The First Practical Catalytic Asymmetric Addition of Alkyl Groups to Ketones

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Supporting Information

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General Methods. All reactions using diethylzinc and titanium(IV) isopropoxide were carried out in a Vacuum Atmospheres dry box or under nitrogen using standard Schlenck techniques. NMR spectra were obtained on a Bruker 250, 360 or 500 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were referenced to tetramethylsilane; $^{13}C\{^{1}H\}$ NMR spectra were referenced to residual solvent. All reagents were obtained from Aldrich Chemical Company; ketone substrates were obtained from Aldrich or Acros Organics unless otherwise specified. Titanium(IV) isopropoxide and all liquid ketone substrates were distilled prior to use. Solid 3-chloropropiophenone was recrystallized from pentane. 1.0 M diethylzinc and 1.4 M titanium(IV) isopropoxide solutions were prepared and stored in a Vacuum Atmospheres dry box.

Synthesis and Characterization of Ligands.

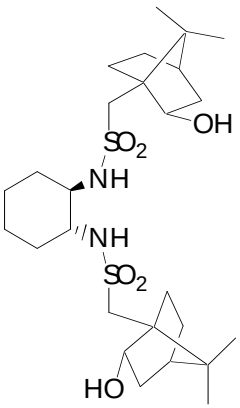
Preparation of Bis(sulfonamide) 4. Bis(sulfonamide) **4** was prepared according to literature procedure.[1]

Preparation of Bis(sulfonamide) 5. Bis(sulfonamide) **5** was prepared according to literature procedure.[1]

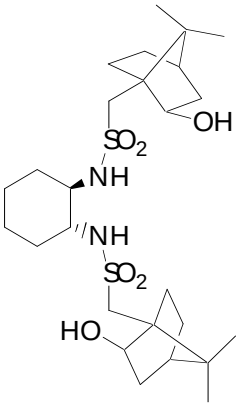
Preparation of Bis(sulfonamides) 6, 6b, ent-6 and ent-6b. Bis(sulfonamide) **4** (12 g, 22 mmol, 1.0 equiv) was charged to the reaction vessel with a 1 : 1 mixture of isopropyl alcohol and THF (400 mL). The bis(sulfonamide) was only partially soluble in this mixture. $NaBH_4$ (5.8 g, 150 mmol, 6.9 equiv) was added portionwise over 5 min and the turbid gray mixture quickly became homogeneous. The reaction mixture was stirred until the foaming subsided (about 0.5 h), then quenched carefully with sat. NH_4Cl (70 mL). The organic solvents were removed from the two-phase mixture under reduced pressure. Dichloromethane (100 mL) was added to the resulting aqueous mixture, then the organic layer was separated from the aqueous layer and washed with H_2O (2 x 20 mL). The aqueous fractions were combined and extracted with CH_2Cl_2 (2 x 50 mL). The organic fractions were combined, dried over Na_2SO_4, and concentrated to give 12 g of white foam. The diastereomers were separated by column chromatography (hexanes /

EtOAc : 70 / 30) to yield 6.7 g (55%) of **6** and 1.93 g (16%) of **6b** (**6** : **6b** = 3.5 : 1). The combined yield of **6** and **6b** was 8.6 g (71%).

The diastereomeric bis(sulfonamides) **ent-6** and **ent-6b** are the enantiomers of **6** and **6b** respectively. They were prepared by the same methods, except that the opposite enantiomers of the starting materials were used.



Data for 6: mp 181.5 - 182.3 °C; $[\alpha]_D^{20}$ = -34.4 (*c* 3.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84 (s, 6H), 1.07 (s, 6H), 1.08-1.2 (m, 2H), 1.26-1.43 (m, 4H), 1.43-1.56 (m, 2H), 1.66-1.88 (m, 12H), 2.09-2.21 (m, 2H), 2.92 (d, *J* = 13.6 Hz, 2H), 3.05-3.12 (m, 2H), 3.32 (d, *J* = 3.5 Hz, 2H), 3.50 (d, *J* =13.6 Hz, 2H), 4.01-4.12 (m, 2H), 5.07 (d, *J* = 7.3 Hz, 2H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 20.3, 20.9, 25.1, 27.7, 31.0, 35.1, 39.5, 44.9, 49.2, 51.0, 53.8, 54.4, 58.1 ppm; IR (KBr) 3528, 3298, 2938, 1456, 1390, 1372, 1319, 1146, 1075, 1058, 1028, 982, 903, 771, 701, 580 cm^{-1}; HRMS calcd for $C_{26}H_{46}N_2O_6S_2Na$ $(M + Na)^+$: 569.2695, found 569.2668.



Data for 6b: mp 203.8 - 204.2 °C; $[\alpha]_D^{20}$ = +0.73 (*c* 3.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.84 (s, 3H), 0.91 (s, 6H), 1.07 (s, 3H), 1.10-1.14 (m, 2H), 1.27-1.48 (m, 4H), 1.47-1.87 (m, 12H), 2.08-2.18 (m, 2H), 2.27-2.43 (m, 2H), 2.94 (d, *J* = 13.7 Hz, 1H), 3.03-3.18 (m, 4H), 3.31 (d, *J* = 3.3 Hz, 1H), 3.40 (d, *J* = 3.7 Hz, 1H), 3.52 (d, *J* = 13.7 Hz, 1H), 4.05-4.11 (m, 1H), 4.29-4.36 (m, 1H), 5.18 (d, *J* = 7.1 Hz, 1H), 5.42 (d, *J* = 7.1, 1H) ppm; ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 19.22, 20.34, 20.85, 20.89, 24.04, 25.08, 27.73, 28.61, 30.96, 34.78, 34.98, 38.69, 39.43, 44.46, 44.83, 49.15, 50.98, 51.70, 51.96, 54.40, 57.99, 58.09, 58.36, 75.91, 77.02 (one peak could not be located due to overlapping resonances) ppm; IR (KBr) 3519, 3289, 2940, 1452, 1391, 1372, 1317, 1147, 1075, 1023, 981, 905, 843, 772, 736, 702, 680 cm^{-1}; HRMS calcd for $C_{26}H_{46}N_2O_6S_2Na$ $(M + Na)^+$: 569.2695, found 569.2700.

Enantioselective Addition of Diethylzinc to Ketones.

General Procedure A. The bis(sulfonamide) ligand **6** (2 - 10 mol%) was weighed into the reaction vessel, and the diethylzinc solution (1.0 M toluene solution, 1.4 - 1.6 equiv) and the titanium(IV) isopropoxide (1.4 M toluene solution , 1.2 equiv) were added at room temperature. After 5 - 10 min, the substrate ketone (1.0 equiv) was added neat. The homogeneous reaction mixture was stirred at room temperature. After completion, it was quenched with saturated aqueous solution NH_4Cl, extracted into CH_2Cl_2, concentrated under reduced pressure, and purified by column chromatography or column filtration.

General Procedure B. General Procedure A was followed, except that the substrate (a solid) was added as a solution in toluene.

Preparation of 2-Phenyl-2-butanol (S1). [2, 3] The reaction with acetophenone (400 μL, 3.43 mmol) was performed according to general procedure A using 2 mol% (37.4 mg) of the bis(sulfonamide) ligand **6**. Chromatography on neutral alumina (hexanes / EtOAc : 99 / 1) afforded 293 mg (71% yield, 96% ee, (*S*)) of a colorless oil: $[\alpha]_D^{20}$ = -16.7 (*c* 0.72, Acetone). [Published $[\alpha]_D^{20}$ = -15.9 (*c* 1.50, Acetone, 96% ee)].[4]

Preparation of 2-(3-Methylphenyl)-2-butanol (S2). The general procedure A was applied to 3-methylacetophenone on a 0.15 mL (1.09 mmol) scale, using 10 or 2 mol% of the bis(sulfonamide) ligand **ent-6** (60 or 12 mg, respectivily). The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S2** (147 mg, 82.0% yield and 140 mg, 78% yield respectivily, 99.0% ee) as an oil: $[\alpha]_D^{20}$ = -4.08 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.71 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.44 (s, 3H), 1.73 (dq, *J* = 7.4, 7.4, 7.4, 14.9 Hz, 1H), 1.76 (dq, *J* = 7.4, 7.4, 7.4, 14.9 Hz, 1H), 2.27 (s, 3H), 6.95-6.97 (m, 1H), 7.11-7.17 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 8.7, 22.0, 30.0, 37.0, 75.3, 122.3, 126.0, 127.6, 128.4, 138.0, 148.2 ppm; IR (NaCl) 3420, 2970, 1606, 1456, 1373, 1162 cm^{-1}.

Preparation of 2-(4-Methoxyphenyl)-2-butanol (S3). The general procedure A was applied to 4-methoxyacetophenone on a 112 mg (0.73 mmol) scale, using 10 mol% of the bis(sulfonamide) ligand **6** (40 mg). The crude product was purified by column chromatography on silica gel (hexanes / EtOAc : 8 / 2) to give **S3** (112 mg, 85.2% yield, 94.0% ee) as an oil: $[\alpha]_D^{20}$ = -13.32 (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.50 (s, 3H), 1.76-1.82 (m, 2H), 3.78 (s, 3H), 6.83-6.86 (m, 2H), 7.31-7.34 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 8.8, 29.9, 37.1, 55.6, 75.0, 113.7, 126.5, 140.3, 158.5 ppm; IR (NaCl) 3444, 2967, 1610, 1300, 1179 cm^{-1}; MS (*m/z* relative intensity) 180 $(M)^+$ (7), 165 $(M-CH_3)^+$ (5), 163 $(M-OH)^+$ (49), 162 $(M-H_2O)$ (15); HMRS calcd for $C_{11}H_{15}$ $(M - OH)^+$: 163.1122, found 163.1129.

