Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Asymmetric synthesis of quaternary α-hydrazino aldehydes via an organocatalytic Michael/α-amination sequence.

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General methods

All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh). Yields refer to chromatographically and spectroscopically pure compounds.The ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signal of the solvent ($CHCl_3$). Coupling constants are given in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal. High Resolution Mass spectra and X-ray data were obtained from the ILV-UVSQ. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). HPLC analysis was performed using chiral AS-H columns with i-PrOH/heptane as the eluent. HPLC traces were compared with racemic samples obtained by using DL-proline and benzylamine as catalyst.

Commercial grade reagents and solvents were used without further purification. Chiral primary amine catalyst, 9-Amino(9-deoxy)*epi*-cinchonine **2** and 9-Amino(9-deoxy)*epi*-cinchonidine **7** were prepared from commercially available cinchonine and cinchonidine following the literature procedure. [1] (*rac*)-α-Isopropylbenzylamine and (*rac*)-α-*tert*-butylbenzylamine were obtained following the literature procedure.[2] 2-nitrovinyl naphthalene (Table 1, entry 2), 4-fluoro-nitrostyrene (Table 1, entry 6), 3-chloro-nitrostyrene (Table 1, entry 7) and 3-methoxy-nitrostyrene (Table 1, entry 8) were synthetized following the literature procedure.[3] All other nitroolefines employed are commercially available.

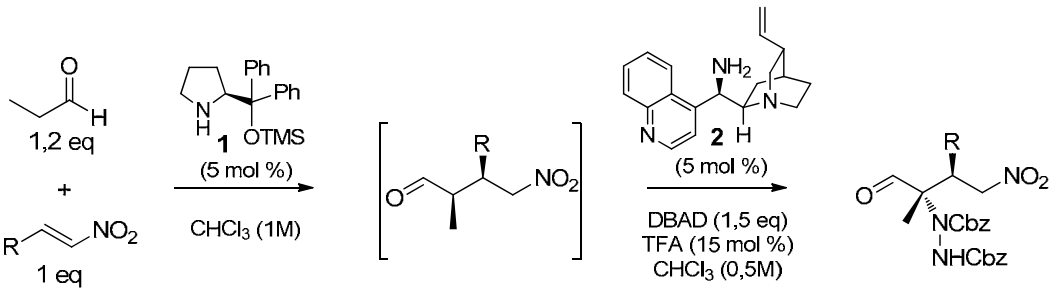
[1] Brunner, H.; Bügler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699

[2] Weiberth, F.J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901.

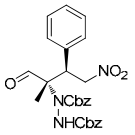
[3] Denmark, S. E.; Marcin, L. R. *J. Org. Chem* **1993**, *58*, 3850.

Experimental procedures

General procedure for the asymmetric organocatalytic Michael/amination cascade sequence of aldehydes.



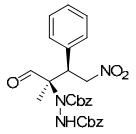
Diphenylprolinol silyl ether **1** (0.05 mmol, 16 mg), nitroalkene (1 mmol) and propionaldehyde (1.2 mmol, 107 µL) in $CHCl_3$ (1 mL) were stirred at 0°C until completion of the reaction (monitored by TLC). Then, DBAD (1.5 mmol, 447 mg), 9-Amino(9-deoxy)*epi*-cinchonine **2** (0.05 mmol, 14,7 mg) and a solution of TFA in $CHCl_3$ (0.3M, 0.15 mmol, 0.5 mL) were added sequentially at 0°C. The reaction mixture was stirred at room temperature until completion of the reaction (monitored by TLC). Solvent was removed *in vacuo* and the residue was purified by flash chromatography ($CHCl_3$ to CH_2Cl_2) to yield the desired product.



Dibenzyl-1-((*2S*,*3S*)-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl) hydrazine-1,2-dicarboxylate (5). The reaction was carried out over 4 hours for the Michael addition and 30 hours for the electrophilic amination.

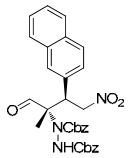
Yield : 90%; Ee: 96%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 46.3 min.(major), t_R = 85.0 min (minor); $[\alpha]_D^{20}$ = -85 (*c* 1, CH_2Cl_2); m.p. = 109-111°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.10 (s, $3H_{(rot\ min.)}$) 1.21 (s, $3H_{(rot\ maj)}$), 4.03-4.13 (m, 1H), 4.64-4.83 (m, 1H), 4.82-5.01 (m, 1H), 5.10-5.26 (m, 4H), 5.55 (s, $1H_{(rot\ min.)}$), 5.86 (s, $1H_{(rot\ maj)}$), 7.08-7.24 (m, 4H), 7.31-7.42 (m, 11H), 9.35 (s, $1H_{(rot\ min.)}$), 9.62 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 19.9 (CH_3), 48.9 (CH), 68.2 (CH_2), 69.5 (CH_2), 70.6 (C), 75.9 (CH_2), 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 129.2, 129.4 ($15CH_{arom}$), 134.7 (C), 134.7 (C), 134.8 (C), 155.9 (C), 156.6 (C), 195.6 (C); IR : γ 3306, 3032, 2942, 1729, 1694, 1506, 1330, 1228, 742, 699; HRMS: (*m/z*) calculated for $C_{27}H_{27}N_3O_7Na$: 528.1747 ,

found: 528.1767.



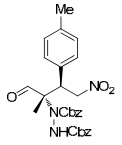
Dibenzyl-1-((*2R,3S*)-2-methyl-4-nitro-1-oxo-3-phenylbutan-2-yl)hydrazine-1,2-dicarboxylate (6). The reaction was carried out over 4 hours for the Michael addition and 15 hours for the electrophilic amination.

Yield : 76%; Ee: 96%, the ee was determined on the single diastereoisomer by HPLC analysis on a OD-H column: heptane/*i*-PrOH 95/5, flow rate 1 mL/min, λ = 254 nm, 30°C : t_R = 41.9 min.(major), t_R = 48.8 min (minor); $[\alpha]_D^{20}$ = 73.3 (*c* 1, CH_2Cl_2);^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.18 (s, $3H_{(rot\ min.)}$) 1.28 (s, $3H_{(rot\ maj)}$), 4.45-4.51 (m, 8H), 7.08-7.40 (m, 14H), 9.38 (s, $1H_{(rot\ min.)}$), 9.59 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 14.1 (CH_3), 44.2 (CH), 68.1 (CH_2), 69.0 (CH_2), 69.7 (C), 75.0 (CH_2), 128.1, 128.3, 128.6, 129.2, ($15CH_{arom}$), 134.9 (C), 135.1 (C), 135.3 (C), 155.6 (C), 156.1 (C), 197.0 (C); IR : γ 3302, 3024, 2923, 1731, 1699, 1554, 1341, 1222, 735, 699; HRMS: (*m/z*) calculated for $C_{27}H_{27}N_3O_7Na$: 528.1747, found: 528.1720.



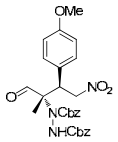
Dibenzyl-1-((*2S,3S*)-2-methyl-4-nitro-1-oxo-3-naphtylbutan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 4 hours for the Michael addition and 65 hours for the electrophilic amination.

Yield : 73%; Ee: 96%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 40.5 min.(major), t_R = 71.2 min (minor); $[\alpha]_D^{20}$ = -96.7 (*c* 1, CH_2Cl_2); m.p. = 177-179°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.13 (s, $3H_{(rot\ min.)}$) 1.24 (s, $3H_{(rot\ maj)}$), 4.19-4.28 (m, 1H), 4.75-5.29 (m, 6H), 5.43 (s, $1H_{(rot\ min.)}$), 5.81 (s, $1H_{(rot\ maj)}$), 7.13-7.19 (m, 3H), 7.30-7.62 (m, 11H), 7.74-7.84 (m, 3H), 9.37 (s, $1H_{(rot\ min.)}$), 9.65 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 20.1 (CH_3), 49.2 (CH), 68.3 (CH_2), 69.6 (CH_2), 70.8 (C), 76.2 (CH_2), 125.0, 126.7, 126.8, 127.7, 127.8, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.2 (17 CH_{arom}), 132.0 (C), 132.9 (C), 133.2 (C), 134.7 (C), 134.8 (C), 156.0 (C), 156.7 (C), 195.8 (C); IR : γ 3329, 2840, 1748, 1716, 1546, 1495, 1345, 1223, 749, 730, 691; HRMS: (*m/z*) calculated for $C_{31}H_{29}N_3O_7Na$: 578.1903, found: 578.1890.



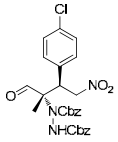
Dibenzyl-1-((*2S*,*3S*)-2-methyl-4-nitro-1-oxo-3-tolylbutan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 6 hours for the Michael addition and 25 hours for the electrophilic amination.

Yield : 85%; Ee: 96%, the ee was determined on the single diastereoisomer by HPLC analysis on a OD-H column: heptane/*i*-PrOH 95/5, flow rate 1 mL/min, λ = 254 nm : t_R = 41.6 min.(major), t_R = 54.7 min (minor); $[\alpha]_D^{20}$ = -93 (*c* 1, CH_2Cl_2); m.p. = 129-130°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.08 (s, $3H_{(rot\ min.)}$) 1.20 (s, $3H_{(rot\ maj)}$), 2.31 (s, 3H), 3.97-4.07 (m, 1H), 4.58-4.70 (m, 1H), 4.82-5.01 (m, 1H), 5.07-5.25 (m, 4H), 5.47 (s, $1H_{(rot\ min.)}$), 5.83 (s, $1H_{(rot\ maj)}$), 6.90-6.97 (m, 2H), 7.10-7.25 (m, 4H), 7.33-7.41 (8H), 9.34 (s, $1H_{(rot\ min.)}$), 9.61 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 20.0 (CH_3), 21.0 (CH_3), 48.7 (CH), 68.3 (CH_2), 69.5 (CH_2), 70.7 (C), 76.1 (CH_2), 128.3, 128.4, 128.7, 128.9, 130.0, 130.1 (14 CH_{arom}), 131.6 (C), 134.7 (C), 134.9 (C), 138.4 (C), 155.9 (C), 156.6 (C), 195.8 (C); IR : γ 3345, 3023, 2954, 1740, 1685, 1548, 1348, 1227, 753, 729; HRMS: (*m/z*) calculated for $C_{28}H_{29}N_3O_7Na$: 542.1903 , found: 542.1883.



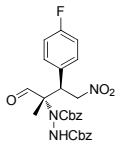
Dibenzyl-1-((*2S*,*3S*)-2-methyl-4-nitro-1-oxo-3-(4-methoxyphenyl)butan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 8 hours for the Michael addition and 22 hours for the electrophilic amination.

Yield : 85%; Ee: 97%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 74.7 min.(major), t_R = 117.2 min (minor); $[\alpha]_D^{20}$ = -87.8 (*c* 1, CH_2Cl_2); m.p. = 120-122°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.08 (s, $3H_{(rot\ min.)}$) 1.20 (s, $3H_{(rot\ maj)}$), 3.78 (s, 3H), 3.98-4.05 (m, 1H), 4.56-4.68 (m, 1H), 4.82-5.25 (m, 5H), 5.46 (s, $1H_{(rot\ min.)}$), 5.81 (s, $1H_{(rot\ maj)}$), 6.81-7.00 (m, 4H), 7.15-7.25 (m, 2H), 7.33-7.41 (m, 8H), 9.34 (s, $1H_{(rot\ min.)}$), 9.61 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 19.9 (CH_3), 48.2 (CH), 55.1 (CH_3), 68.2 (CH_2), 69.4 (CH_2), 70.7 (C), 76.2 (CH_2), 114.5 (2CH), 126.2 (C), 128.2, 128.3 , 128.5, 128.6, 128.7, 128.8, 129.8 (12 CH_{arom}), 134.7 (C), 134.9 (C), 155.9 (C), 156.6 (C), 159.4 (C), 195.9 (C); IR : γ 3305, 3031, 2958, 1727, 1703, 1549, 1252, 901, 727; HRMS: (*m/z*) calculated for $C_{28}H_{29}N_3O_8Na$: 558.1852, found: 558.1840.



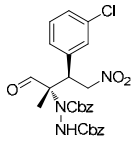
Dibenzyl-1-((*2S*,*3S*)-2-methyl-4-nitro-1-oxo-3-(4-chlorophenyl)butan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 5 hours for the Michael addition and 70 hours for the electrophilic amination.

Yield : 85%; Ee: 98%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 43.1 min.(major), t_R = 58.3 min (minor); $[\alpha]_D^{20}$ = -76 (*c* 1, CH_2Cl_2); m.p. = 146-148°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.08 (s, $3H_{(rot\ min.)}$) 1.19 (s, $3H_{(rot\ maj)}$), 4.02-4.11 (m, 1H), 4.57-4.70 (m, 1H), 4.84-5.24 (m, 5H), 5.73 (s, $1H_{(rot\ min.)}$), 5.96 (s, $1H_{(rot\ maj)}$), 6.97-7.42 (m, 14H), 9.32 (s, $1H_{(rot\ min.)}$), 9.61 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 19.9 (CH_3), 48.4 (CH), 68.4 (CH_2), 69.6 (CH_2), 70.4 (C), 75.9 (CH_2), 128.4, 128.6, 128.7, 128.8, 128.9, 129.4, 130.1 (14 CH_{arom}), 133.1 (C), 133.4 (C), 134.5 (C), 134.7 (C), 156.1 (C), 156.6 (C), 195.4 (C); IR : γ 3332, 3031, 2958, 1723, 1697, 1551, 1334, 1228, 728; HRMS: (*m/z*) calculated for $C_{27}H_{26}ClN_3O_7Na$: 562.1357, found: 562.1364.



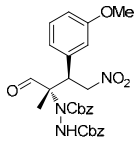
Dibenzyl-1-((*2S*,*3S*)-2-methyl-4-nitro-1-oxo-3-(4-fluorophenyl)butan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 4 hours for the Michael addition and 140 hours for the electrophilic amination.

