Tandem Functionalization of Non-activated Alkenes and Alkynes in Intramolecular *N*-Acyloxyiminium Ion Carbocyclization. Synthesis of 6-Substituted Hydroindole 2-Carboxylic acids

Stephen Hanessian,* Martin Tremblay

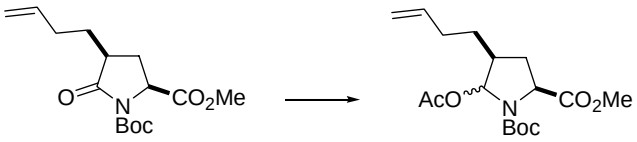
Supplemental Information

1. Experimental procedures (21 pages)
2. X-ray crystal structure data (6 pages)
3. Copies of ^{1}H and ^{13}C NMR spectra (54 pages)

(Spectra of *N*-Boc derivatives consist of two rotamers in most cases)

General information

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods; THF and ether, from Na/benzophenone; and CH_2Cl_2, from $CaCl_2$. All commercially available reagents were used without further purification. All reactions were performed under nitrogen atmosphere. NMR (^1H, ^{13}C) spectra were recorded on AMX-300, ARX-400, AV-400 and DMX-600 spectrometers. Low- and high-resolution mass spectra were recorded on VG Micromass, AEI-MS 902 or Kratos MS-50 spectrometers using fast atom bombardement (FAB) or electrospray techniques. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ pre-coated silica gel plates. Visualization was performed by ultraviolet light and/or by staining with ceric ammonium molybdate, ninhydrine or potassium permanganate. Flash column chromatography was performed using (40-60 μm) silica gel at increased pressure.



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(2S,4S)-5-Acetoxy-4-but-3-enyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (2). To a solution of the N-Boc lactam (3.00 g, 10.0 mmol) in THF (70 mL) at –78°C, was added a solution of $LiHBEt_3$ (11.1 mL, 1.0 N in THF), stirred of 1h, quenched with $NaHCO_3$ (sat.), 2 drops of H_2O_2 (30% in H_2O) were added and the solution was concentrated under vacuum. The aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The resulting oil was dissolved in CH_2Cl_2 (25 mL) and Et_3N (2.81 mL, 20.2 mmol), Ac_2O (2.86 mL, 30.3 mmol) and DMAP (cat.) were added successively. After stirring overnight, the solution was quenched with $NaHCO_3$ (sat.),

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the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 15:85) to give the corresponding hemiaminal derivative **2** (3.13 g, 91%) as a mixture of diastereoisomeres.

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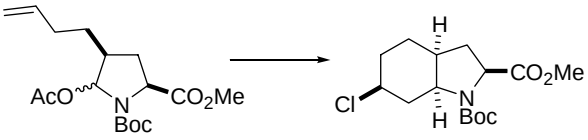

2 **3a**

(2S,3aS,6S,7aS)-6-Chloro-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3a). To a solution of the hemiaminal **2** derivative (0.400 g, 1.17 mmol) in CH_2Cl_2 (8 mL) at –78°C, was added a solution of $SnCl_4$ (1.52 mL, 1.0 M in CH_2Cl_2) dropwise. After stirring for 10 min., the solution was quenched with $NaHCO_3$ (sat.), warmed up to RT, filtered on a small celite pad, the filtrated was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 10:90 to 15:85) to give **3a** (0.245 g, 66%) as a colorless oil; ^{1}H RMN (400 MHz, DMSO-d_6) δ (rotamers) 4.20-4.15 (m, 1H), 4.05-3.92 (m, 1H), 3.85-3.75 (m, 1H), 3.64 (s, 1.5H), 3.61 (s, 1.5H), 2.42-2.20 (m, 2H), 2.16-2.05 (m, 1H), 1.95-1.80 (m, 2H), 1.75-1.60 (m, 4H), 1.17 (s, 4.5H), 1.13 (s, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (rotamers) 174.4, 173.9, 153.8, 153.1, 80.1, 59.9, 58.0, 57.9, 57.8, 57.4, 52.9, 52.8, 39.3, 39.2, 38.9, 35.9, 35.2, 32.5, 32.0, 31.7, 29.1, 28.9, 24.8; $[\alpha]_D$ +2.0° (c 0.98, $CHCl_3$); HRMS for $C_{15}H_{25}NO_4Cl$ calculated ($M + H^+$) 318.14860 found 318.14722.