Preparation of 2-(3-Trifluoromethylphenyl)-2-butanol (S4). The general procedure A was applied to 3-(trifluoromethyl)acetophenone on a 0.14 mL (0.91 mmol) scale, using 2 mol% of the bis(sulfonamide) ligand **ent-6** (10 mg). The crude was purified by neutral alumina column chromatography (hexanes / EtOAc : 9 / 1) to give **S4** (107 mg, 55.5% yield, 98.0% ee) as an oil: $[\alpha]_D^{20}$ = +8.82 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.54 (s, 3H), 1.81-1.87 (m, 2H), 7.42-7.43 (m, 1H), 7.47 (m, 1H), 7.57-7.59 (m, 1H), 7.70 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 8.5, 30.0, 37.0, 75.1, 122.2, 123.7, 124.7 (q, *J* = 270.5 Hz), 128.8, 128.9, 130.8 (q, *J* = 31.8 Hz), 149.1 ppm; IR (NaCl) 3409, 2974, 1613, 1166 cm^{-1}; MS (*m/z* relative intensity) 218 $(M)^+$ (29), 217 $(M-1)^+$ (78), 200 $(M-H_2O)^+$ (10), 185 (12); HRMS calcd for $C_{11}H_{12}$ $(M - OH)^+$: 201.0891, found 201.0889.

Preparation of 2-(2-Methylphenyl)-2-butanol (S5).[5] The general procedure A was applied to 2-methylacetophenone on a 0.14 mL (1.09 mmol) scale, using 10 mol% of the bis(sulfonamide) ligand **ent-6** (60 mg). The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S5** (44 mg, 24.4% yield, 96.0% ee) as an oil: $[\alpha]_D^{20}$ = +7.0 (*c* 1.8, $CHCl_3$).

Preparation of 1-Ethyl-1,2,3,4-tetrahydro-naphthalen-1-ol (S6).[2, 3] Diethylzinc addition to α-tetralone (133 μL, 1.00 mmol) was performed according to general procedure A using 10 mol% of the bis(sulfonamide) ligand **6** (54.7 mg). The resulting oil was purified by column chromatography (hexanes / EtOAc : 96 / 4) to yield 35% of a yellow oil (>99% ee): $[\alpha]_D^{20}$ = -0.67 (*c* 2.2, MeOH). [Published $[\alpha]_D^{20}$ = -1.61 (*c* 2.3, MeOH, 89% ee)].[3]

Preparation of 3-Phenyl-3-heptanol (S7).[3] The general procedure A was applied to valerophenone on a 0.15 mL (0.91 mmol) scale, using 10 or 2 mol% of the bis(sulfonamide) ligand **ent-6** (50 or 10 mg). The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S7** (146 mg, 83% yield and 138 mg, 79% yield respectivily, 87-88% ee) as an oil: $[\alpha]_D^{20}$ = +2.42 (*c* 2.2, $CHCl_3$);

Preparation of 1-Chloro-3-phenyl-3-pentanol (S8). Diethylzinc addition to 3-chloropropiophenone (0.5 g, 2.97 mmol) was performed according to general procedure B using 10 mol% of the bis(sulfonamide) ligand **6** (162.1 mg). The crude product was filtered through a pad of basic alumina with EtOAc (200 mL) to yield 485 mg of **S8** (82% yield, 88% ee) as a colorless oil: $[\alpha]_D^{20}$ = -21.0 (*c* 3.0, MeOH); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 0.76 (dd, *J* = 7.6, 7.6 Hz, 3H), 1.76-1.90 (m, 2H), 2.25-2.34 (m, 2H), 3.20-3.29 (m, 1H), 3.48-3.60 (m, 1H), 7.20-7.39 (m, 5H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 90 MHz) δ 7.55, 36.08, 40.58, 45.46, 77.00, 125.20, 126.92, 128.45, 144.33 ppm; IR (KBr) 3566, 3462, 3087, 3060, 3027, 2969, 2936, 2879, 1602, 1494, 1446, 1340, 1251, 1173, 1124, 1074, 1055, 1031, 1014, 989, 900, 762, 702, 611 cm^{-1}; HRMS calcd for $C_{11}H_{14}Cl$ $(M - OH)^+$: 181.0784, found 181.0789 (chlorine splitting pattern observed).

Preparation of 2-(1-Cyclohexenyl)-2-butanol (S9).[2, 3] Diethylzinc addition to 1-(1-cyclohexenyl)-ethanone (1.04 mL, 8.05 mmol) was performed according to general procedure A using 2 mol% of bis(sulfonamide) ligand **ent-6** (88 mg). The product was purified by column

chromatography (hexanes / EtOAc : 96 / 4) to give 697.1 mg of **S9** (56% yield, 96% ee) of a colorless oil: $[\alpha]_D^{20}$ = +5.9 (*c* 3.0, MeOH). [Published $[\alpha]_D^{20}$ = +0.7 (*c* 3.0, MeOH, 51% ee)].[3]

Preparation of (1*E*)-3-Methyl-1-phenyl-1-penten-3-ol (S10).[3] The general procedure A was applied to *trans*-4-phenyl-3-buten-2-one on a 134 mg (0.91 mmol) scale, using 2 mol% of the bis(sulfonamide) ligand **6** (10 mg). The crude was purified by column chromatography on silica gel (hexanes / EtOAc : 95 / 5) to give **S10** (128 mg, 79.7% yield, 90.3% ee) as an oil: $[\alpha]_D^{20}$ = -14.7 (*c* 1.9, $CHCl_3$).

Preparation of 3-Methyl-1-phenyl-3-pentanol (S11). The general procedure A was applied to 4-phenyl-2-butanone on a 0.16 mL (1.09 mmol) scale, using 10 mol% of the bis(sulfonamide) ligand **6** (60 mg). The crude was purified by column chromatography on silica gel (Hexanes / EtOAc : 80 / 20) to give **S11** (132 mg, 67.6% yield, 70.0% ee) as an oil: $[\alpha]_D^{20}$ = -1.7 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (dd, *J* = 7.5, 7.5 Hz, 3H), 1.21 (s, 3H), 1.53-1.58 (m, 2H), 1.73-1.77 (m, 2H), 2.65-2.68 (m, 2H), 7.17-7.20 (m, 3H), 7.25-7.28 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 8.6, 26.7, 30.7, 34.8, 43.6, 73.2, 126.1, 128.7, 128.8, 143.1 ppm; IR (NaCl) 3393, 3025, 1603, 1454, 1147 cm^{-1}; MS (*m/z* relative intensity) 200 $(M+Na-1)^+$ (32), 165 (18), 164 (15), 159 $(M-H_2O)^+$ (12), 145 (8); HMRS calcd for $C_{12}H_{17}$ $(M-OH)^+$: 161.1330, found 161.1329.

Conditions for the Determination of Enantiomeric Excess.

The racemic alcohols were prepared by addition of ethylmagnesium bromide to the corresponding ketone. The tertiary alcohols **S1**, **S2**, **S4 - S7**, and **S9** were analyzed by chiral capillary GC. The specifications for the GC analyses were as follows: Fused silica chiral capillary column (Supelco β-Dex 120): 30 m x 0.25 mm (id) x 0.25 μm film thickness. Carrier gas: nitrogen. Inlet temperature: 250 °C. Detector: FID, 270 °C. The conditions for the resolution of the racemates by GC are given below.

2-Phenyl-2-butanol (S1). t_1 = 25.8 min, t_2 = 26.7 min (110 °C, 1.0 mL/min).

2-(3-Methylphenyl)-2-butanol (S2). t_1 = 38.1 min, t_2 = 40.6 min (105 °C, 1.5 mL/min).

2-(3-Trifluoromethylphenyl)-2-butanol (S4). t_1 = 21.2 min, t_2 = 22.7 min (110 °C, 1.0 mL/min).

2-(2-Methylphenyl)-2-butanol (S5). t_1 = 47.3 min, t_2 = 49.6 min (110 °C, 1.0 mL/min).

1-Ethyl-1,2,3,4-tetrahydro-naphthalen-1-ol (S6). t_1 = 38.2 min, t_2 = 41.9 min (125 °C, 2.5 mL/min).

3-Phenyl-3-heptanol (S7). t_1 = 57.1 min, t_2 = 59.5 min (110 °C, 1.5 mL/min).

2-(1-Cyclohexenyl)-2-butanol (S9). t_1 = 20.8 min, t_2 = 21.9 min (110 °C, 1.0 mL/min).

Chiral HPLC analyses of **S3**, **S8**, **S10** and **S11** were performed using a Chiralcel OD-H column. The conditions for the resolution of the racemates are described below.

2-(4-Methoxyphenyl)-2-butanol (S3). t_1 = 23.7 min, t_2 = 28.2 min (hexane / 2-propanol : 99 / 1, 0.8 mL/min).

