Supporting Information

New Chiral Derivatizing Agents: Convenient Determination of Absolute Configurations of Free Amino Acids by ^{1}H-NMR

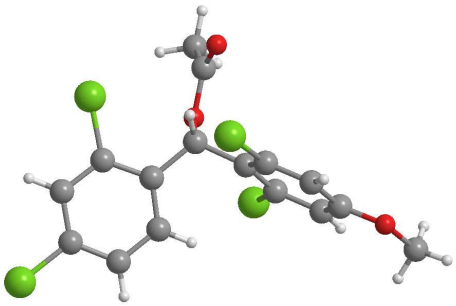
Michio Kurosu, and Kai Li

Department of Microbiology, Immunology, and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 1682 Campus Delivery, Fort Collins, CO 80523-1682

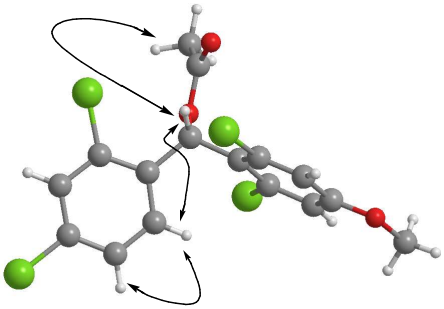
michio.kurosu@ColoState.edu

General Procedures and Methods: All glassware was oven dried, assembled hot and cooled under a stream of nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques. Commercially available reagents were used as received without further purification. Thin layer chromatography was performed using 0.25 mm silica gel 60 plates visualizing at 254 nm, or developed with anisaldehyde or ninhydrin solutions by heating with a hot-air gun. Specified products were purified by flash column chromatography using silica gel 60. IR absorptions were run on NaCl plates. ^{1}H NMR spectral data were recorded on 300 or 400 MHz NMR spectrometer. The residual solvent signal was utilized as an internal reference $CDCl_3$ (7.26). ^{13}C NMR spectral data were recorded at 75, 100 MHz instruments. The residual solvent signal was utilized as an internal reference $CDCl_3$ (77.23). For all NMR spectra, δ values are given in ppm and *J* values in Hz.

X-ray structure and NOESY correlations of the acetate of 1



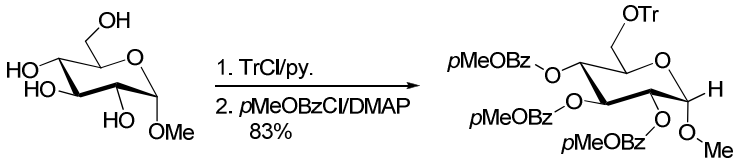
Chem3D representation of the X-ray crystal structure of theacetate of **1**



The NOE correlations observed for theacetate of **1** in the NOESY experiment.

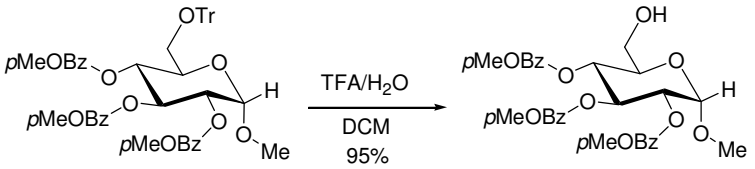
Experimental Procedures

Methyl 2,3,4-tri-*O*-4-methoxybenzoyl-6-*O*-trityl-α-D-glucoside



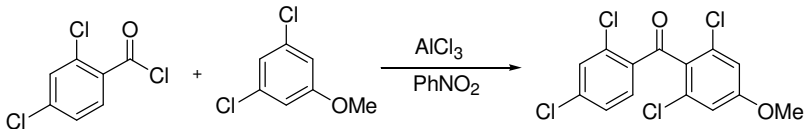
To a stirred solution of methyl α-D-glucoside (7.8 g, 40 mmol) in dry pyridine (64 mL) was added trityl chloride (12.2 g, 44 mmol) and DMAP (488 mg, 4 mmol). The reaction mixture was stirred at 60 °C for 10 h. The reaction mixture was cooled to 0 °C, and 4-methoxylbenzoyl chloride (27.4g, 160 mmol) was added. After 12 h at rt, all volatiles were removed by evap. *in vacuo*. The partition between EtOAc and water was conducted. The EtOAc phase was washed with 1 N HCl and brine. The combined organic phase was dried over Na_2SO_4, and evap. *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 3/1) gave the desired product (27.8 g, 83%). $[\alpha]^{20}_D$ = +19.7 (*c* 1.5 in $CHCl_3$); IR (film) 1725, 1606, 1257, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (g, *J* = 9.2 Hz, 2H), 7.81 (d, *J* = 9.2 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.42-7.40 (m, 6H), 7.20-7.08 (m, 9H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.75 (g, *J* =9.2 Hz, 2H), 6.00 (t, *J* = 9.6 Hz, 1H), 5.45 (t, *J* = 10.0Hz, 1H), 5.26-5.20 (m, 2H), 4.14 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.52 (s, 3H), 3.27 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 165.9, 165.7, 164.9, 163.8, 163.6, 163.5, 143.9, 132.2, 132.0, 128.8, 127.9, 127.1, 122.0, 121.9, 121.8, 113.8, 113.6, 113.6, 97.186.9, 72.3, 70.6, 69.5, 62.9, 55.6, 55.5; HRMS (ESI) Calcd. for $C_{50}H_{46}NaO_{12}$ $(M+Na)^+$: 861.2887; found: 861.2883.

Methyl 2,3,4-tri-*O*-4-methoxybenzoyl glucoside



To a stirred solution of methyl 2,3,4-tri-*O*-4-methoxybenzoyl-6-*O*-trityl-α-D-glucoside (8.5 g, 10 mmol) in CH_2Cl_2 (100 mL) was added trifluoroacetic acid (80% in water, 10 mL) at rt. After 1 h at rt, all volatiles were removed by evap. *in vacuo*. The partition between $CHCl_3$ and water was conducted. The $CHCl_3$ phase washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, and evap. i*n vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 5/1) gave the desired product (5.4 g, 95%). $[\alpha]^{20}_D$ = +23.8 (*c* 1.7 in $CHCl_3$); IR (film) 3519, 1722, 1606, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 4H), 7.84 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.16 (m, 1H), 5.40 (t, *J* = 10.0Hz, 1H), 5.24 (s, 1H), 5.22 (m, 1H), 3.99 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (m, 1H), 3.76 (s, 3H), 3.74-3.70 (m, 1H), 3.45 (s, 3H), 2.34 (broad, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.8, 165.7, 164.1, 163.8, 163.6, 132.4, 132.2, 131.9, 121.8, 121.6, 121.0, 114.0, 113.9, 113.7, 97.4, 72.0, 70.0, 69.9, 69.6, 61.2, 55.8, 55.65, 55.59, 55.52; HRMS (ESI) Calcd. for $C_{31}H_{32}NaO_{12}$ $(M+Na)^+$: 619.1791; found: 619.1794.

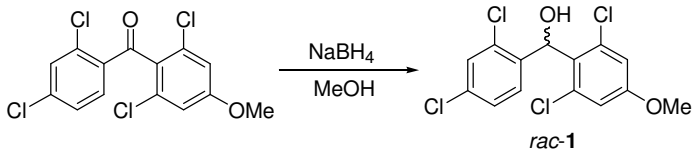
(2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanone



Anhydrous $AlCl_3$ (4.5 g, 33.9 mmol) was placed in a round bottom flask and $PhNO_2$ (150 mL) was added. At –78 °C, 2,4-dichlorobenzoyl chloride (4.7 mL, 33.9 mmol) and 3,5-dichloroanisole (5.0 g, 28.2 mmol) were added. The reaction mixture was kept at the same temperature for 1 h and warmed to rt over 24 h. The

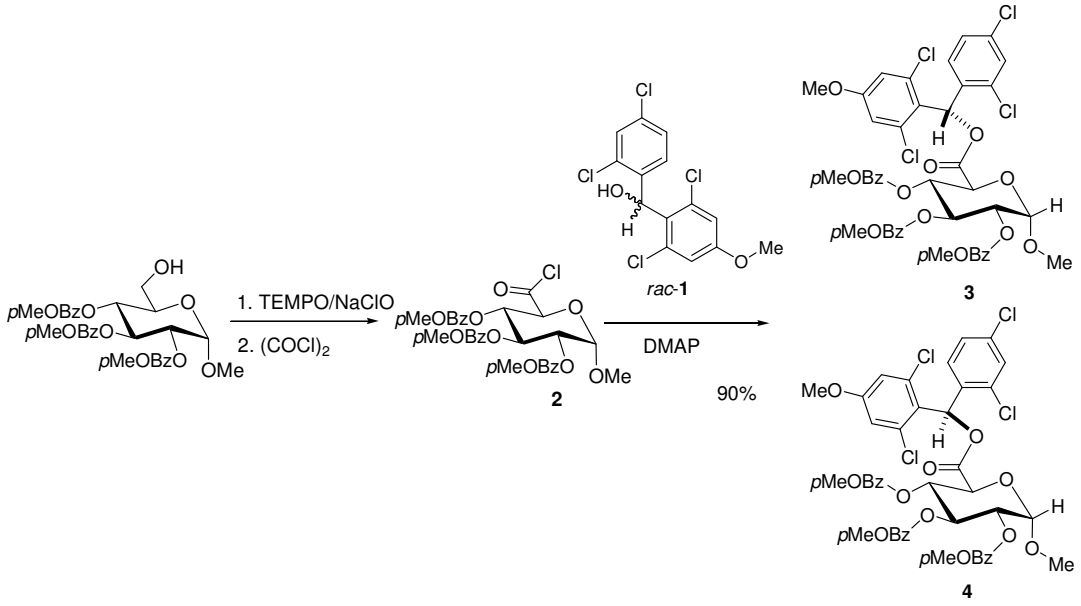
reaction mixture was diluted with Et_2O (50 mL) at 0 °C and quenched with 1 N NaOH (~30 mL). The reaction mixture was stirred vigorously until a white precipitate had been formed. The precipitates were filtered and washed with CH_2Cl_2 (50, 30, and 20 mL). The combined organic solvents were dried (Na_2SO_4), filtered, and concentrated under vacuum at ~10 mmHg. Purification by silica gel chromatography (hexanes/$CHCl_3$ = 4/1,) to provide (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanone (8.3 g, 85 %). IR (film): 1619 1584, 1553, 1400, 1309 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.37 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.95 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 163.8, 142.0, 138.3, 137.7, 136.4, 130.3, 129.9, 127.8, 122.9, 118.4, 117.9, 114.6, 56.1;; HRMS (ESI) Calcd. for $C_{14}H_8Cl_4NaO_2$ $(M + Na)^+$: 370.9176, found: 370.9177.

(2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol (*rac*-1)[1]



(2,6-Dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanone (1.0 g, 2.8 mmol) was dissolved in MeOH (15 mL) and cooled to 0 °C. $NaBH_4$ (318 mg, 8.4 mmol) was added. The reaction mixture was quenched by aq. NH_4Cl (15 mL) and extracted with EtOAc (100, 30, and 20 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 5:1) gave *rac*-**1** (980 mg, 97%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 3.0 Hz, 1H), 7.31 (dd, *J* = 8.2, 3.0 Hz, 1H), 6.91 (s, 2H), 6.61 (d, *J* = 2.1 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 137.8, 136.3, 133.9, 133.0, 130.5, 129.6, 129.6, 128.0, 126.6, 115.4, 115.4, 70.2, 55.9; IR (film): 3482, 1438, 1410, 1325 cm^{-1}; HRMS (ESI) Calcd. for $C_{14}H_{10}Cl_4NaO_2$ $(M + Na)^+$: 372.9333, found: 372.9332.

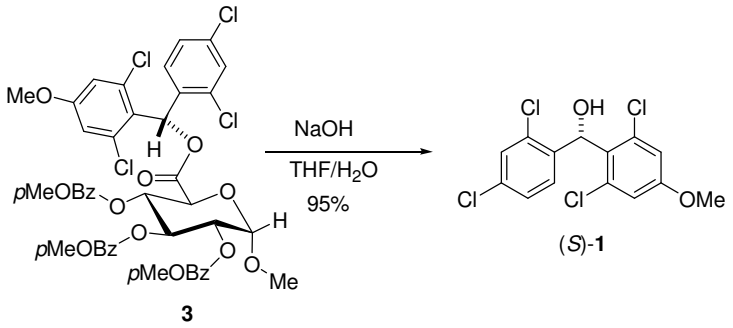
Resolution of *rac*-1



To a stirred suspension of methyl 2,3,4-tri-*O*-4-methoxybenzoyl-α-D-glucoside (5.9 g, 10 mmol), KBr (170 mg) and NBu_4Cl (210 mg) in the mixture of CH_2Cl_2 (50 mL) and sat. aq. $NaHCO_3$ (30 mL), was added the mixture of NaClO (30% aqueous, 30mL), $NaHCO_3$ (sat. aqueous, 15 mL), and brine (30 mL) during 30 min. at 0 °C. After 2 h at 0 °C, the reaction mixture was acidified with HCl (2 N) to pH 4.0. The water phase was extracted with $CHCl_3$ (50 mL x 2). The combined $CHCl_3$ phase was dried over Na_2SO_4, and evap. *in vacuo*. Purification by passing through short silica gel pad (hexanes/EtOAc = 5/1 to 0/1) gave the acid as white solid (5.5 g).

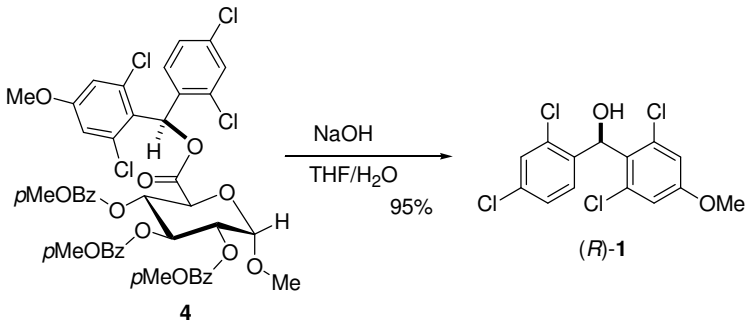
To a stirred solution of acid (5.5 g, 8.9 mmol) in dry CH_2Cl_2 (40 mL) was added oxalyl dichloride (2.20 g, 18 mmol) and dry DMF (64 mg, 0.9 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and all volatile components were removed by vacuum evaporation to give the crude acid chloride.
To a stirred solution of the crude acid chloride in dry CH_2Cl_2 (40 mL) was added alcohol *rac*-**1** (2.5 g, 7.1 mmol) and DMAP (2.2 g, 18 mmol). The reaction mixture was stirred at 0 °C for 30 min and quenched with HCl (1 N, 70 mL). The water phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, and evap. *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 3/2) gave the two diastereomers (3.1 g and 2.9 g, allover yield upon racemic alcohol **1** is 90%). Data for **3**: $[\alpha]^{20}_D$ = +16 (*c* 1.8 in $CHCl_3$); IR (film) 1728, 1606, 1257, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.2 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.54 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.86-6.83 (m, 3H), 6.81 (s, 2H), 6.78-6.73 (m, 3H), 6.06 (t, *J* = 10.0 Hz, 1H), 5.72 (t, *J* = 10.0 Hz, 1H), 5.30 (d, *J* = 3.2 Hz, 1H), 5.25 (dd, *J* = 10.0, 3.6 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.7, 165.6, 164.4, 163.9, 163.7, 163.6, 160.0, 136.9, 134.7, 134.1, 132.7, 132.2, 132.0, 131.99, 130.9, 129.6, 126.4, 123.9, 121.7, 121.5, 121.4, 115.5, 113.8, 113.7, 113.5, 97.7, 72.2, 71.5, 70.0, 69.7, 68.9, 56.3, 55.9, 55.6, 55.5; HRMS (ESI) Calcd. for $C_{45}H_{38}Cl_4NaO_{14}$ $(M+Na)^+$: 965.0913; found: 965.0914.
Data for **4**: $[\alpha]^{20}_D$ = -15 (*c* 1.5 in $CHCl_3$); IR (film) 1725, 1606, 1257, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92, (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.69 (d, 9.2 Hz, 2H), 7.61 (s, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.77-6.72 (m, 4H), 6.61 (s, 2H), 6.04 (t, *J* = 10.0 Hz, 1H), 5.76 (t, *J* = 10.0 Hz, 1H), 5.33 (d, *J* = 3.6 Hz, 1H), 5.23 (dd, *J* = 10, 3.6 Hz, 1H), 4.76 (d, *J* = 10.4 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.71 (s, 3H), 3.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 165.7, 165.5, 164.3, 163.9, 163.6, 163.5, 159.8, 137.0, 134.7, 133.7, 133.3, 132.3, 132.0, 131.99, 130.5, 129.9, 126.6, 123.6, 121.7, 121.5, 121.3, 115.2, 113.9, 113.7, 113.4, 97.7, 72.0, 71.5, 70.0, 69.4, 68.8, 56.4, 55.7, 55.6, 55.55; HRMS (ESI) Calcd. for $C_{45}H_{38}Cl_4NaO_{14}$ $(M+Na)^+$: 965.0913; found: 965.0915.

(*S*)-(2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol ((*S*)-1)



To a stirred solution of NaOH (2M in THF/H_2O = 4/1, 2 mL) was added glucosyluronate **3** (94 mg, 0.1 mmol). After 12 h at rt, the reaction mixture was diluted with EtOAc and quenched with HCl (1 N) at 0 °C. The water phase was extracted with EtOAc. The combined organic phase was dried over Na_2SO_4, and evap. *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 10/1 to 5/1) gave the alcohol (*S*)-**1** (33 mg, 95%). $[\alpha]^{20}_D$ = +173 (*c* 1.0 in $CHCl_3$); IR (film) 3337, 1600, 1557, 1468, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.25 (, *J* = 8.4 Hz, 1H), 6.87 (s, 2H), 6.55 (d, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 2.77 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 137.8, 136.3, 133.9, 133.1, 130.5, 129.6, 128.0, 126.6, 115.5, 70.3, 56.0; HRMS (ESI) calcd. for $C_{14}H_{10}Cl_4NaO_2$ $(M + Na)^+$: 372.9333, found 372.9333.

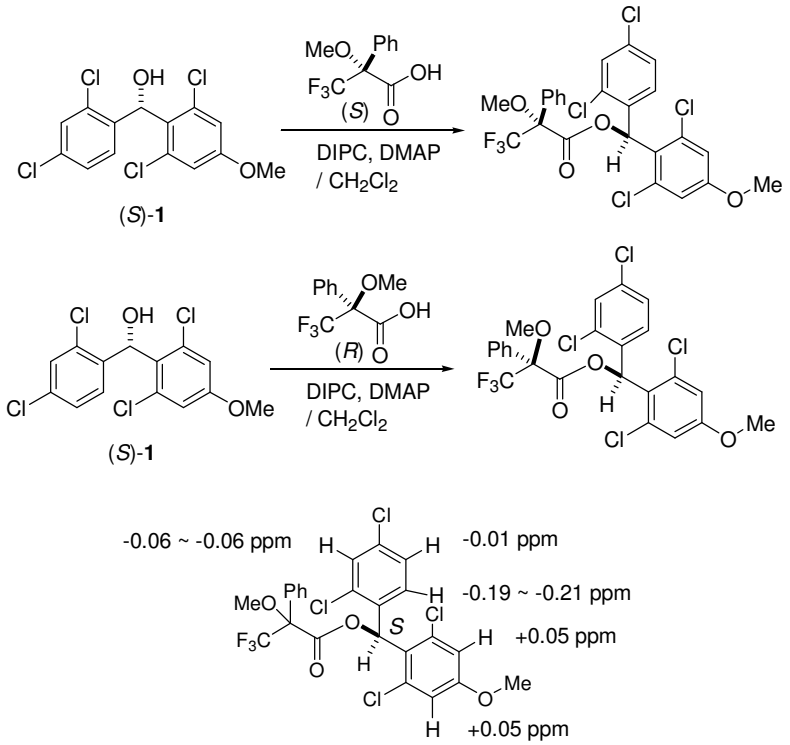
(*R*)-(2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol ((*R*)-1)



The same procedure as preparing (*S*)-**1** gave (*R*)-**1**. $[\alpha]^{20}_{D}$ = -177 (*c* 1.0 in $CHCl_3$); IR (film) 3337, 1600, 1557, 1468, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.25 (, *J* = 8.4 Hz, 1H), 6.87 (s, 2H), 6.55 (d, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 2.77 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 137.8, 136.3, 133.9, 133.1, 130.5, 129.6, 128.0, 126.6, 115.5, 70.3, 56.0; HRMS (ESI) calcd. for $C_{14}H_{10}Cl_4NaO_2$ $(M + Na)^+$: 372.9333, found 372.9332.

Determination of the absolute stereochemistry of (*S*)-1

1. via the advanced Mosher method.[2]

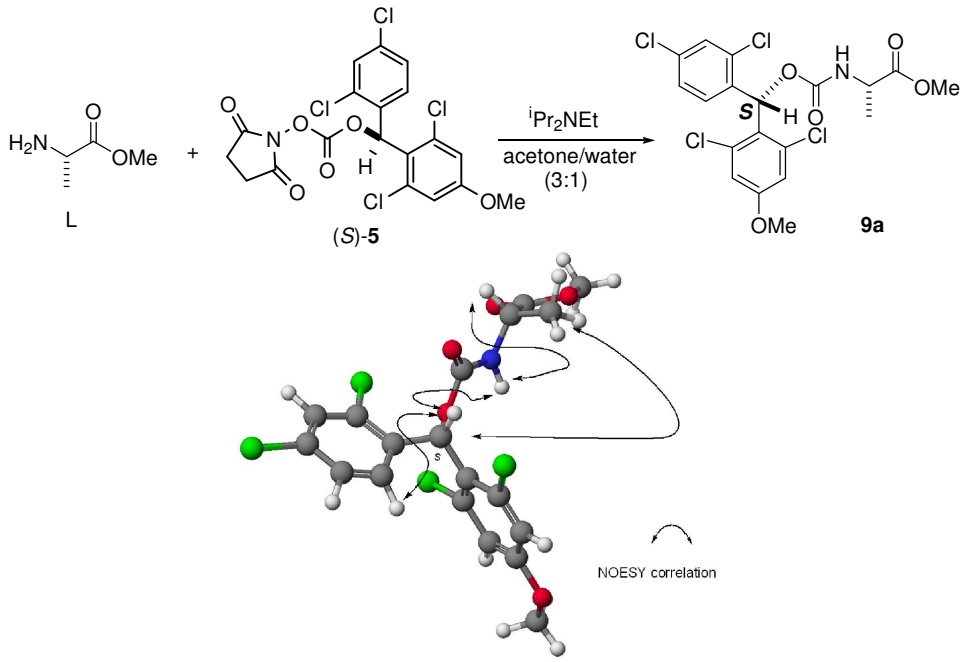


chemical shift differences between the (*R*) and (*S*)- Mosher esters (Δδ (*R*-*S*))

To a stirred solution of (*R*)- or (*S*)-Mosher acid (2.3 mg, 0.01 mmol) and chiral (2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol (2.8 mg, 0.008 mmol) in dry CH_2Cl_2 (0.3 mL) was added *N,N'*-diisopropylcarbodiimide (DIPC) (2 mg, 0.016 mmol) and DMAP (2.7 mg, 0.024 mmol) at rt. After 1 h at rt, the reaction mixture was diluted with CH_2Cl_2 and quenched with HCl (1 N). The water phase was extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, and evap. *in vacuo*. Purification by silica gel TLC (hexanes/EtOAc = 5/1) gave the desired (*R*)- or (*S*)-Mosher ester.

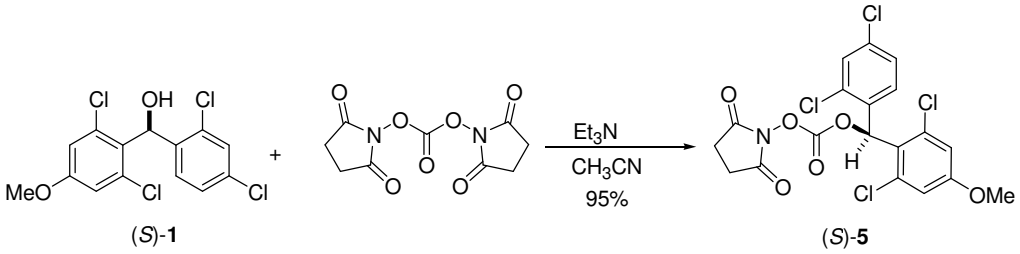
(*R*)-Mosher acid ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.43-7.34 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.32 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.88 (s, 2H), 3.81 (s, 3H), 3.50 (s, 3H).
(*S*)-Mosher acid ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.71-7.40 (m, 5H), 7.34-7.30 (m, 2H), 7.20 (dd, *J* = 8.8, 2.4Hz, 1H), 6.83 (s, 2H), 3.81 (s, 3H), 3.55 (s, 3H).

2. via a NOESY experiment of the L-Ala derivative.



To a stirred solution of H-L-Ala-OMe (1.3 mg, 0.01 mmol) in acetone/H_2O (3/1, 0.3 mL) was added (*S*)-(2,6-dichloro-4-methoxyphenyl)-(2,4-dichlorophenyl)methyl-*N*-succinimidyl carbonate ((*S*)-**5**) (10 mg, 0.02 mmol) and $^iPr_2NEt$ (5 mg, 0.04 mmol) at rt. After 4 h at rt, the reaction mixture was evaporated *in vacuo*. The partition between EtOAc (1 mL) and HCl (aq. 1 N, 1mL) was conducted. The water phase was extracted with EtOAc (1 mL x 2). The combined organic phase was dried over Na_2SO_4, and evap. *in vacuo*. Purification by silica gel TLC plate (hexanes/EtOAc = 5/1) gave the desired carbamate (4.6 mg, 95%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.38 (d, *J* = 1.6 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.88 (s, 2H), 5.52 (d, *J* = 7.2 Hz, 1H), 4.38 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H).