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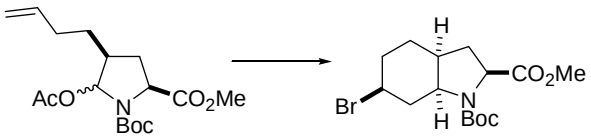

2 **3b**

(2S,3aS,6S,7aS)-6-Bromo-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (3b). Same procedure as **3a**. (78%); ^{1}H RMN (400 MHz, DMSO-d_6) δ (rotamers) 4.21-4.08 (m, 2H), 3.85-3.79 (m, 1H), 3.67 (s, 1.5H), 3.64 (s, 1.5H), 2.62-2.41 (m, 1H), 2.39-2.21 (m, 1H), 2.17-1.60 (m, 7H), 1.37 (s, 4.5H), 1.30 (s, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (rotamers) 174.3, 173.8, 153.6, 152.9, 80.0, 79.9, 59.7, 59.3, 58.0, 57.6, 52.8, 52.7, 50.1, 50.0, 39.6, 35.6, 35.0, 32.7, 32.6, 32.3, 31.5, 29.0, 28.7, 25.6; $[\alpha]_D$ +5.9^{o} (c 1.5, $CHCl_3$); HRMS for $C_{15}H_{24}NO_4Br$ calculated 361.088870 found 361.088652.

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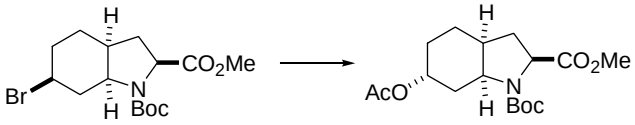

3b **4a**

(2S,3aS,6R,7aS)-6-Acetoxy-2,3,3a,4,5,6,7,7a-octahydroindole-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester (4a). To a solution of **3b** (0.500 g, 1.38 mmol) in toluene (12 mL), was added Bu_4NOAc (6.20 g, 20.7 mmol) and the mixture was heated at 40-50^{o}C for 2h. After cooling down to RT, the solution was diluted with Hexanes, the organic solution was washed with H_2O, brine and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 15:85) to give **4a** (0.368 g, 78%) as a colorless oil; ^{1}H RMN (400 MHz, DMSO-d_6) δ 4.97-4.90 (m, 1H), 4.22-4.12 (m, 1H), 3.95-3.82 (m, 1H), 3.67 (s, 3H), 2.40-2.28 (m, 1H), 2.20-2.10 (m, 2H), 2.05 (s, 3H), 1.96-1.80 (m, 2H), 1.66-1.47 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.3, 170.6, 79.7, 69.8, 59.7, 59.2, 53.9, 52.7, 36.3, 35.8, 32.5, 31.9, 30.9, 28.7, 24.0, 21.8, 20.4; $[\alpha]_D$ -47.5^{o} (c 1.55, $CHCl_3$); HRMS for $C_{17}H_{28}NO_6$ calculated (M + H^+) 342.191663 found 342.193100.

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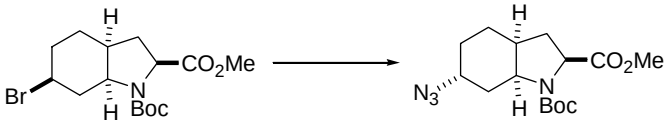
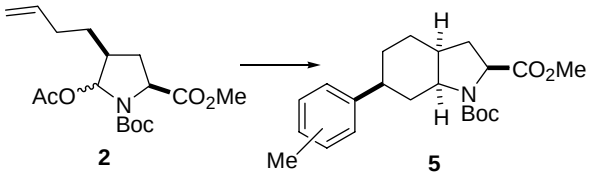