1-Chloro-3-phenyl-3-pentanol (S8). t_1 = 42.7 min, t_2 = 53.2 min (hexane / 2-propanol : 98 / 2, 0.7 mL/min).

(1*E*)-3-Methyl-1-phenyl-1-penten-3-ol (S10). t_1 = 25.8 min, t_2 = 29.8 min (hexane / 2-propanol : 95 / 5, 0.5 mL/min).

3-Methyl-1-phenyl-3-pentanol (S11). t_1 = 59.1 min, t_2 = 64.7 min (Hexane / 2-propanol : 99.4 / 0.6, 1.0 mL/min).

References.

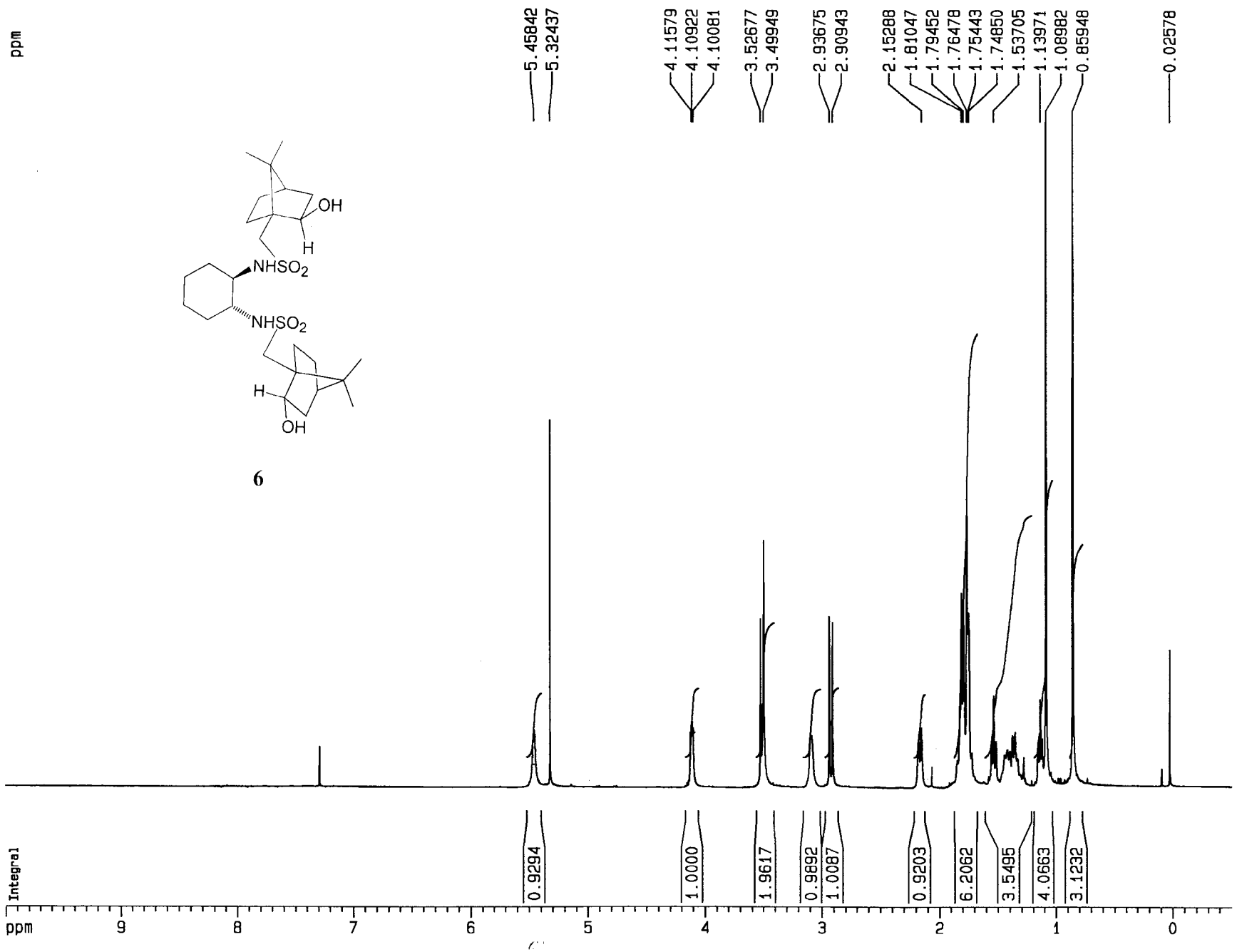
1) Balsells, J. ; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250-3251.

2) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 6117-6128.

3) Ram n, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651-5666.

4) Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112-6114.

5) Musser, C. A.; Richer Jr., H. G. *J. Org. Chem.* **2000**, *65*, 7750-7756.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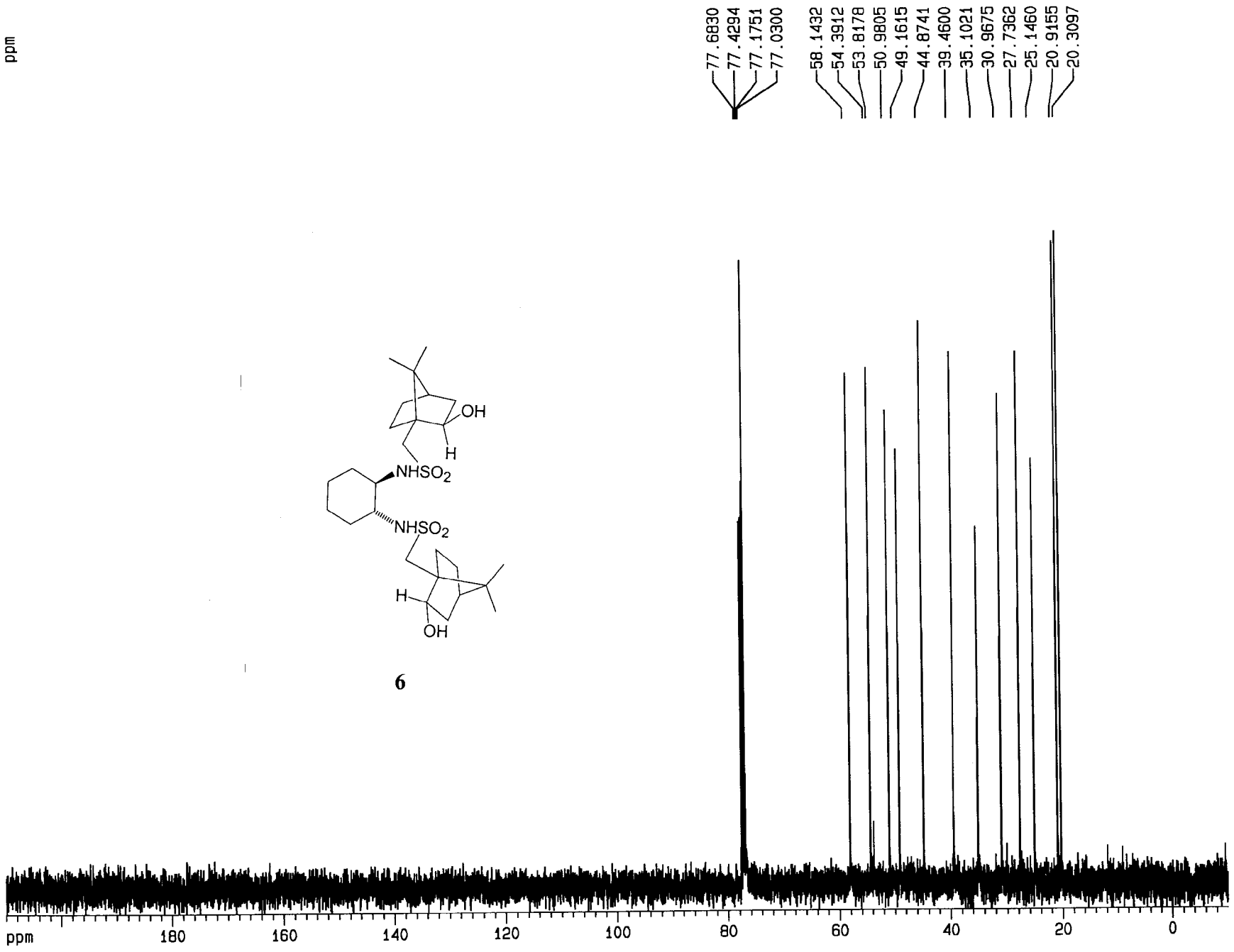
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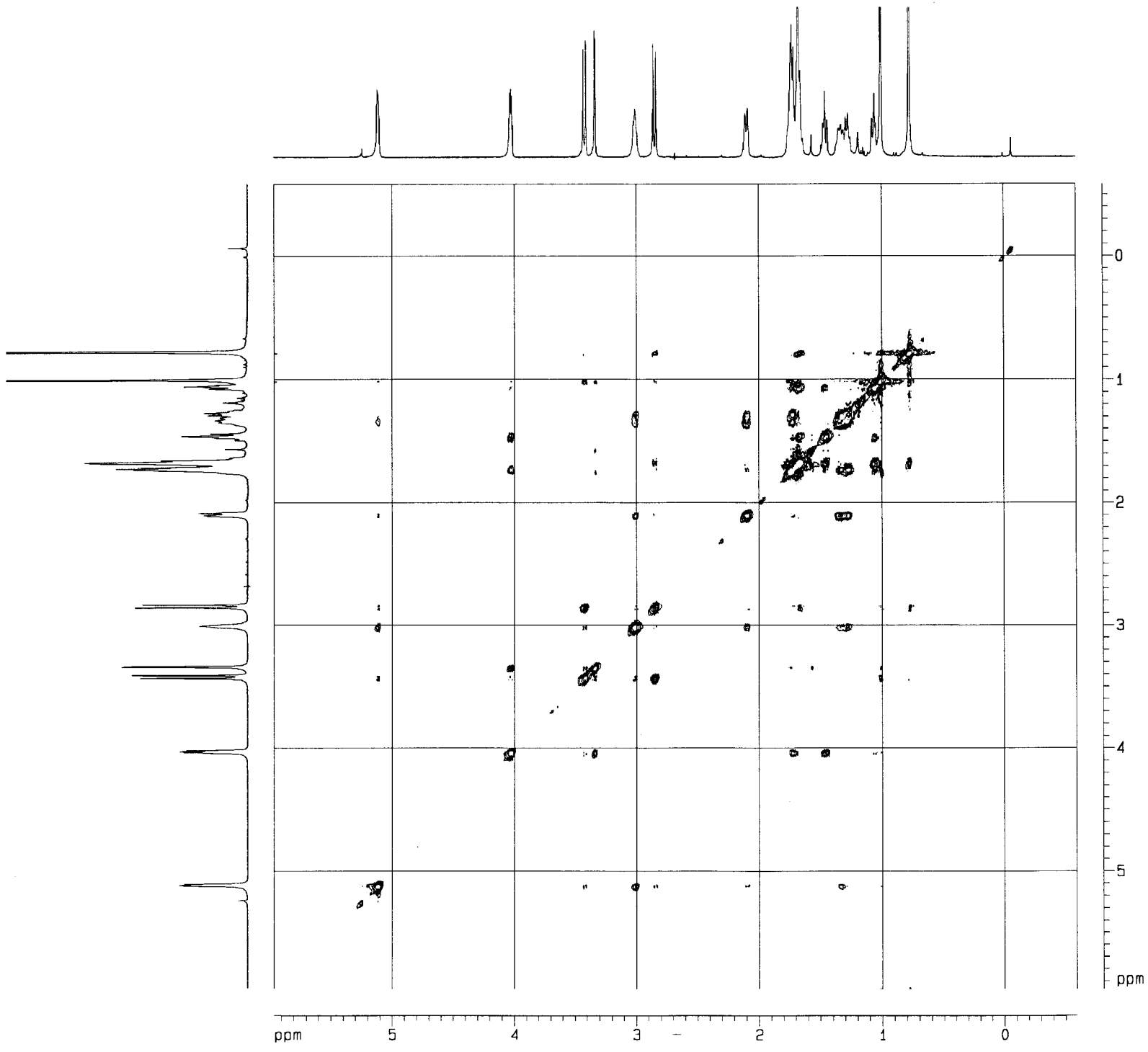