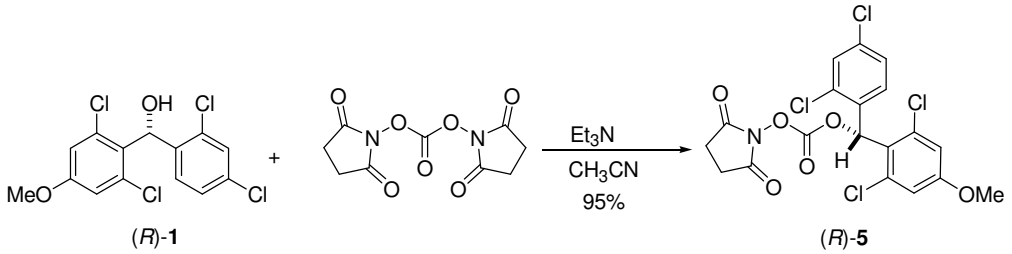
(*S*)-(2,6-dichloro-4-methoxyphenyl)-(2,4-dichlorophenyl)methyl-*N*-succinimidyl carbonate ((*S*)-5)



To a stirred solution of (*S*)-(2,6-dichloro-4-methoxyphenyl)(2,4-dichlorophenyl)methanol (100 mg, 0.28 mmol) and triethylamine (56 mg, 0.55 mmol) in dry CH_3CN (4 mL) was added *N,N′*-disuccinimidyl carbonate (108 mg, 0.42 mmol) at 0 °C. After 10 h at rt, the reaction mixture was evaporated *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 5:1) gave desired compound (*S*)-**5** (131 mg, 95%). $[\alpha]^{20}_D$ = +71 (*c* 0.6 in $CHCl_3$); IR (film): 3447, 1744, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52

(s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 8.8, 2.0 Hz, 1H), 6.91 (s, 2H), 3.82 (s, 3H), 2.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 160.7, 151.1, 137.3, 135.5, 133.9, 131.9, 130.7, 130.1, 126.9, 122.5, 115.7, 77.7, 56.0, 25.6; HRMS (FAB) calcd. for $C_{19}H_{14}Cl_4NO_6$ $(M + H)^+$: 491.9575, found 491.9577.

(*R*)-(2,6-dichloro-4-methoxyphenyl)-(2,4-dichlorophenyl)methyl-*N*-succinimidyl carbonate ((*R*)-5)



(*R*)-**5**, yield: 95%. $[\alpha]^{20}_D$ = -71 (*c* 0.8 in $CHCl_3$); IR (film): 3447, 1744, 1223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 2.0, 8.8 Hz, 1H), 6.91 (s, 2H), 3.82 (s, 3H), 2.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 160.7, 151.1, 137.3, 135.5, 133.9, 131.9, 130.7, 130.1, 126.9; HRMS (FAB) calcd. for $C_{19}H_{14}Cl_4NO_6$ $(M + H)^+$: 491.9575, found 491.9579.

General procedure for carbamate formation:

To a stirred solution of amino acid or amino acid hydrochloride salt (0.01 mmol) in acetone/H_2O (3/1, 0.3 mL) was added (*S*)-(2,6-dichloro-4-methoxyphenyl)-(2,4-dichlorophenyl)methyl-*N*-succinimidyl carbonate (*S*)-**5** (10 mg, 0.02 mmol) and ^{i}Pr$_2$NEt (5 mg, 0.04 mmol) at rt. After 4 h (for α,α-disubstituted amino acids 10 h is needed) at rt, the reaction mixture was evaporated *in vacuo*. The partition between EtOAc (1 mL) and HCl (aq. 1 N, 1mL) was conducted. The water phase was extracted with EtOAc (1 mL x 2). The combined organic phase was dried over Na_2SO_4, and evap. *in vacuo*. If necessary the crude materials were purified by preparative TLC plate ($CHCl_3$/MeOH/HOAc = 100/10/1) to give the desired carbamate.

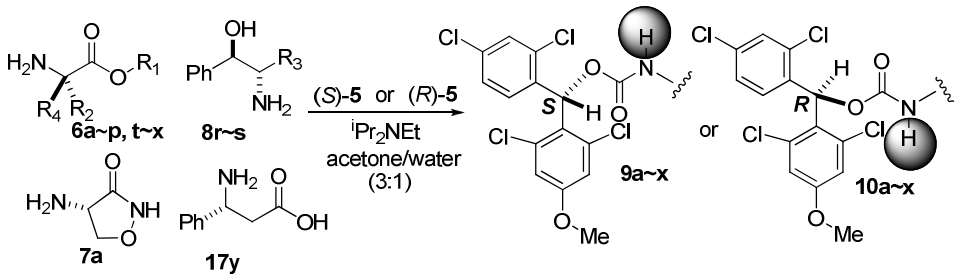


Table 1. The chemical shift of the -O(CO)N<u>H</u>- proton.

entry	substrate	δ (*S*), δ (*R*)[a]	□Δδ (*S*-*R*)
1	**6a**: R_1 = CH_3, R_2 = CH_3, R_4 = H	5.52, 5.41	+0.11
2	**6b**: R_1 = ^{t}Bu, R_2 = CH_2Ph, R_4 = H	5.45, 5.38	+0.07
3	**6c**:R_1 = CH_3, R_2 = $(CH_2)_2CO_2CH_3$, R_4 = H	5.56, 5.54	+0.02
4	**6d**: L-Ala	5.63, 5.55	+0.08
5	**6e**: L-His[b]	6.10, 6.04	+0.06
6	**6f**: L-Phe	5.57, 5.47	+0.10
7	**6g**: L-Thr[b]	5.85, 5.83	+0.02
8	**6h**: L-Trp[b]	5.60, 5.50	+0.10
9	**6i**: L-Tyr[b]	5.71, 5.53	+0.18
10	**6J**: L-Lys[c]	5.51, 5.42	+0.09
11	**6k**: L-Val	5.48, 5.41	+0.07
12	**6l**: R_1 = H, R_2 = ^{t}Bu, R_4 = H	5.50, 5.45	+0.05
13	**6m**: R_1 = H, R_2 = CH_2CN, R_4 = H	5.53, 5.49	+0.04
14	**6n**: R_1 = H, R_2 = CH_2CH_3, R_4 = H	5.53, 5.42	+0.11
15	**6o**: R_1 = H, R_2 = CH_2-2-furyl, R_4 = H	5.66, 5.61	+0.05
16	**6p**: R_1 = H, R_2 = CH_2-cyclohexyl, R_4 = H	5.37, 5.28	+0.09
17	**7a**	5.99, 5.53	+0.46
18	**8r**: R_3 = Ph	5.79, 5.68	+0.11
19	**8s**: R_3 = Me	5.11, 5.03	+0.08
20	**6t**: R_1 = Bn, R_2 = Bn, R_4 = H	5.43, 5.36	+0.07
21	**6u**: R_1 = H, R_2 = CH_2-2-thienyl, R_4 = H	5.56, 5.52	+0.04
22	**6v**: R_1 = H, R_2 = $CHPh_2$	5.22, 5.16	+0.06
23	**6w** R_1 = H, R_2 = ^{i}Pr, R_4 = Me	5.53, 5.46	+0.07
24	**6x**: R_1 = H, R_2 = Ph, R_4 = Me	6.35, 6.21	+0.14
25	**17y**	5.92, 5.78	+0.14

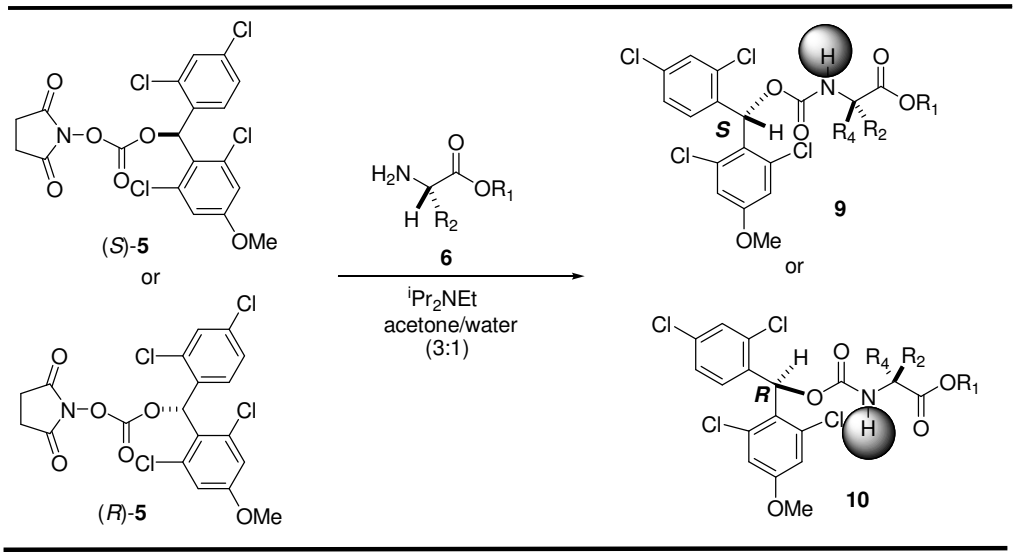
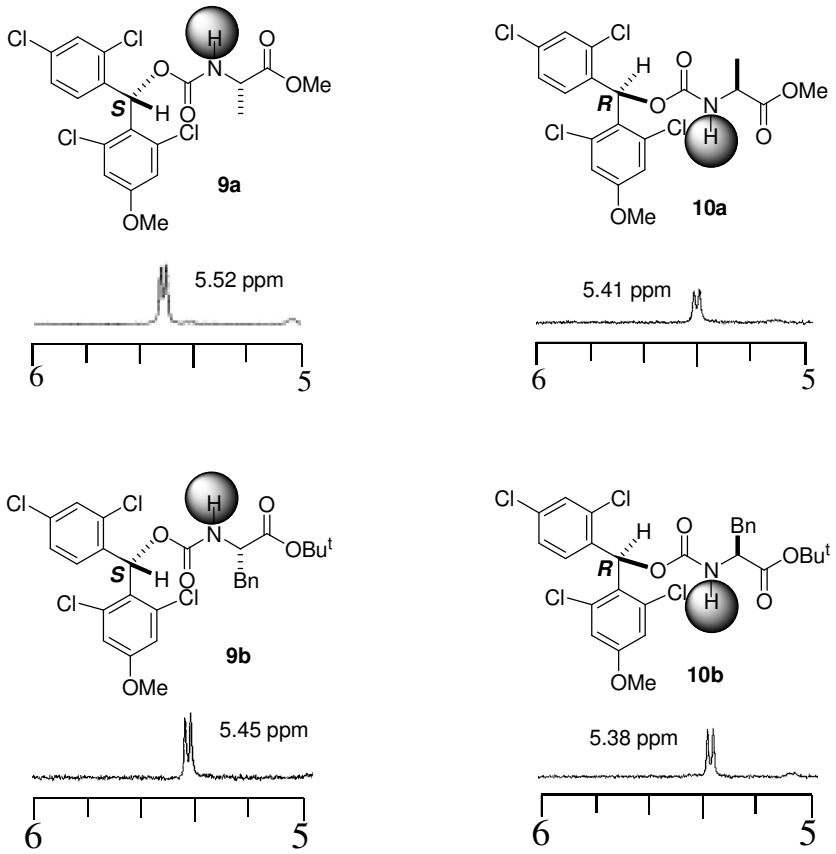
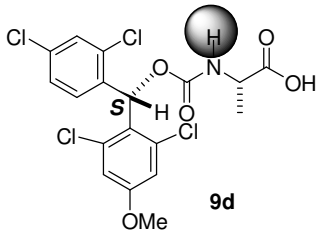
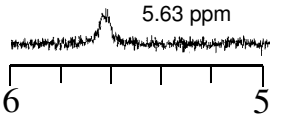
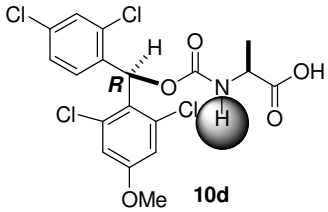


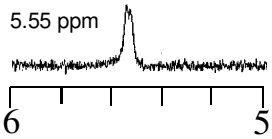
Figure 1. The carbamate formation with (*S*)-**5** or (*R*)-**5**.

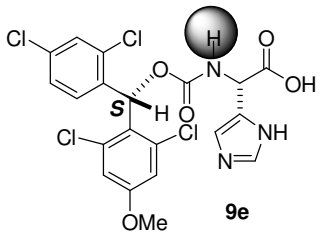


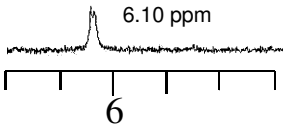

9d

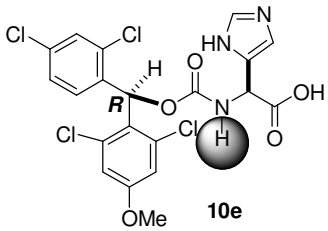

5.63 ppm
6
5

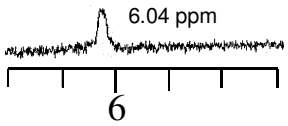

10d

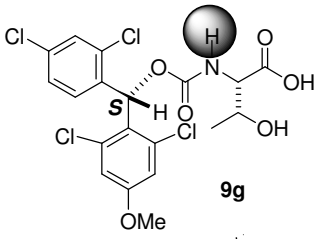

5.55 ppm
6
5

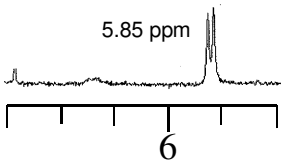

9e

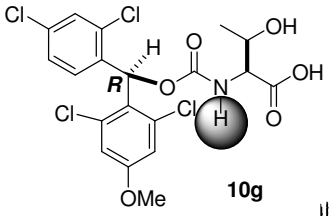

6.10 ppm
6

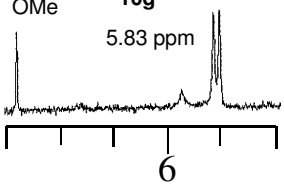

10e

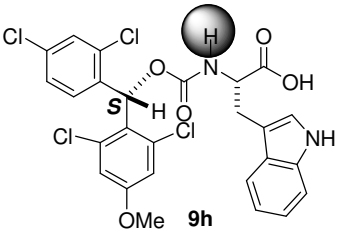

6.04 ppm
6

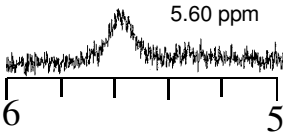

9g

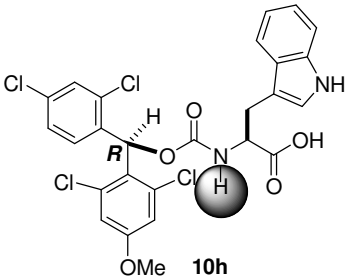

5.85 ppm
6

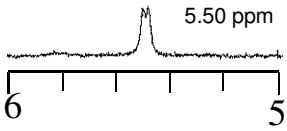

10g

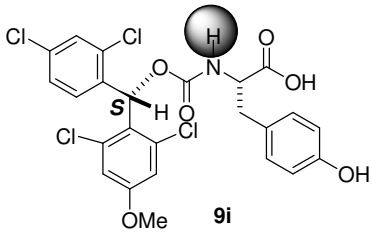

5.83 ppm
6


9h

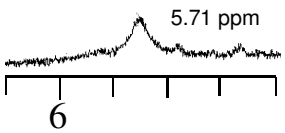

5.60 ppm
6
5

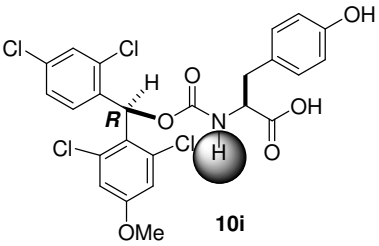

10h


5.50 ppm
6
5

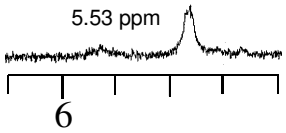


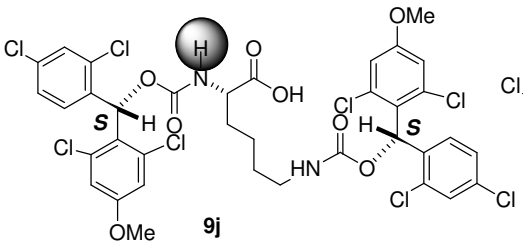
9i



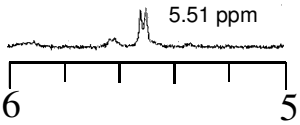


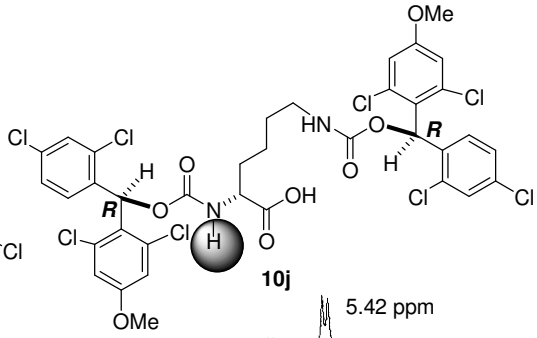
10i



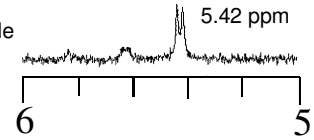


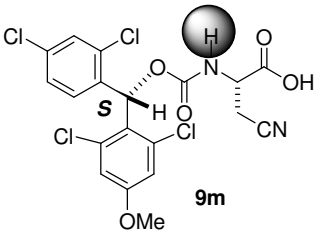
9j



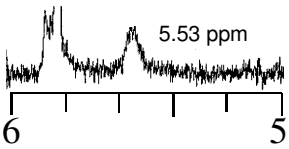


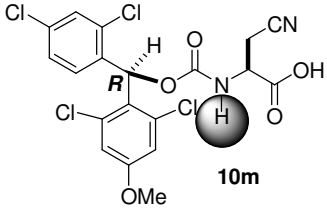
10j



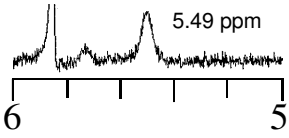


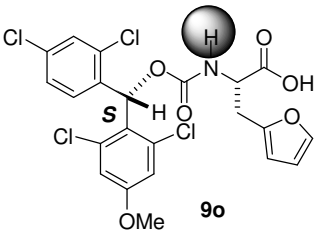
9m



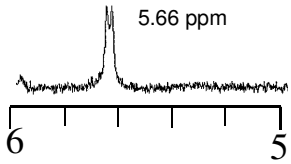


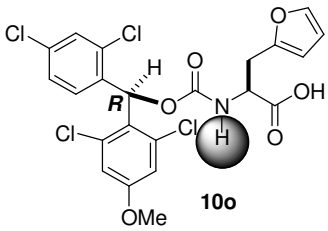
10m



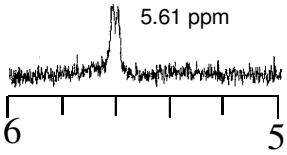


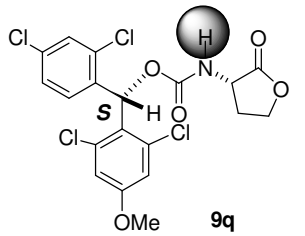
9o



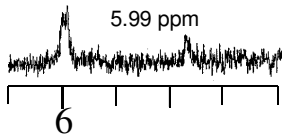


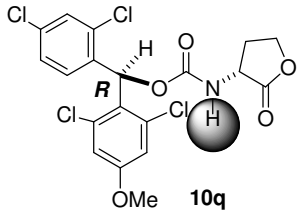
10o



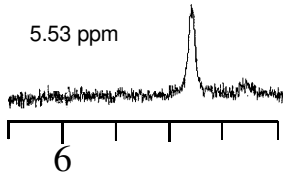


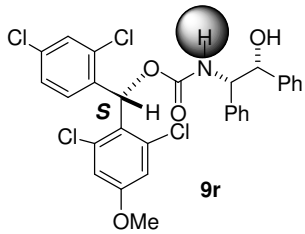
9q



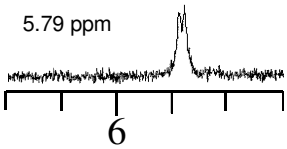


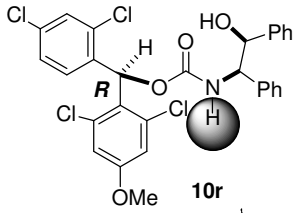
10q



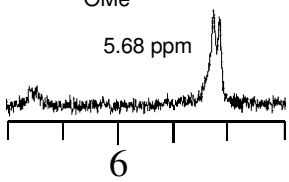


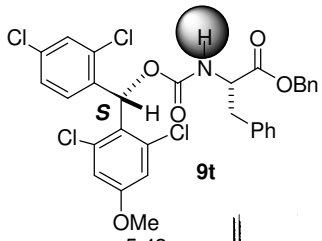
9r



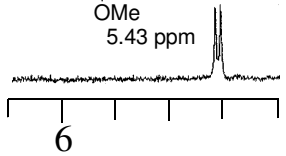


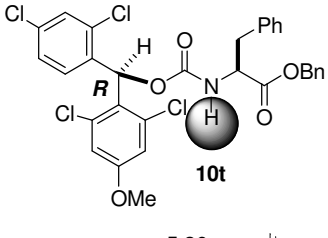
10r



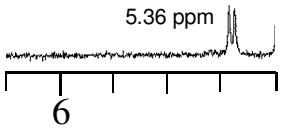


9t





10t



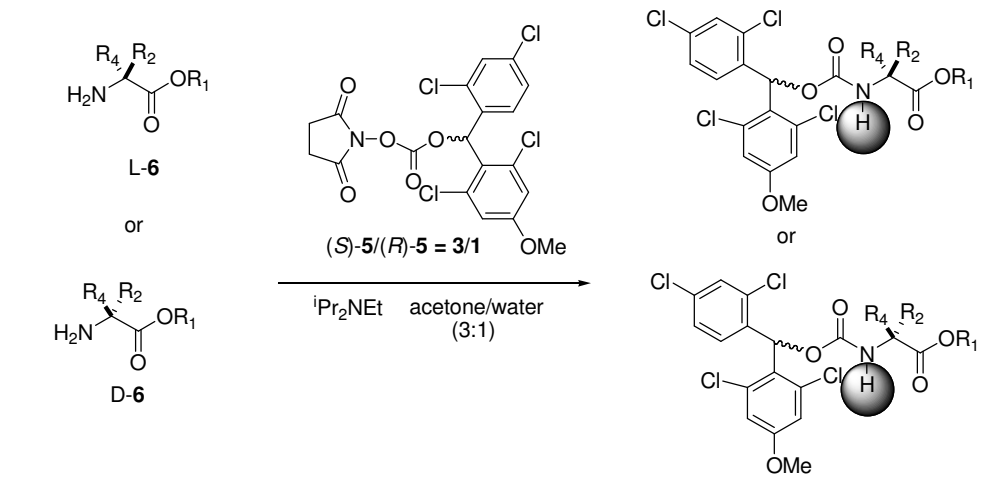
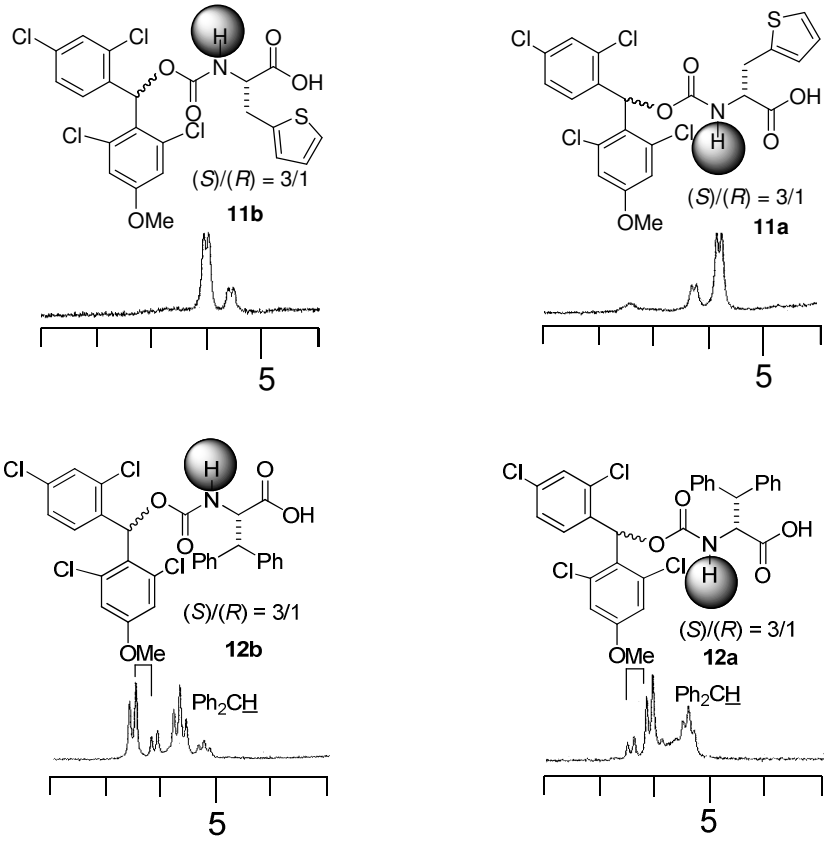
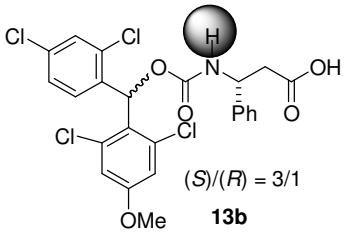
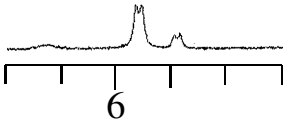
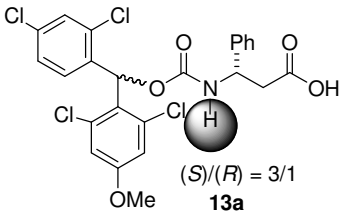


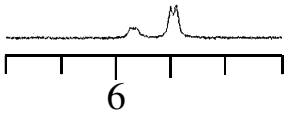
Figure 2. The carbamate formation via a 3:1 mixture of (*S*)-**5** and (*R*)-**5.**