3b **4b**

(2S,3aS,6R,7aS)-6-Azido-*N*-*tert*-butyloxycarbonyl-octahydroindole-2-carboxylate de méthyle (4b). To a solution of the bromide 3b (0.051 g, 0.141 mmol) in DMF (1 mL), was added NaN_3 (0.183 g, 2.82 mmol) and the solution was heated at 100°C for 24h. After cooled down to RT, the solution was diluted with EtOAc, the organic layer was washed with H_2O (3X), brine and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 15:85) to give the azido 4b (0.032 g, 71%) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.20-4.10 (m, 1H), 4.08-4.01 (m, 1H), 3.63-3.57 (broad s, 3H), 2.37-2.20 (m, 1H), 2.12-2.04 (m, 2H), 1.90-1.72 (m, 2H), 1.70-1.40 (m, 4H), 1.38-1.20 (m, 10H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 173.8, 153.8, 153.1, 80.0, 59.6, 59.1, 57.5, 57.1, 54.1, 53.7, 52.7, 36.3, 35.7, 30.5, 28.8, 24.0, 20.6; IR cm^{-1} 2936, 2104, 1751, 1699, 1399, 1167; $[\alpha]_D$ -43.8° (c 1.60, $CHCl_3$); HRMS for $C_{15}H_{24}N_4O_4$ calculated (M^+) 324.179756, found 324.180101.



(2S,3aS,6S,7aS)-6-(o/p-Tolyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (5). To a solution of the hemiaminal derivative 2 (0.095 g, 0.278 mmol) in toluene (3 mL) at –78°C, was added BF_3OEt_2 (52 μL, 0.417 mmol) dropwise. After stirring for 10 min., the solution was quenched with $NaHCO_3$ (sat.), warmed up to RT, diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 20:80) to give 5 (0.079 g, 77%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.28-6.93 (m, 4H), 4.34-4.18 (m, 1H), 4.09-3.88 (m, 1H), 3.78-3.68 (m, 3H), 2.70-2.60 (m, 0.5H), 2.50-2.23 (m, 4.5H), 2.22-1.98 (m, 2H), 1.95-1.78 (m, 2H), 1.77-1.48 (m, 3H), 1.42 (s, 4.5H), 1.37 (s, 4.5H), 1.30-1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.4, 174.3, 153.6,

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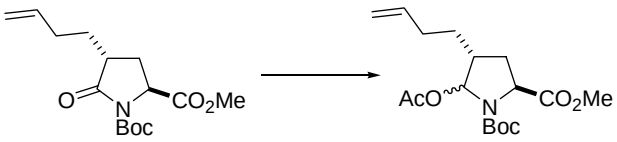

(2S,4R)-5-Acetoxy-4-but-3-enyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester. Same procedure as for **2** (80%).

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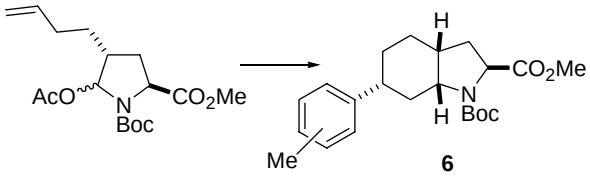

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(2S,3aR,6R,7aR)-6-(o/p-Tolyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (6). Same procedure as for **5** (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.20-6.90 (m, 4H), 4.38-4.30 (m, 0.5H), 4.29-4.22 (m, 0.5H), 4.17-3.93 (m, 1H), 3.76-3.70 (m, 3H), 2.68-2.50 (m, 1H), 2.48-2.09 (m, 5H), 1.90-1.77 (m, 3H), 1.75-1.28 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.2, 173.8, 154.4, 153.5, 144.6, 143.8, 143.7, 135.6, 130.8, 130.7, 129.6, 129.4, 128.6, 127.9, 127.4, 127.2, 127.0, 126.7, 126.4, 126.3, 126.2, 124.2, 124.1, 80.2, 80.1, 60.8, 58.7, 58.3, 58.3, 58.0, 57.8, 57.6, 52.6, 52.4, 37.3, 36.4, 35.2, 35.1, 34.3, 34.2, 32.4, 31.5, 31.4, 28.8, 28.7, 26.3, 26.0, 21.4; HRMS for $C_{22}H_{32}NO_4$ calculated (M + H^+) 374.233134, found 374.232887.