Yield : 81%; Ee: 97%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 33.0 min.(major), t_R = 43.1 min (minor); $[\alpha]_D^{20}$ = -76.3 (*c* 1, CH_2Cl_2); m.p. = 136-138°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.09 (s, $3H_{(rot\ min.)}$) 1.20 (s, $3H_{(rot\ maj)}$), 4.05-4.11 (m, 1H), 4.58-4.71 (m, 1H), 4.85-5.24 (m, 5H), 5.67 (s, $1H_{(rot\ min.)}$), 5.92 (s, $1H_{(rot\ maj)}$), 6.98-7.40 (m, 14H), 9.34 (s, $1H_{(rot\ min.)}$), 9.62 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 19.9 (CH_3), 48.4 (CH), 68.5 (CH_2), 69.7 (CH_2), 70.7 (C), 76.2 (CH_2), 116.3 (d, J = 21 Hz, 2CH), 128.4, 128.7, 128.8, 129.0 (10 CH_{arom}), 130.6 (d, J = 7.6 Hz, 2CH), 130.7 (d, J = 3.2 Hz, C), 134.7 (C), 134.9 (C), 156.2 (C), 156.7 (C), 162.5 (d, J = 247 Hz, C), 195.6 (C); IR : γ 3321, 2836, 1743, 1720, 1546, 1408, 1345, 1219, 749, 722, 698; HRMS: (*m/z*) calculated for $C_{27}H_{26}FN_3O_7Na$: 546.1652, found: 546.1642.



Dibenzyl-1-((*2S,3S*)-2-methyl-4-nitro-1-oxo-3-(3-chlorophenyl)butan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 4 hours for the Michael addition and 90 hours for the electrophilic amination.

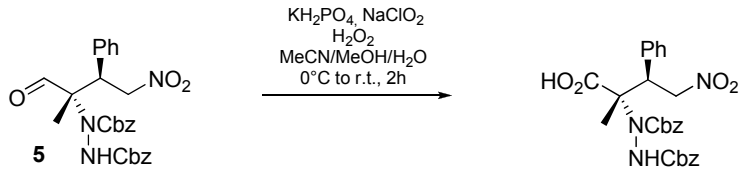
Yield : 85%; Ee: 98%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm : t_R = 30.6 min.(major), t_R = 46.0 min (minor); $[\alpha]_D^{20}$ = -76.5 (*c* 1, CH_2Cl_2); m.p. = 180-181°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.09 (s, $3H_{(rot\ min.)}$) 1.21 (s, $3H_{(rot\ maj)}$), 4.00-4.09 (m, 1H), 4.52-4.66 (m, 1H), 4.82-5.25 (m, 5H), 5.51 (s, $1H_{(rot\ min.)}$), 5.84 (s, $1H_{(rot\ maj)}$), 6.93-7.40 (m, 14H), 9.30 (s, $1H_{(rot\ min.)}$), 9.59 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 20.0 (CH_3), 48.8 (CH), 68.5 (CH_2), 69.7 (CH_2), 70.5 (C), 75.9 (CH_2), 126.4 (2CH), 128.4, 128.7, 128.8, 128.9, 129.0, 129.7 (11 CH_{arom}), 130.4 (CH), 134.6 (C), 134.8 (C), 135.1 (C), 137.2 (C), 156.1 (C), 156.6 (C), 195.3 (C); IR : γ 3305, 2832, 1748, 1732, 1672, 1558, 1412, 1345, 1227, 753, 738, 694; HRMS: (*m/z*) calculated for $C_{27}H_{26}ClN_3O_7Na$: 562.1357, found: 562.1332.



Dibenzyl-1-((*2S,3S*)-2-methyl-4-nitro-1-oxo-3-(3-methoxyphenyl)butan-2-yl) hydrazine-1,2-dicarboxylate. The reaction was carried out over 4 hours for the Michael addition and 88 hours for the electrophilic amination.

Yield : 76%; Ee: 96%, the ee was determined on the single diastereoisomer by HPLC analysis on a AS-H column: heptane/*i*-PrOH 9/1, flow rate 0.8 mL/min, λ = 254 nm, 35°C : t_R = 32.0 min.(major), t_R = 66.3 min (minor); $[\alpha]_D^{20}$ = -76.2 (*c* 1, CH_2Cl_2); m.p. = 98-100°C; ^{1}H NMR (300 MHz, $CDCl_3$) Mixture of rotamers : δ 1.12 (s, $3H_{(rot\ min.)}$) 1.24 (s, $3H_{(rot\ maj)}$), 3.74 (s, 3H), 4.00-4.09 (m, 1H), 4.60-4.73 (m, 1H), 4.84-5.26 (m, 5H), 5.62 (s, $1H_{(rot\ min.)}$), 5.94 (s, $1H_{(rot\ maj)}$), 6.60-6.86 (m, 3H), 7.18-7.40 (m, 11H), 9.35 (s, $1H_{(rot\ min.)}$), 9.62 (s, $1H_{(rot\ maj)}$); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 20.0 (CH_3), 49.0 (CH), 55.1 (CH_3) 68.5 (CH_2), 69.5 (CH_2), 70.6 (C), 76.0 (CH_2), 113.7 (CH), 116.0 (CH), 120.2 (CH) 128.3, 128.6, 128.7, 128.8, 130.2 (11 CH_{arom}), 134.7 (C), 134.9 (C), 136.4 (C), 156.0 (C), 156.6 (C), 159.9 (C), 195.6 (C); IR : γ 3314, 2836, 1744, 1680, 1550, 1451, 1341, 1219, 749, 726, 695; HRMS: (*m/z*) calculated for $C_{28}H_{29}N_3O_8Na$: 558.1852, found: 558.1833.

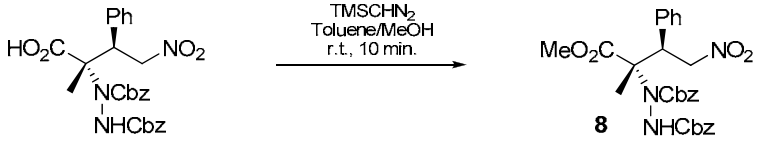
Procedure for the oxidation of aldehyde 5



To a solution of aldehyde **5** (190 mg, 0.38 mmol) in $CH_3OH/CH_3CN/H_2O$ (1/2/1, 8 mL) was added KH_2PO_4 (200 mg, 1.47 mmol), $NaClO_2$ (140 mg, 1.30 mmol) and 30% H_2O_2 (1.4 mL) at 0°C. The mixture was allowed warm to room temperature and stirred 2 hours. The solution was acidified with 2 M HCl till pH = 3. Saturated Na_2SO_3 aqueous (1 mL) was added at 0°C and the mixture was acidified with 2 M HCl till pH = 3 again. The aqueous phase was extracted by ethyl acetate. The combined organic layer was washed by brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 96/4) to give the corresponding carboxylic acid as a colorless oil (160 mg, 83 %).

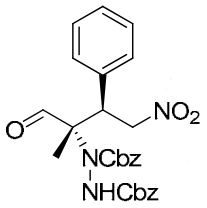
Yield : 83%; $[\alpha]_D^{20}$ = -161.5 (*c* 1, CH_2Cl_2);^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 4.17 (dd, J= 11.7 and 2.8 Hz, 1H), 4.70 (t, J=12.7 Hz, 1H), 5.07-5.26 (m, 4H), 5.44-5.48 (d, J=12.7 Hz, 1H), 6.28 (s, 1H), 7.03-7.05 (m, 2H), 7.25-7.41 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 24.0 (CH_3), 51.2 (CH), 68.8 (CH_2), 70.0 (CH_2), 70.2 (CH_2), 77.4 (C), 128.7, 128.8, 128.9, 129.0, 129.2, 129.3, 129.4, (15CH_{arom}), 134.0 (C), 134.5 (C), 135.4 (C), 155.6 (C), 159.8 (C), 171.4 (C); IR : γ 3286, 3065, 2950, 1716, 1550, 1495, 1451, 1262, 734, 690; HRMS: (*m/z*) calculated for $C_{27}H_{27}N_3O_8Na$: 544.1696, found: 544.1672.

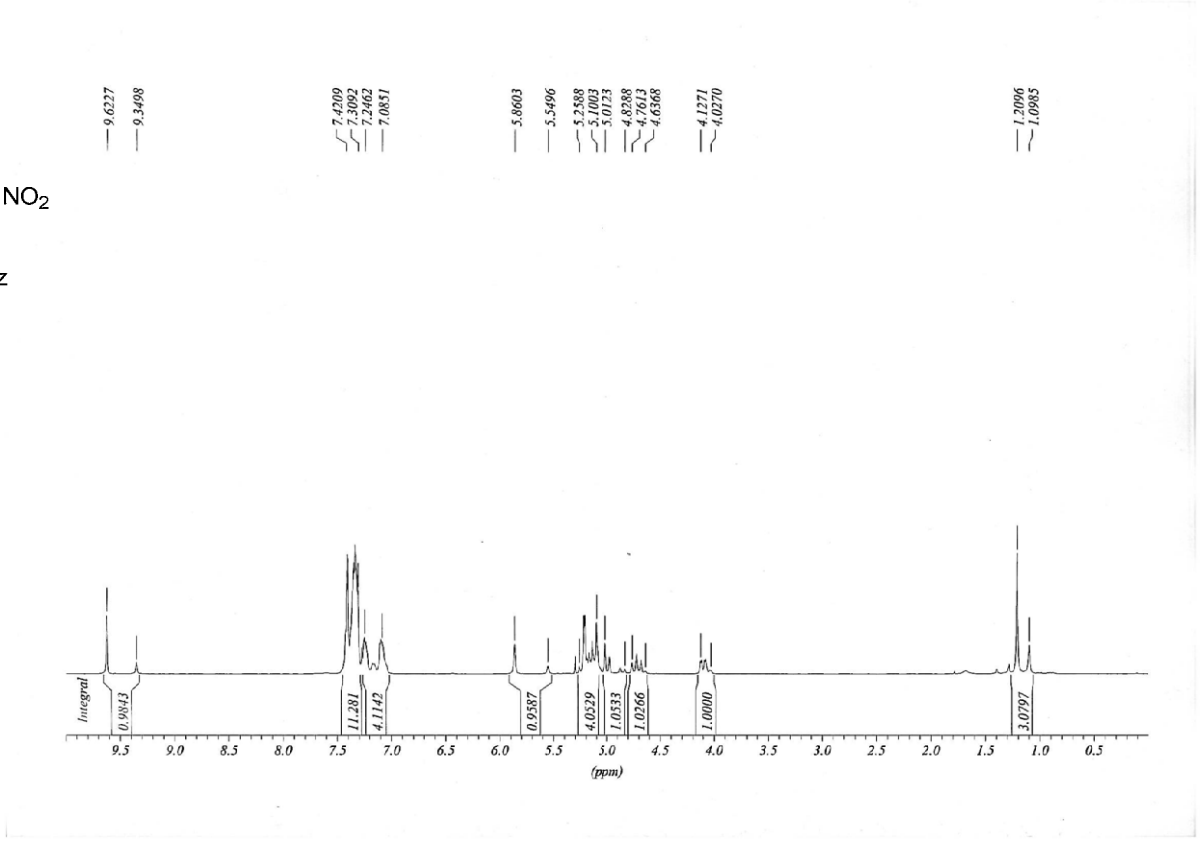
Procedure for the synthesis of compound 8

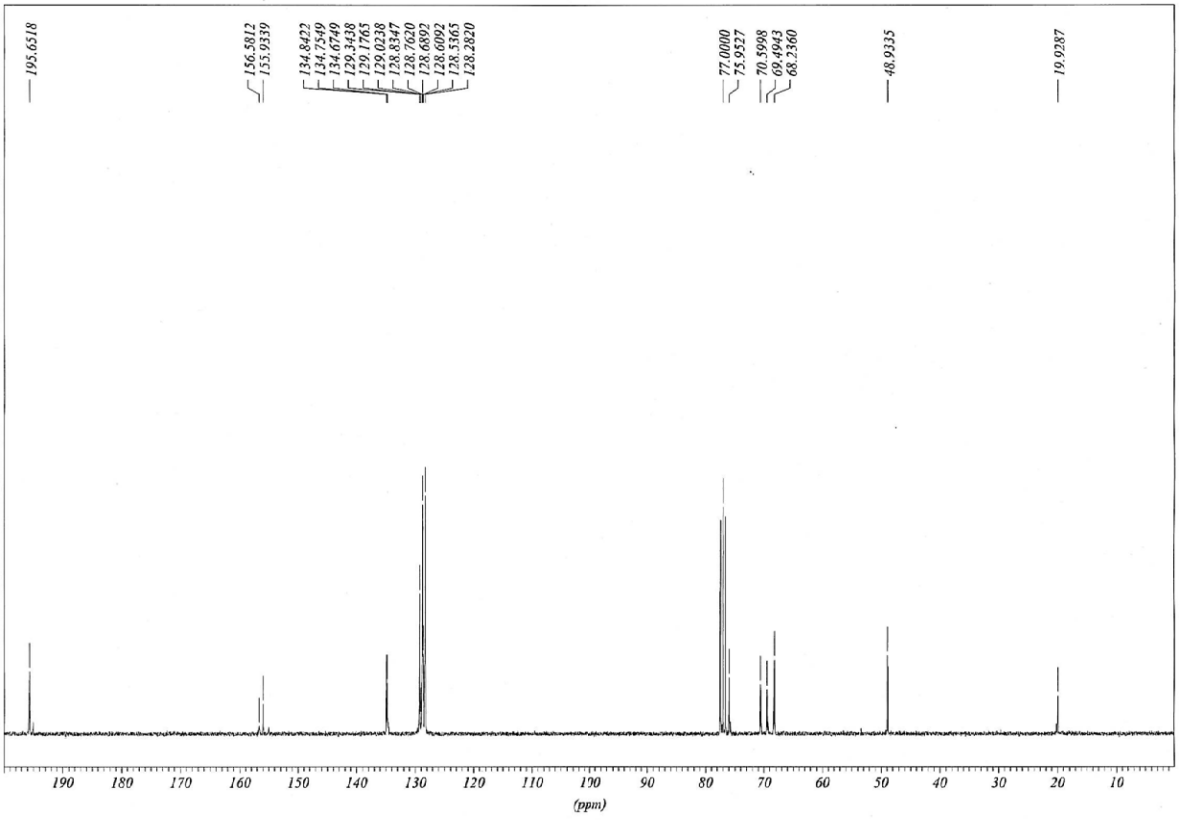


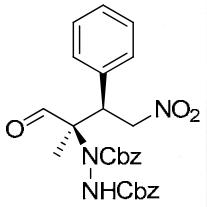
To a solution of carboxylic acid (52 mg, 0.1 mmol) in toluene/MeOH (2/1, 1 mL) was added dropwise a solution of $TMSCHN_2$ (2M in hexanes, 0.1 mL, 0.2 mmol) at room temperature. The solution was stirred 10 minutes and the excess of $TMSCHN_2$ was quenched with few drops of AcOH. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel (Pentane/EtOAc 4/1) to afford the corresponding ester **8** as a colorless oil (32 mg, 60 %).