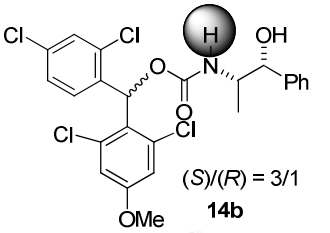


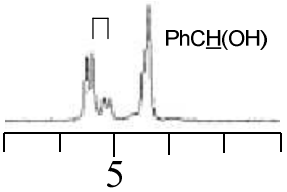

(S)/(R) = 3/1
13b

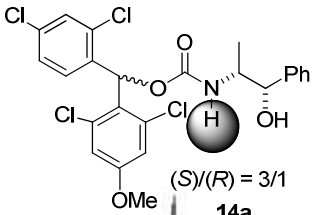

6

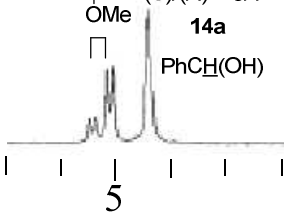

(S)/(R) = 3/1
13a

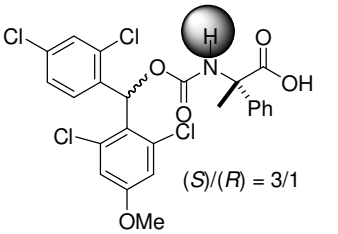

6

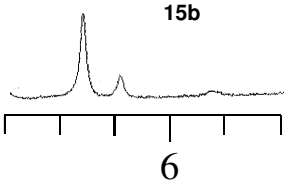

(S)/(R) = 3/1
14b

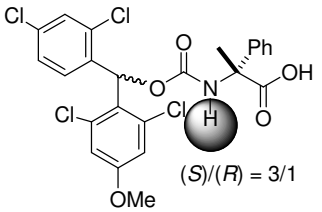

PhCH(OH)
5

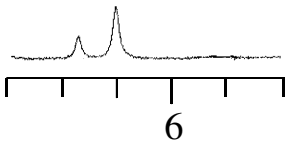

(S)/(R) = 3/1
14a

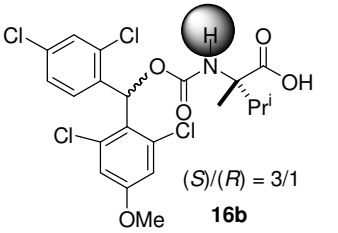

PhCH(OH)
5

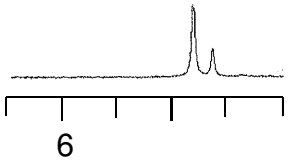

(S)/(R) = 3/1
15b

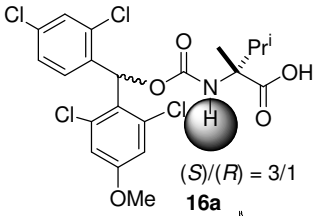

6

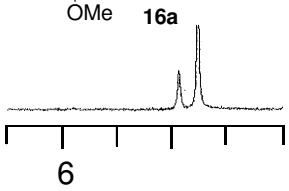

(S)/(R) = 3/1
15a

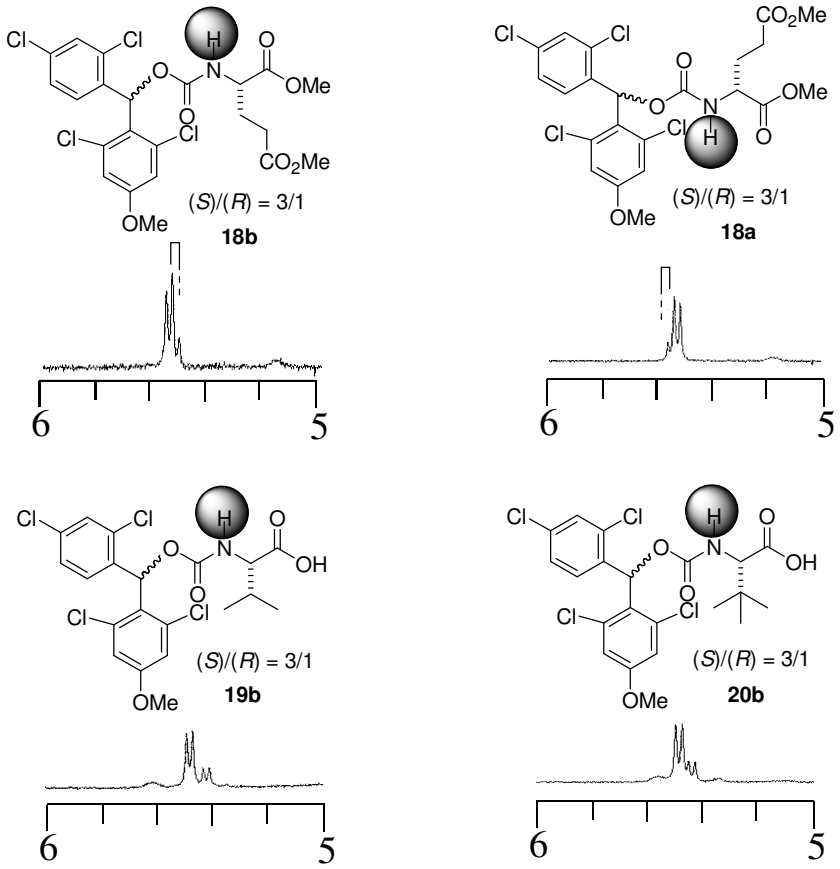

6


(S)/(R) = 3/1
16b


6

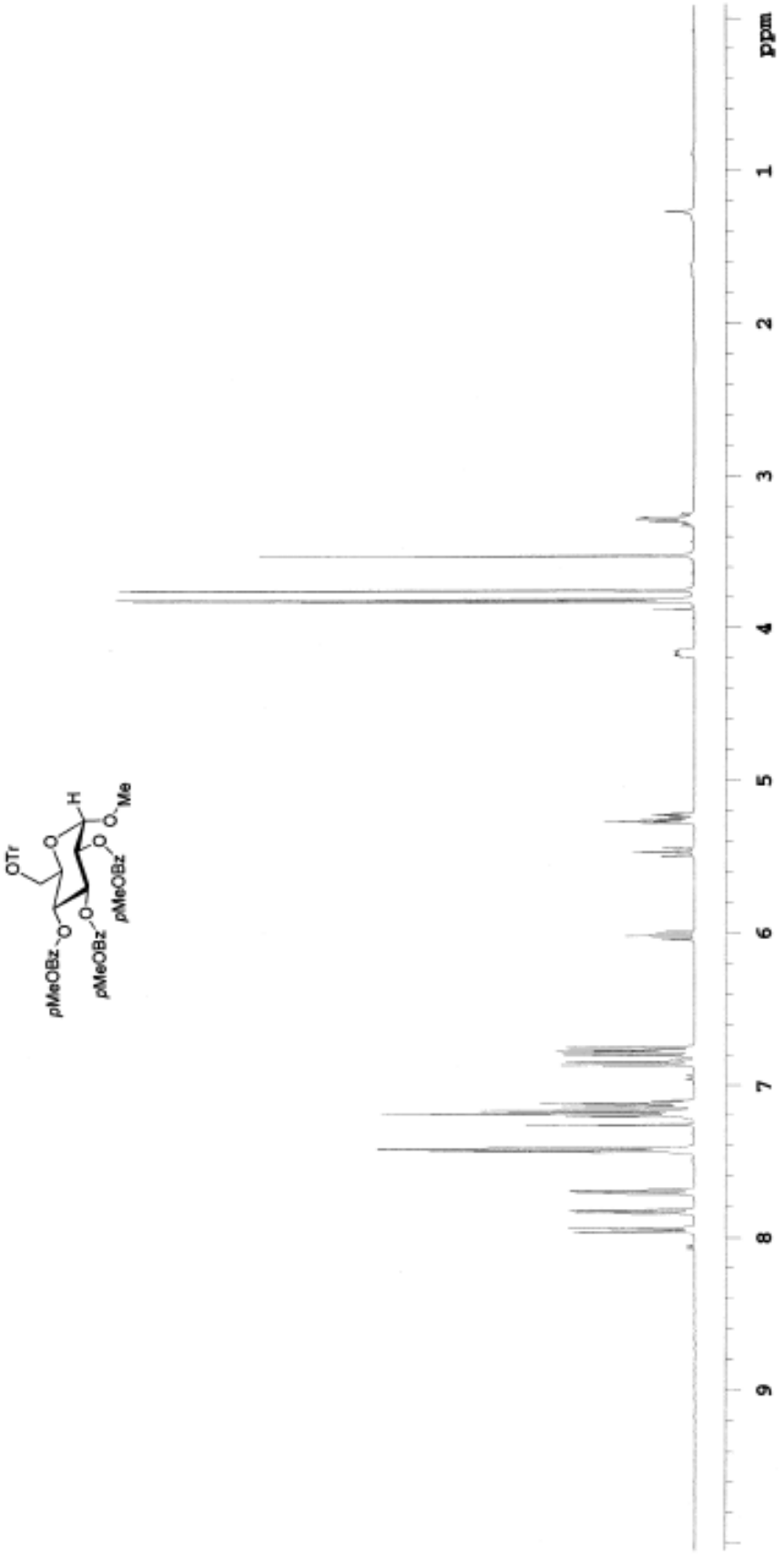

(S)/(R) = 3/1
16a

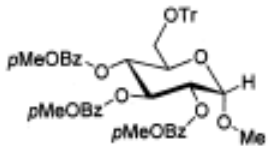

6

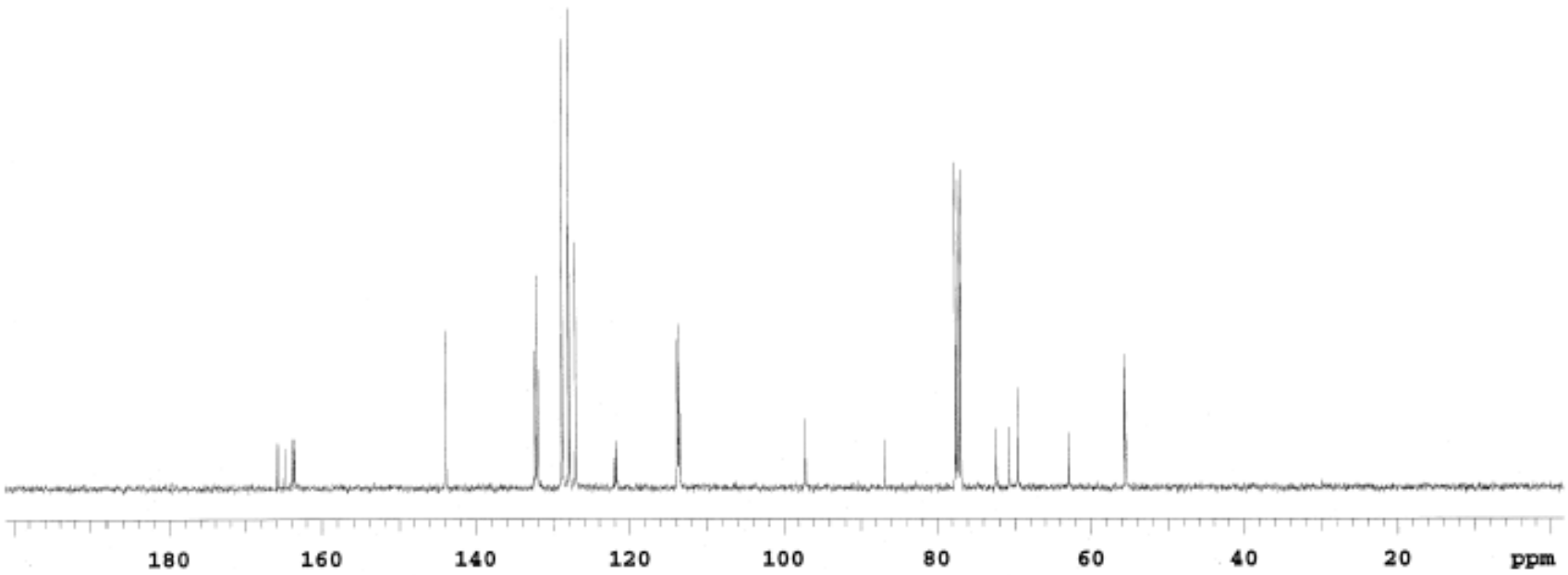


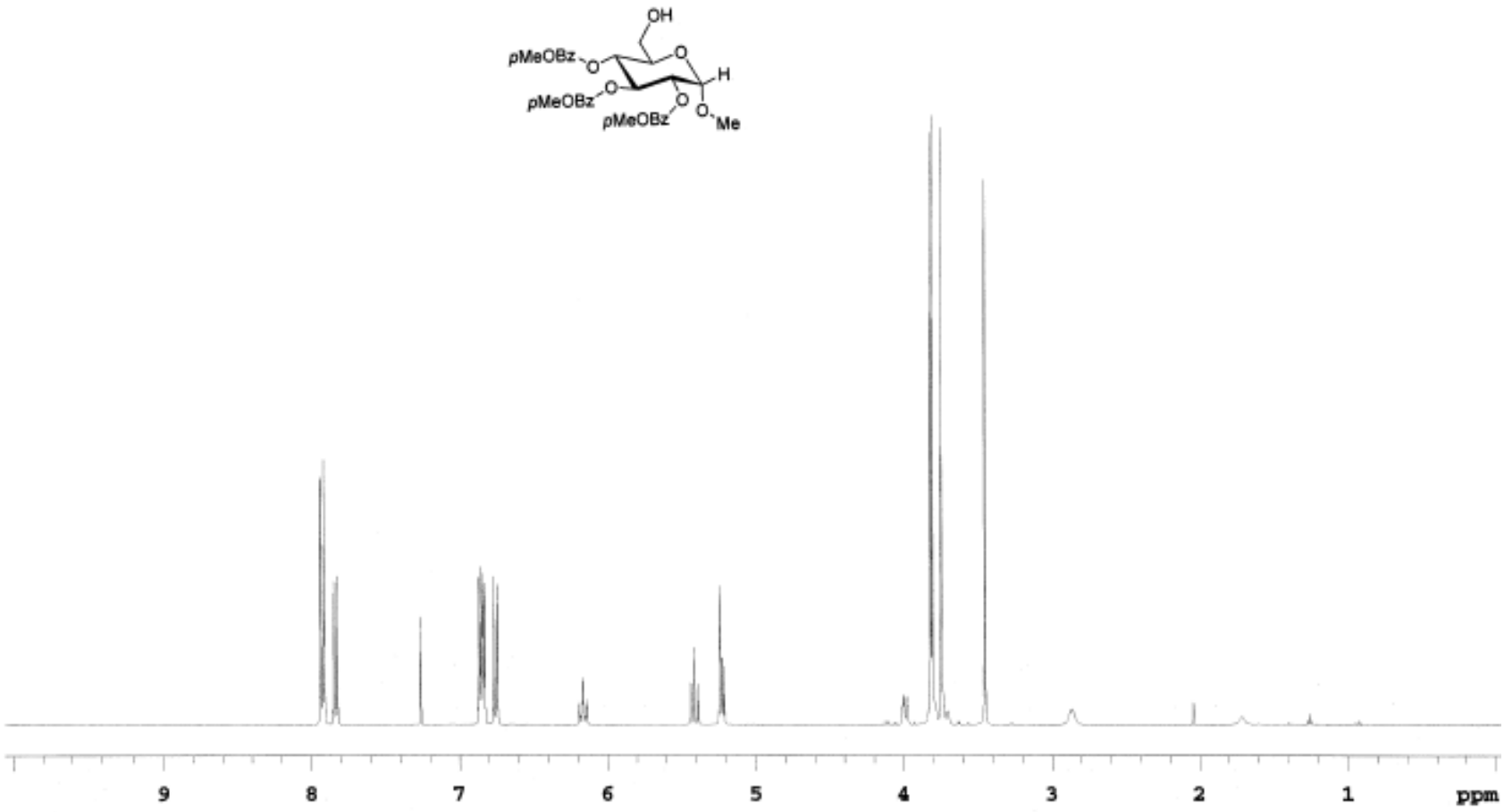
References

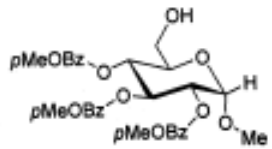
1. Kurosu, M.; Biswas, K.; Narayanasamy, P.; Crick, D. C. *Synthesis* **2007**, *16*, 2513.
2. Ohtani, I.; Kusumi, T.; kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.