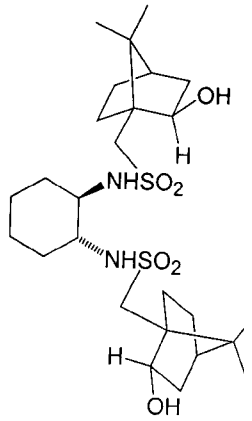

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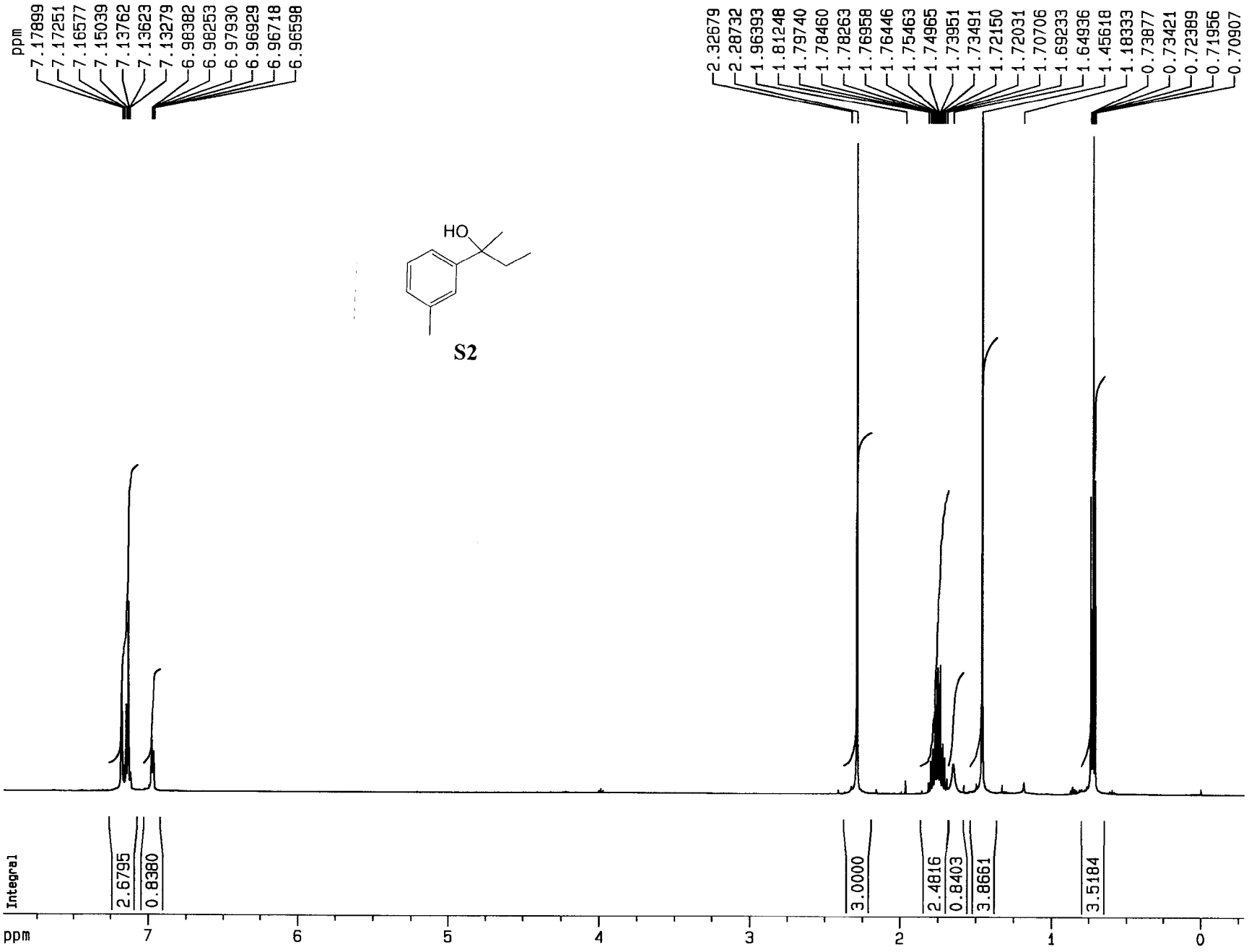

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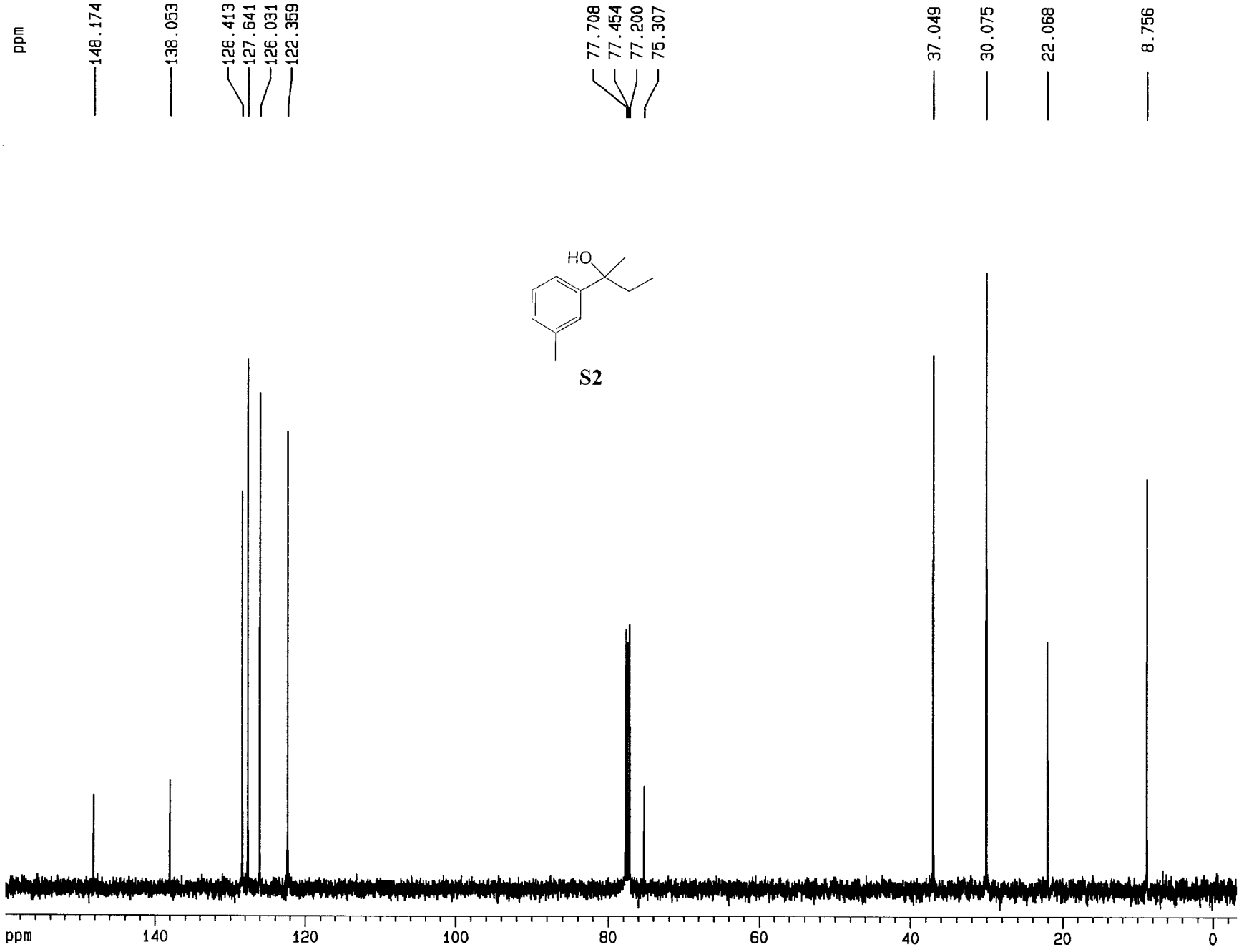