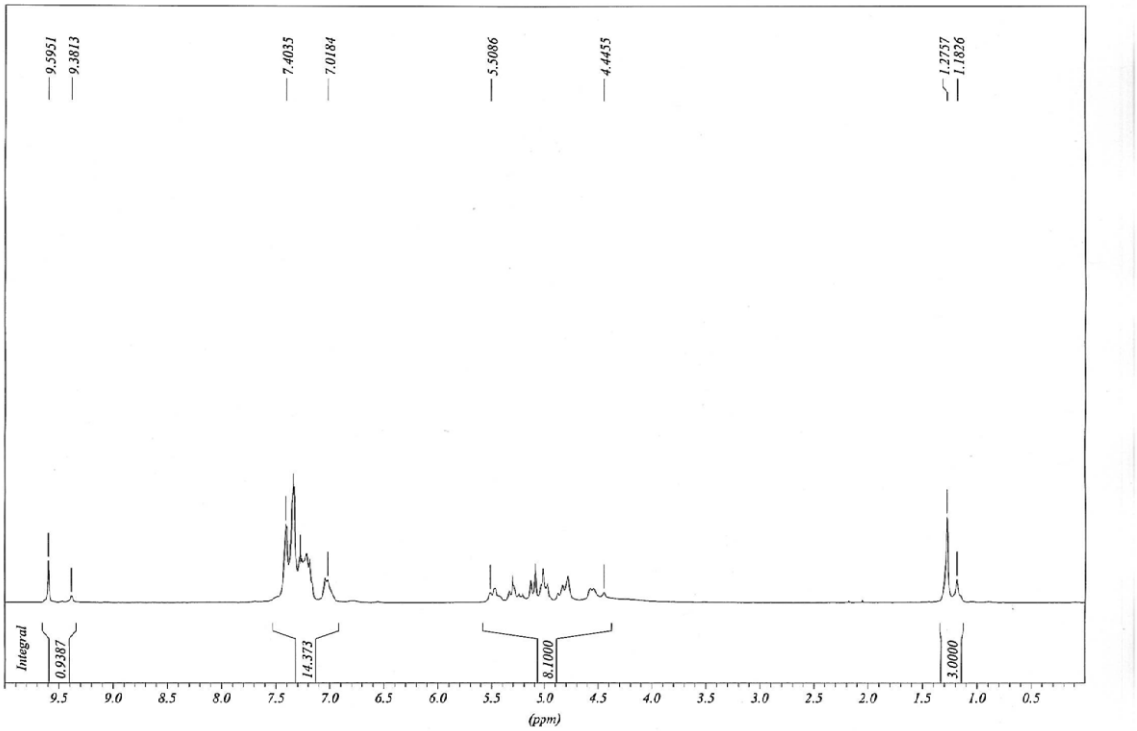
Yield : 60%; $[\alpha]_D^{20}$ = -89.0 (*c* 1, CH_2Cl_2);^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 3H), 3.63 (s, 3H), 4.02-4.21 (m, 1H), 4.72-5.43 (m, 6H), 5.96 (s, 1H), 7.05-7.12 (m, 2H), 7.21-7.41 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) Major rotamer : δ 22.3 (CH_3), 50.8 (CH), 52.9 (CH_3), 68.2 (CH_2), 68.5 (CH_2), 69.0 (CH_2), 76.6 (C), 128.2, 128.4, 128.6, 128.6, 128.8, 128.8, 129.2 ($15CH_{arom}$), 135.1 (C), 135.3 (C), 135.4 (C), 155.9 (C), 155.9 (C), 172.4 (C); IR : γ 3294, 3025, 2939, 1708, 1542, 1451, 1215, 738, 698; HRMS: (*m/z*) calculated for $C_{28}H_{29}N_3O_8Na$: 558.1852, found: 558.1831.