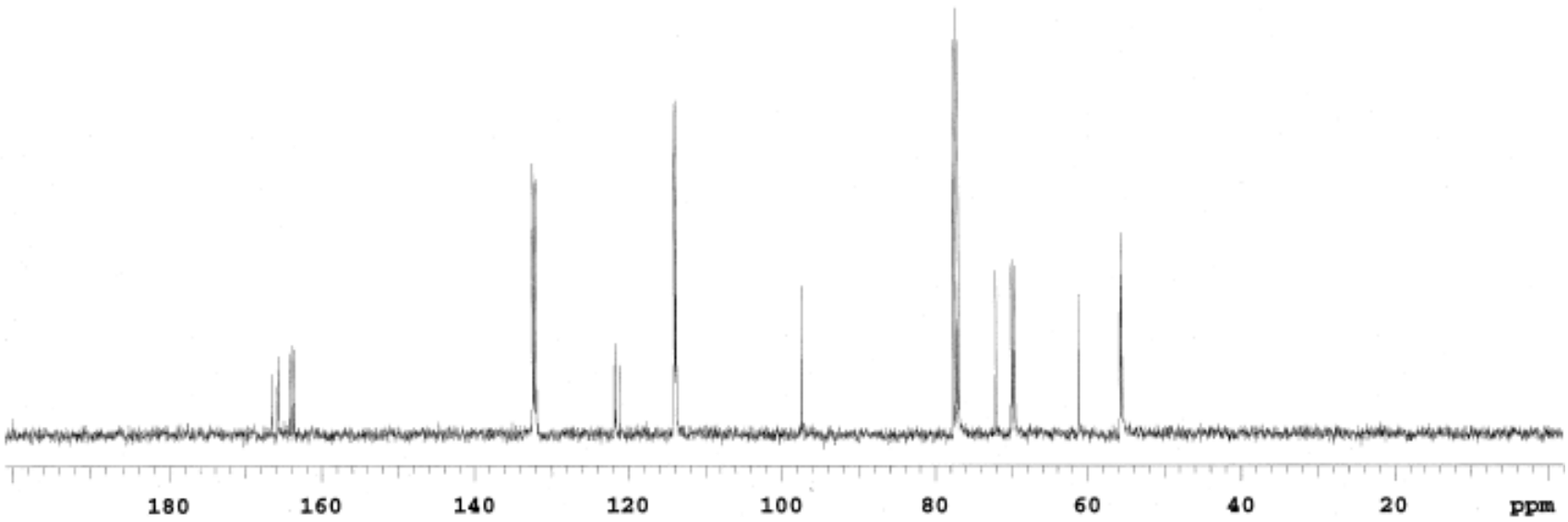

OTr
H
O
Me
O
O
pMeOBz
O
pMeOBz
O
pMeOBz
ppm
1
2
3
4
5
6
7
8
9

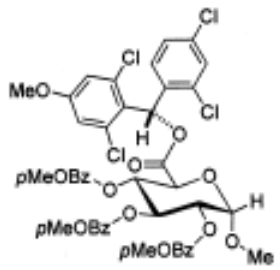

OTr
pMeOBz
O
O
H
pMeOBz
O
O
pMeOBz
O
Me


180
160
140
120
100
80
60
40
20
ppm

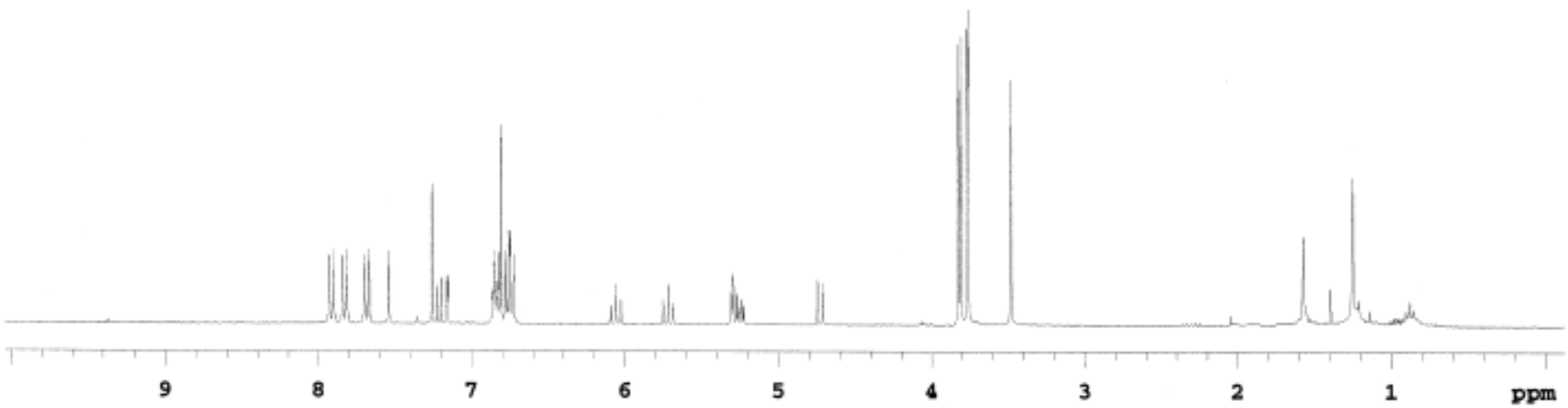

OH
pMeOBz
O
O
H
pMeOBz
O
O
pMeOBz
O
Me
9
8
7
6
5
4
3
2
1
ppm

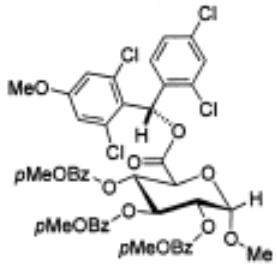

OH
pMeOBz
O
O
H
pMeOBz
O
O
pMeOBz
O
Me


180
160
140
120
100
80
60
40
20
ppm

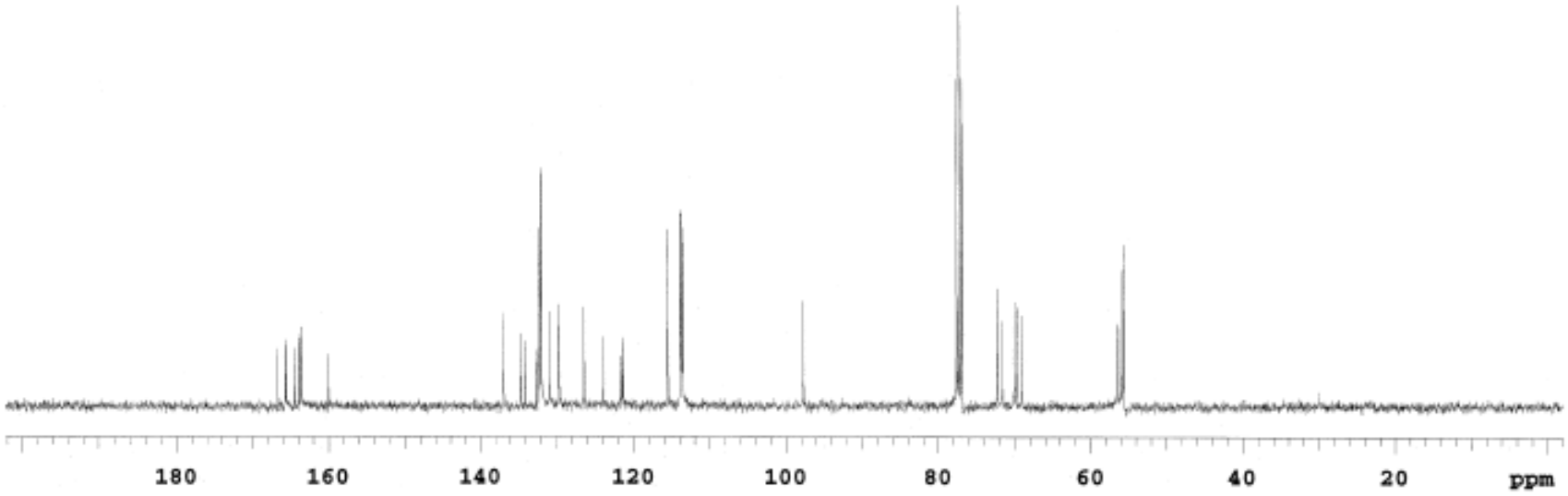

Cl
Cl
MeO
Cl
Cl
H
O
O
pMeOBz
O
O
H
pMeOBz
O
O
pMeOBz
O
Me

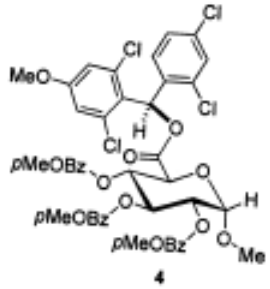
3

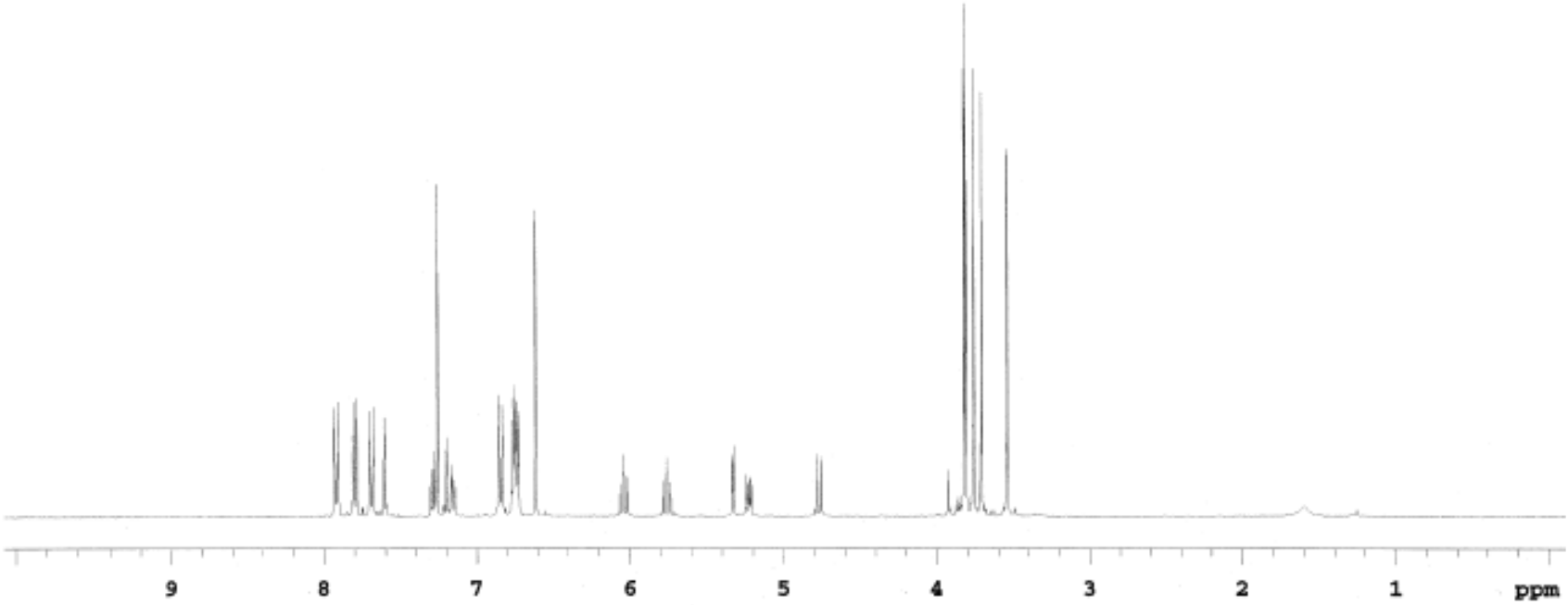

9
8
7
6
5
4
3
2
1
ppm


MeO
Cl
Cl
Cl
Cl
H
O
O
O
O
pMeOBz
O
O
pMeOBz
O
O
pMeOBz
H
O
Me

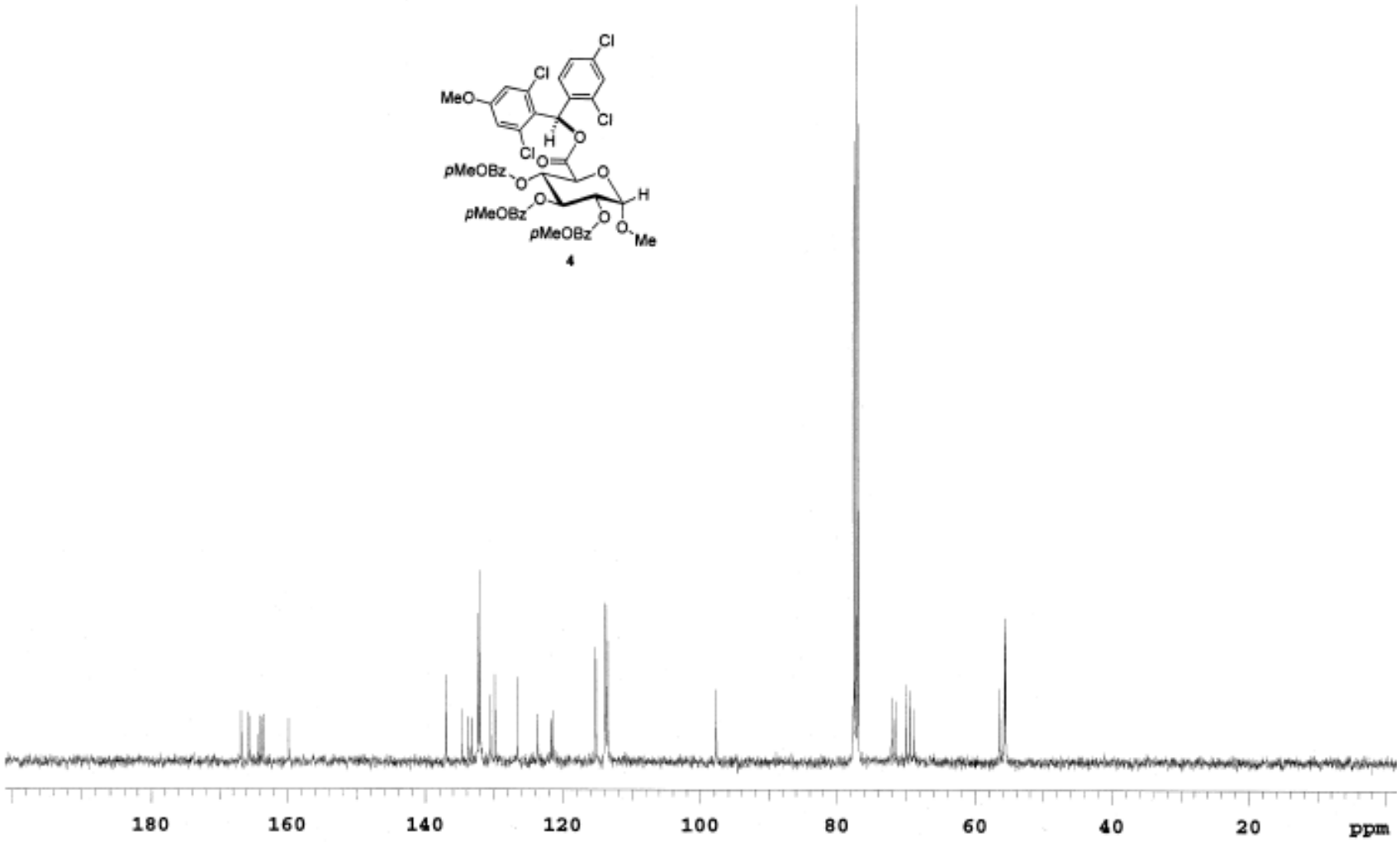
3

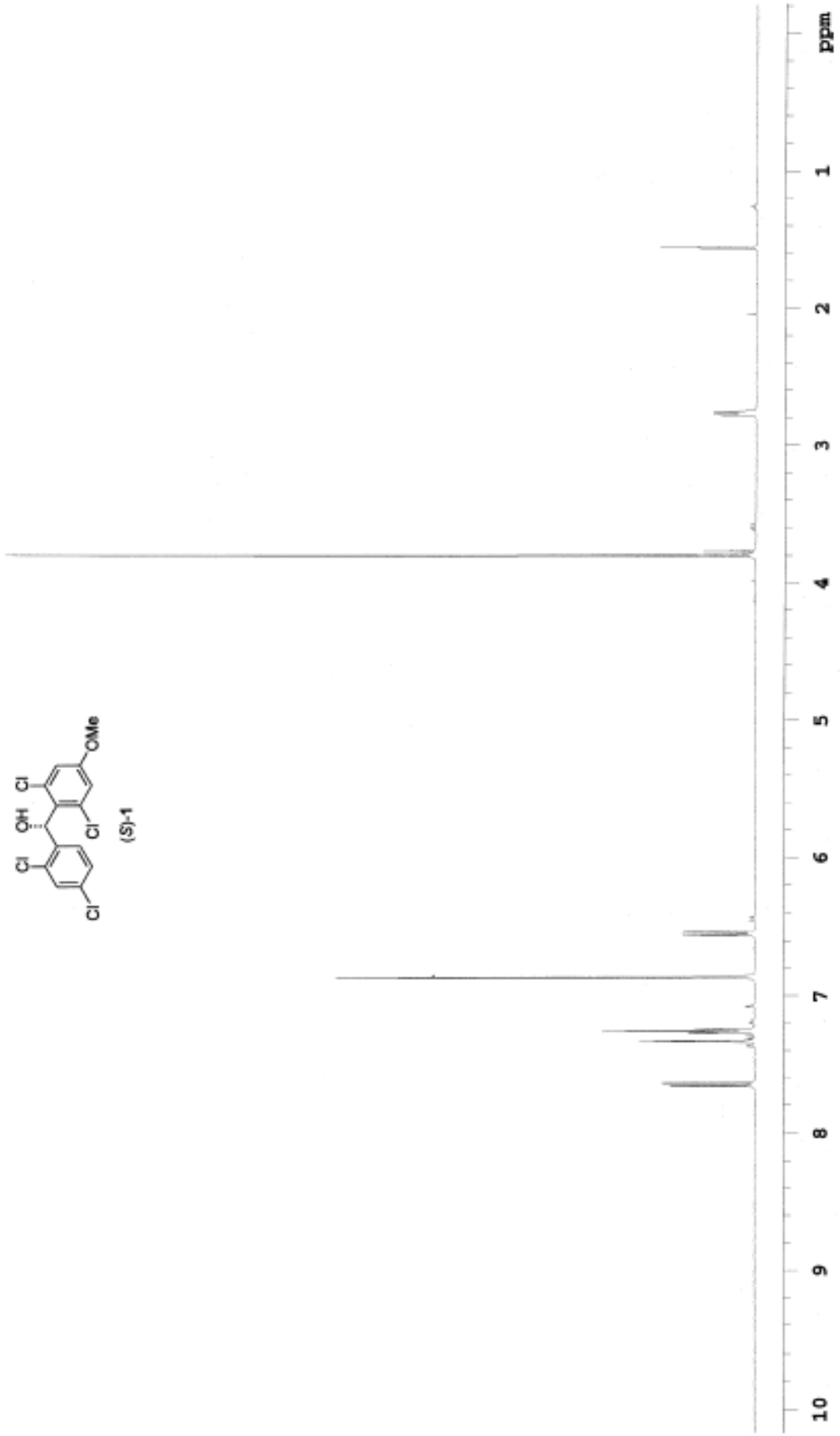

180
160
140
120
100
80
60
40
20
ppm

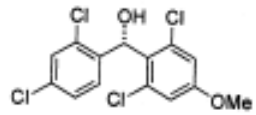

MeO
Cl
Cl
Cl
Cl
H
O
O
O
pMeOBz
O
O
pMeOBz
O
pMeOBz
O
H
O
Me
4


9
8
7
6
5
4
3
2
1
ppm

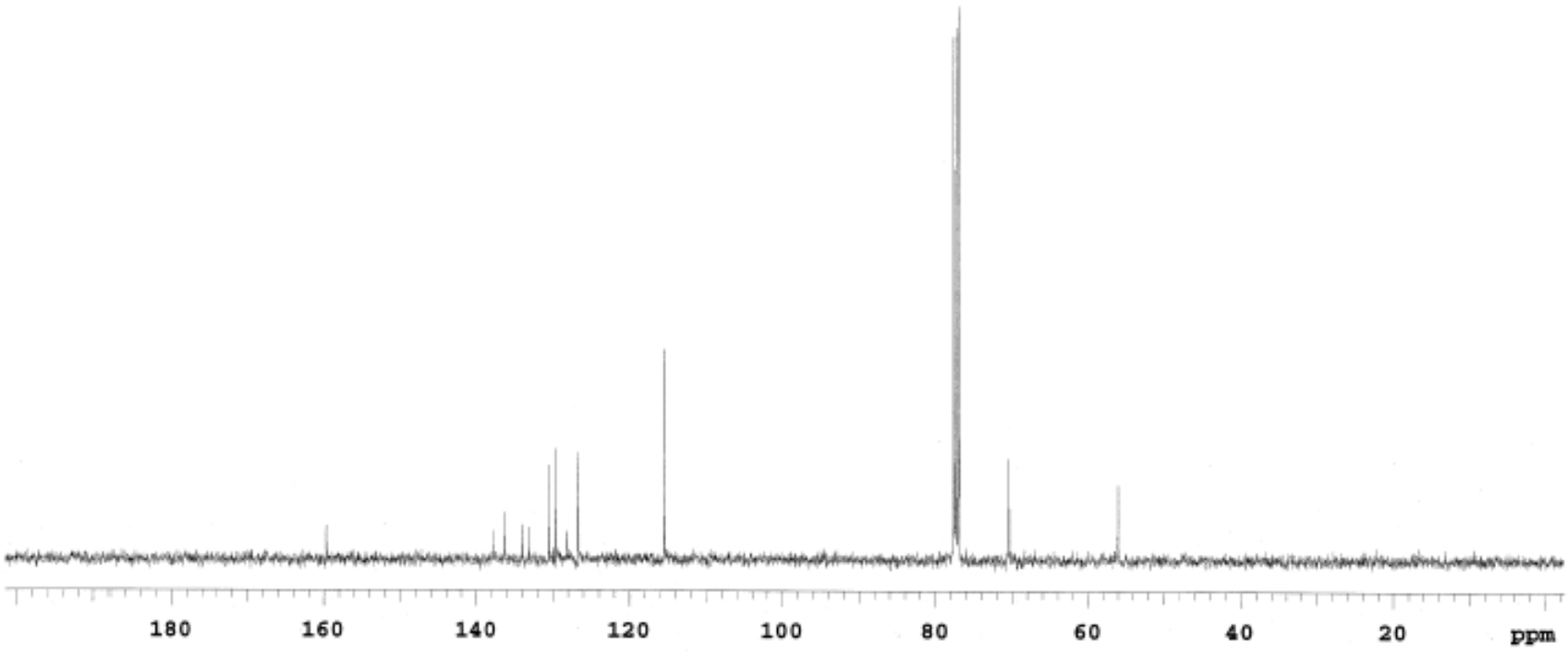
MeO
Cl
Cl
Cl
Cl
H
O
O
pMeOBz
O
O
O
H
pMeOBz
O
O
pMeOBz
O
Me
4