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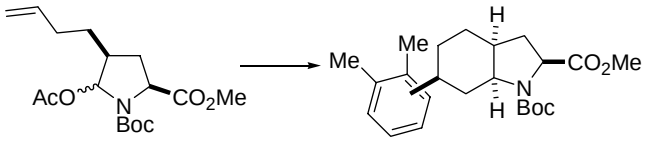

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(2S,3aS,6S,7aS)-6-(o/p-1,2-Dimethyl-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **1**, table 1**)**. Same procedure as for **5**, except that the reaction was done in *o*-xylene at –20°C (67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.12-6.89 (m, 3H), 4.32-4.18 (m, 1H), 4.10-3.88 (m, 1H), 3.80-3.69 (m, 3H), 2.80-2.68 (m, 0.4H), 2.50-1.95 (m, 10.6H), 1.93-1.80 (m, 2H), 1.75-1.25 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 173.8, 173.7, 173.6, 153.7, 152.9, 143.8, 143.6, 136.6, 136.4, 134.2, 133.6, 129.5, 129.4, 128.0, 127.6, 127.4, 125.5, 125.3, 124.0, 123.9, 122.9, 105.0, 79.6, 59.3, 58.8, 58.1, 57.8, 57.6, 52.0, 51.8, 41.3, 40.9, 37.4, 36.4, 35.7, 35.3, 34.8, 32.5, 31.7, 31.6, 28.3, 28.1, 27.6, 26.2, 26.0, 20.9, 19.7, 19.2, ; HRMS for $C_{23}H_{34}NO_4$ calculated (M + H^+) 388.248784, found 388.247856.

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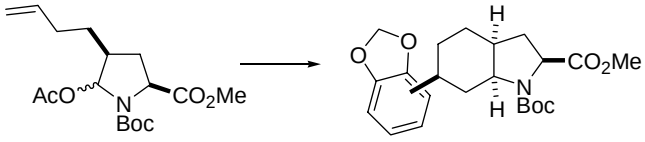

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(2S,3aS,6S,7aS)-6-(o/p-Benzo[1,3]dioxolyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **2**, table 1**)**. Same procedure as for **5**, except that the reaction was done in phthalane at –15°C (58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 6.80-6.60 (m, 3H), 5.95-5.88 (m, 2H), 4.30-4.18 (m, 1H), 4.07-3.97 (m, 0.6H), 3.96-3.87 (m, 0.4H), 3.74-3.67 (m, 3H), 2.68-2.58 (m, 0.4H), 2.42-2.29 (m, 2.6H), 2.20-2.05 (m, 3H), 1.88-1.50 (m, 4H), 1.48-1.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.4, 154.3, 153.5, 147.9, 140.9, 140.8, 128.2, 121.9, 120.2, 119.9, 108.6, 108.5, 107.8, 106.8, 101.1, 100.8, 80.2, 60.8, 59.8, 59.3, 57.8, 52.4, 52.3, 41.9, 41.7, 36.4,

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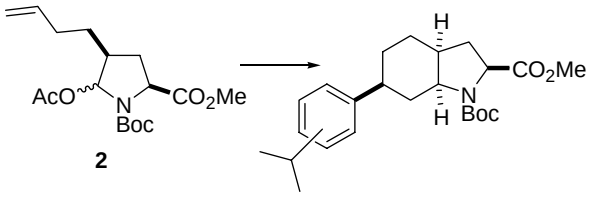
36.2, 36.1, 35.7, 32.9, 28.8, 28.7, 26.6, 26.2, 14.6; HRMS for $C_{22}H_{29}NO_6$ calculated (M^+) 403.199488, found 403.201268.



(2S,3aS,6S,7aS)-6-(o/p-Isopropyl-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **3**, table 1**)**. Same procedure as for **5**, except that the reaction was done in cumene at –78°C (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.28-7.00 (m, 4H), 4.37-4.18 (m, 1H), 4.08-3.88 (m, 1H), 3.79-3.68 (m, 3H), 2.93-2.82 (m, 1H), 2.50-2.30 (m, 2H), 2.25-2.00 (m, 2H), 1.90-1.78 (m, 2H), 1.77-1.34 (m, 13H), 1.30-1.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.4, 174.2, 154.4, 153.6, 153.5, 149.2, 147.0, 146.6, 144.1, 144.0, 128.8, 128.7, 127.1, 127.0, 126.8, 125.8, 125.7, 124.5, 124.4, 80.2, 59.3, 58.4, 58.2, 58.1, 52.6, 52.4, 41.5, 36.9, 36.2, 35.9, 35.4, 34.6, 34.0, 32.9, 32.1, 29.3, 28.9, 28.8, 28.2, 26.5, 26.3, 24.5; HRMS for $C_{24}H_{36}NO_4$ calculated ($M + H^+$) 402.264434, found 402.263991.