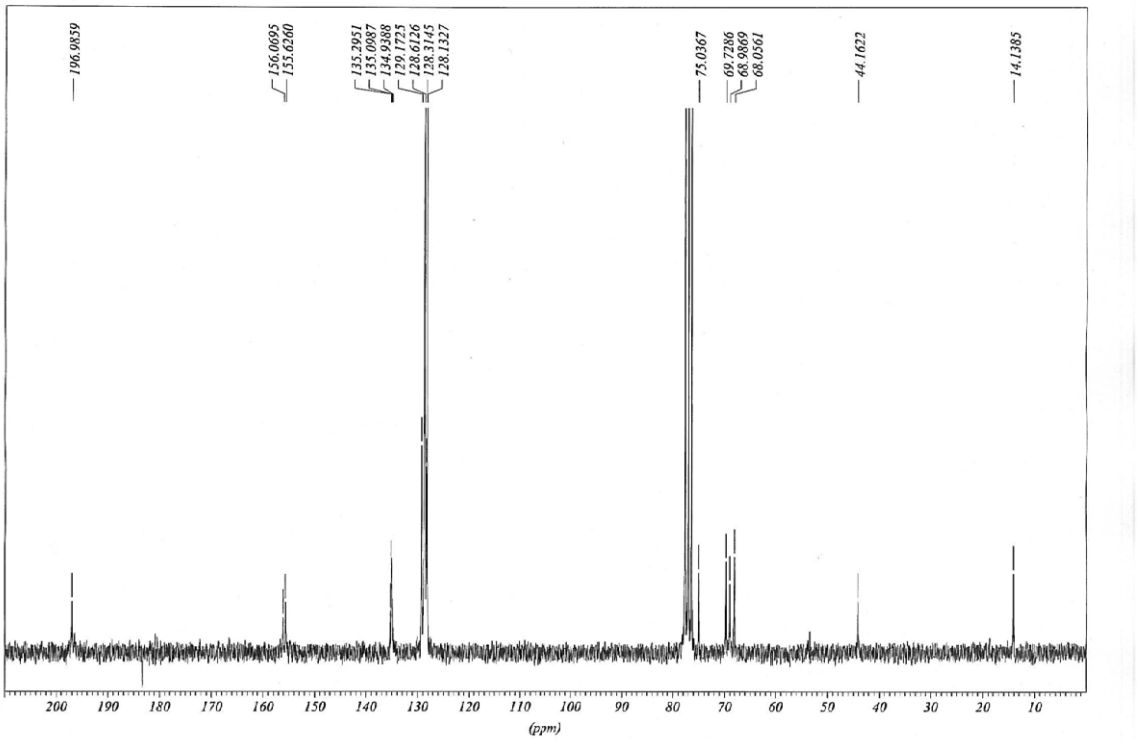


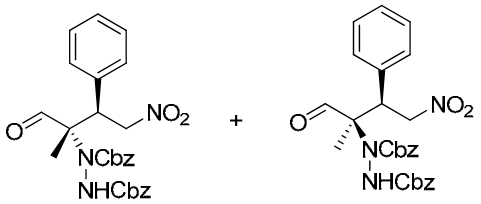


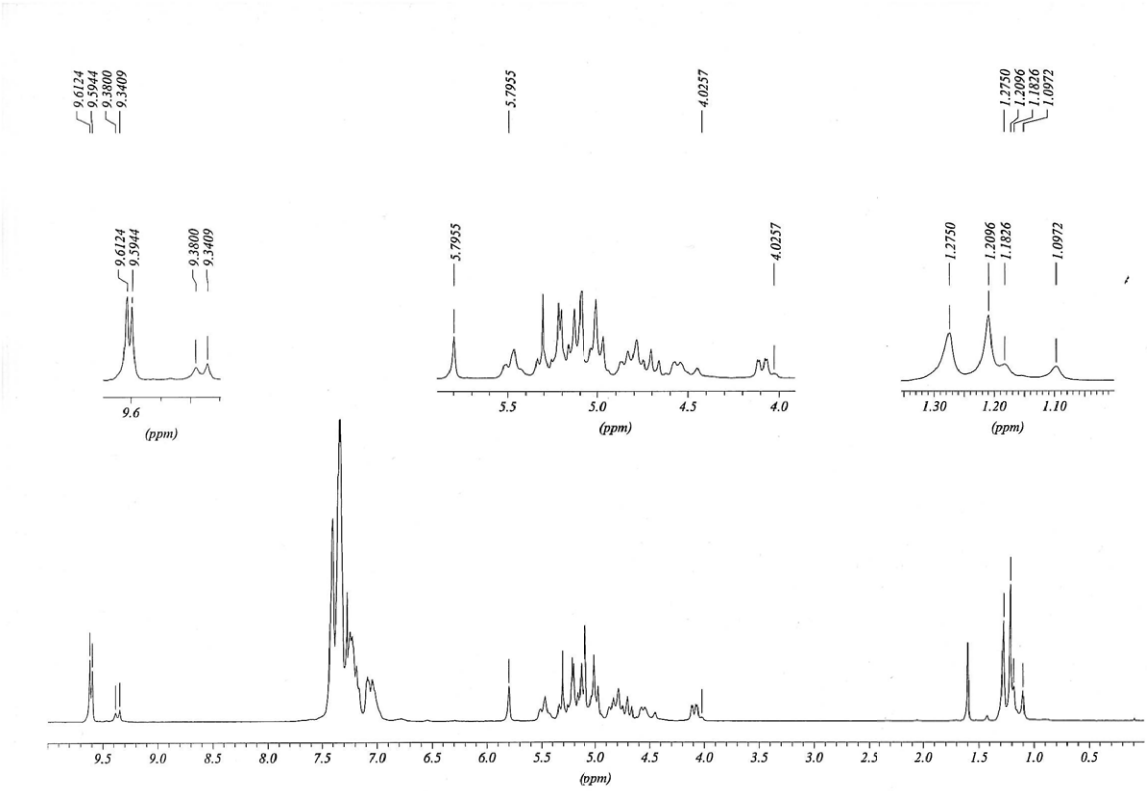


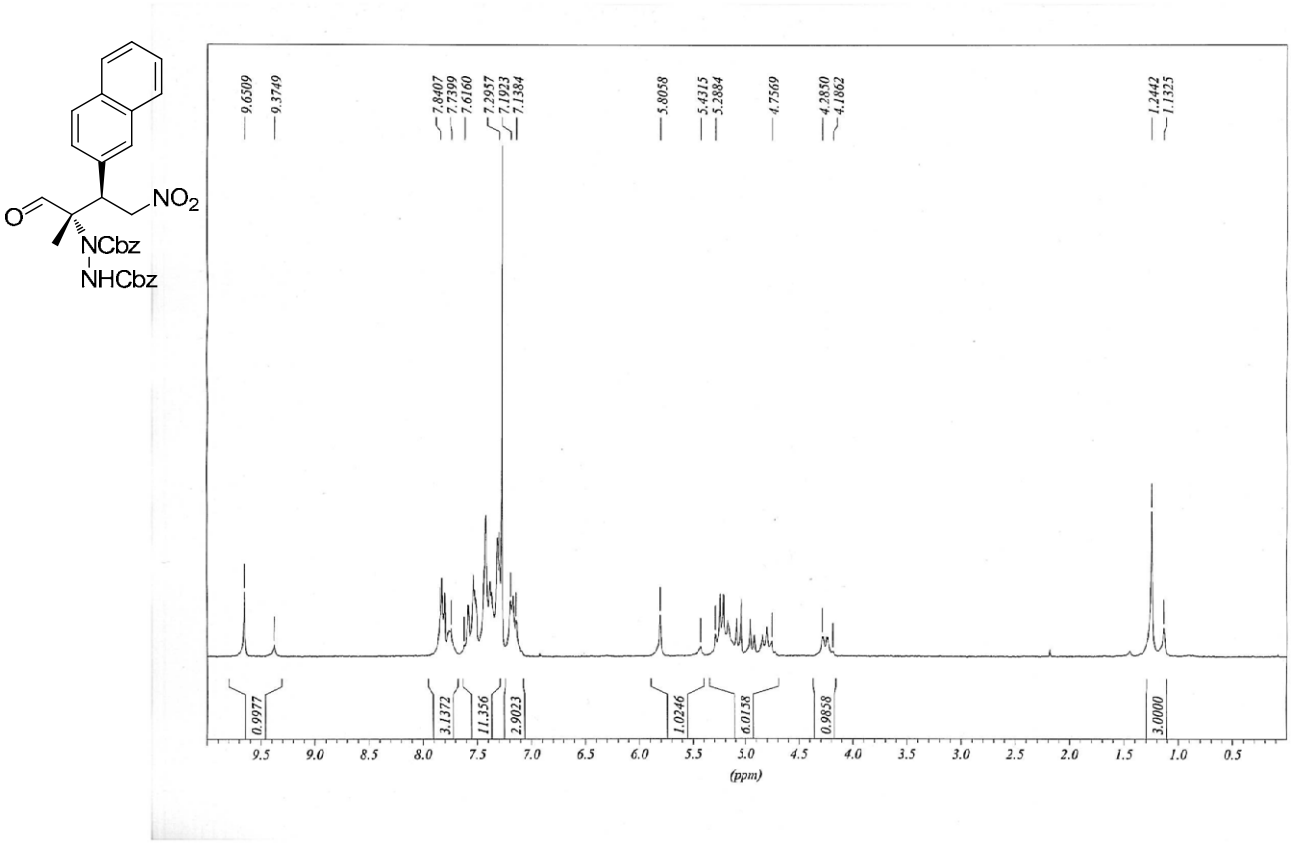


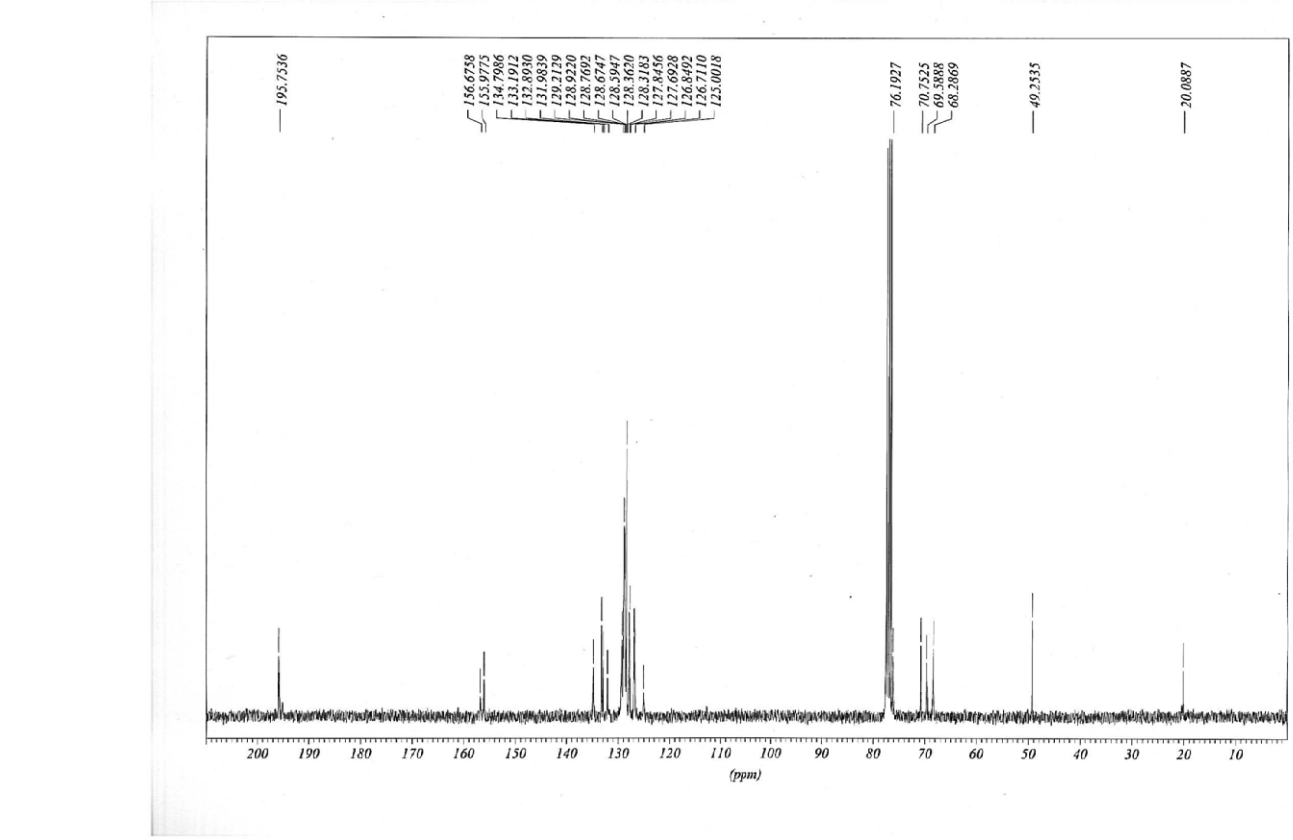


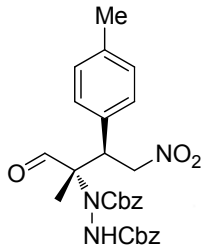


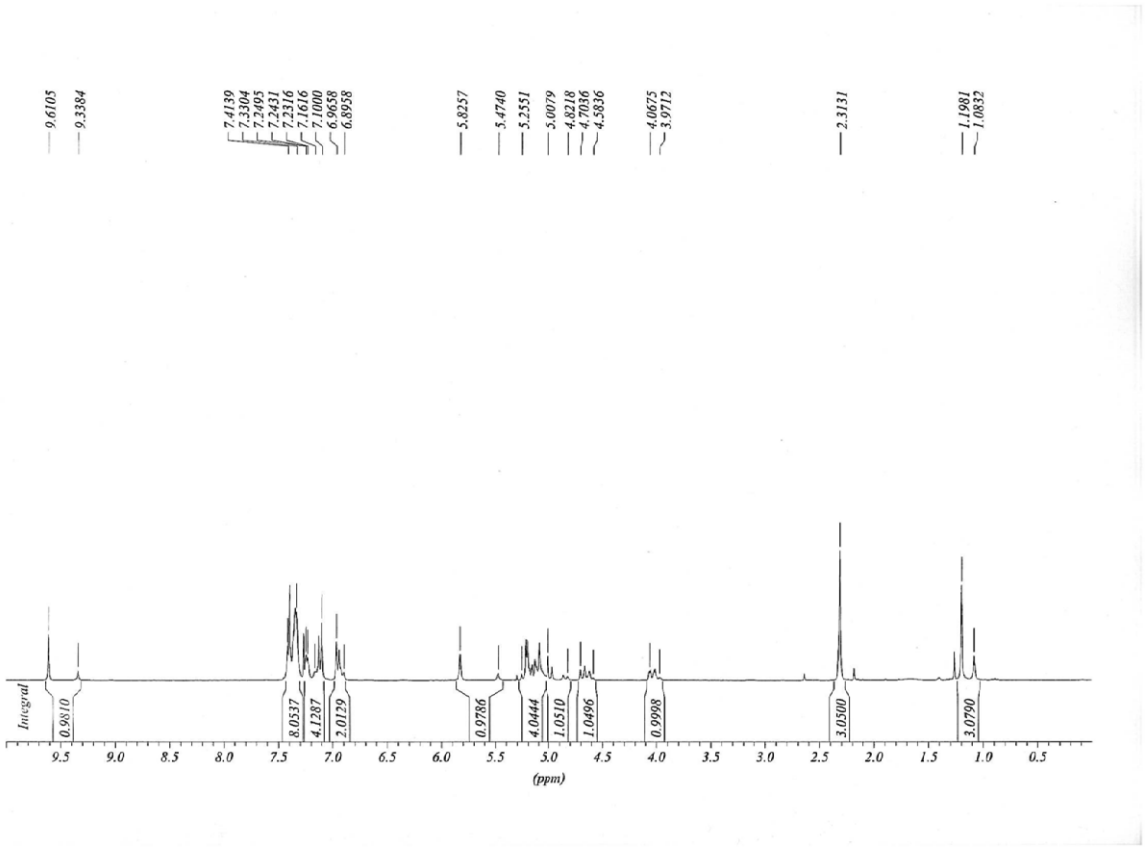


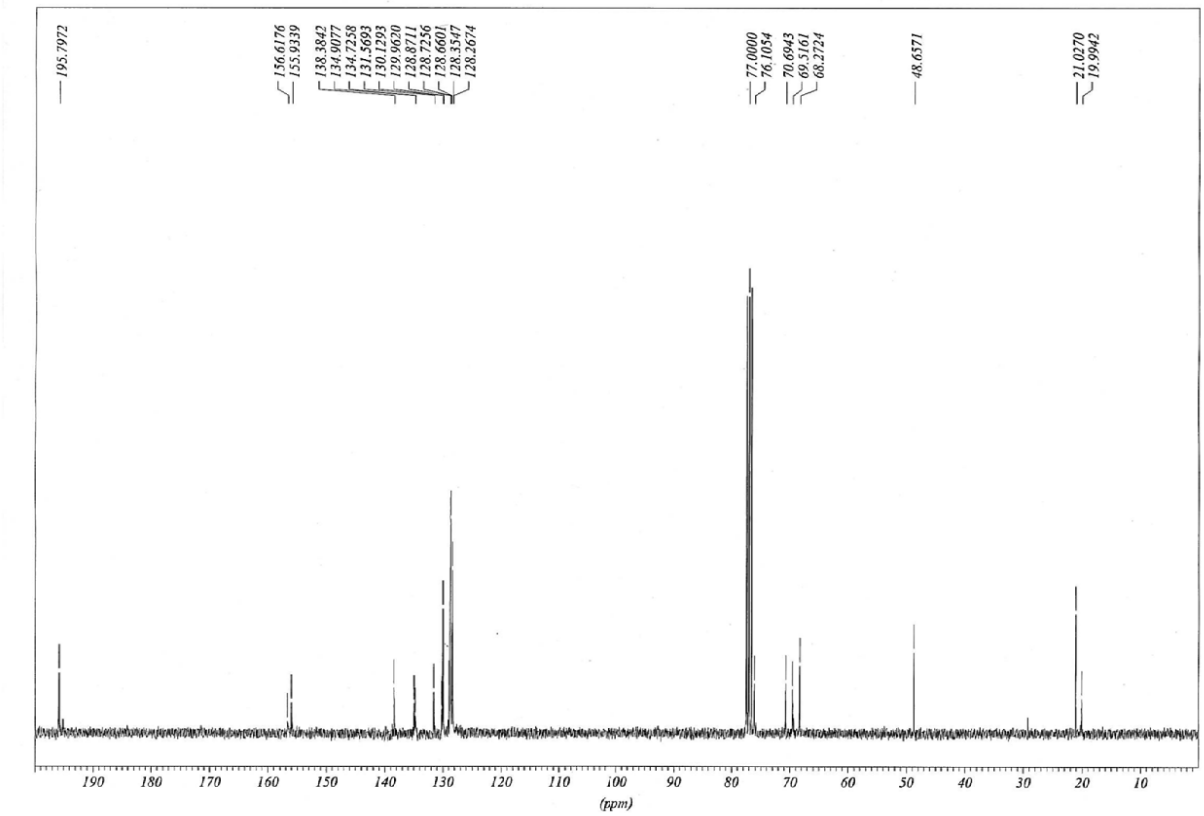


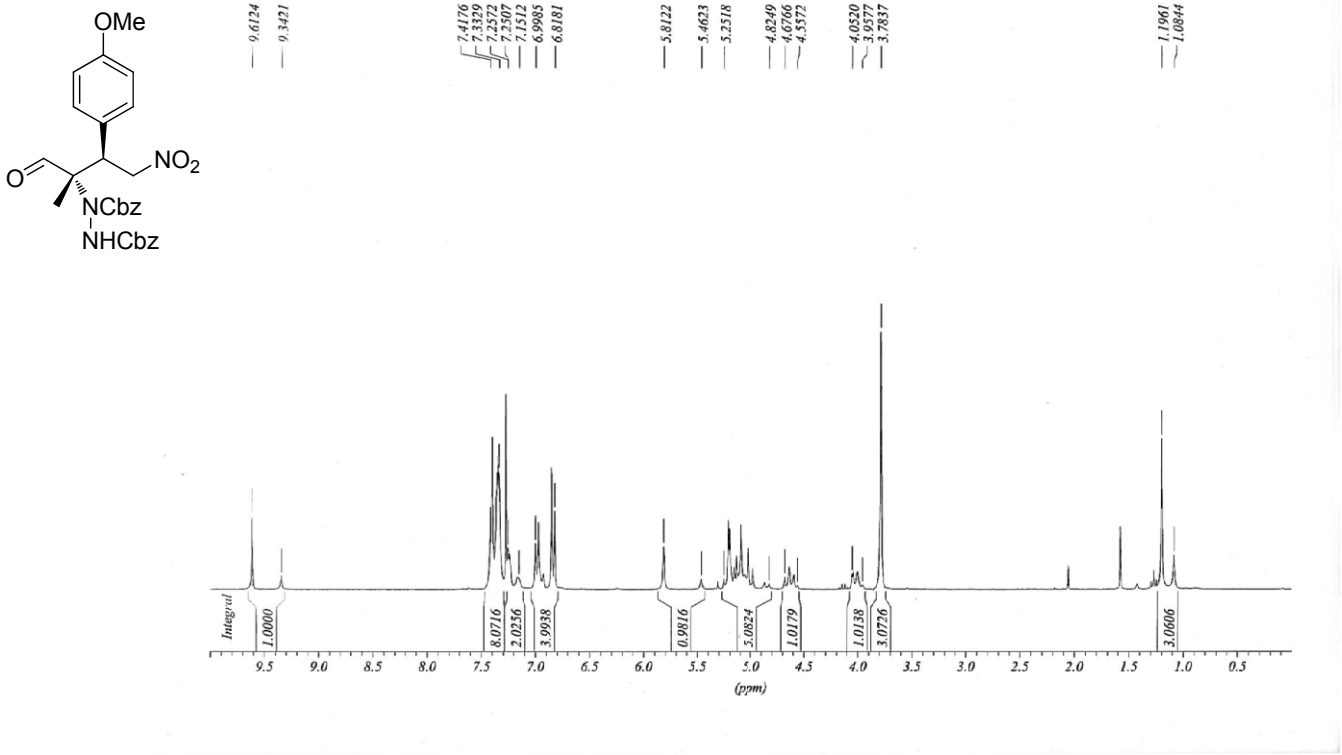


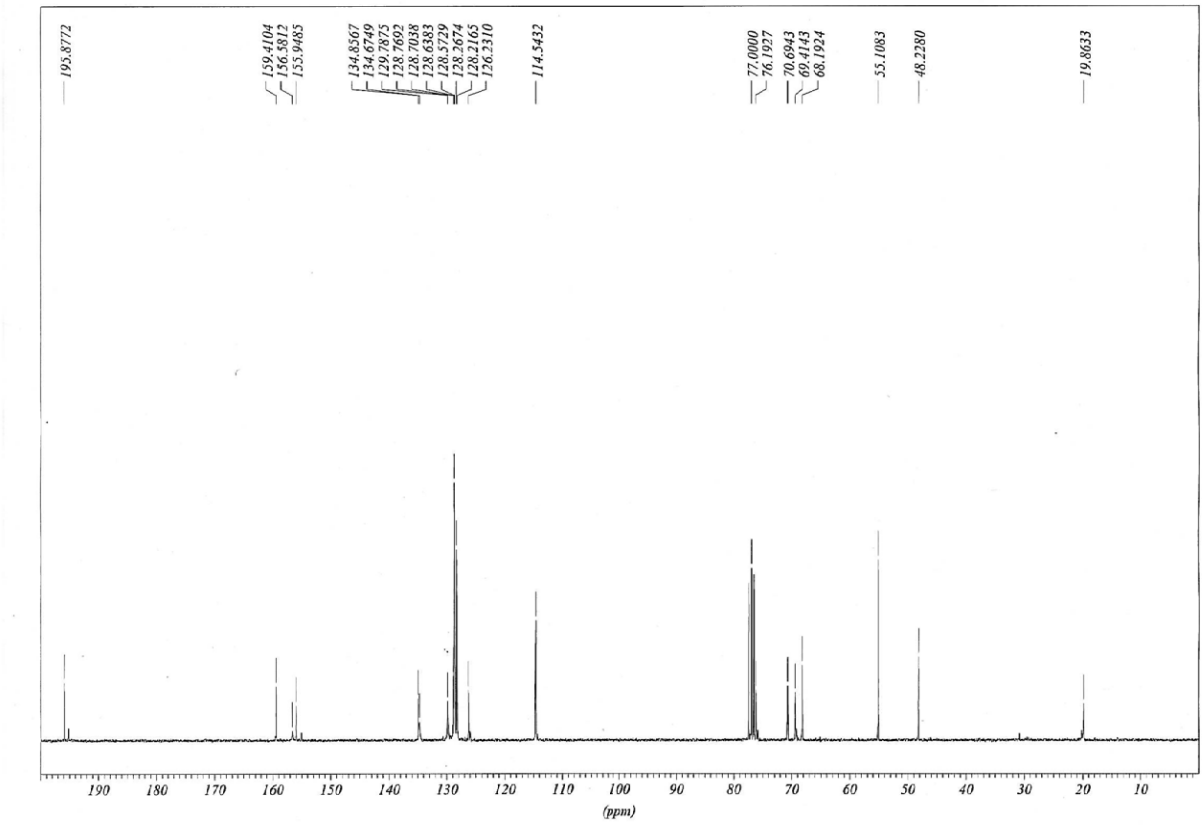


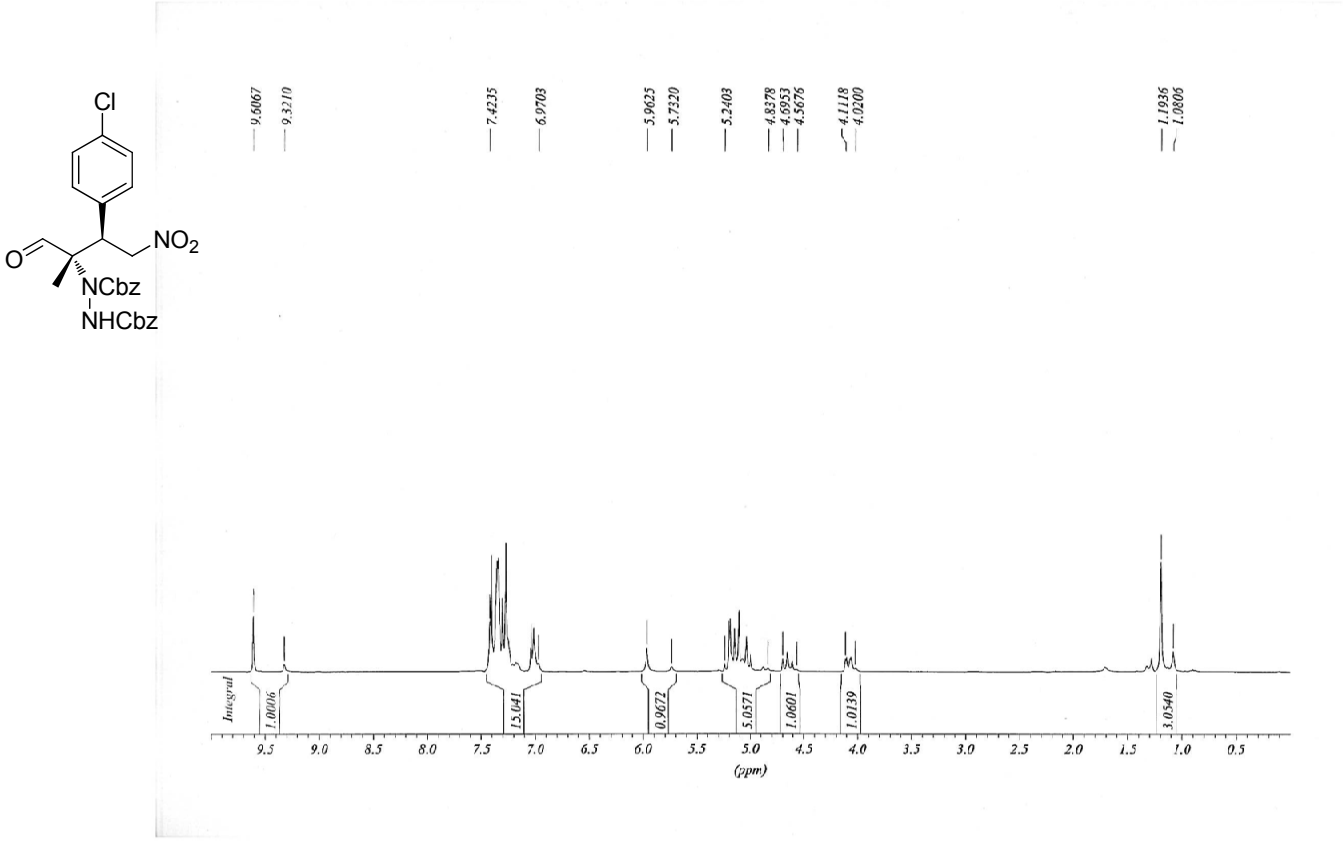


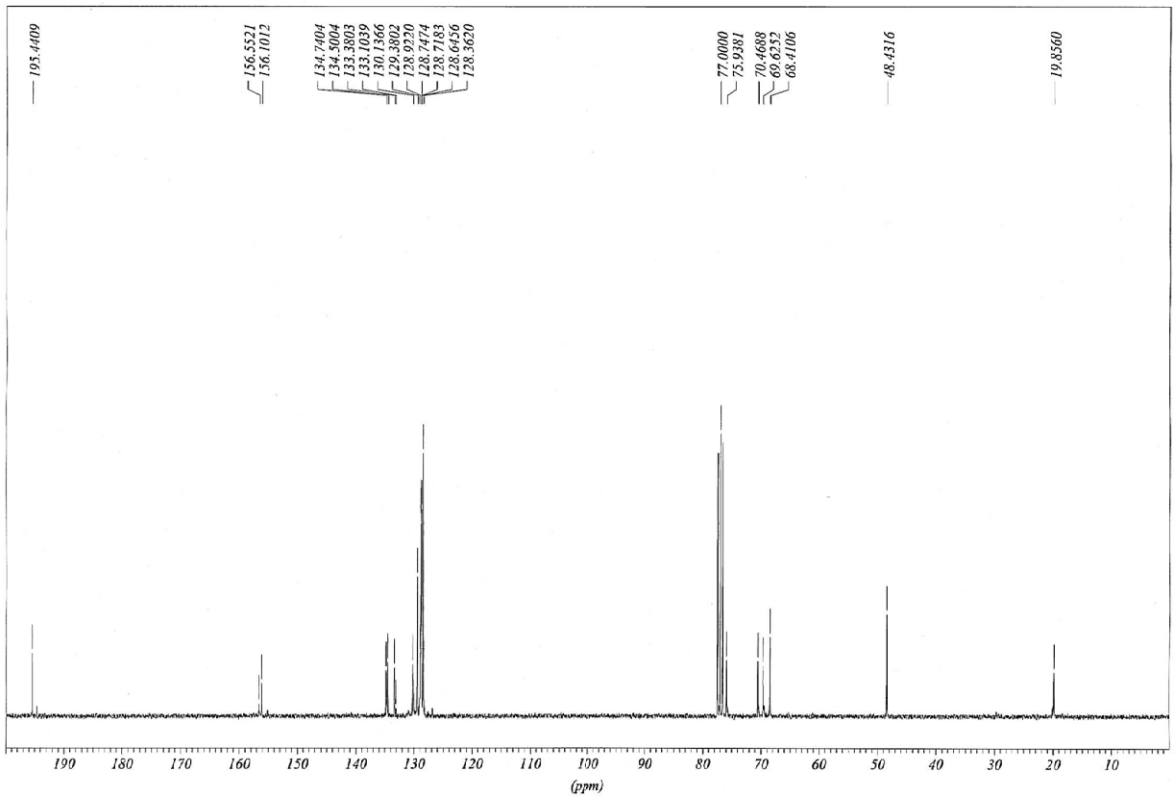


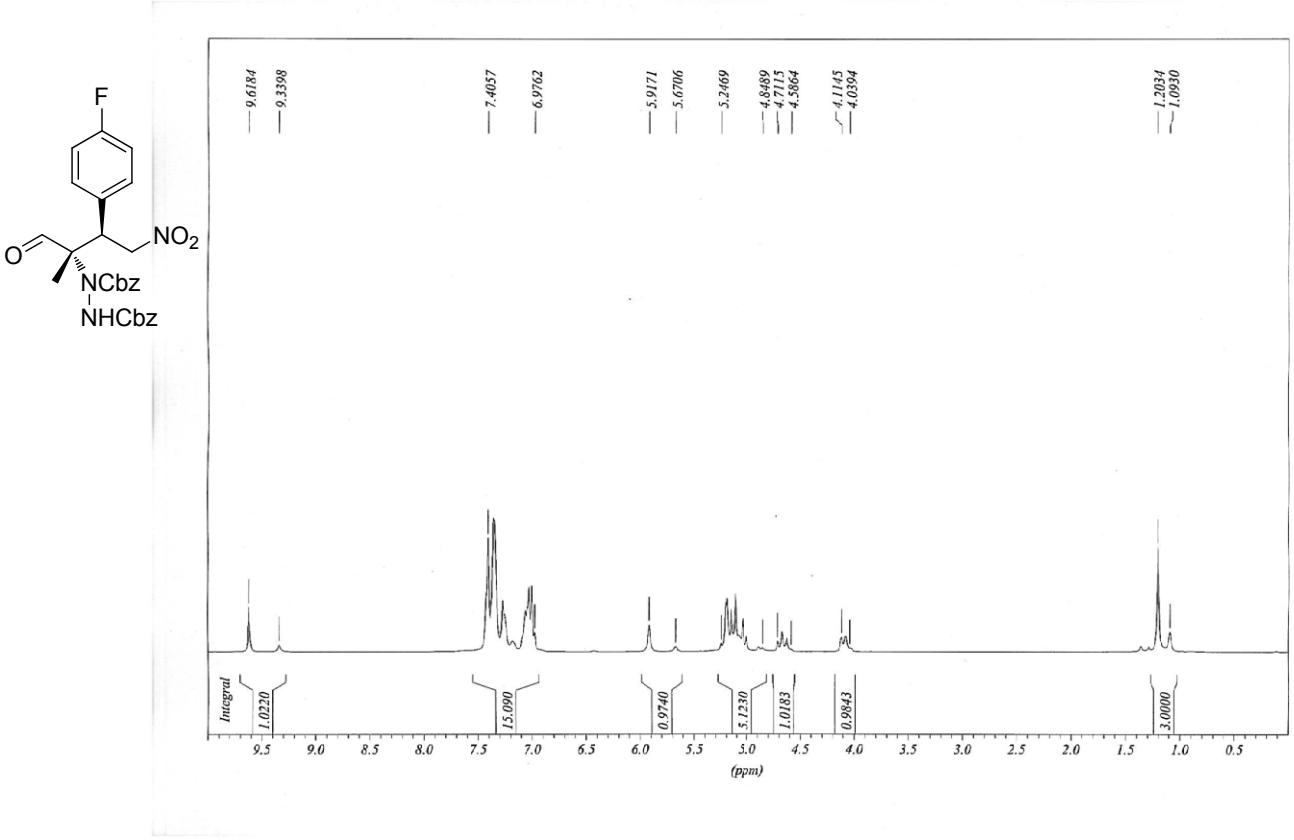


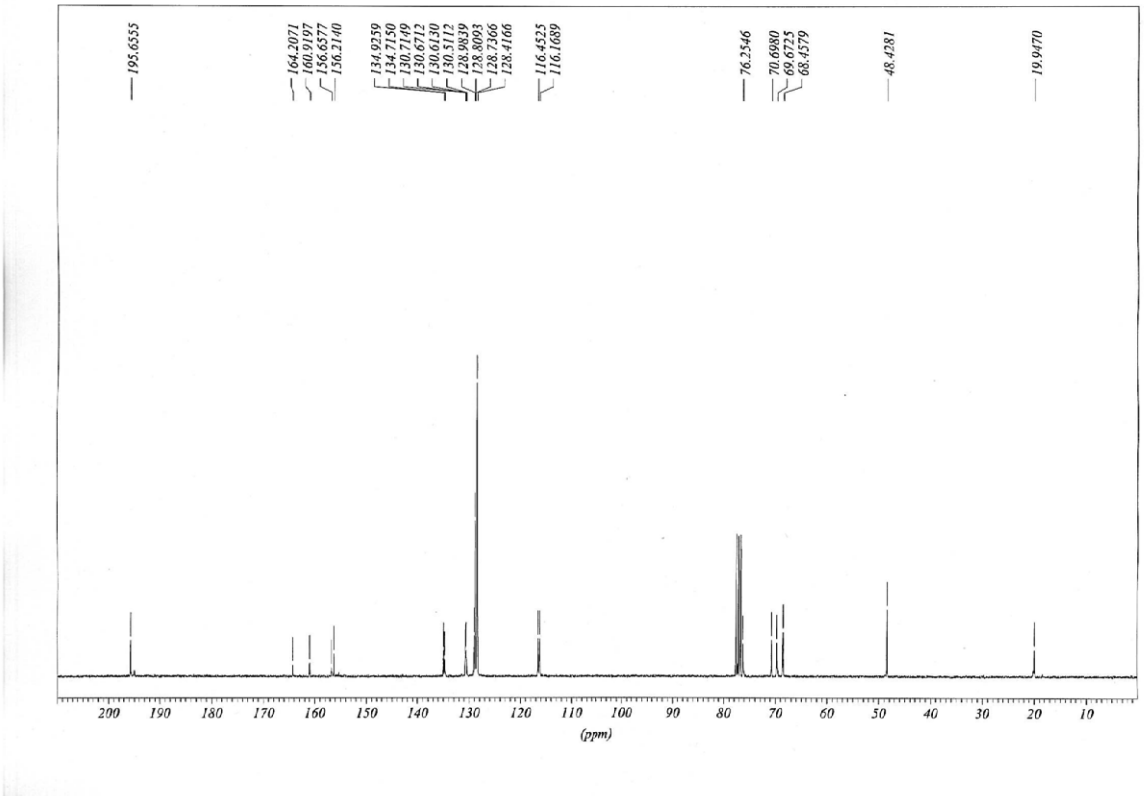


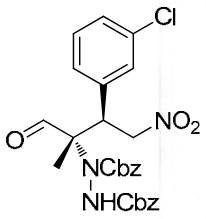


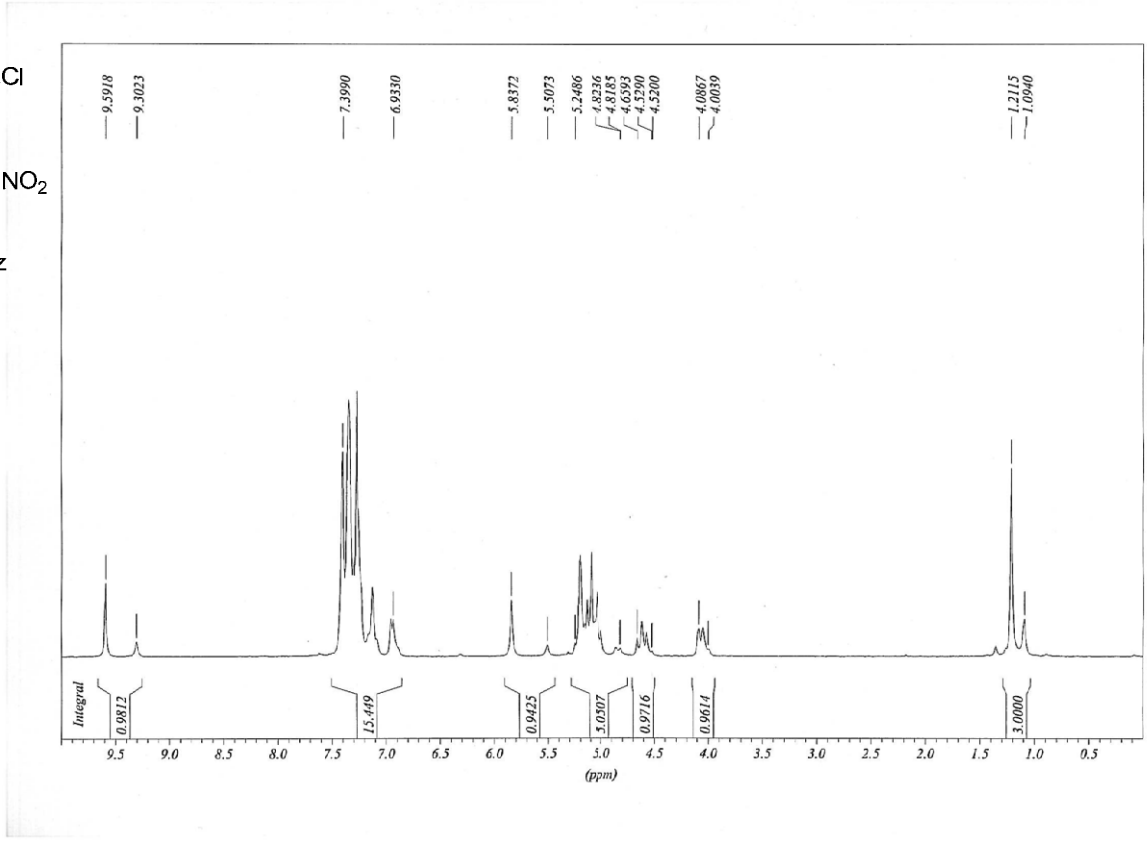


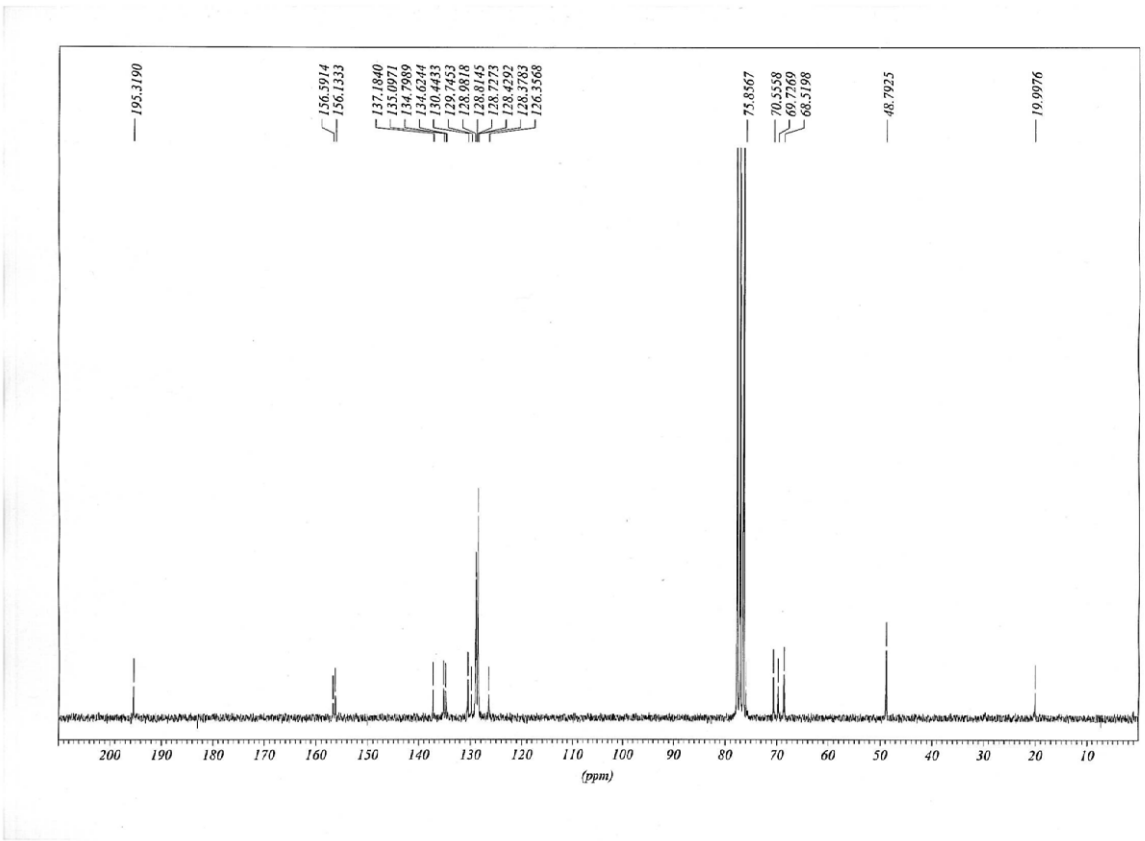


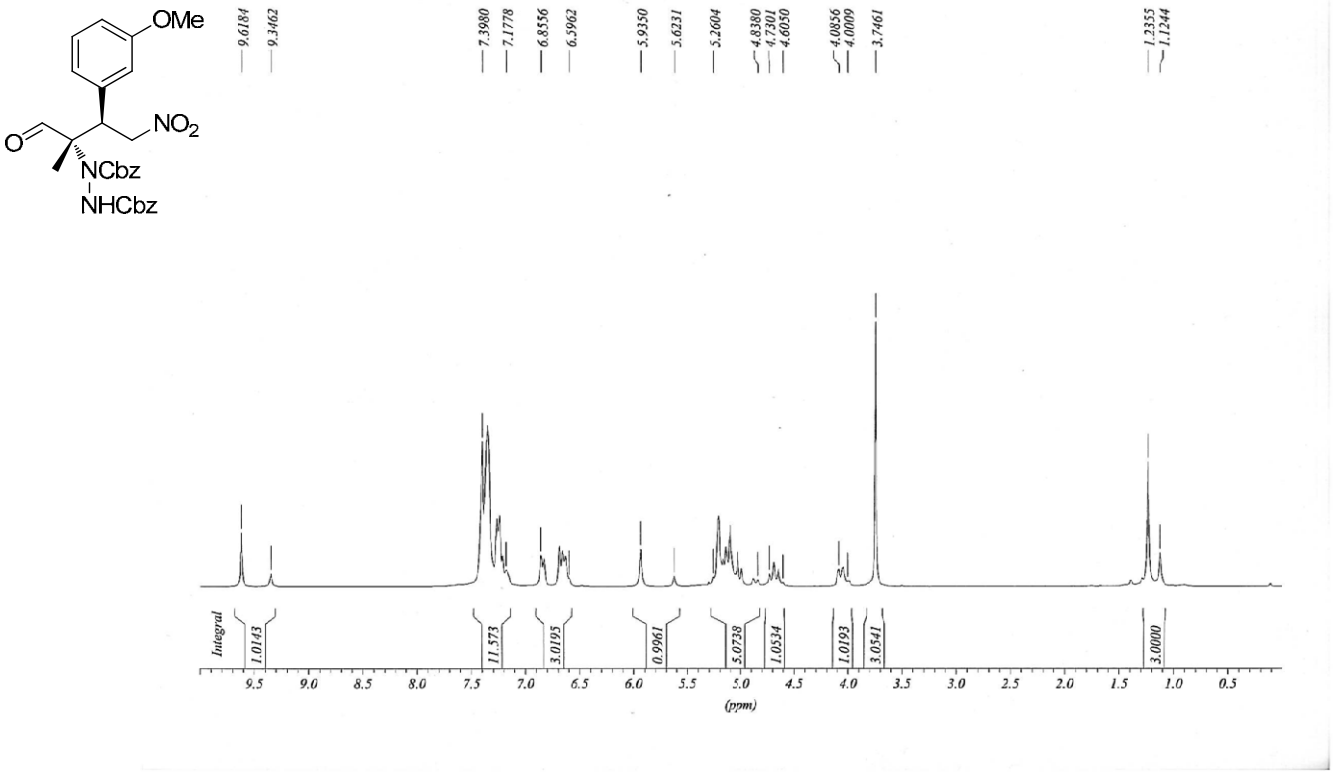