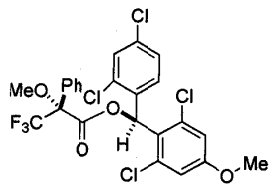

180
160
140
120
100
80
60
40
20
ppm


Cl
OH
Cl
Cl
Cl
OMe
(S)-1
10
9
8
7
6
5
4
3
2
1
ppm

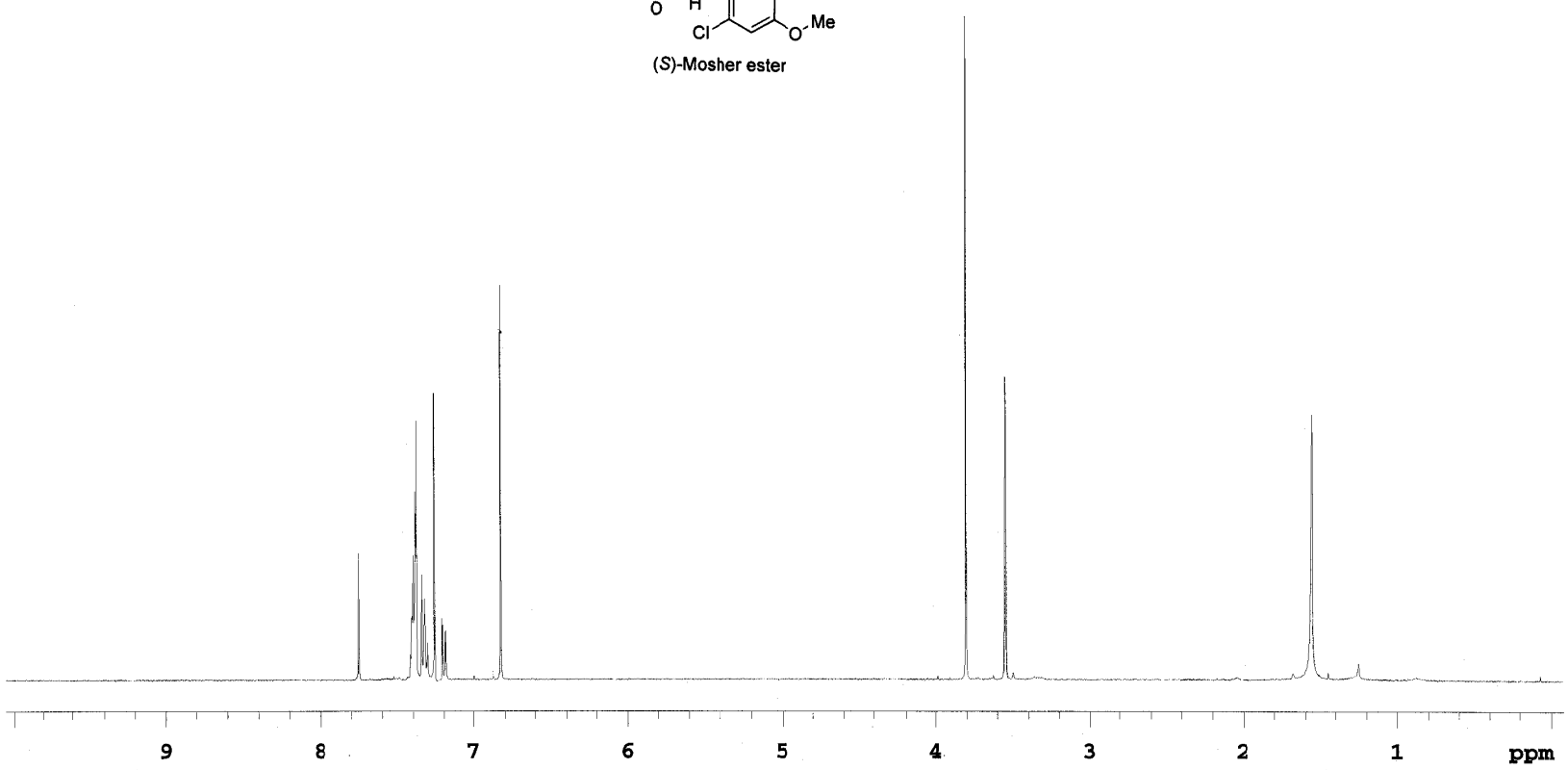


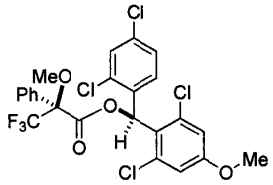
(*S*)-1



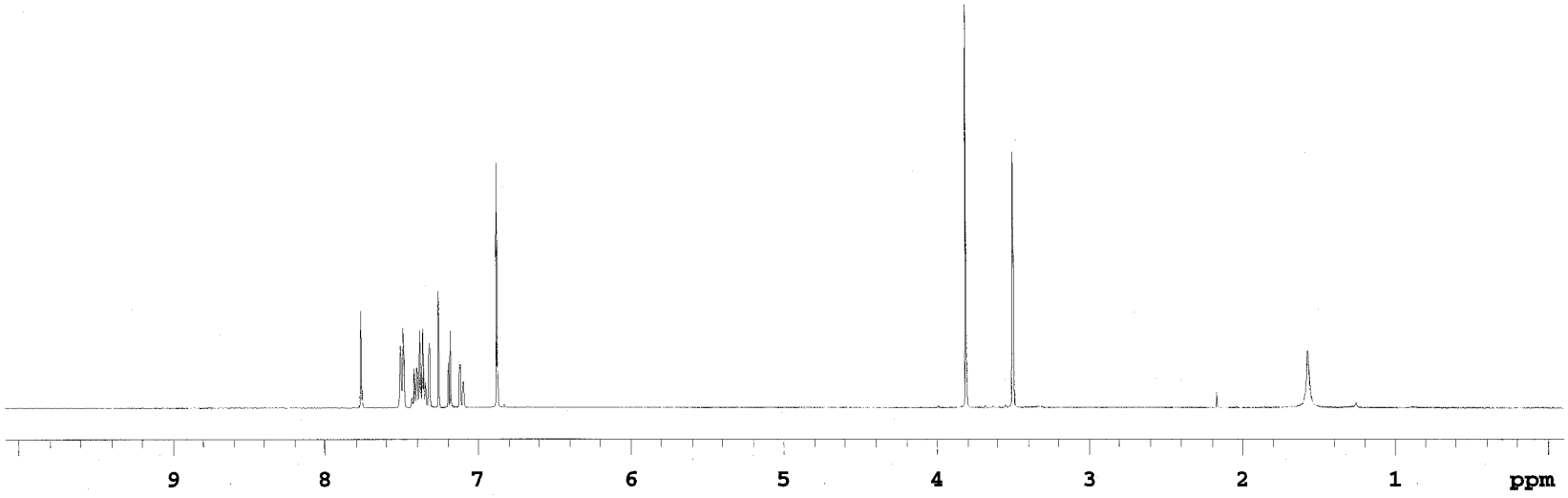


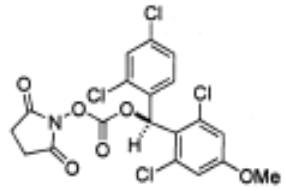
(*S*)-Mosher ester



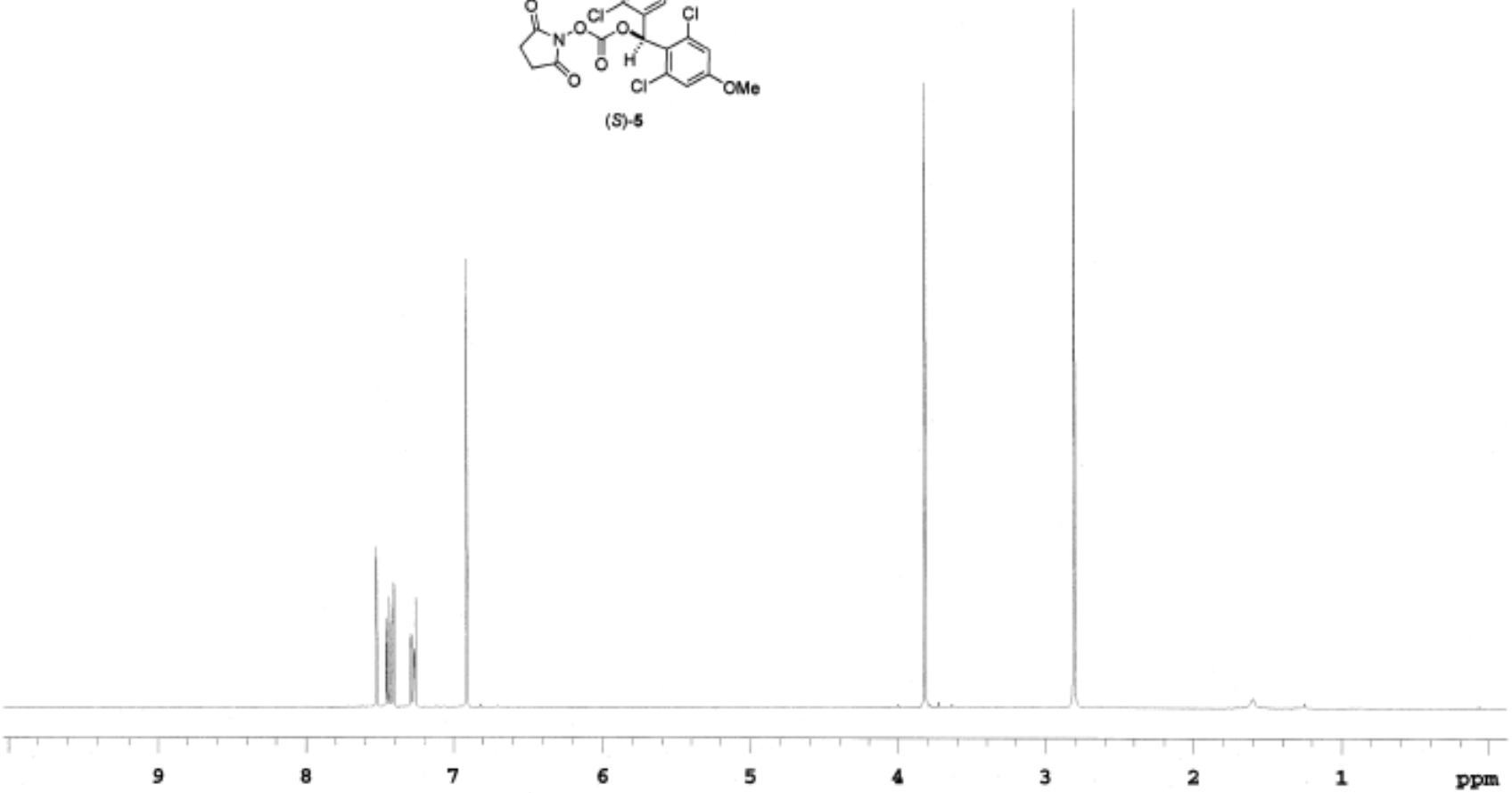


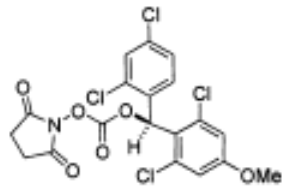
(*R*)-Mosher ester



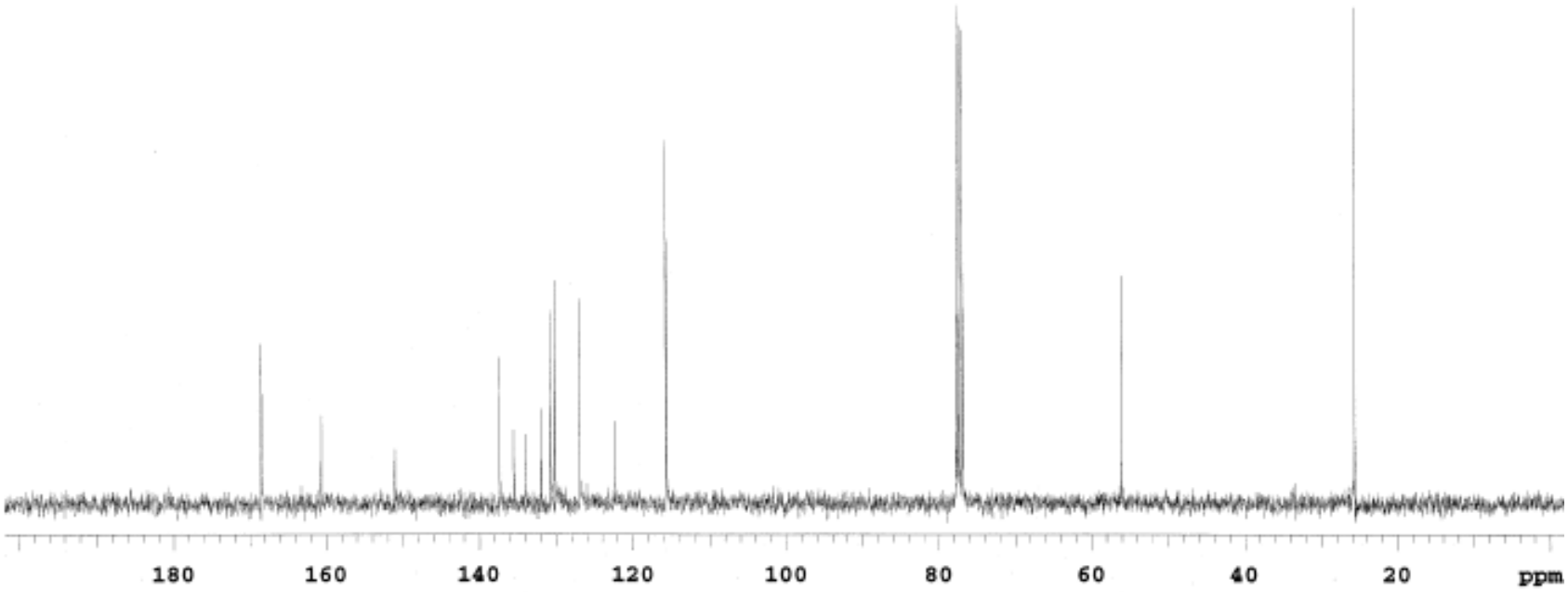


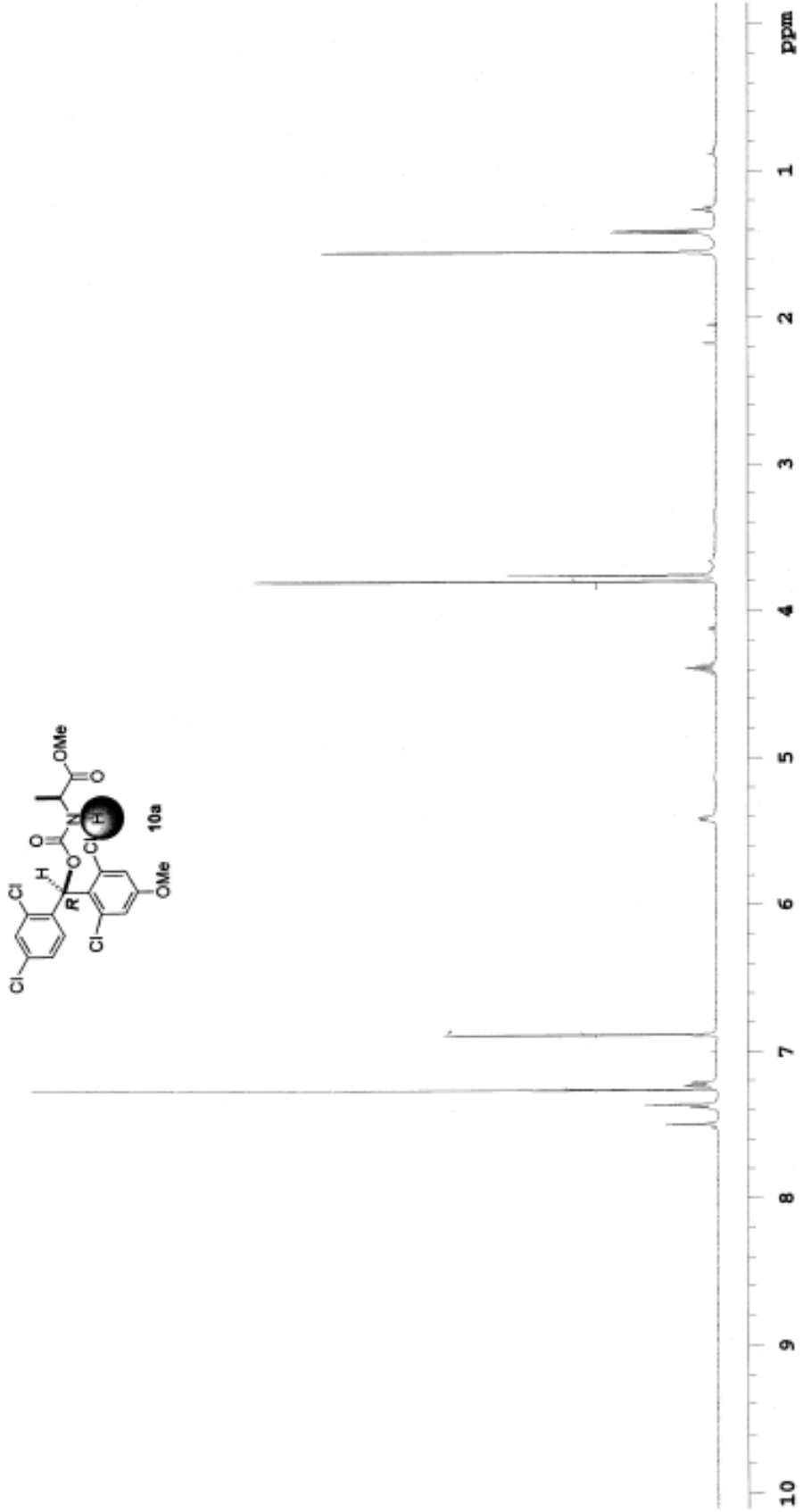
(*S*)-5

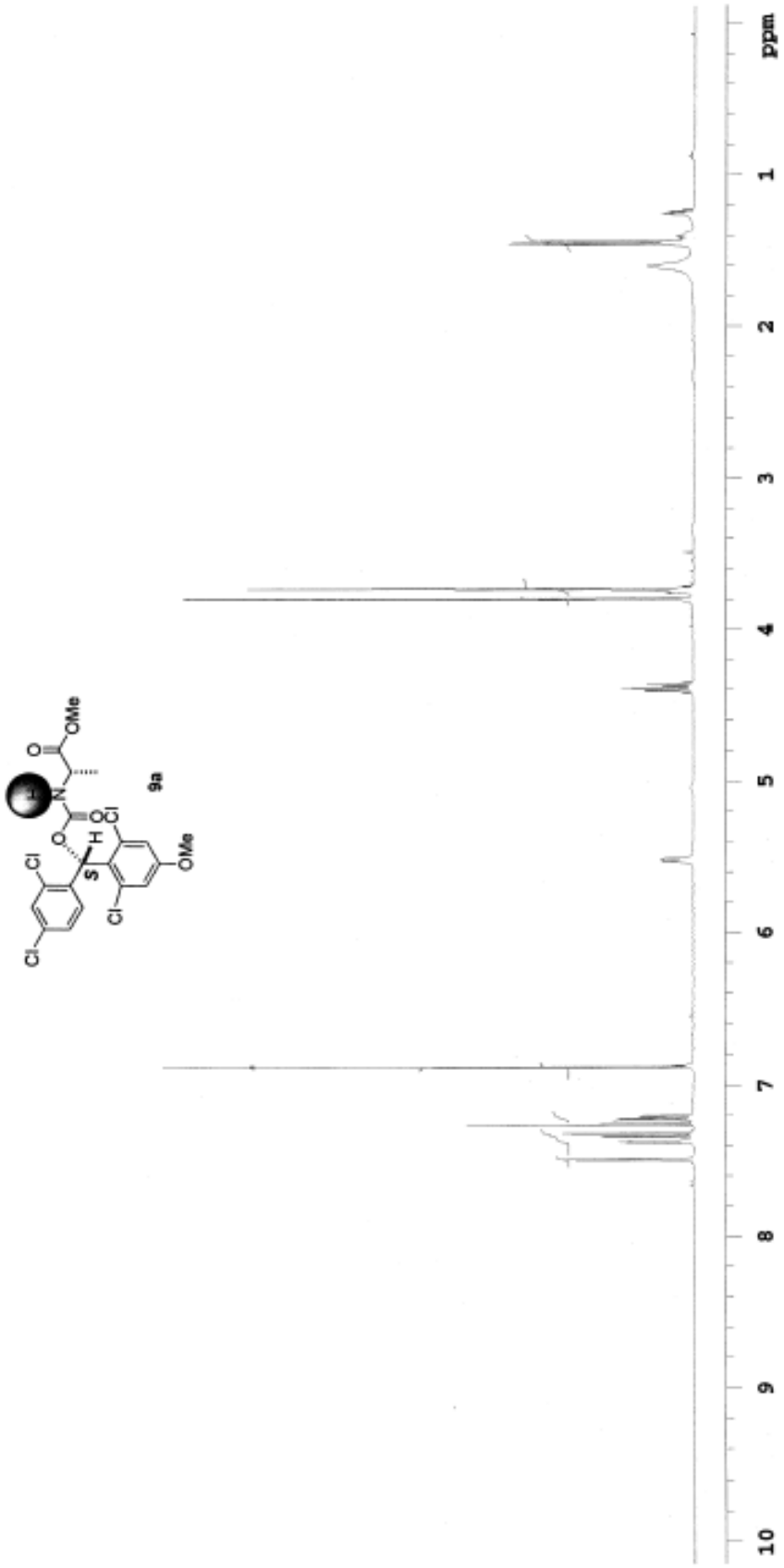


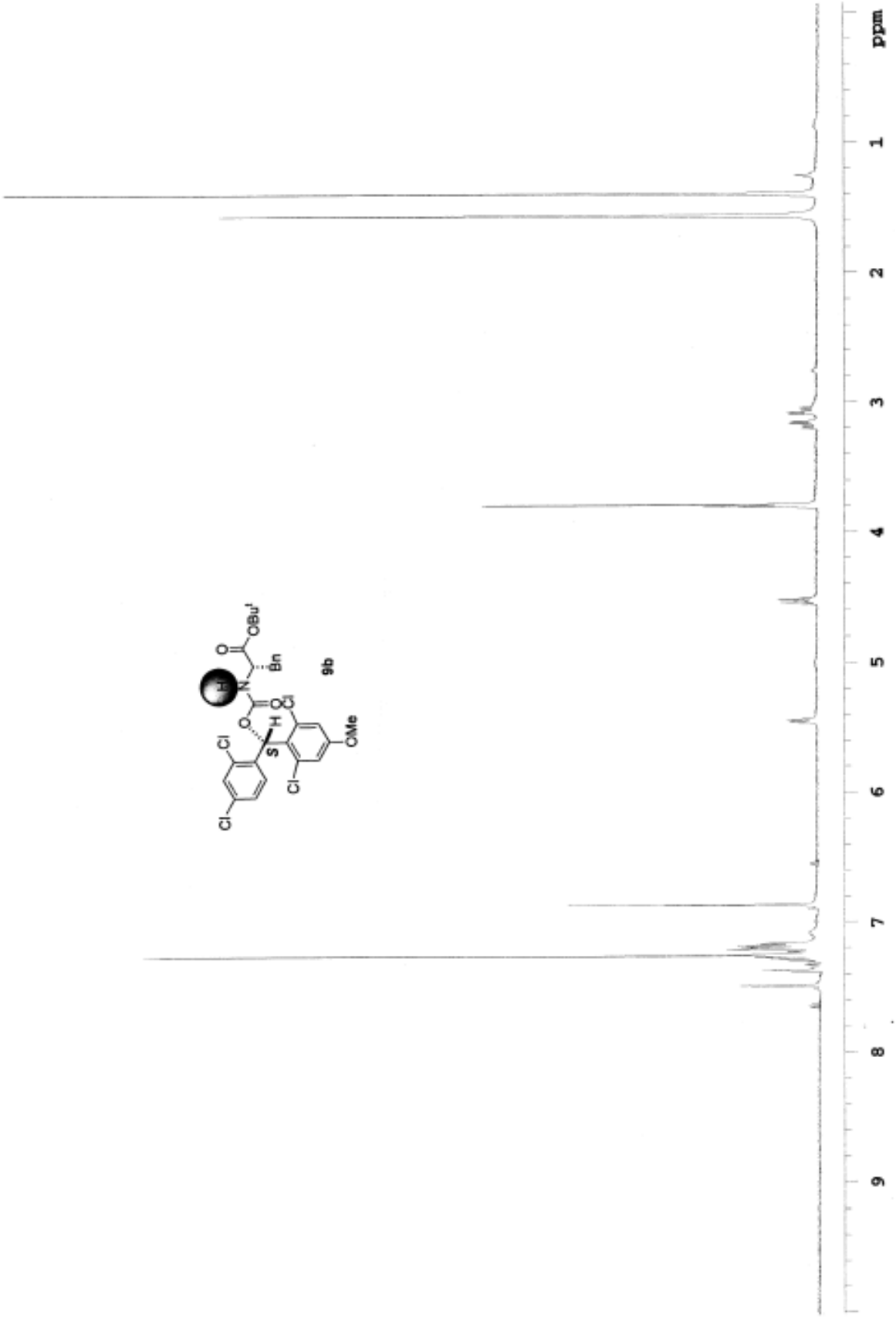


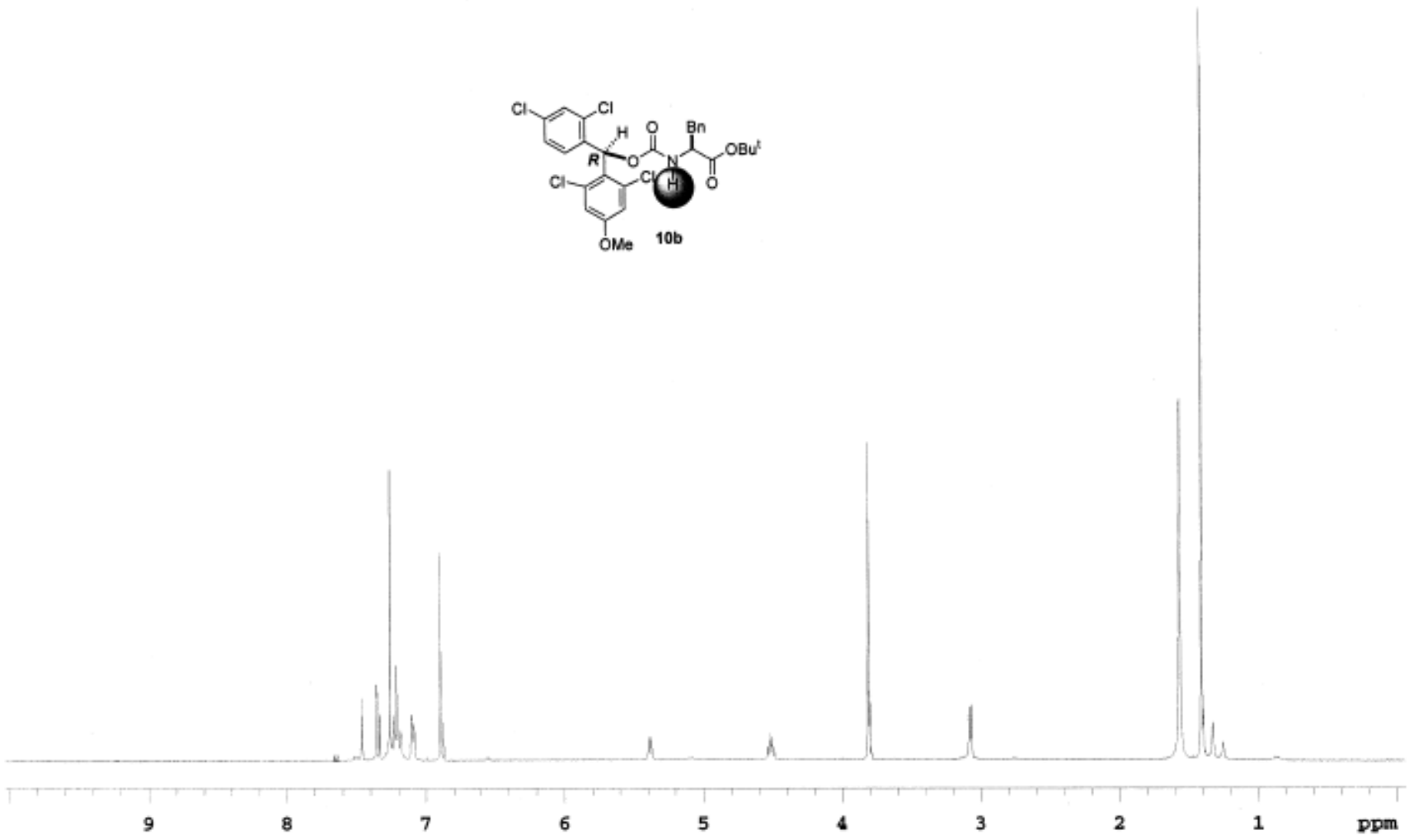
(*S*)-5

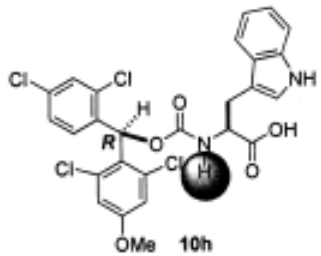


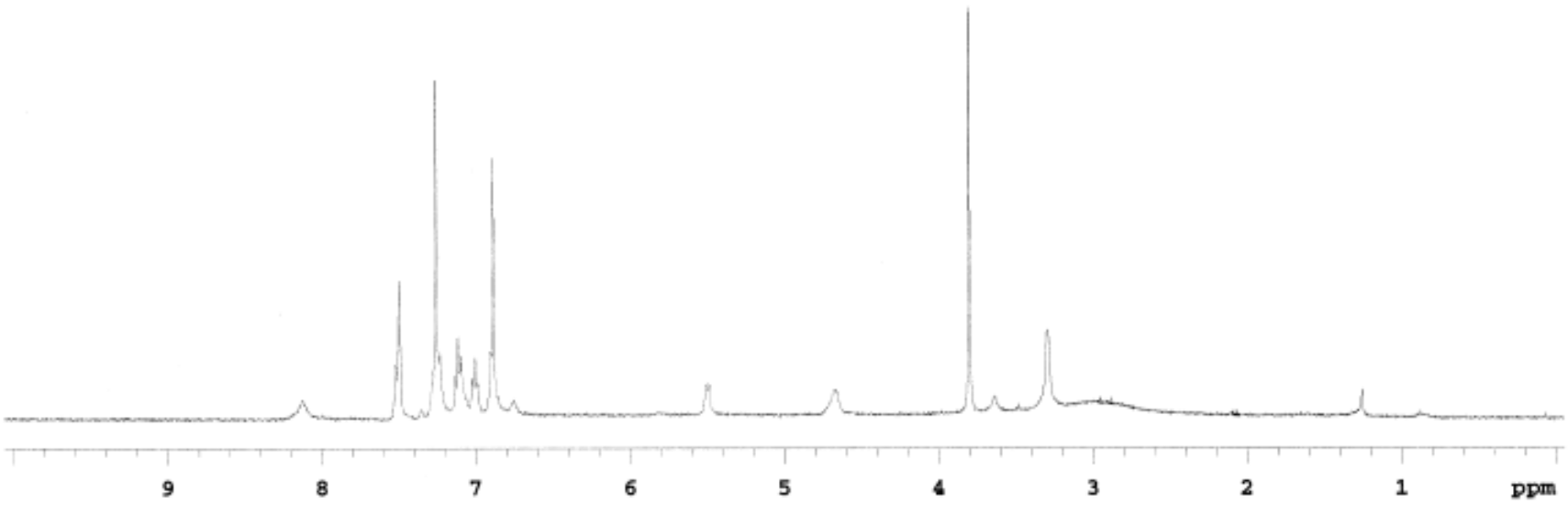

ppm
1
2
3
4
5
6
7
8
9
10
10a

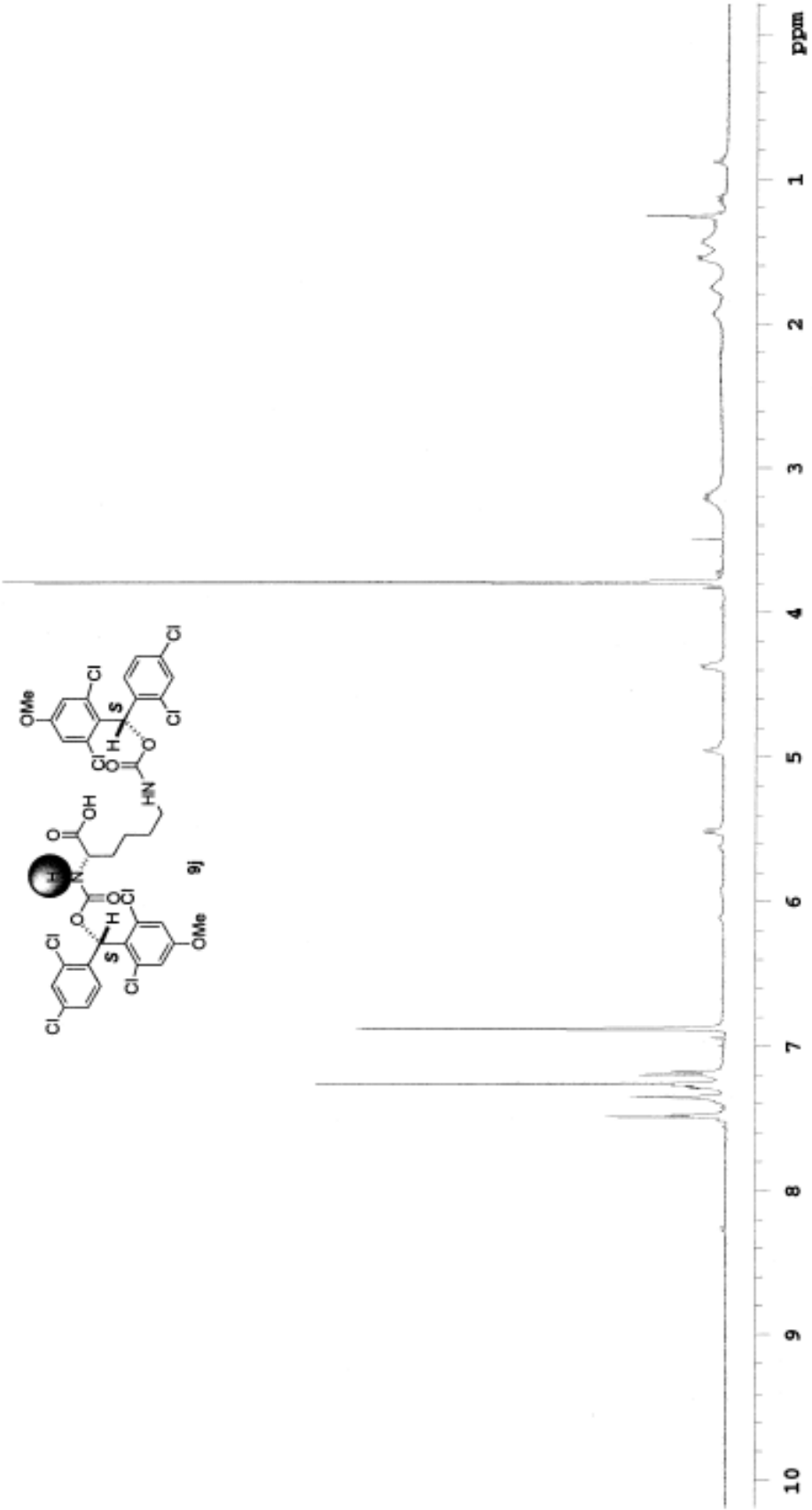

9a
ppm
10
9
8
7
6
5
4
3
2
1