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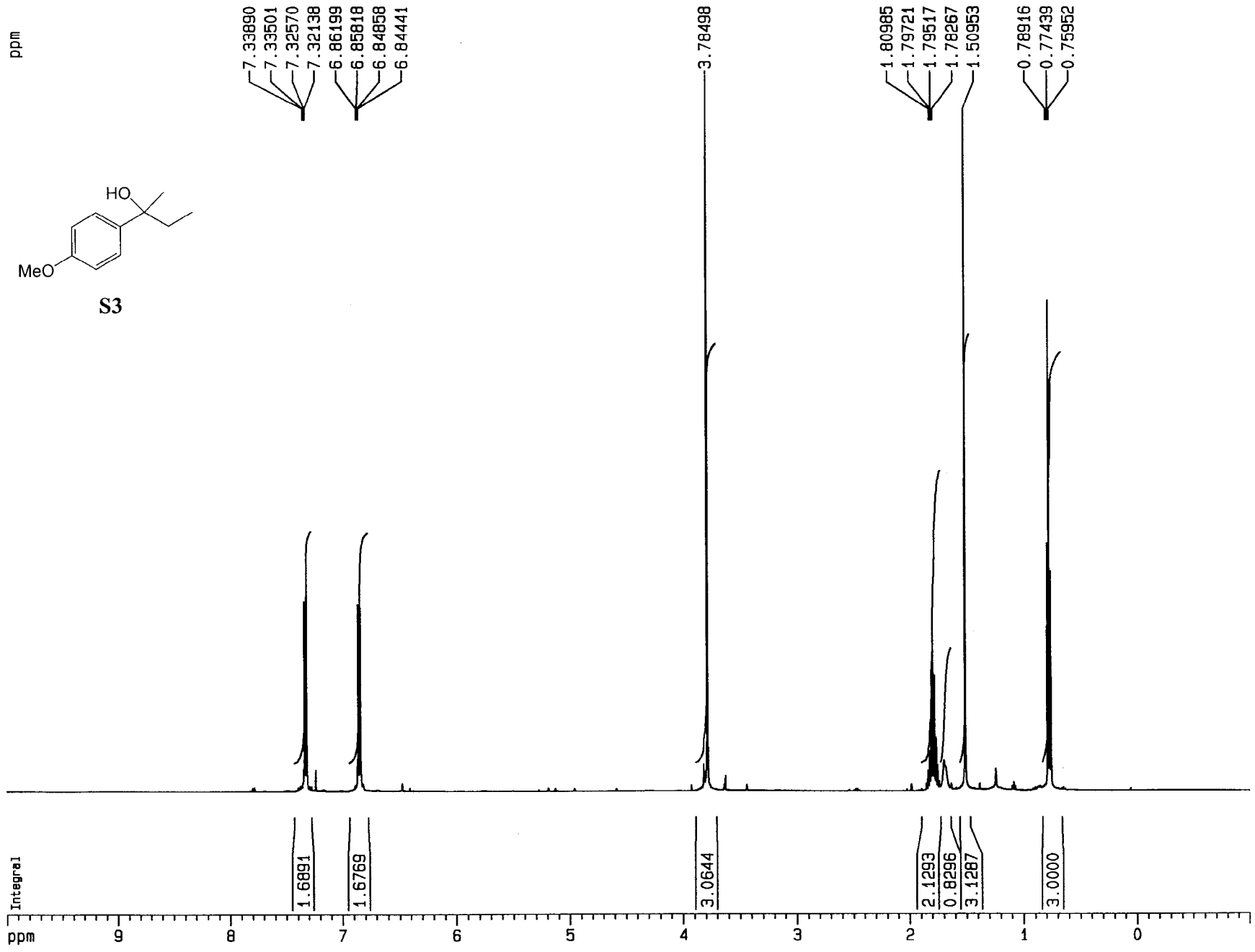

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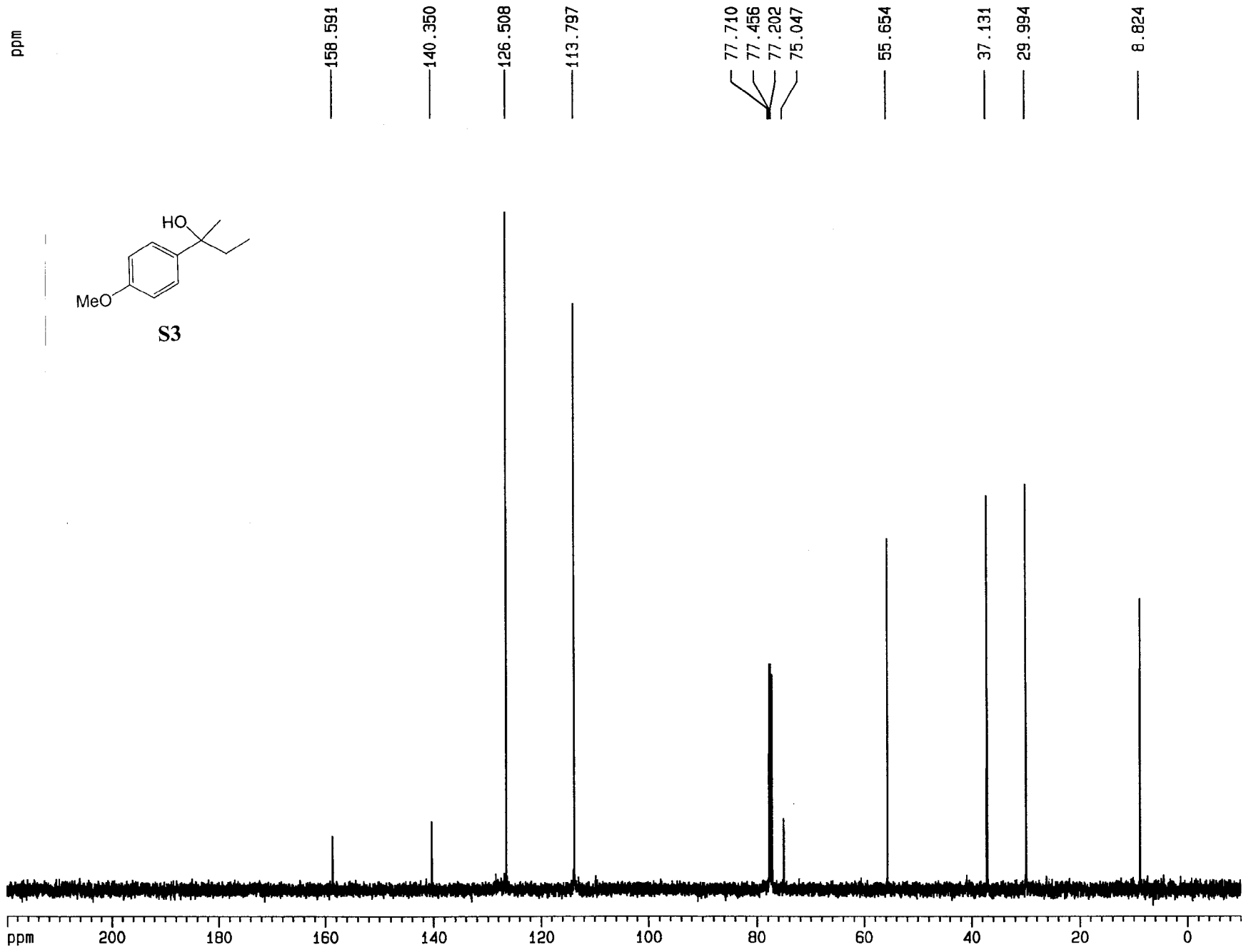