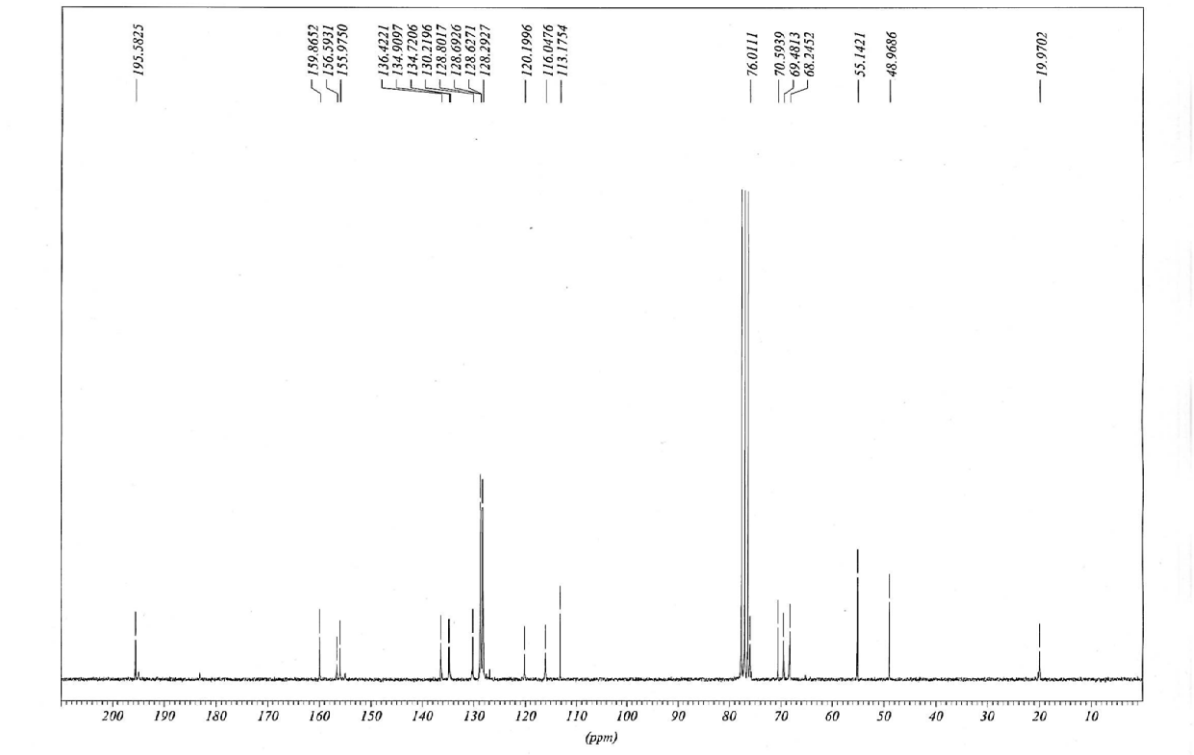


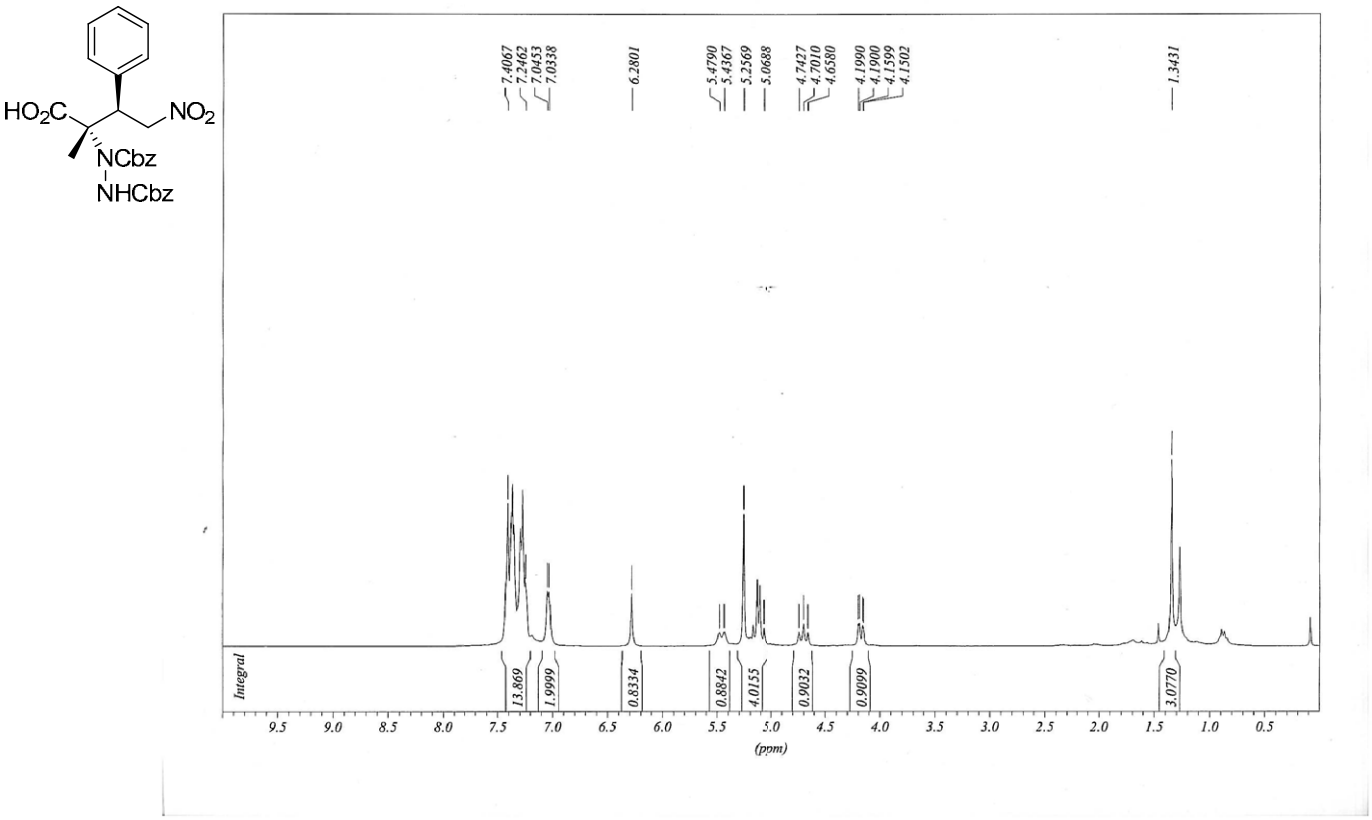


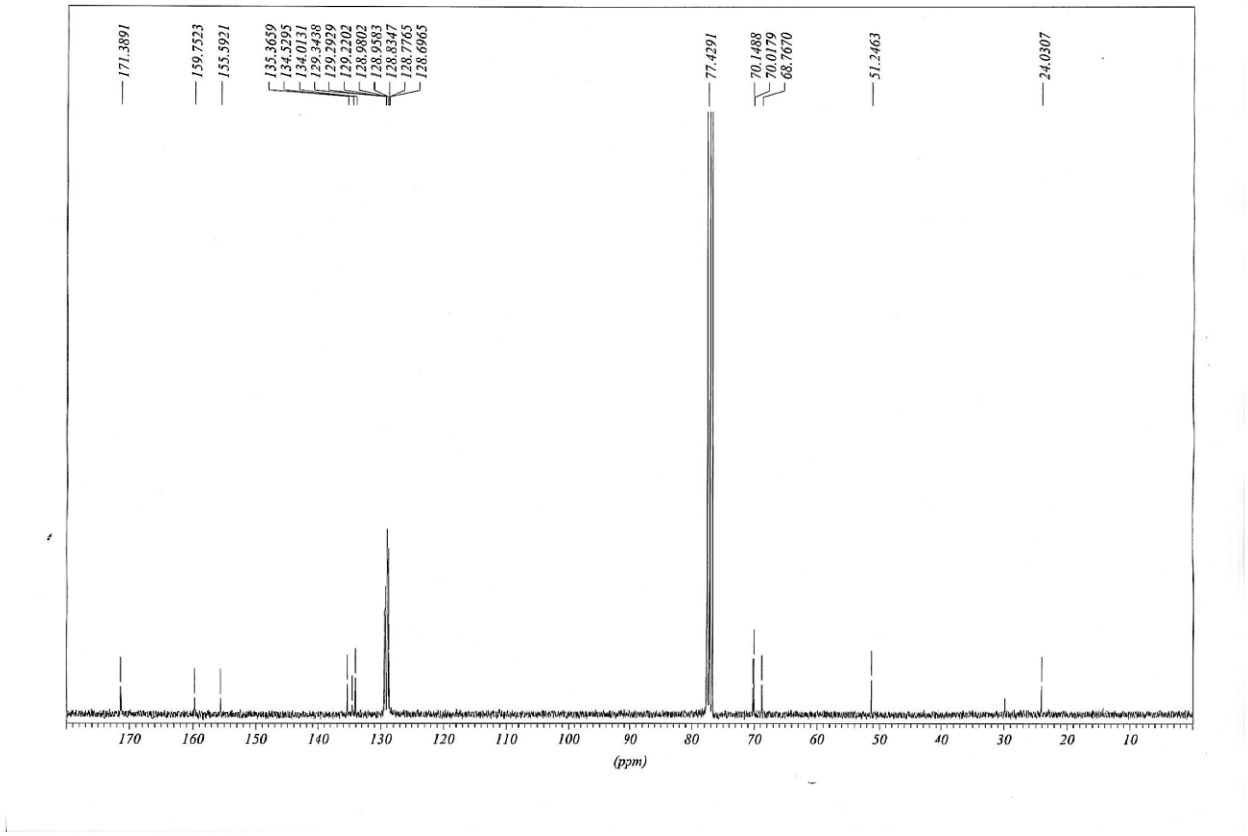


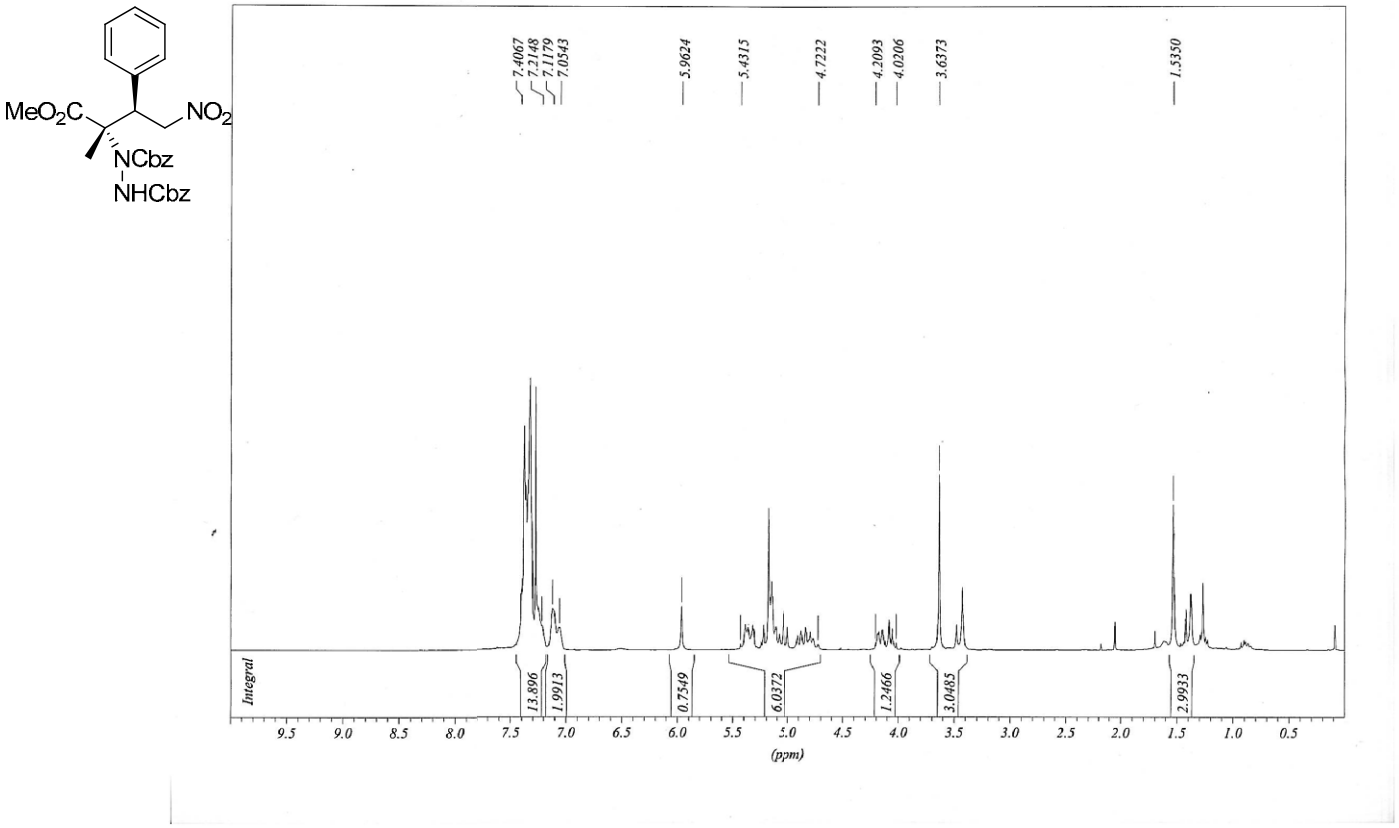


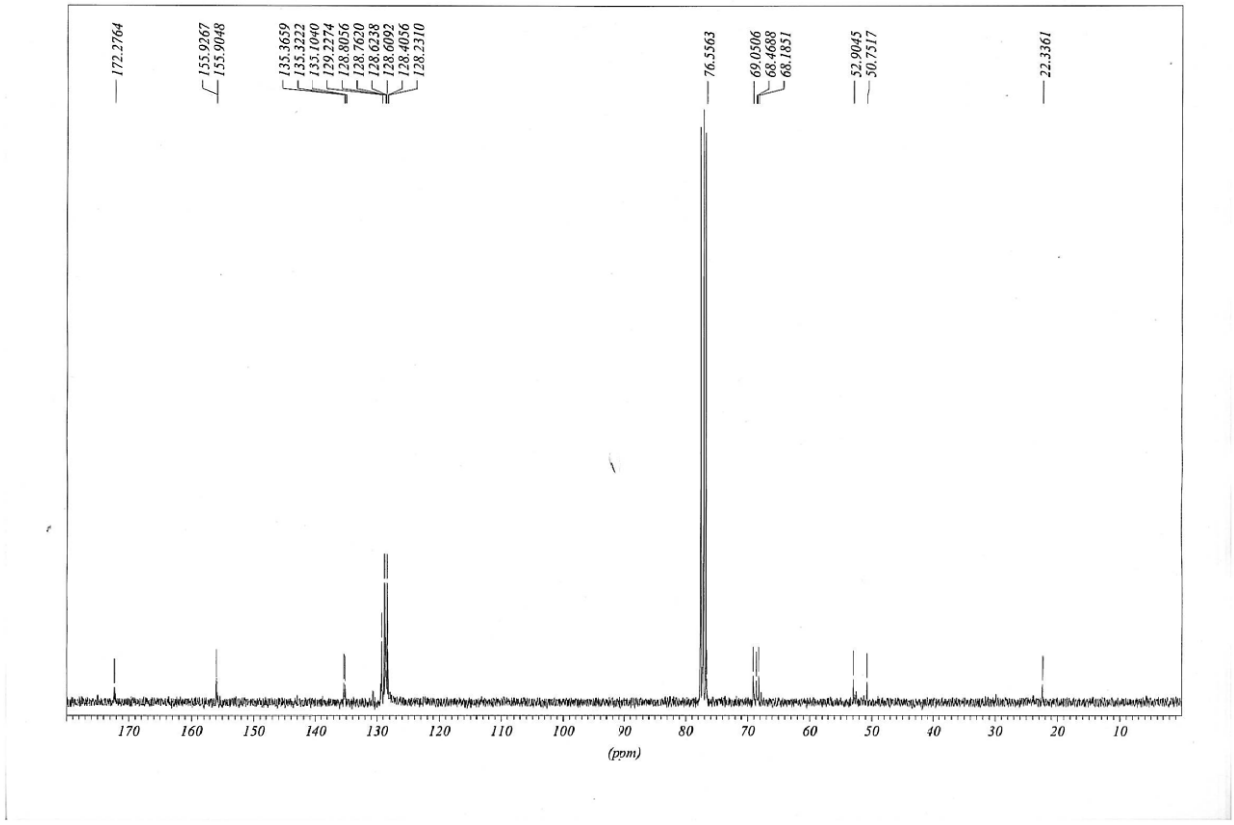












Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	13/01/2010 14:43:40
Description	
HPLC System Name	HPLC-JASCO
Injection Date	13/01/2010 13:03:24
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 19 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 19-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ch	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	46,502	2738334	12431	50,697	69,775	N/A	1045	3,758	1,214	
2	Unknown	2	82,227	2666527	5385	49,338	30,225	N/A	623	N/A	1,201	

Chromatogram

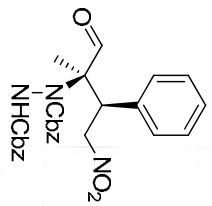