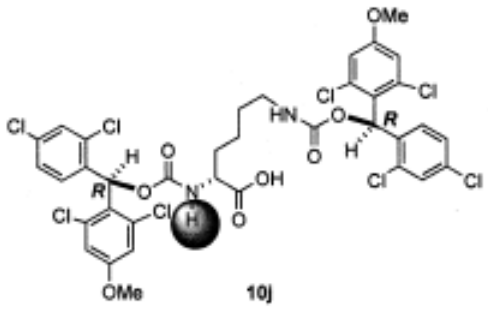

ppm
1
2
3
4
5
6
7
8
9
9b
Cl
Cl
S
H
O
O
Cl
Cl
OMe
N
H
Bn
O
OBu^t

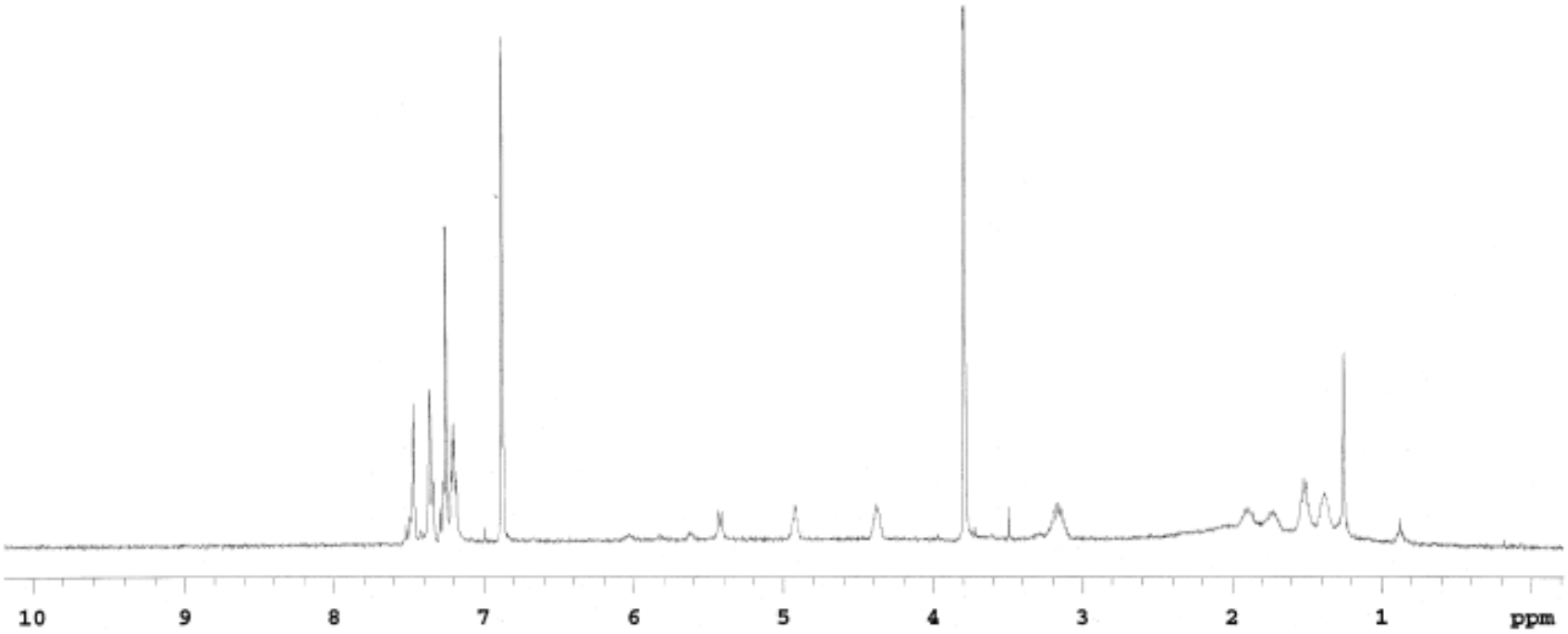

Cl
Cl
H
O
Bn
OBu^t
R
O
N
Cl
Cl
H
O
OMe
10b
9
8
7
6
5
4
3
2
1
ppm

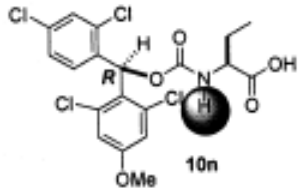

Cl
Cl
H
R
O
O
N
H
NH
OH
O
Cl
Cl
OMe
10h

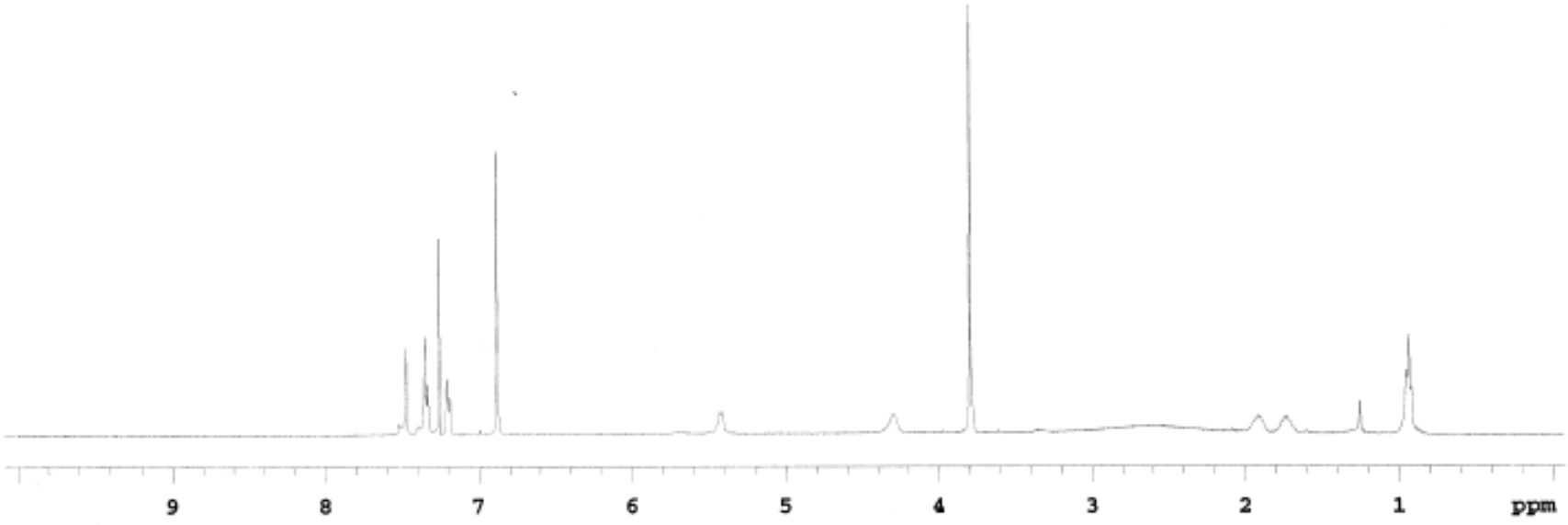

9
8
7
6
5
4
3
2
1
ppm

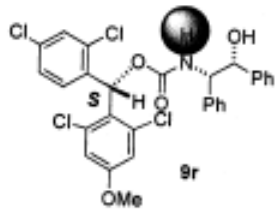

9j
ppm
10
9
8
7
6
5
4
3
2
1

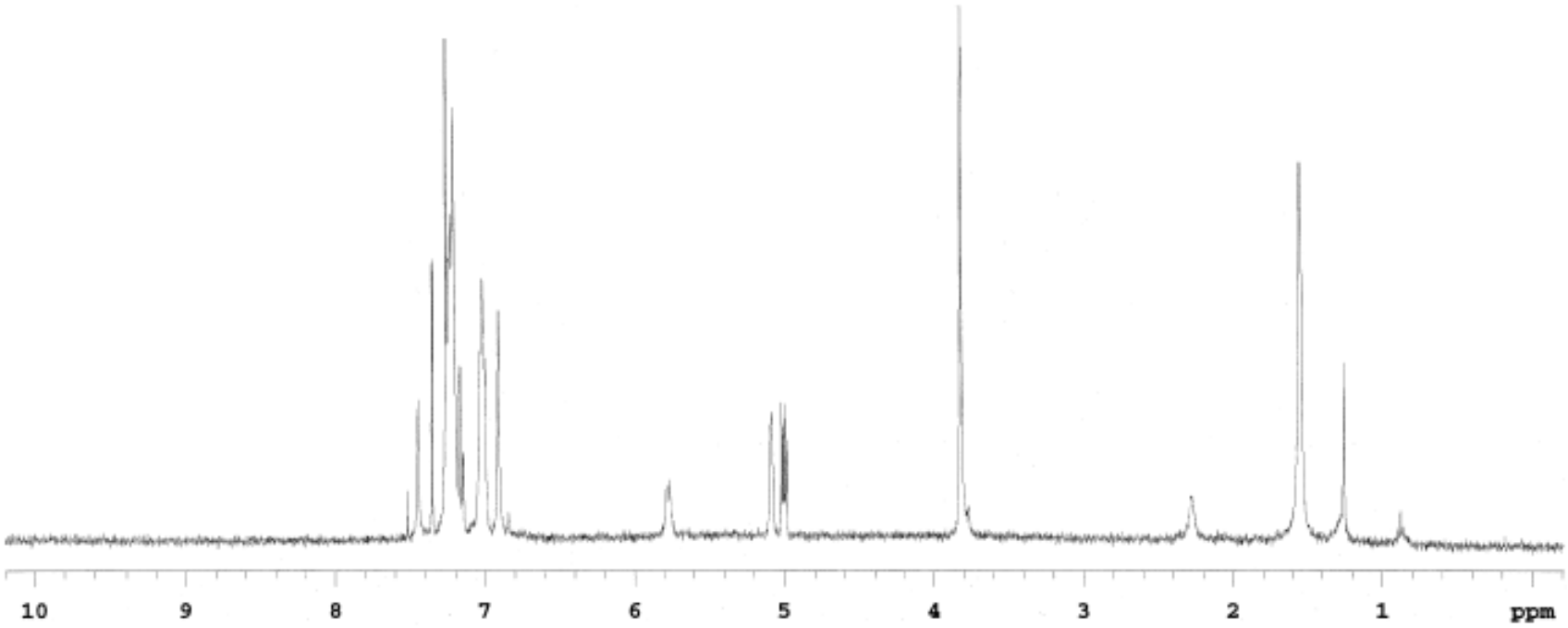

OMe
Cl
Cl
HN
O
R
H
Cl
Cl
Cl
Cl
H
O
R
O
N
OH
Cl
Cl
H
O
OMe
10j

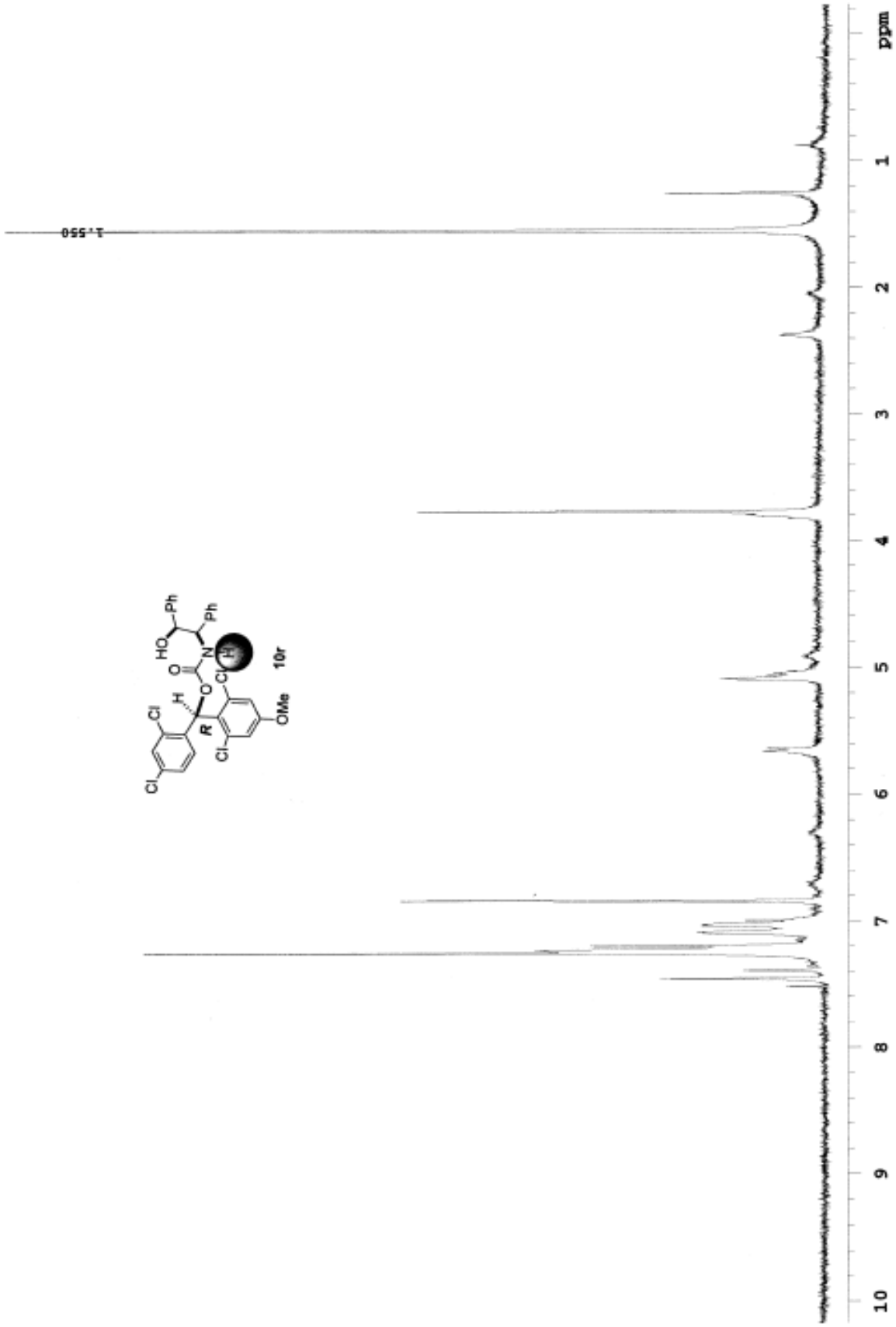

10
9
8
7
6
5
4
3
2
1
ppm

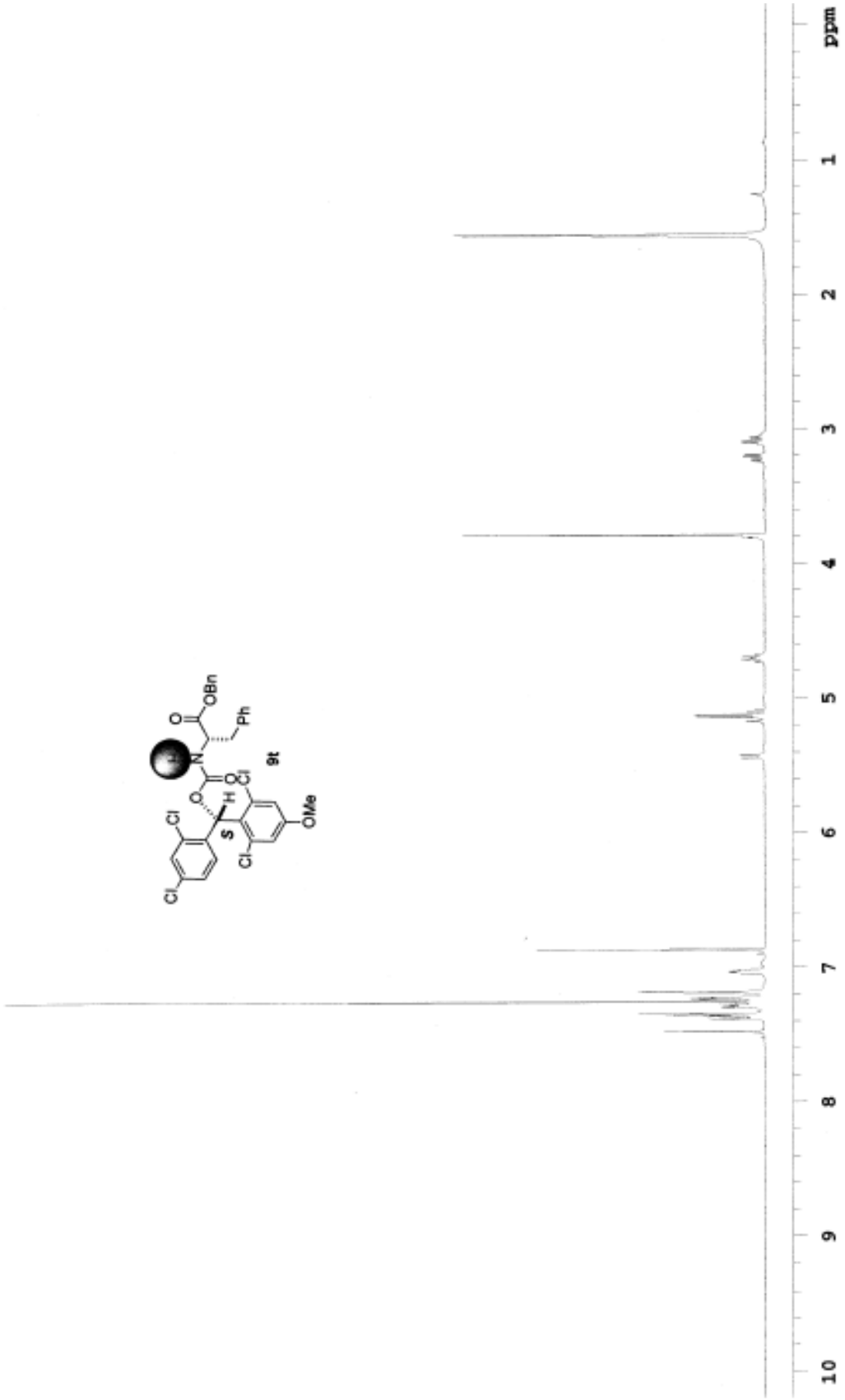

Cl
Cl
H
R
O
O
N
OH
Cl
Cl
H
O
OMe
10n

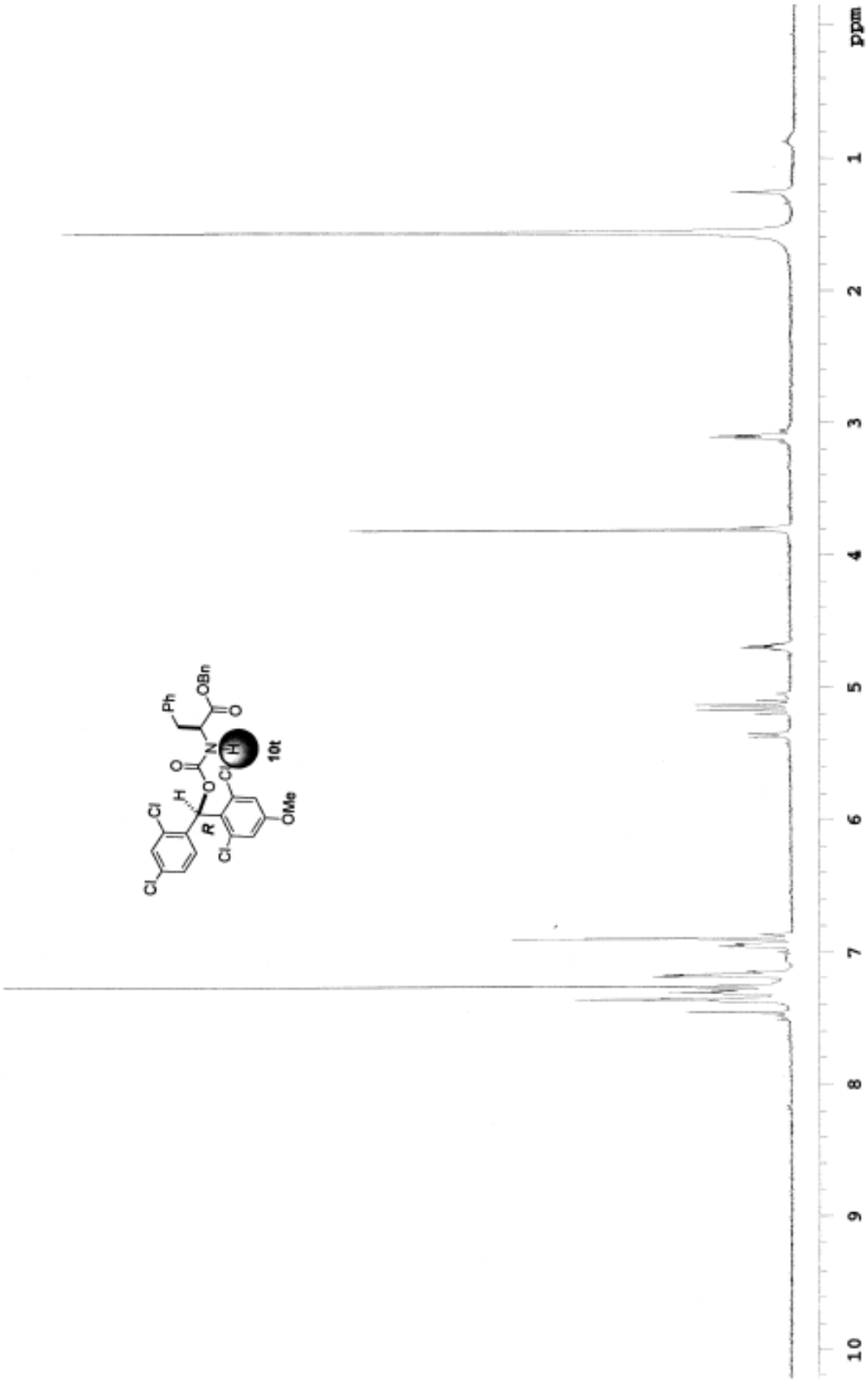

9
8
7
6
5
4
3
2
1
ppm

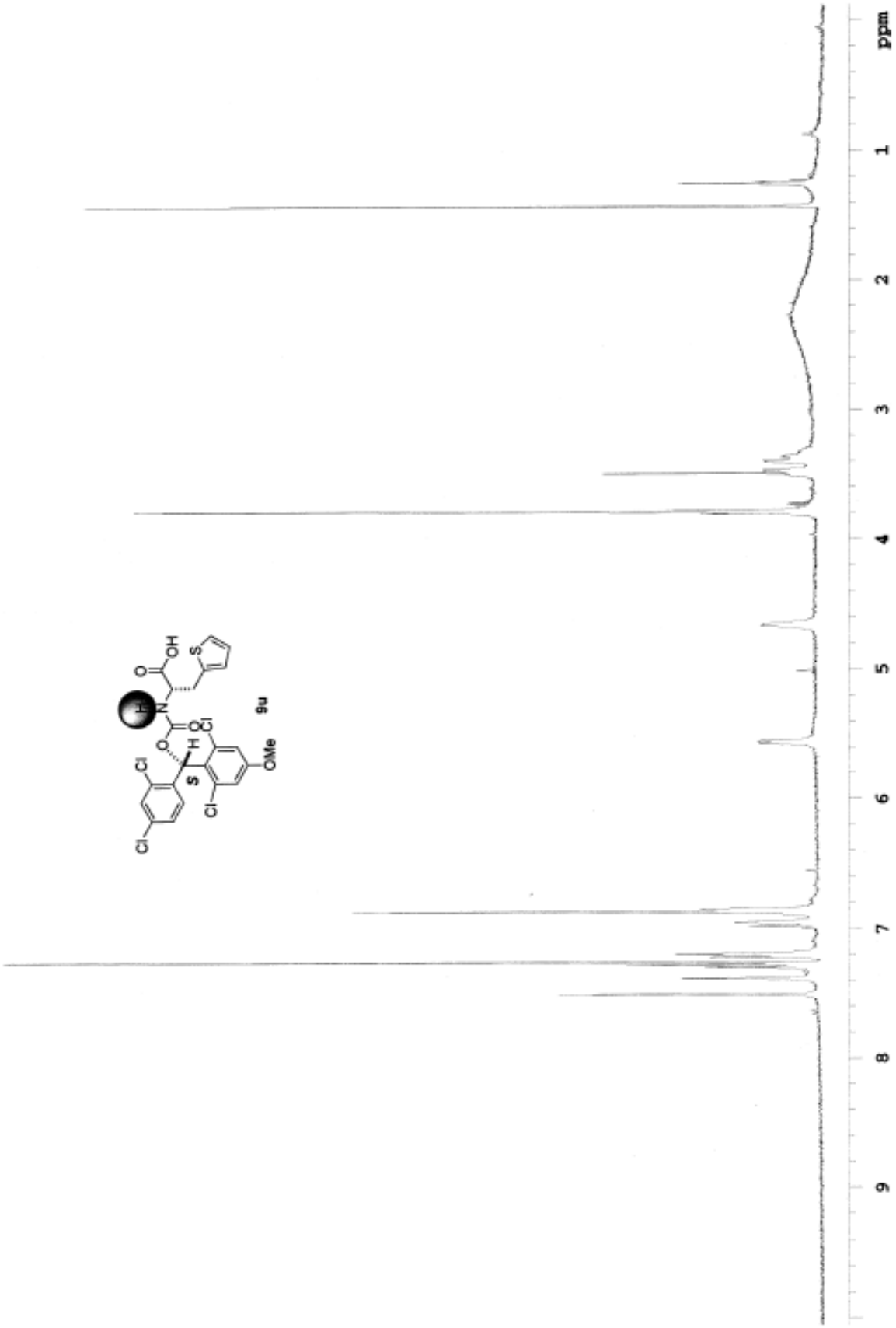

Cl
Cl
O
N
OH
Ph
S
H
O
Ph
Cl
Cl
OMe
9r

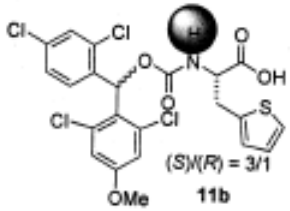