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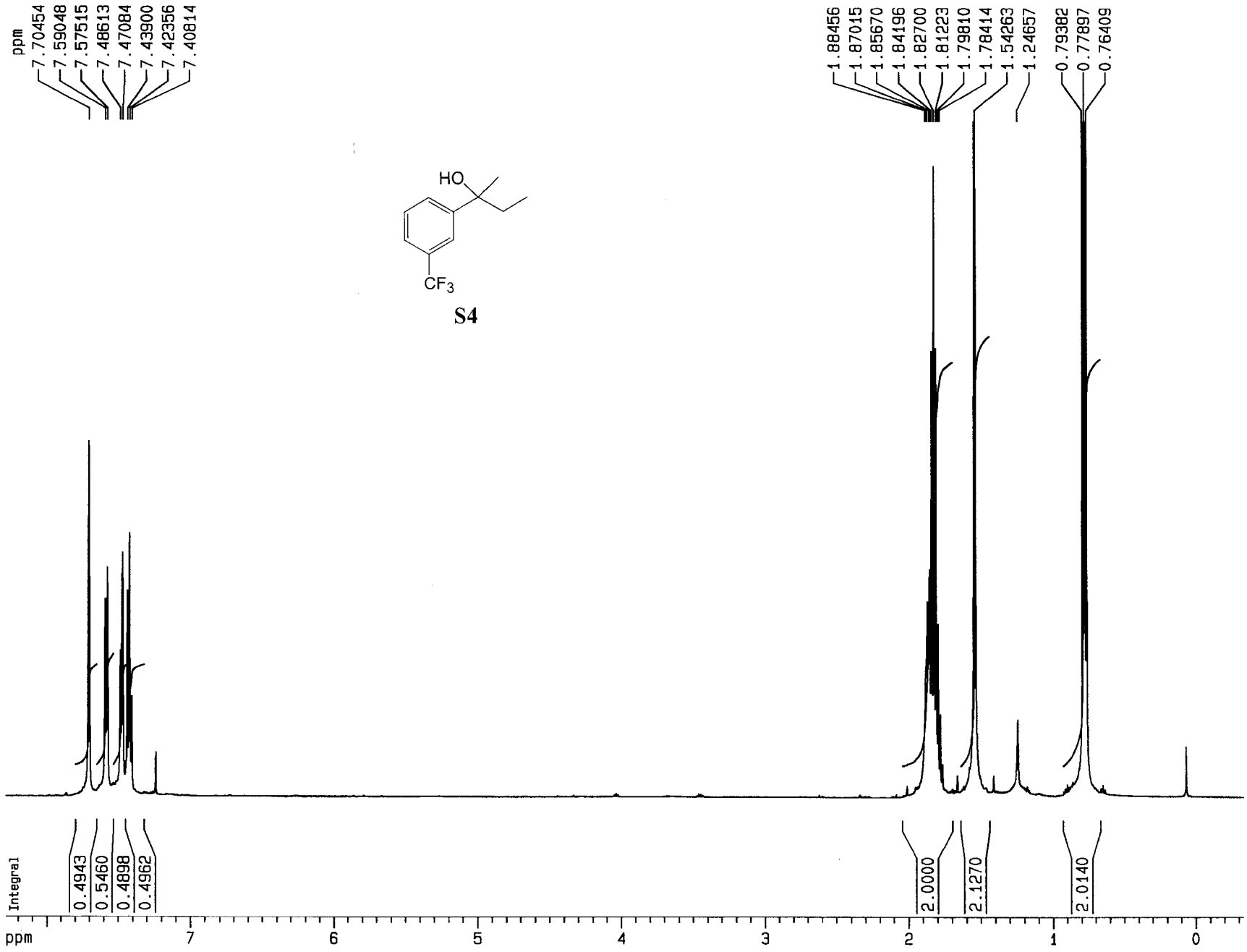