Chromatogram Information

User Name	ilv
Date Modified	13/01/2010 16:33:36
Description	
HPLC System Name	HPLC-JASCO
Injection Date	13/01/2010 14:53:21
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 19 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

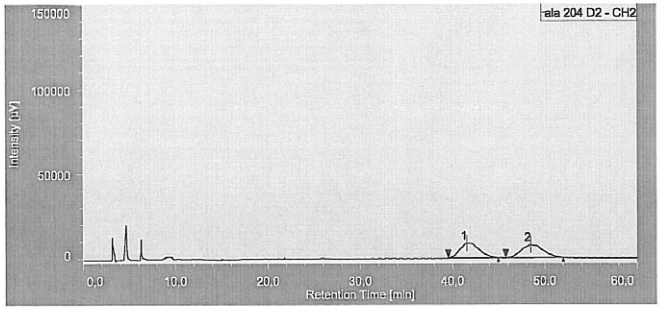
Channel & Peak Information Table

Chromatogram Name	ala 19-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ch	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	46,353	2518351	13379	98,135	99,020	N/A	1455	4,511	1,456	
2	Unknown	2	85,015	47859	133	1,865	0,980	N/A	762	N/A	1,093	



Chromatogram



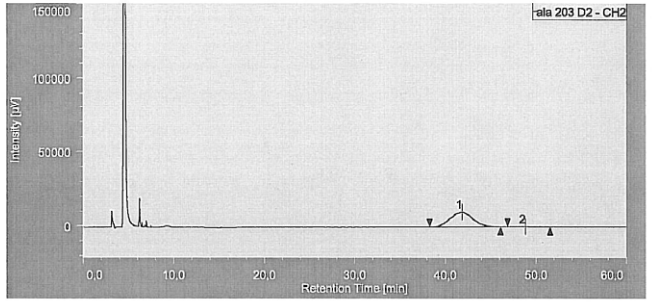
Chromatogram Information	
User Name	ilv
Date Modified	21/10/2010 14:12:16
Description	
HPLC System Name	HPLC-JASCO
Injection Date	21/10/2010 12:42:50
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 204 D2 Rac OD 95-5 H-iPrOH 1ml
Control Method	H-iPrOH 95-5 1 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 204 D2-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	41,560	1267954	8639	50,388	53,231	N/A	1689	1,612	1,315	
2	Unknown	2	48,457	1248420	7590	49,612	46,769	N/A	1827	N/A	1,226	

Chromatogram

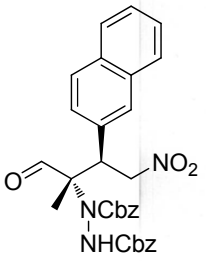


Chromatogram Information	
User Name	ilv
Date Modified	22/10/2010 14:31:22
Description	
HPLC System Name	HPLC-JASCO
Injection Date	22/10/2010 13:15:37
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 203 D2 OD 95-5 H-iPrOH 1ml
Control Method	H-iPrOH 95-5 1 mL
Peak ID Table	
Calibration Method	
Additional Information	

