	14981	7,776
2	45,517	195442	3178	3,128	5,111	12954	10,505
3	66,217	118269	1328	1,893	2,135	12685	5,555
4	80,450	5829813	55223	93,295	88,806	13337	N/A

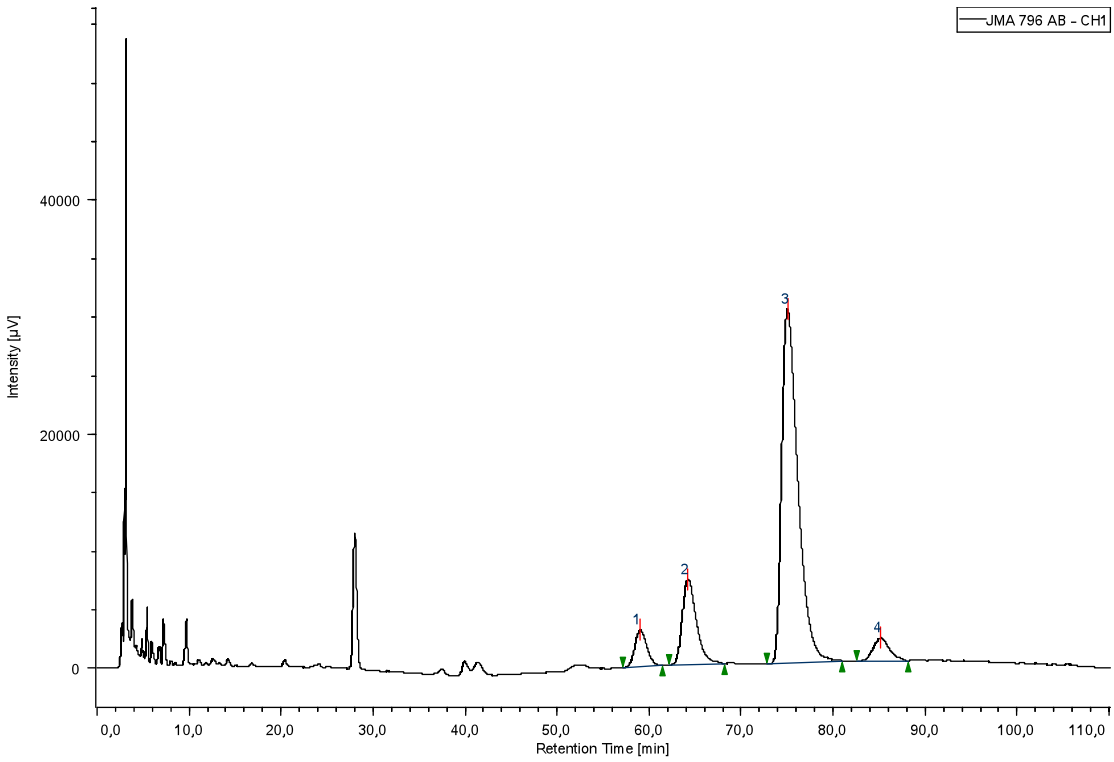


Racemic molecule



#	tR	Area	Height	Area%	Height%	NTP	Resolution
1	66,225	1214203	13767	30,276	34,429	12601	1,504
2	69,900	1239269	12893	30,901	32,243	12109	4,186
3	81,342	773957	6947	19,299	17,373	12245	3,015
4	90,633	782982	6380	19,524	15,955	12523	N/A

HPLC profile for Entry 9, Table 4. 94:6 er



#	tR	Area	Height	Area%	Height%	NTP	Resolution	Symmetry Factor
1	58,975	284593	3139	5,697	7,368	9847	2,044	1,123
2	64,175	779936	7317	15,612	17,174	8879	3,686	1,376
3	74,958	3685239	30182	73,770	70,840	9104	3,178	1,661
4	85,042	245821	1967	4,921	4,618	11164	N/A	1,219

References and Notes

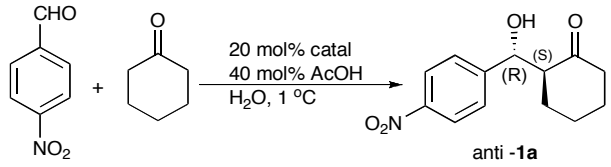
(1) Phikho, P. M.; Laurikainen, K. M.; Usano, A.; Nyoeng, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.

(2) Sakthievel, K.; Notz, W.; Bui, T.; Barbas, C. F. III *J. Am. Chem. Soc*. **2001**, *123*, 5260.

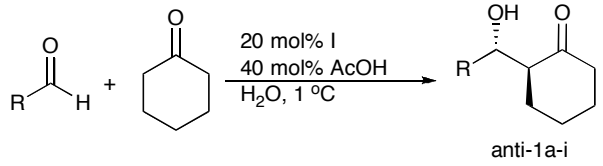
(3) Kojima, S.; Chanayashi, T.; Umeda, Y.; Iwamoto, A.; Tanabe, K.; Ohkata, K. *Heterocycles* **2008**, *75*, 1493.

(4) Hill, A.J.; Aspinal, S.R. *J. Am. Chem. Soc*. **1939**, *61*, 822.

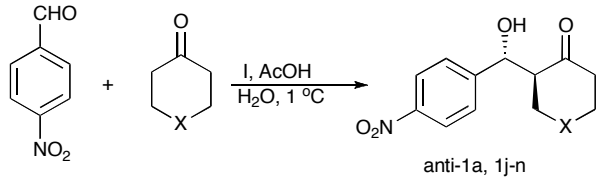
(5) a) Elliot, R.L.; Or, Y.S.; Chu, D.T.; Griesgraber, G.W.; Plattner, J.J.; Pireh, D. From *PCT Int. Appl*. **1997**, WO 9742205 A1 19971113. (b) Graser, F.. From *Ger. Offen*. **1997**, DE 2616486 19771103.



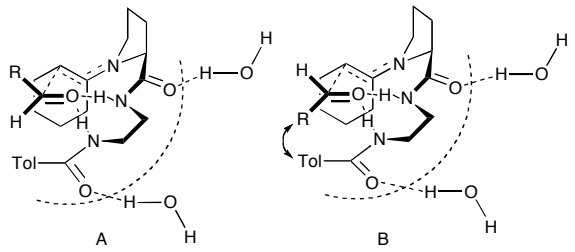
Scheme 1



Scheme 2



Scheme 3



Scheme 4

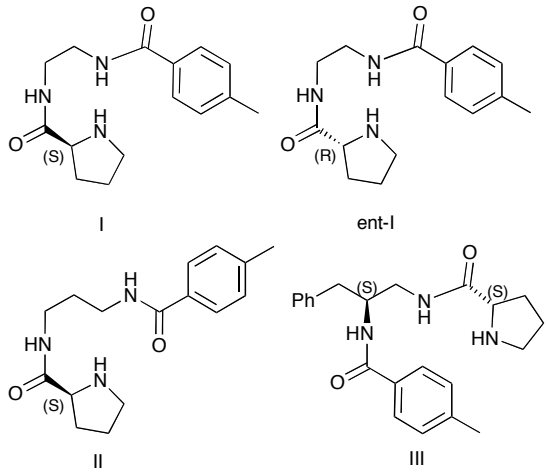


Figure 1