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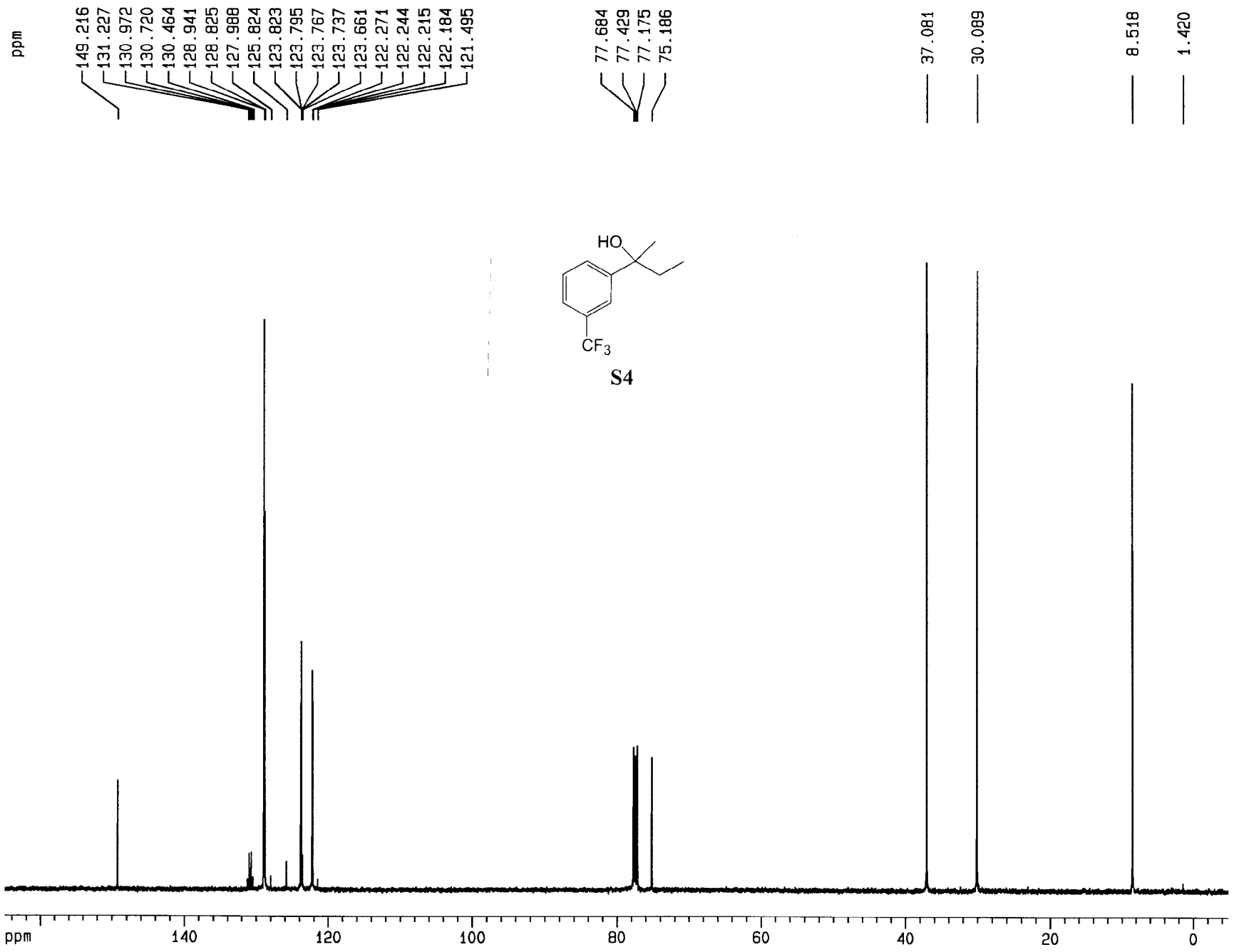
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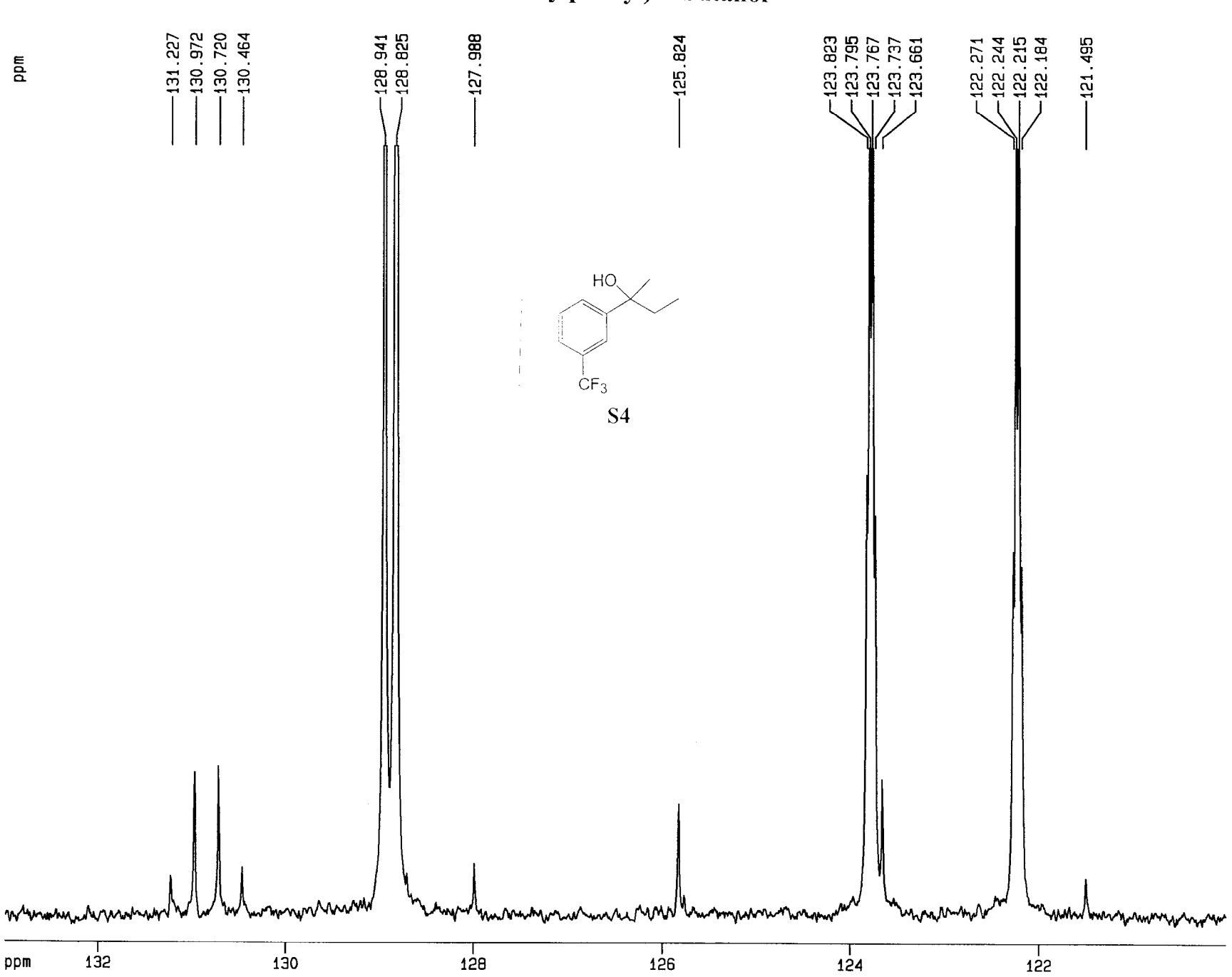
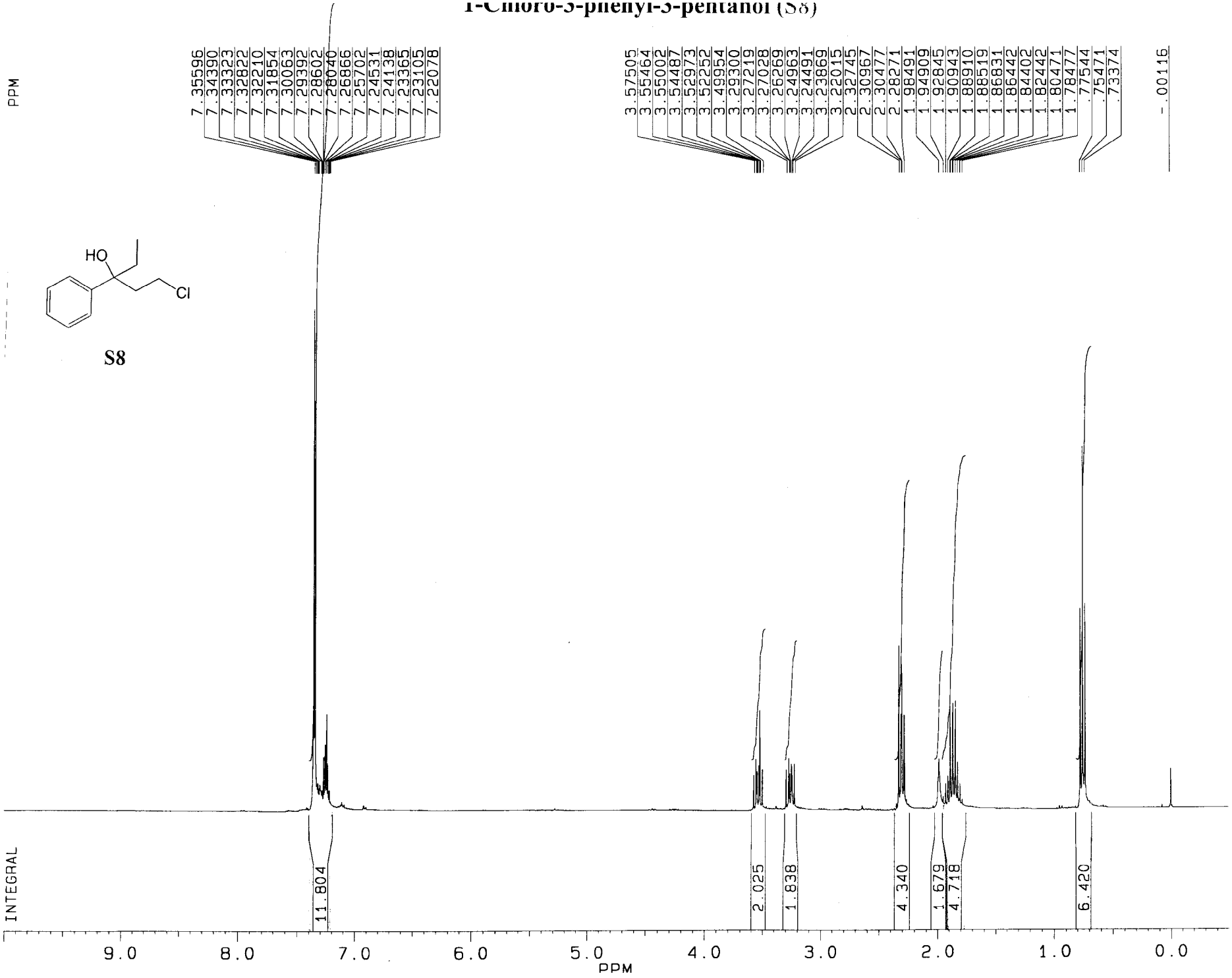
30.089
8.518
1.420
HO
CF3
ppm
140
120
100
80
60
40
20
0

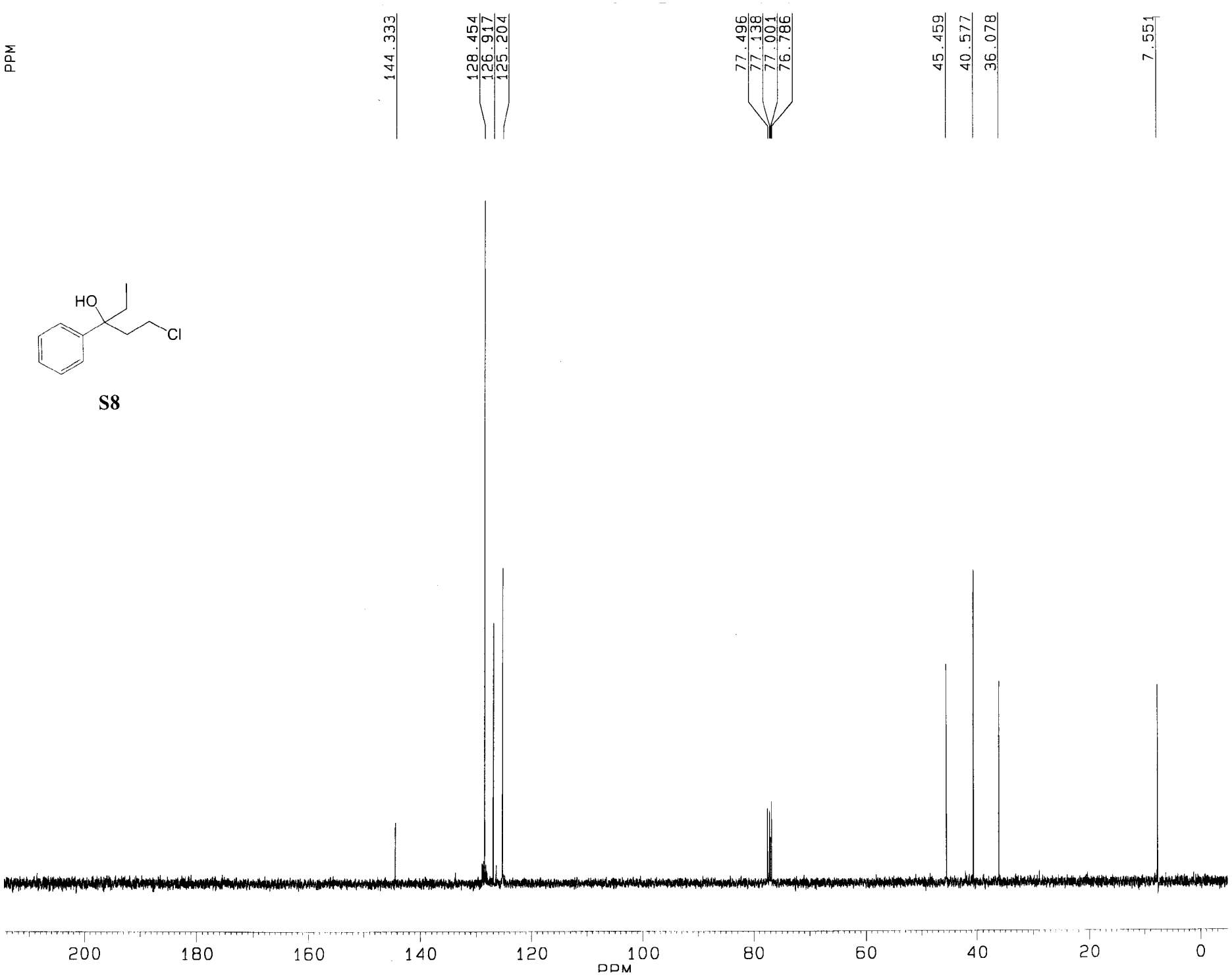
S4


2-(3-Trifluoromethylphenyl)-2-butanol
ppm
131.227
130.972
130.720
130.464
128.941
128.825
127.988
125.824
123.823
123.795
123.767
123.737
123.661
122.271
122.244
122.215
122.184
121.495
HO
CF3
ppm
132
130
128
126
124
122