10
9
8
7
6
5
4
3
2
1
ppm


10r
OMe
Cl
Cl
Cl
Cl
H
R
H
O
O
N
HO
Ph
Ph
1.550
ppm
1
2
3
4
5
6
7
8
9
10


ppm
1
2
3
4
5
6
7
8
9
10
OBn
Ph
9t
Cl
OMe
S
H

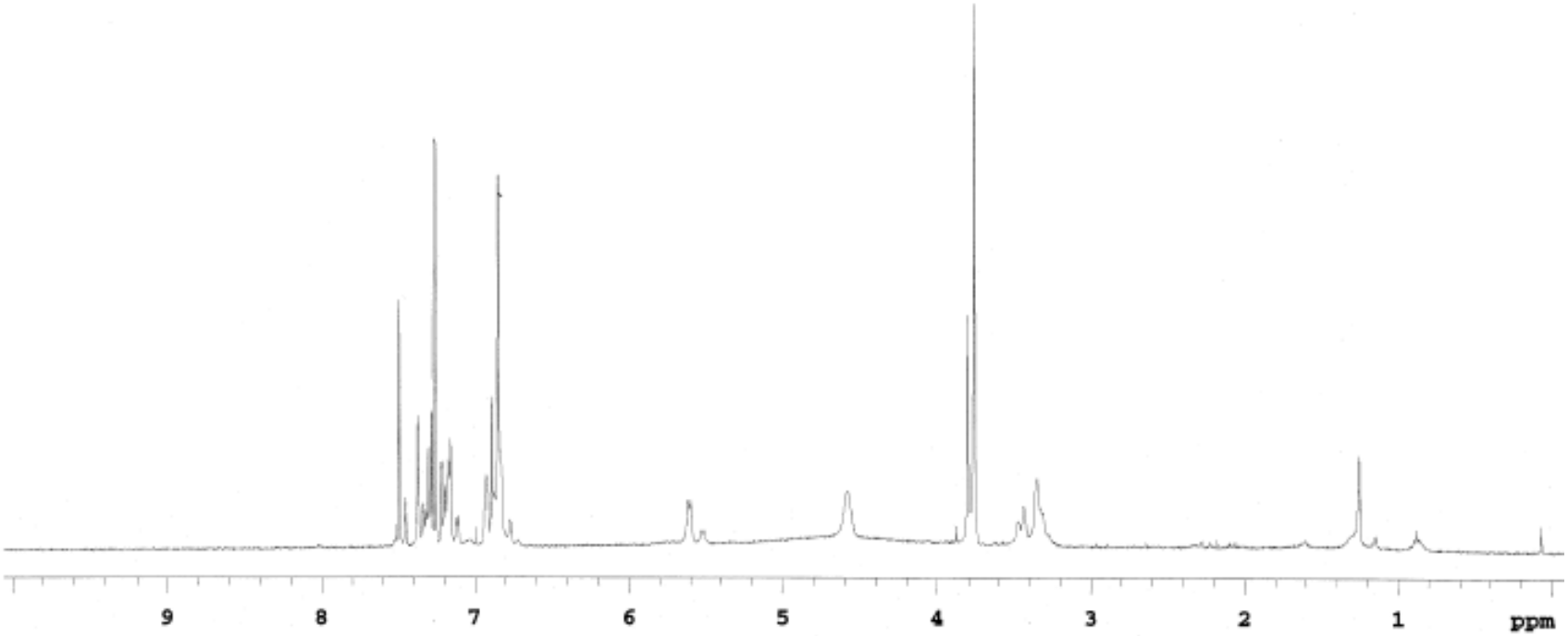

10t
ppm
1
2
3
4
5
6
7
8
9
10

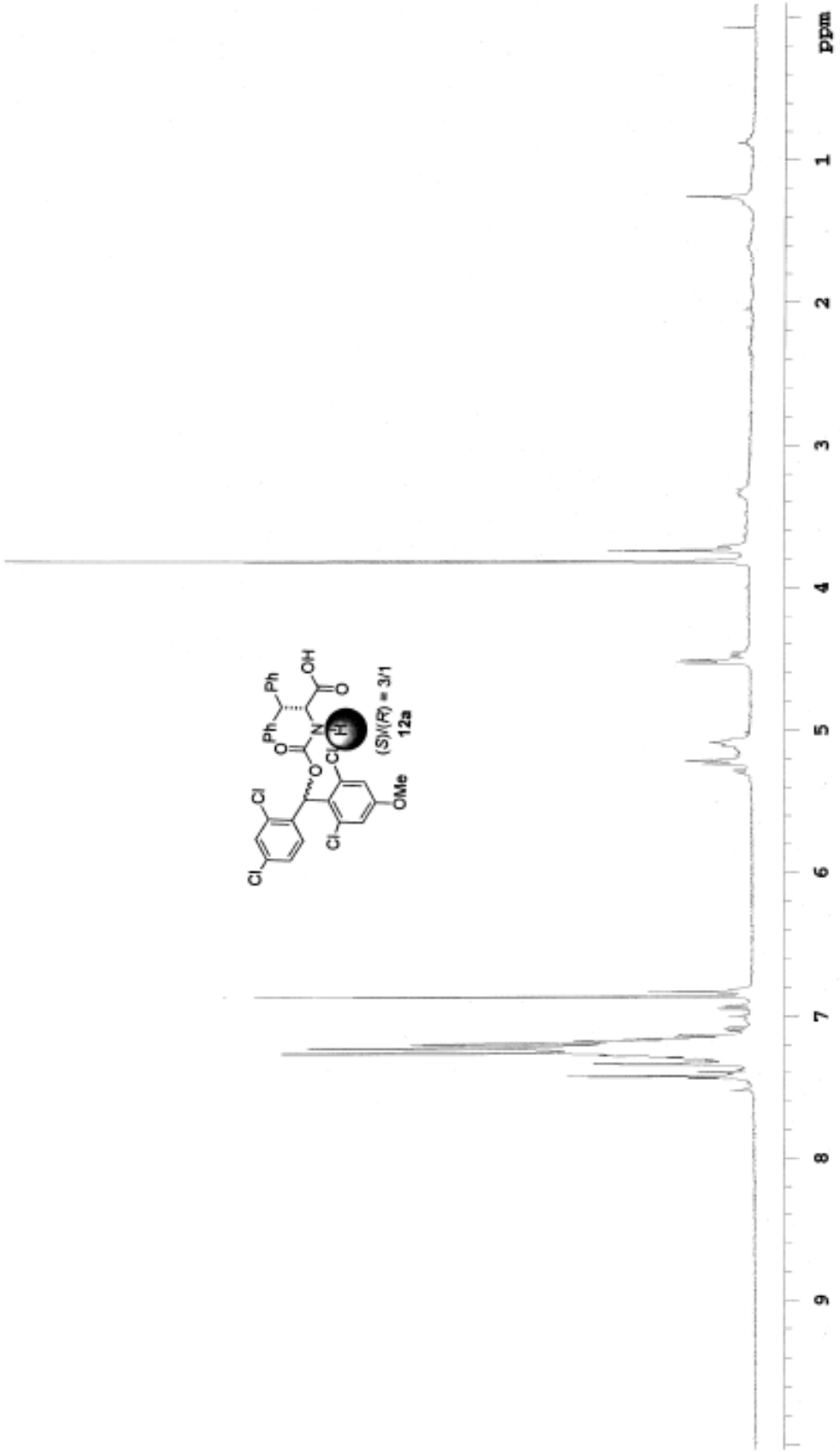

ppm
1
2
3
4
5
6
7
8
9
9u

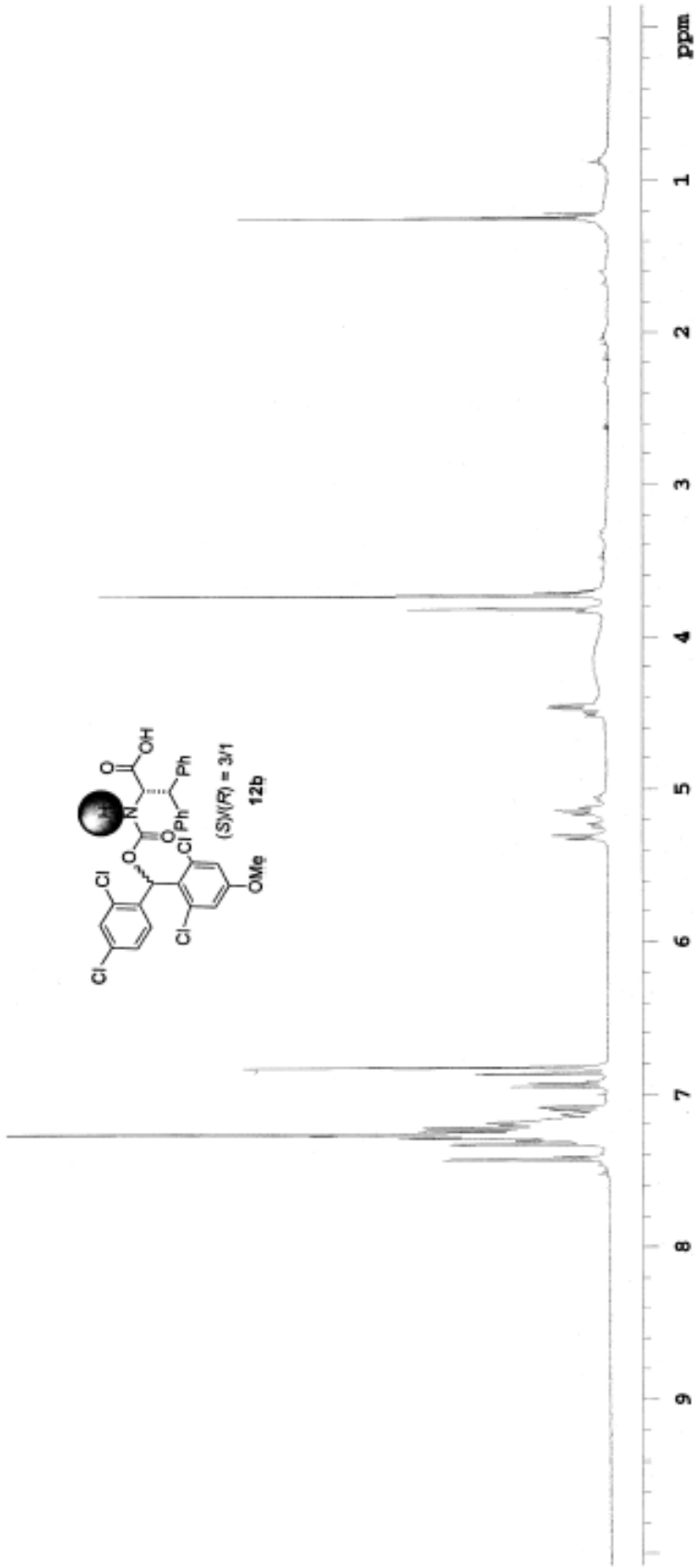


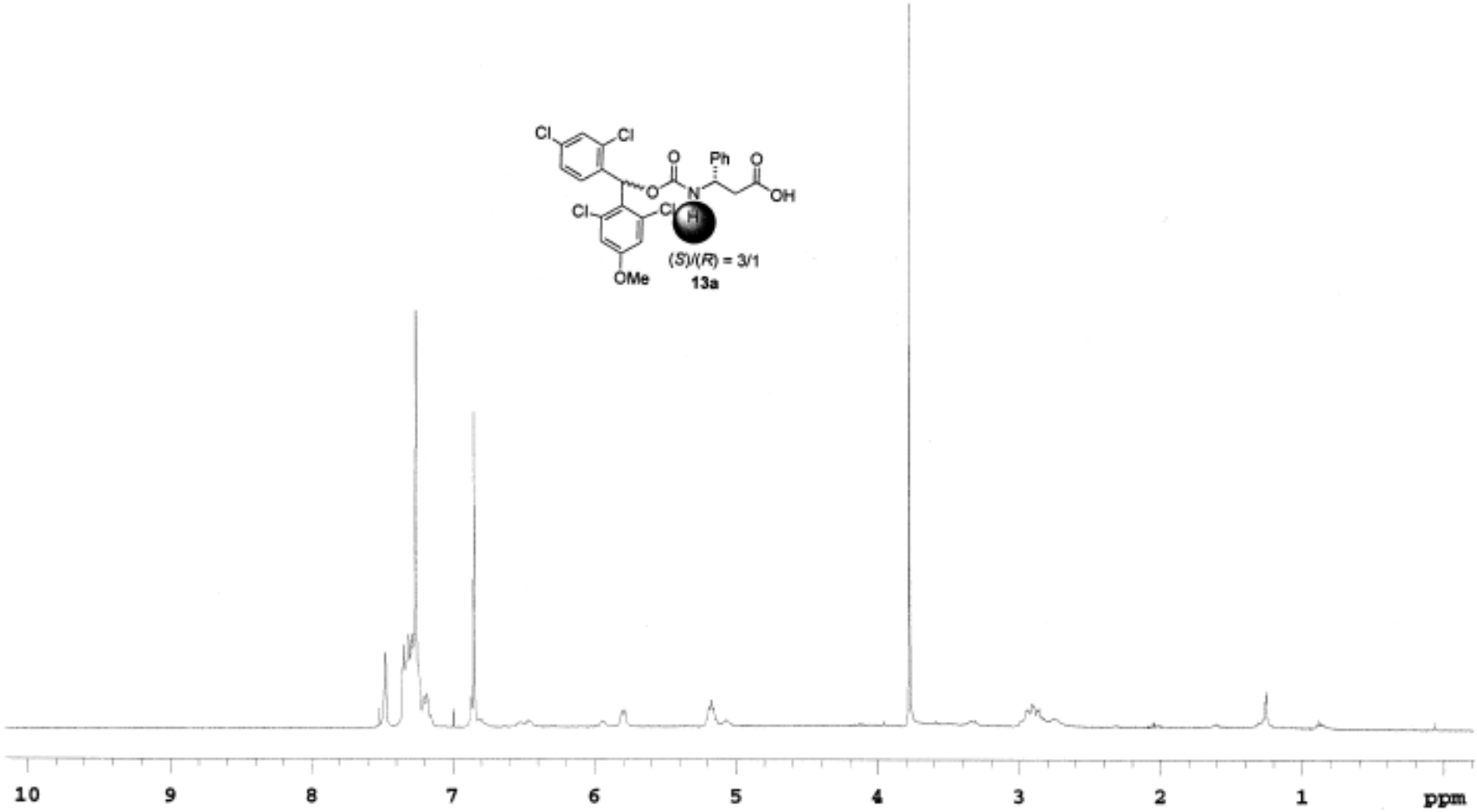
(*S*)/(*R*) = 3/1

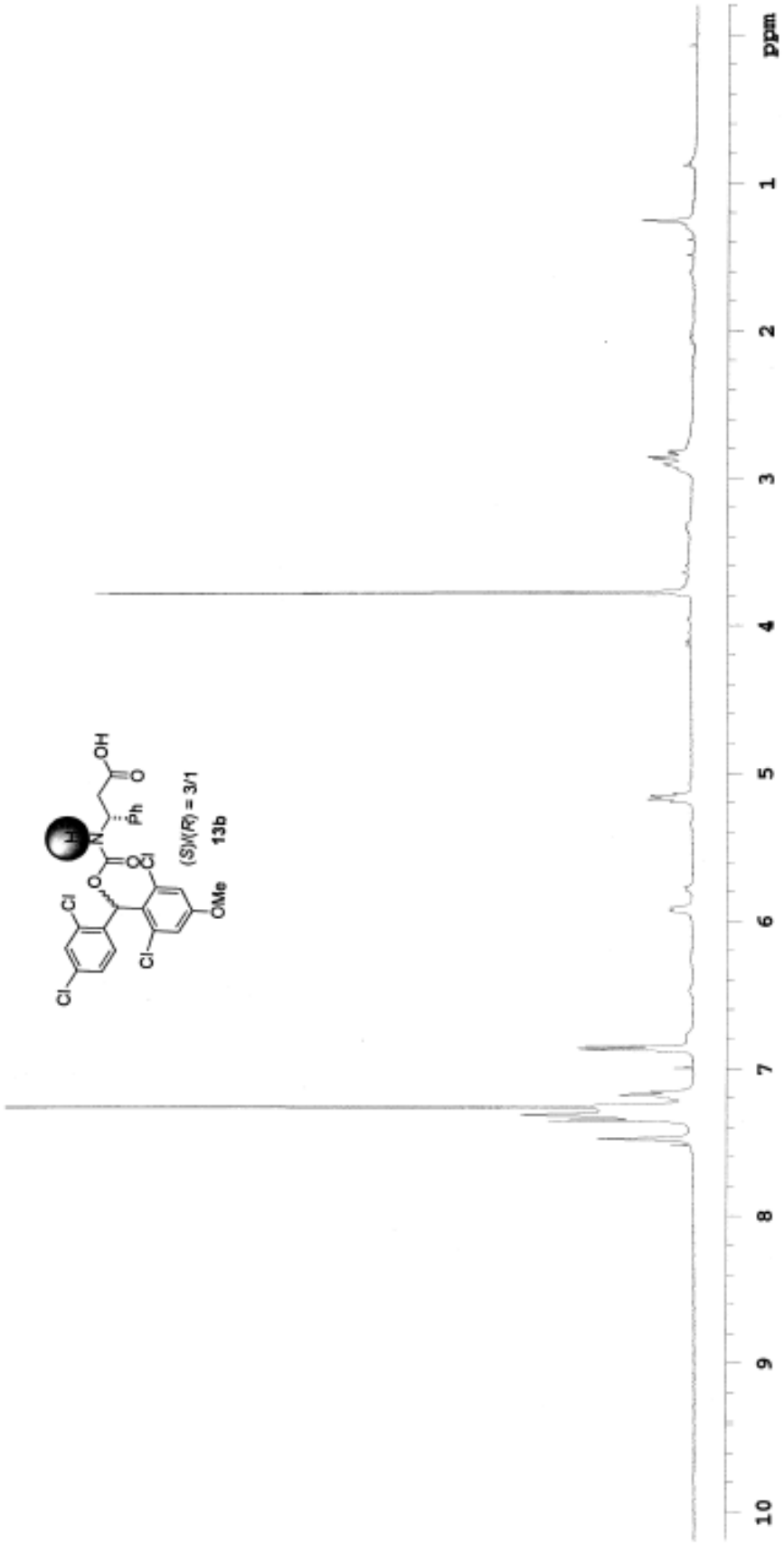
11b

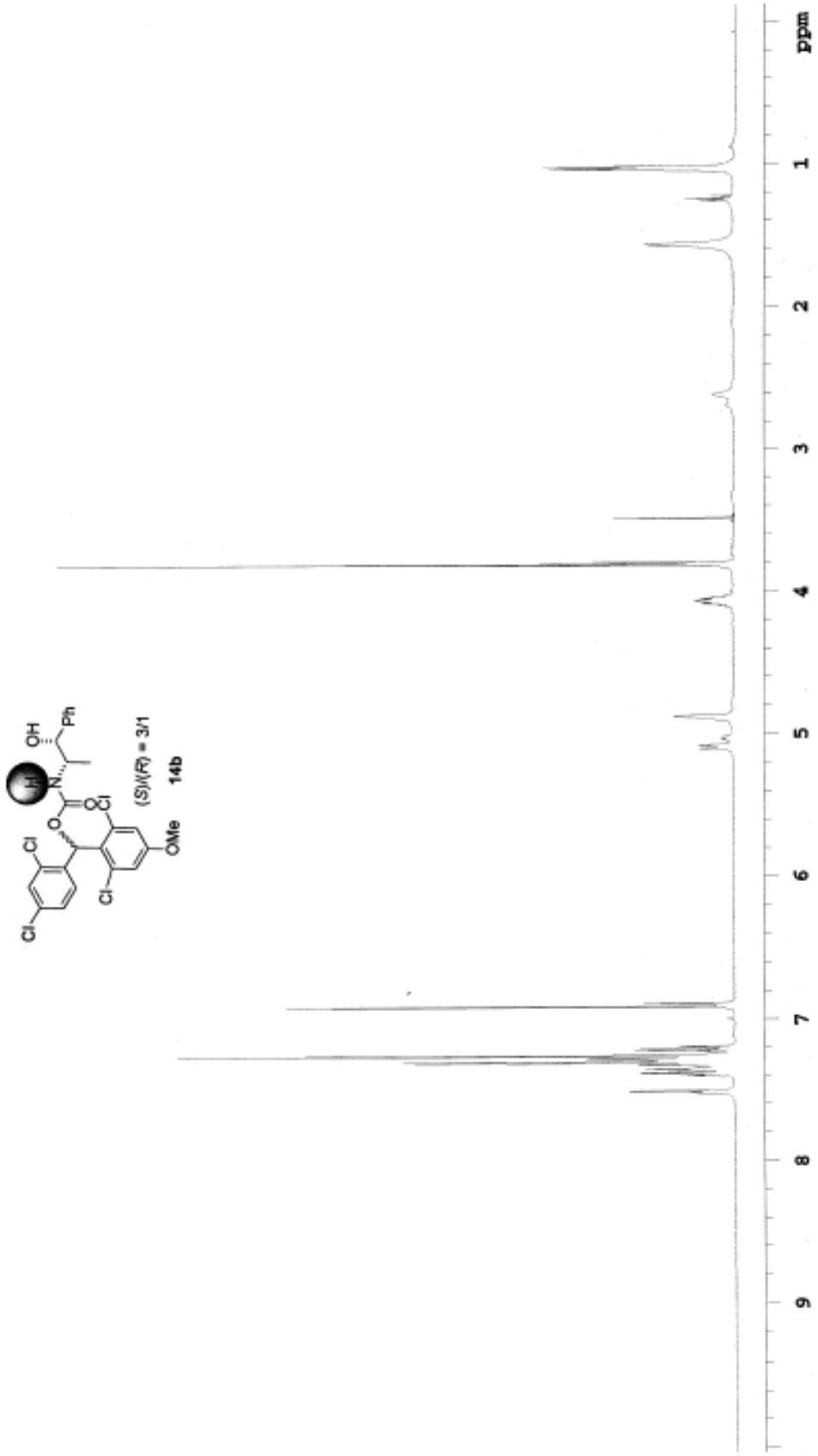


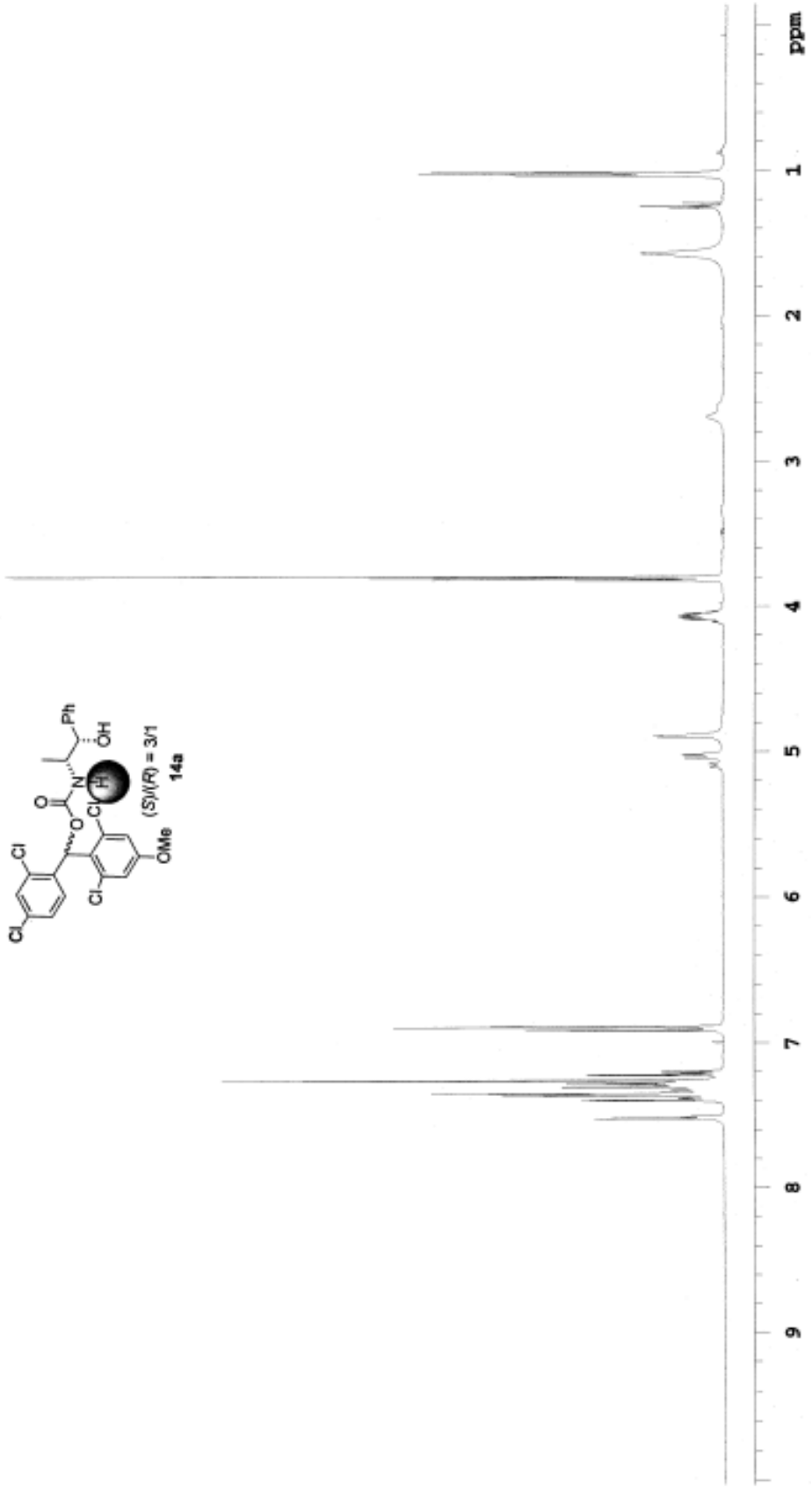

(S)/(R) = 3/1
12a
ppm

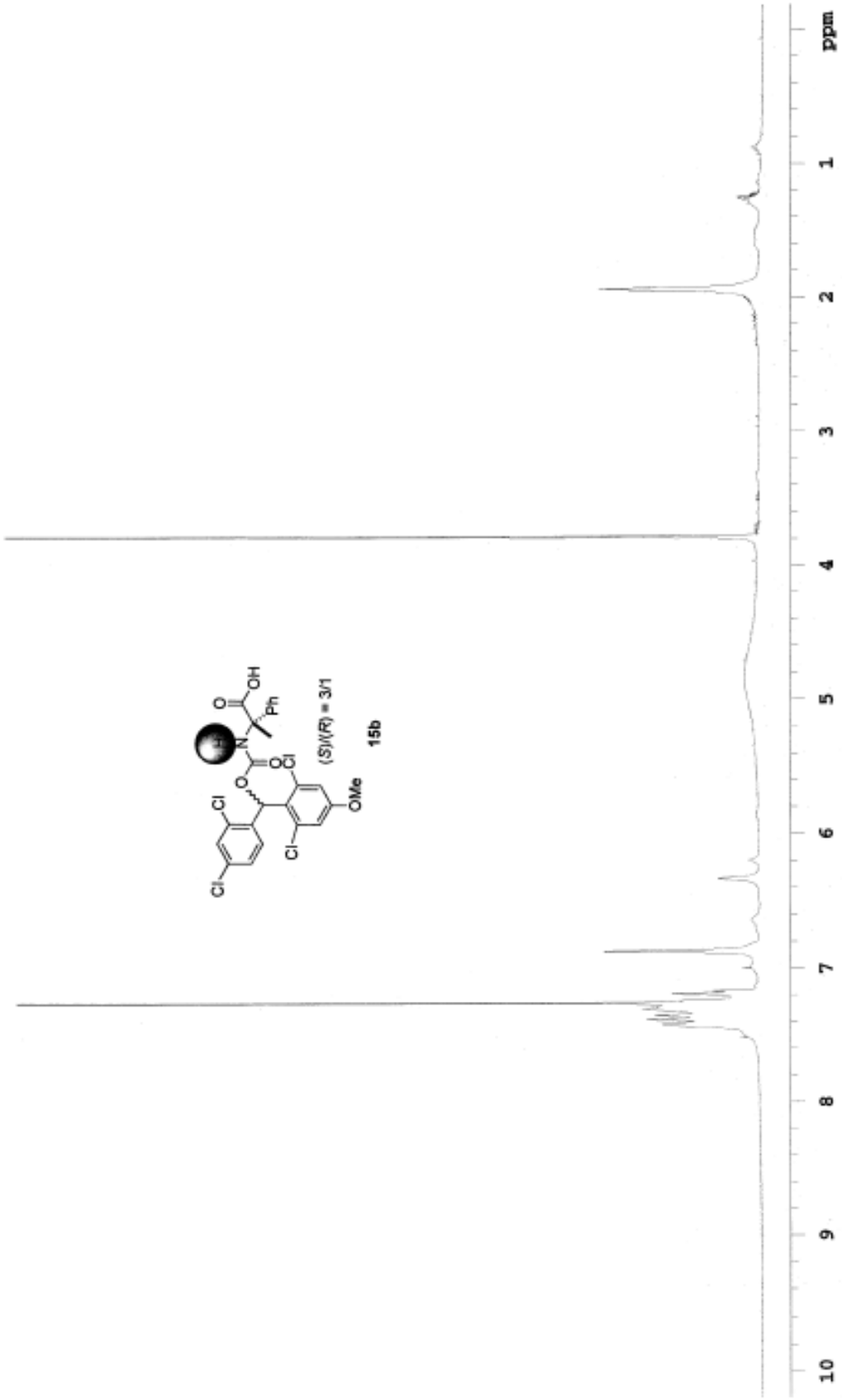

(S)/(R) = 3/1
12b
ppm

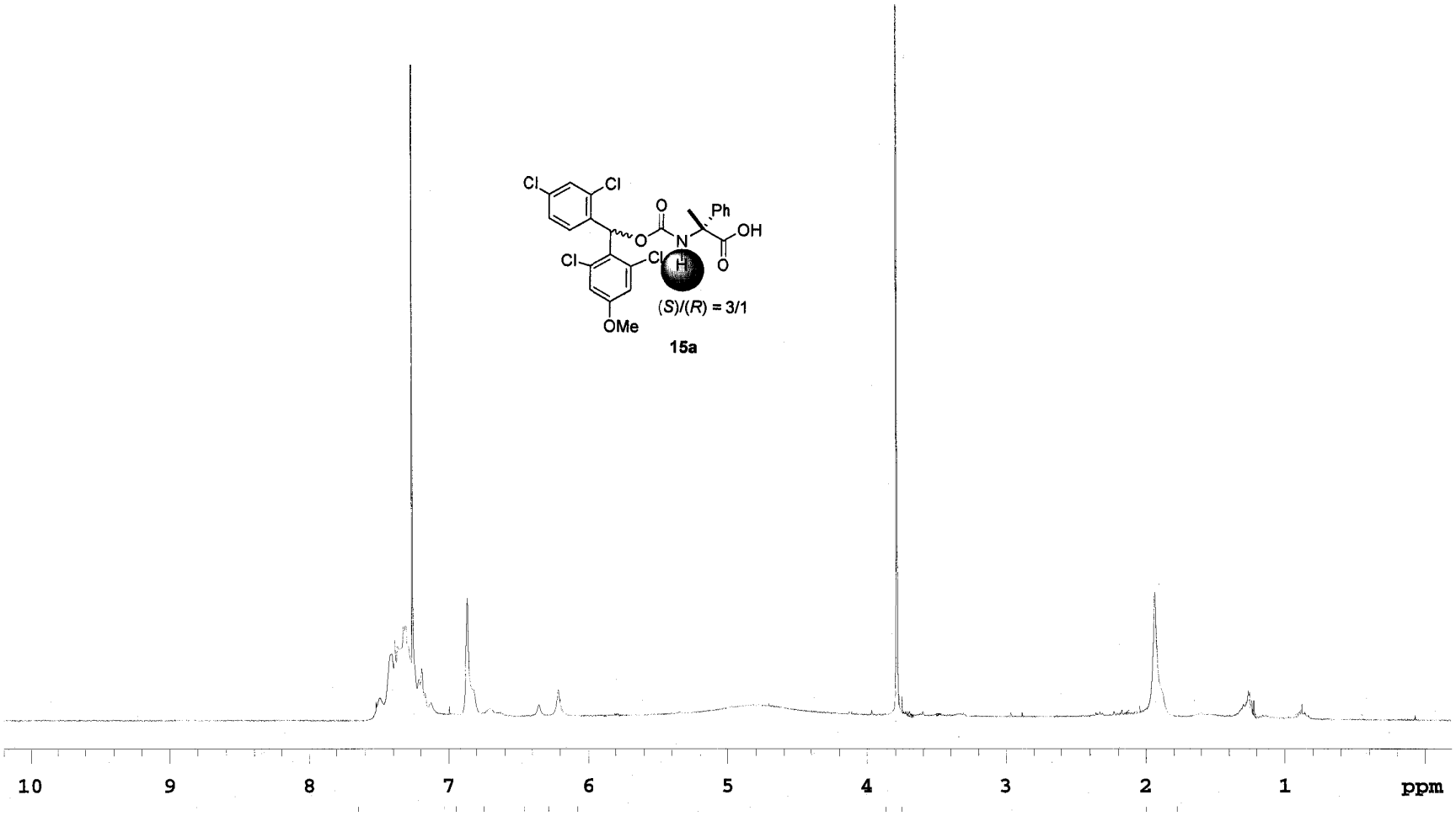

Cl
Cl
O
Ph
O
O
N
OH
Cl
Cl
H
OMe
(S)/(R) = 3/1
13a
10
9
8
7
6
5
4
3
2
1
ppm

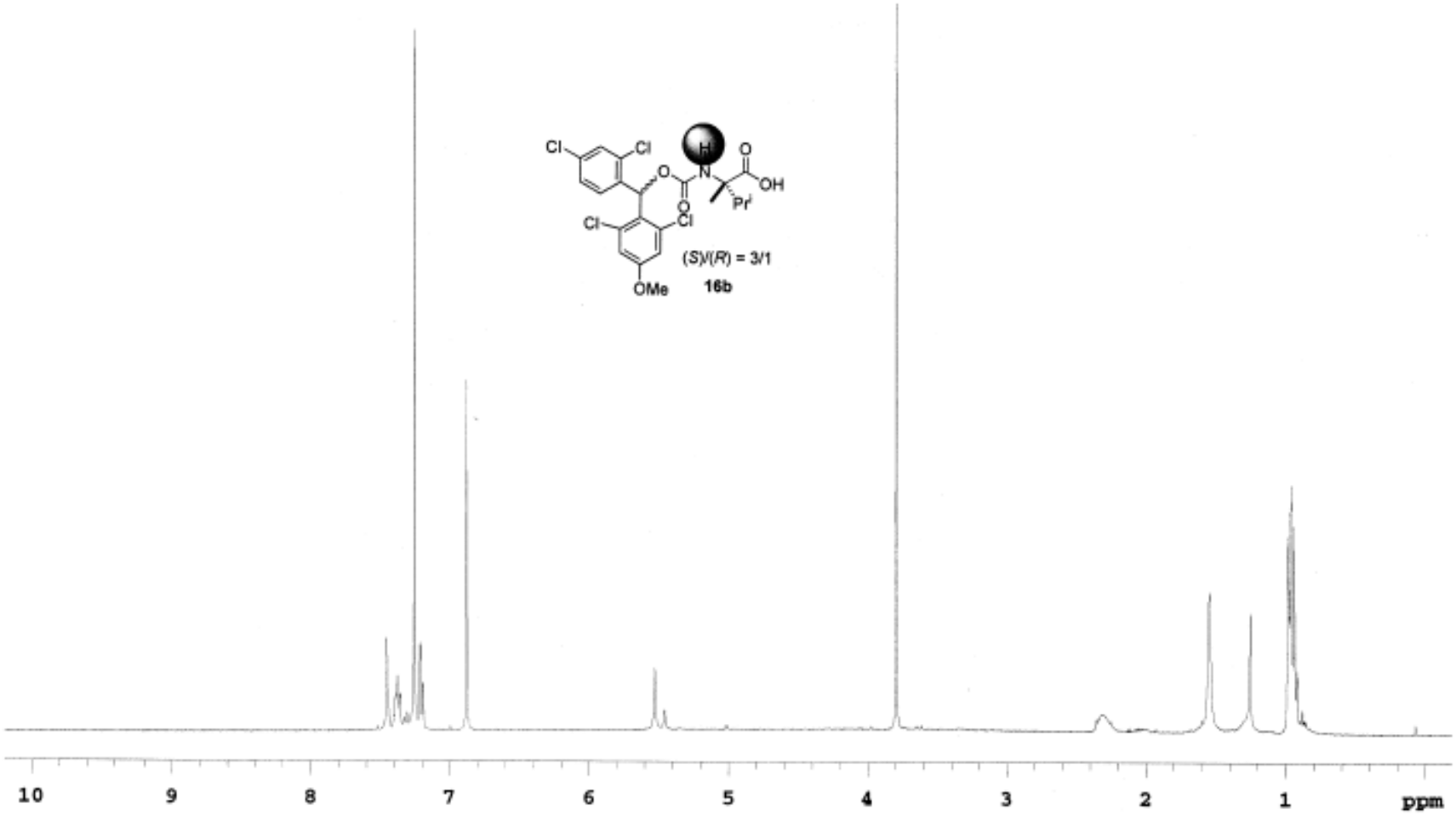

(S)/(R) = 3/1
13b
ppm

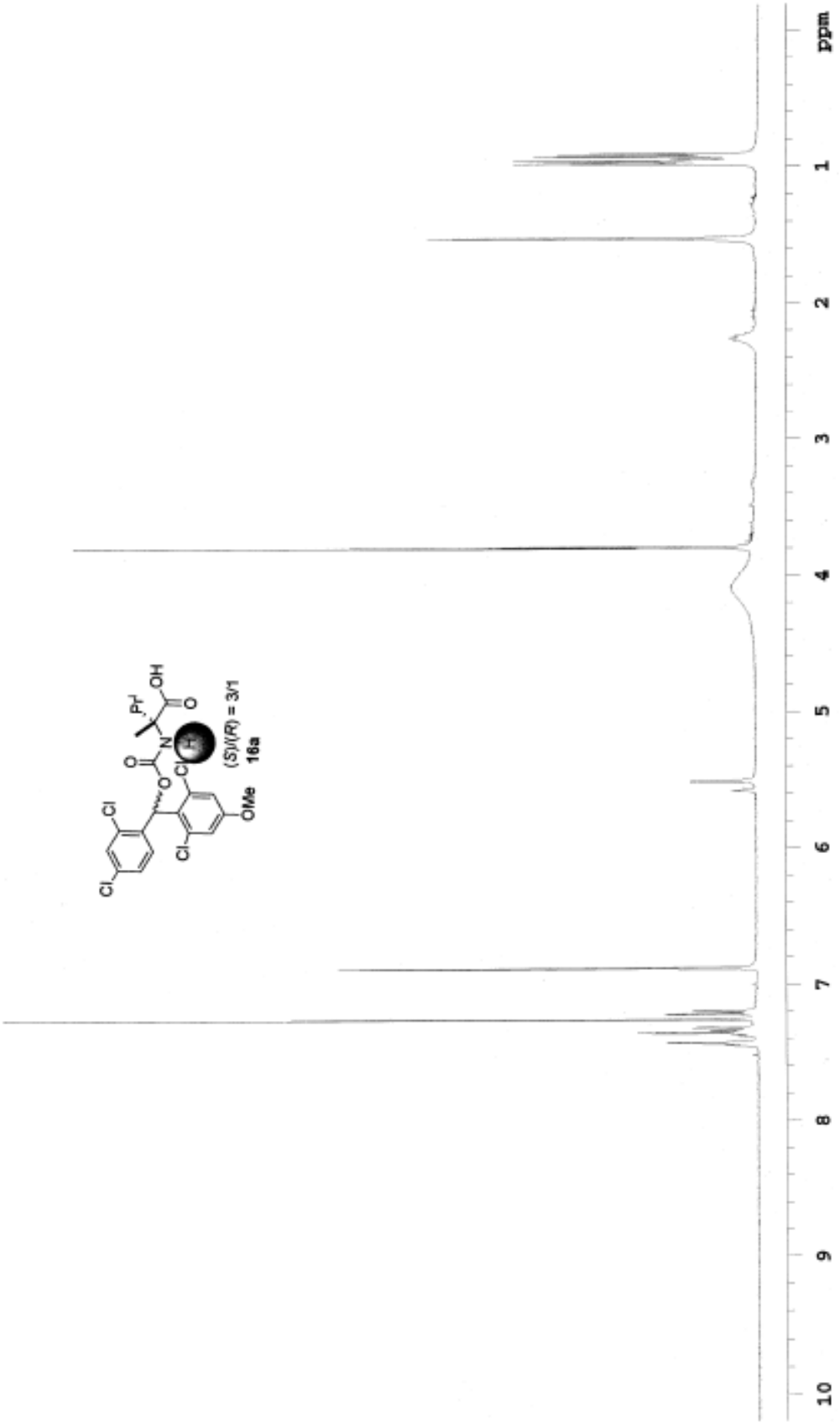

(S)/(R) = 3/1