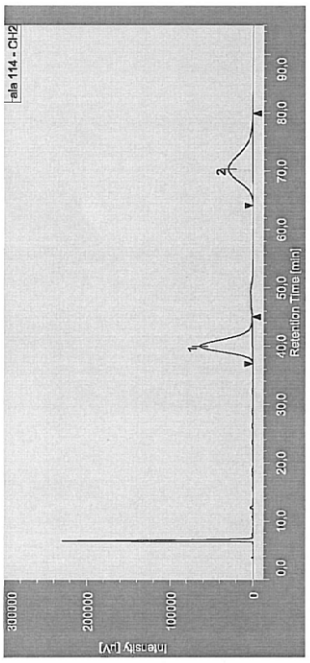
Channel & Peak Information Table

Chromatogram Name	ala 203 D2-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	41,867	1740053	10117	98,007	97,740	N/A	1295	1,234	1,048	
2	Unknown	2	48,835	35379	234	1,993	2,260	N/A	857	N/A	1,189	



Chromatogram



Chromatogram Information

User Name	ilv
Date Modified	08/06/2010 17:45:47
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/06/2010 16:10:27
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 114 Rac AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 114-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ch	Rt [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	39,948	976495	63553	49,314	68,308	N/A	1564	4,675	1,190	
2	Unknown	2	70,303	1003658	29484	50,686	31,693	N/A	988	N/A	1,319	

1 / 1

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	08/06/2010 14:14:00
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/06/2010 12:36:34
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 120 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 120-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	40,558	1136364	67738	97,863	98,665	N/A	1403	5,195	1,185	
2	Unknown	2	71,172	24935	917	2,137	1,335	N/A	1444	N/A	1,279	

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	08/12/2009 13:24:57
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/12/2009 12:03:38
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	nlc20 OD 95-5 H-iPrOH 1ml
Control Method	H-iPrOH 95-5 1 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ALA 20-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	41,622	2640512	16733	97,962	98,003	N/A	776	1,988	2,151	
2	Unknown	2	54,677	54377	219	2,038	1,997	N/A	925	N/A	1,717	

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	08/12/2009 12:01:28
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/12/2009 10:40:25
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	xm300 dia 1 OD 95-5 H-iPrOH 1ml
Control Method	H-iPrOH 95-5 1 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	xm 301 DIA 1-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	43,567	2600706	9833	50,418	52,765	N/A	715	1,709	2,064	
2	Unknown	2	55,178	2554491	8803	49,513	47,235	N/A	966	N/A	1,678	

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	08/01/2010 11:26:02
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/01/2010 08:57:34
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 26 AS 90-10 H-PrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 26-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Area%	Height [µV]	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	74,747	9966183	98,379	29024	98,875	N/A	113	3,360	1,488	
2	Unknown	2	117,223	164167	1,621	330	1,125	N/A	97	N/A	1,117	

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	08/01/2010 14:05:35
Description	
HPLC System Name	HPLC-JASCO
Injection Date	08/01/2010 11:50:14
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	xm304 ala 1 AS 90-10 H-PrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	xm 304 DIA 1-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Area%	Height [µV]	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	75,575	4560704	1,376	50.849	66,585	N/A	1199	3,132	1,379	
2	Unknown	2	115,648	4350888	671,8	49,113	33,415	N/A	74,7	N/A	1,359	

Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	18/01/2010 17:49:12
Description	
HPLC System Name	HPLC-JASCO
Injection Date	18/01/2010 14:45:21
Volume	70,00 [µl]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 23 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 23-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [uV*sec]	Height [uV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	43,105	2080607	[688]	98,801	99,108	N/A	1045	1,944	1,363	
2	Unknown	2	58,295	25257	9]	1,199	0,892	N/A	505	N/A	1,166	

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Chromatogram

Chromatogram Information

User Name	ilv
Date Modified	18/01/2010 17:49:11
Description	
HPLC System Name	HPLC-JASCO
Injection Date	18/01/2010 12:28:33
Volume	70,00 [µl]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	xm302 dia 1 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	xm302 DIA 1-CH1
Sample Name	
Channel Name	CH1
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [uV*sec]	Height [uV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	48,260	1743866	53073	50,234	65,267	N/A	866	1,786	1,451	
2	Unknown	1	57,452	1633718	28248	49,766	34,733	N/A	457	N/A	1,337	

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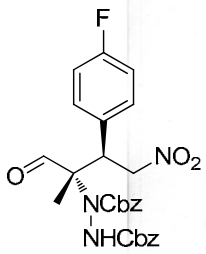

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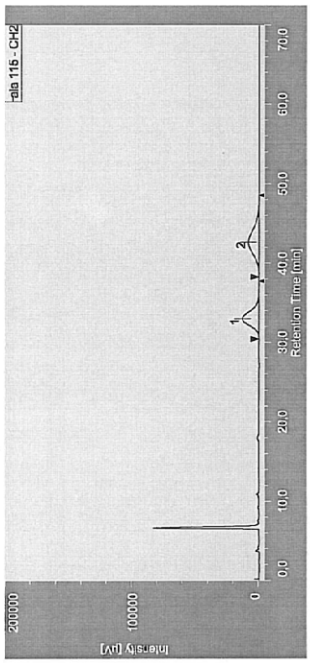


Chromatogram Information

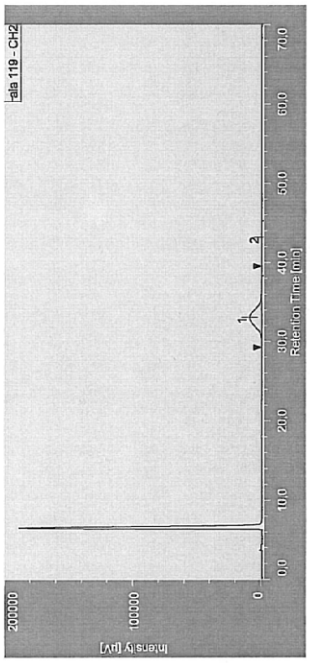
User Name	ilv
Date Modified	09/06/2010 14:53:40
Description	
HPLC System Name	HPLC-JASCO
Injection Date	09/06/2010 13:40:16
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 115 Rac AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 115-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ctrl	tR [min]	Area [uV*sec]	Height [uV]	Area%	Height%	Quantity	N*1'	Resolution	Symmetry Factor	Warning
1	Unknown	2	32,965	1705147	13223	48,014	61,249	N/A	152	2,691	1,165	
2	Unknown	2	42,618	1846248	8364	51,986	38,751	N/A	84	N/A	1,119	

Chromatogram



Chromatogram Information

User Name	ilv
Date Modified	09/06/2010 16:17:36
Description	
HPLC System Name	HPLC-JASCO
Injection Date	09/06/2010 15:03:44
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 119 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 119-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [uV*sec]	Height [uV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	33,023	1447976	9612	98,497	98,885	N/A	1081	2,801	1,037	
2	Unknown	2	43,152	22097	108	1,503	1,115	N/A	792	N/A	0,785	

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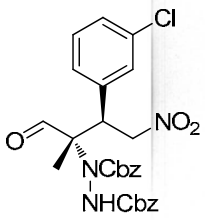

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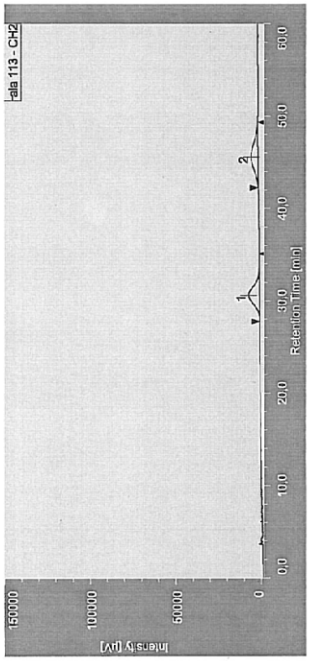

Chromatogram Information

User Name	ilv
Date Modified	10/06/2010 12:43:52
Description	
HPLC System Name	HPLC-JASCO
Injection Date	10/06/2010 11:33:41
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 113 Rac AS 90-10 H-iPrOH 0.8ml
Control Method	H-IPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 113-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	30,594	851210	6326	50,591	60,943	N/A	1194	3,268	1,087	
2	Unknown	2	45,535	831312	4054	49,409	39,057	N/A	1043	N/A	1,067	

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Chromatogram

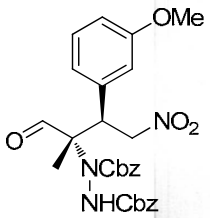
Chromatogram Information

User Name	ilv
Date Modified	09/06/2010 13:25:19
Description	
HPLC System Name	HPLC-JASCO
Injection Date	09/06/2010 12:25:03
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 121 AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ALA 121-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ctrl	tR [min]	Area [µV*sec]	Height [uV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	?	30,618	3680539	28116	98,910	99,298	N/A	1259	3,447	1,174	
2	Unknown	?	46,003	40565	201	1,090	0,710	N/A	1118	N/A	1,303	



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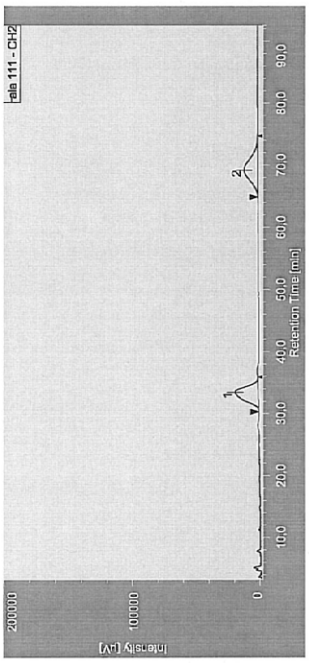

Chromatogram Information

User Name	ilv
Date Modified	01/07/2010 12:33:56
Description	
HPLC System Name	HPLC-JASCO
Injection Date	01/07/2010 10:48:02
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 111 Rac AS 90-10 H-iPrOH 0.8ml
Control Method	H-iPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 111-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	Ch	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	N/1000	Resolution	Symmetry Factor	Warning
1	Unknown	2	33,418	2667117	18169	50,186	62,943	N/A	1025	6,596	0,858	
2	Unknown	2	69,085	2647363	10697	49,814	37,057	N/A	1719	N/A	1,103	

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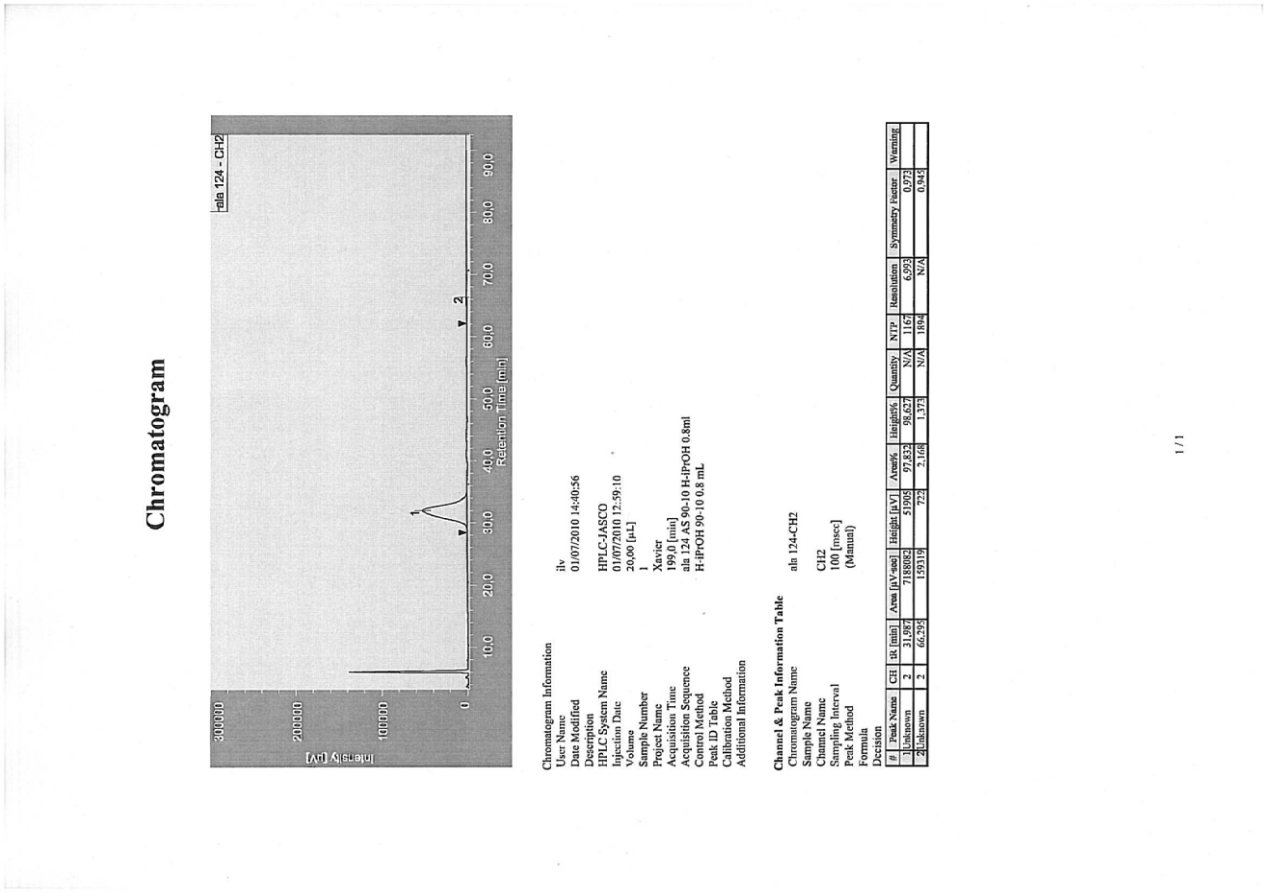

Chromatogram Information

User Name	ilv
Date Modified	01/07/2010 14:40:56
Description	
HPLC System Name	HPLC-JASCO
Injection Date	01/07/2010 12:59:10
Volume	20,00 [µL]
Sample Number	1
Project Name	Xavier
Acquisition Time	199,0 [min]
Acquisition Sequence	ala 124 AS 90-10 Hi-IPrOH 0.8ml
Control Method	Hi-IPrOH 90-10 0.8 mL
Peak ID Table	
Calibration Method	
Additional Information	

Channel & Peak Information Table

Chromatogram Name	ala 124-CH2
Sample Name	
Channel Name	CH2
Sampling Interval	100 [msec]
Peak Method	(Manual)
Formula	
Decision	

#	Peak Name	CH	tR [min]	Area [µV*sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	2	31,987	7188082	51905	97,852	98,627	N/A	1167	6,993	0,973	
2	Unknown	2	66,293	159319	722	2,168	1,373	N/A	1804	N/A	0,943	

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ORTEP diagram of **4**