1-Chloro-3-phenyl-3-pentanol (S8)

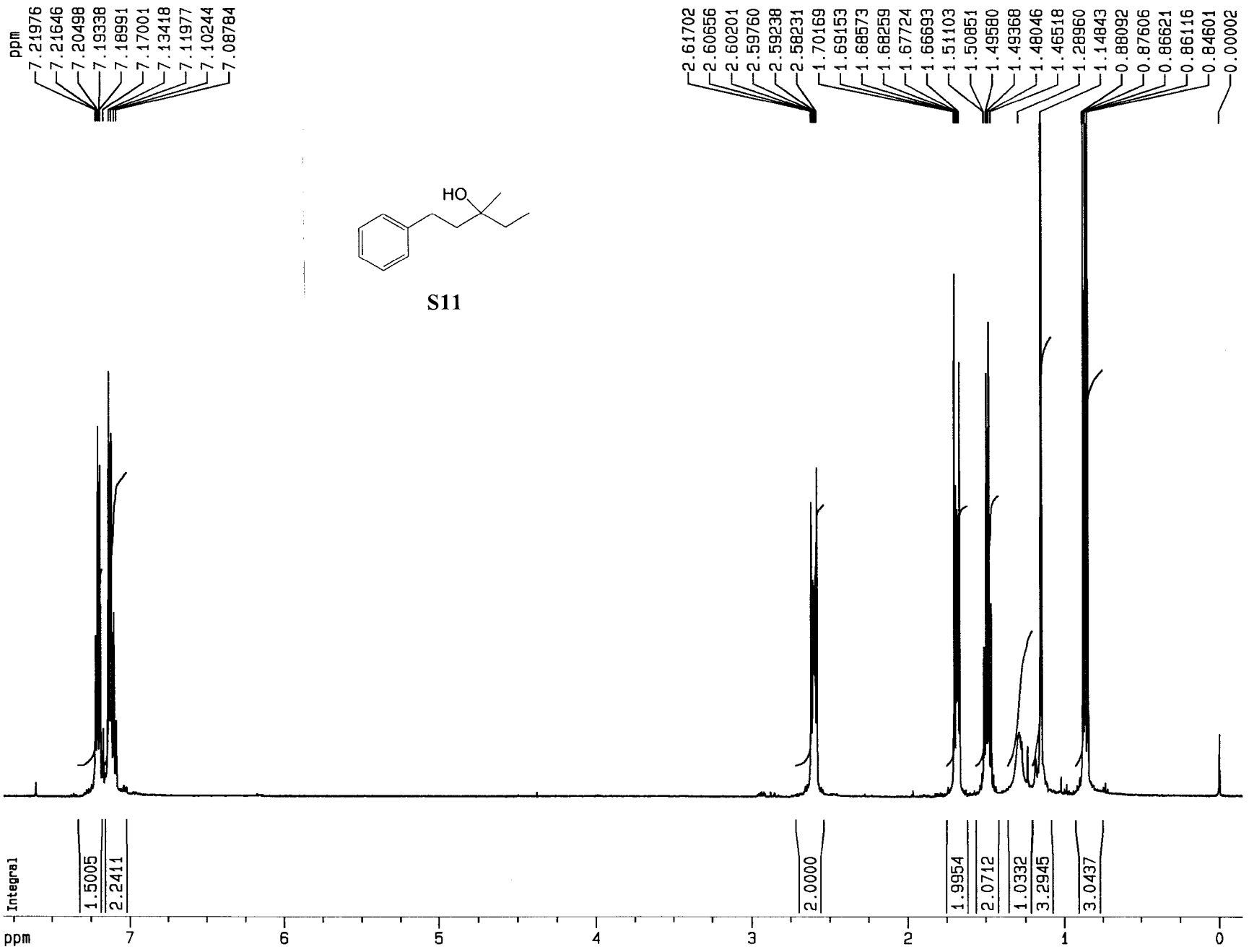


S8

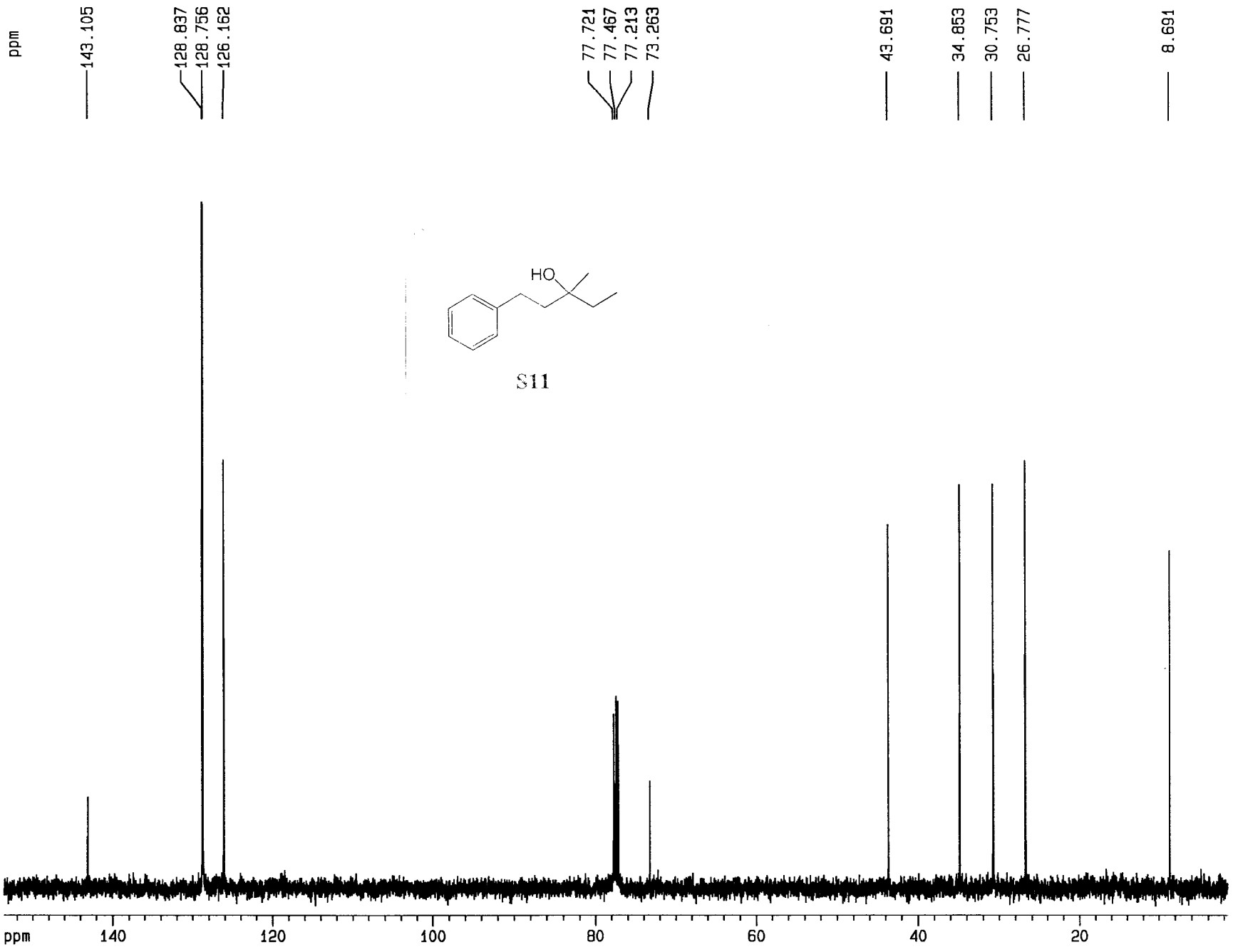

PPM
144.333
128.454
126.917
125.204
77.496
77.138
77.001
76.786
45.459
40.577
36.078
7.551
HO
Cl
200
180
160
140
120
100
80
60
40
20
0
PPM

S8

3-Methyl-1-phenyl-3-pentanol



S11


ppm
143.105
128.837
128.756
126.162
77.721
77.467
77.213
73.263
43.691
34.853
30.753
26.777
8.691
HO
ppm
140
120
100
80
60
40
20