14b
ppm

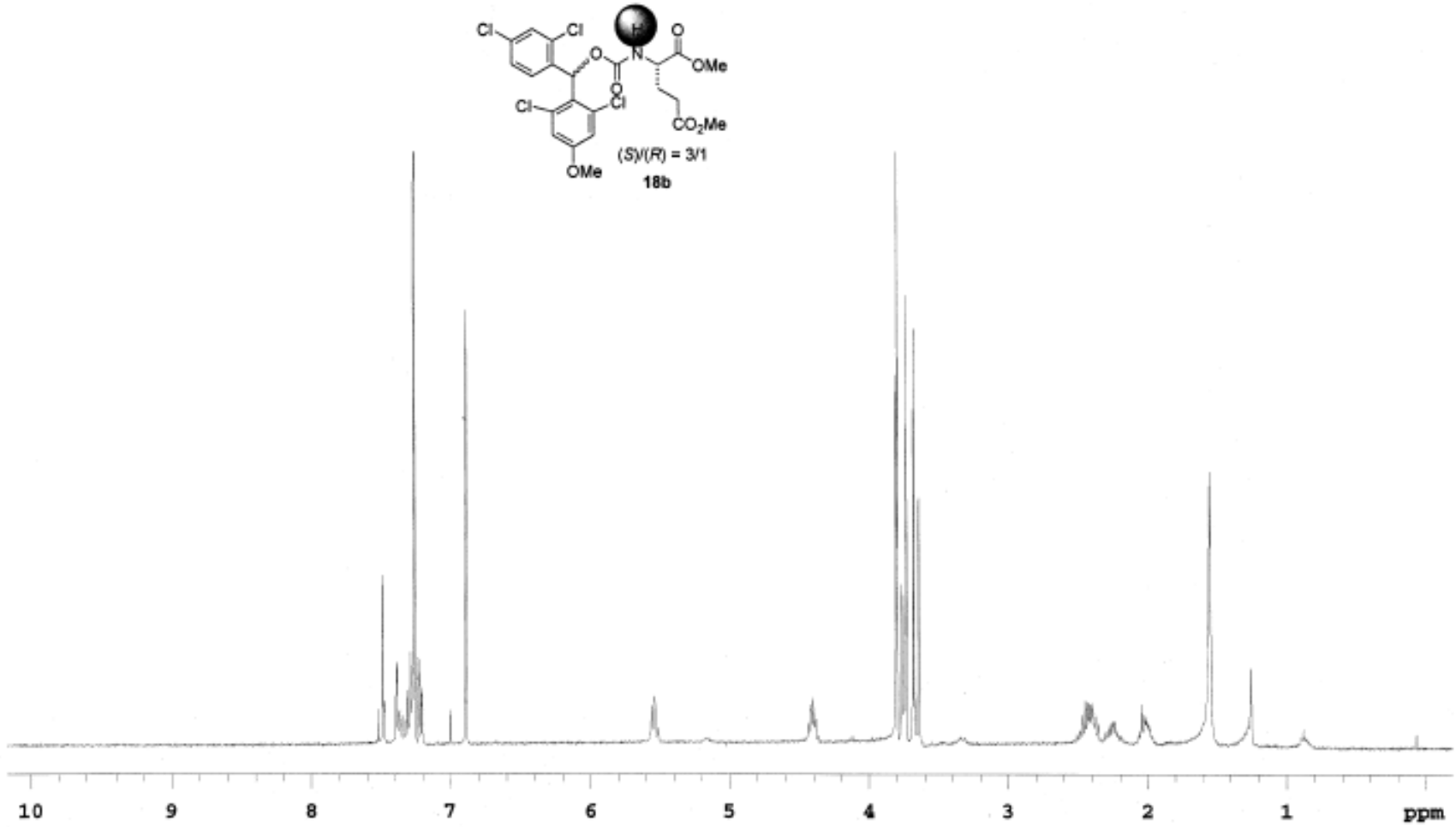

Cl
Cl
O
O
N
H
Cl
Cl
OMe
Ph
OH
(S)/(R) = 3/1
14a
ppm
1
2
3
4
5
6
7
8
9

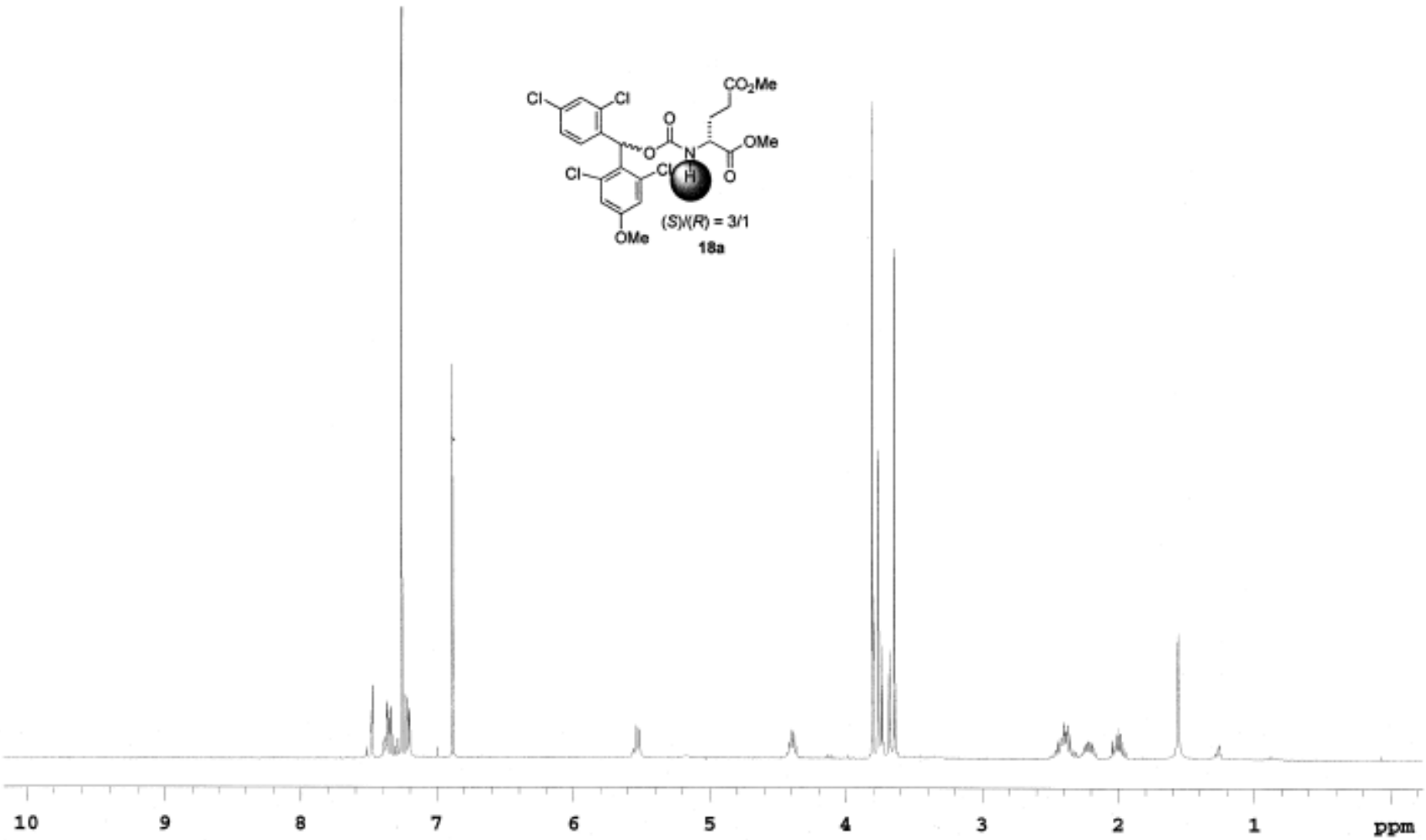

(S)/(R) = 3/1
15b
ppm

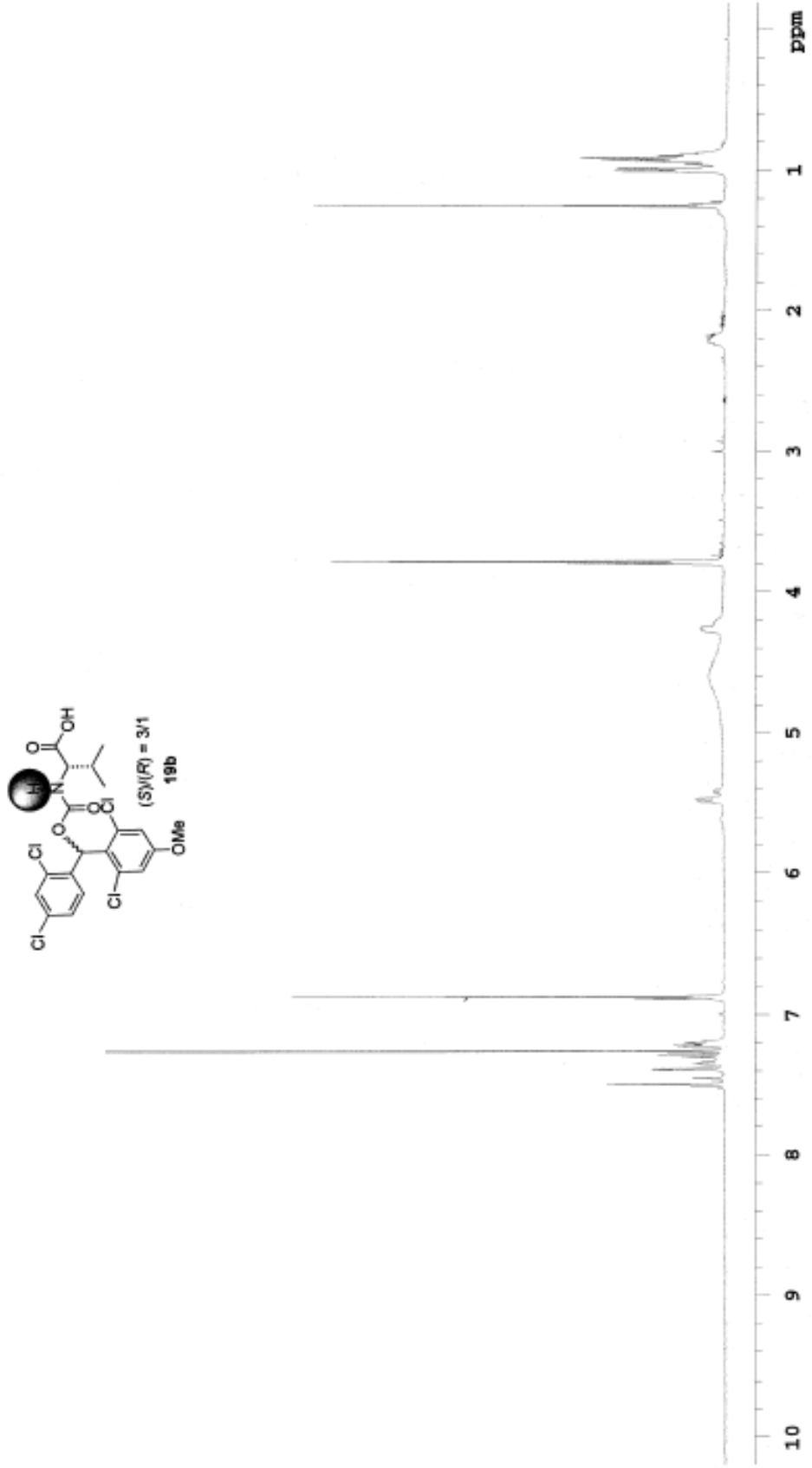

Cl
Cl
O
Ph
OH
O
N
Cl
Cl
H
O
OMe
(S)/(R) = 3/1
15a
10
9
8
7
6
5
4
3
2
1
ppm


Cl
Cl
O
O
H
N
O
OH
Pr^i
Cl
Cl
OMe
(S)/(R) = 3/1
16b
10
9
8
7
6
5
4
3
2
1
ppm

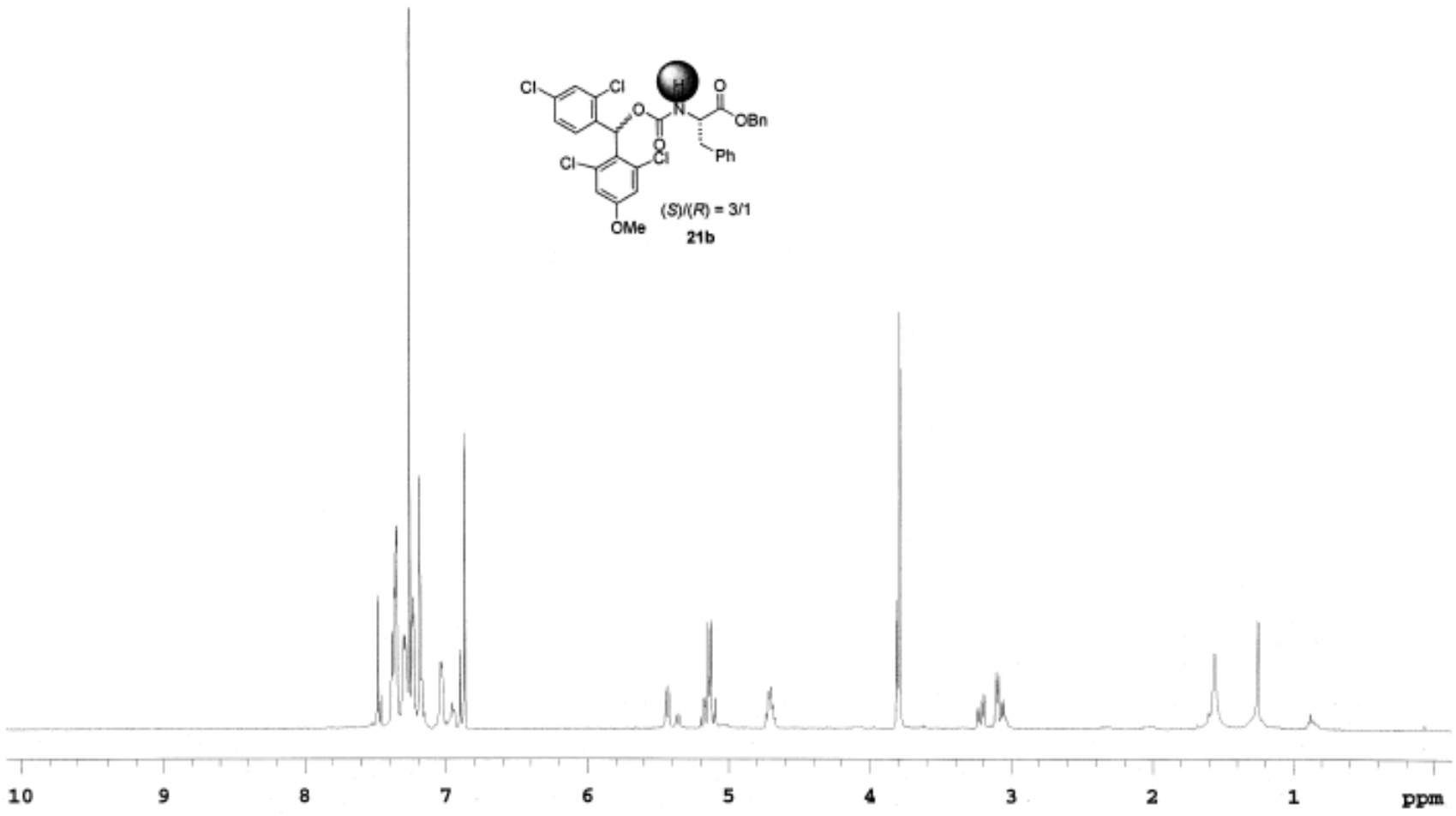

(S)/(R) = 3/1
16a
ppm

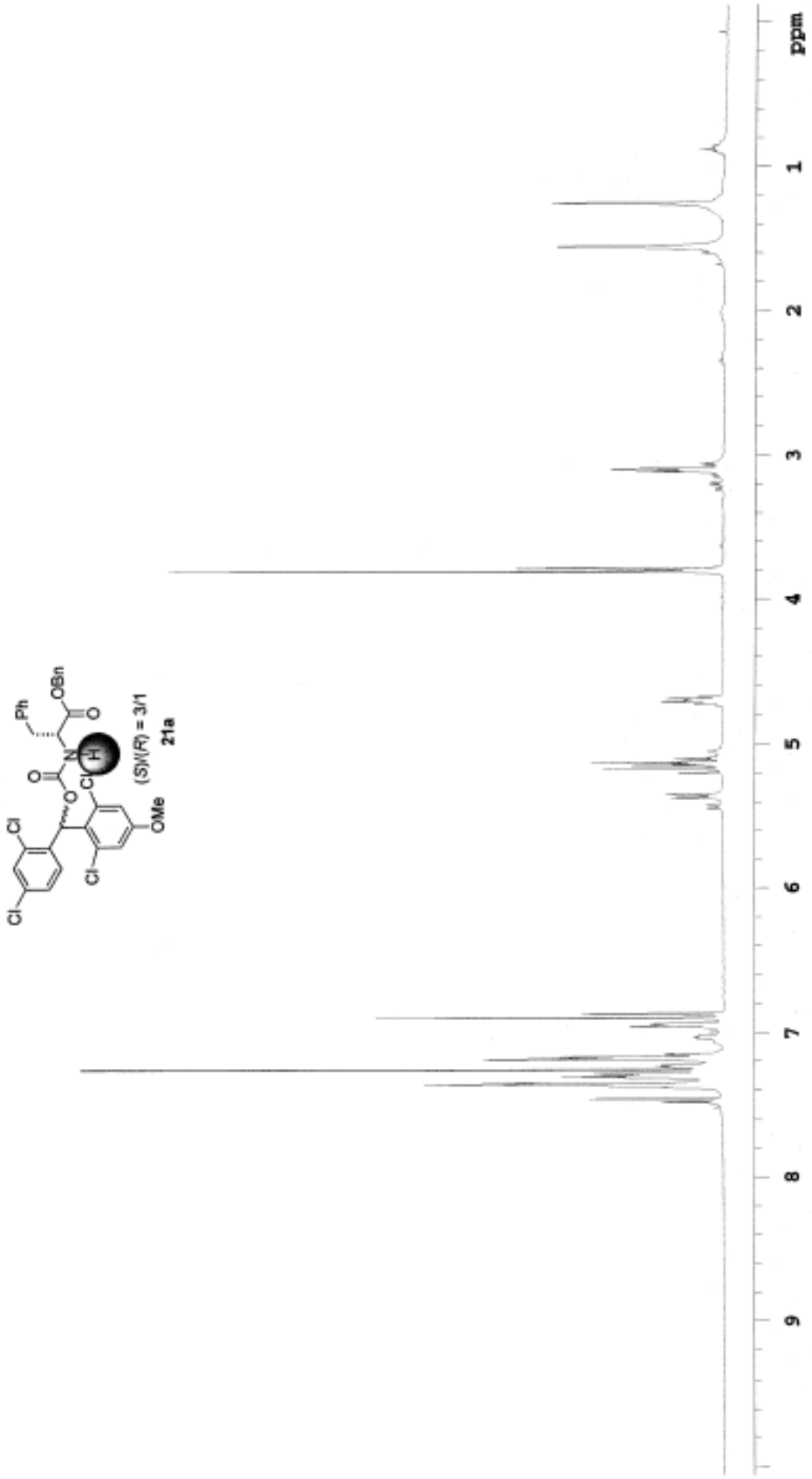

Cl
Cl
O
O
N
H
O
OMe
O
Cl
Cl
CO2Me
OMe
(S)/(R) = 3/1
18b
10
9
8
7
6
5
4
3
2
1
ppm


Cl
Cl
Cl
Cl
O
O
N
H
O
O
OMe
CO2Me
OMe
(S)/(R) = 3/1
18a
10
9
8
7
6
5
4
3
2
1
ppm


(S)/(R) = 3/1
19b
ppm


(S)/(R) = 3/1
20b
ppm


Cl
Cl
O
O
N
H
O
OBn
Ph
Cl
Cl
OMe
(S)/(R) = 3/1
21b
10
9
8
7
6
5
4
3
2
1
ppm


Ph
OBn
O
N
H
O
O
Cl
Cl
Cl
Cl
OMe
(S)/(R) = 3/1
21a
ppm
1
2
3
4
5
6
7
8
9