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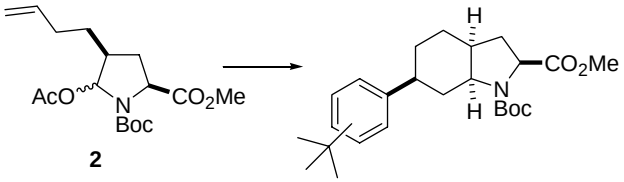

(2S,3aS,6S,7aS)-6-(m/p-*tert*-Butyl-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **4**, table 1**)**. Same procedure as for **5**, except that the reaction was done in *tert*-butylbenzene at –78°C (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.37-7.00 (m, 4H), 4.36-4.20 (m, 1H), 4.10-4.00 (m, 0.5H), 3.98-3.89 (m, 0.5H), 3.77 (s, 1.5H), 3.74 (s,

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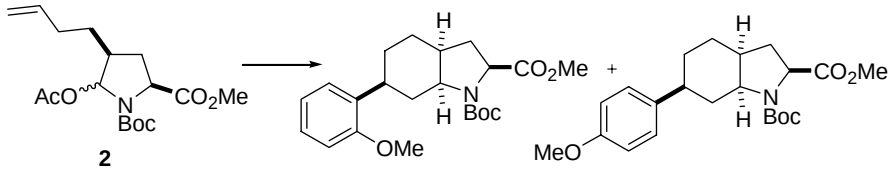
1.5H), 2.55-2.35 (m, 2.5H), 2.34-2.00 (m, 2.5H), 1.92-1.80 (m, 2H), 1.78-1.65 (m, 1.5H), 1.62-1.20 (m, 19.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.4, 174.2, 154.4, 153.6, 153.5, 151.4, 149.3, 149.1, 146.3, 143.7, 143.6, 128.5, 128.4, 126.9, 126.8, 125.7, 125.5, 124.6, 124.5, 123.9, 123.8, 123.6, 123.4, 80.2, 59.9, 59.3, 58.4, 58.2, 58.1, 52.5, 52.3, 41.6, 41.3, 36.9, 36.2, 36.1, 35.9, 35.4, 34.7, 32.9, 32.1, 31.8, 29.2, 28.9, 28.7, 28.1, 28.0, 26.5, 26.3; HRMS for $C_{25}H_{37}NO_4$ calculated (M^+) 415.272259, found 415.272741.



Same procedure as for **5**, except that the reaction was done in anisole at –35°C (69%, 1:1 o/p). **(2S,3aS,6S,7aS)-6-(o-Methoxy-phenyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**Entry **5**, table 1**)**; ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamers) 7.17-7.05 (m, 2H), 6.83-6.78 (m, 2H), 4.30 (t, 0.5H, *J*=8.6 Hz), 4.22 (t, 0.5H, *J*=8.6 Hz), 4.08-3.95 (m, 0.5H), 3.95-3.85 (m, 0.5H), 3.82-3.66 (m, 6H), 2.48-2.26 (m, 2H), 2.22-2.00 (m, 2H), 1.90-1.75 (m, 2H), 1.70-1.30 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (rotamers) 174.5, 174.4, 158.3, 158.2, 154.4, 153.6, 139.0, 128.1, 114.2, 114.1, 80.2, 59.8, 58.4, 58.0, 55.8, 55.7, 52.4, 41.3, 41.0, 36.2, 35.9, 35.5, 32.9, 32.1, 29.4, 28.9, 28.7, 28.6, 26.5, 26.3; $[\alpha]_D$ -21.9° (c 1.05, $CHCl_3$); HRMS for $C_{22}H_{31}NO_5$ calculated (H^+) 389.220223, found 389.221982. **(2S,3aS,6S,7aS)-6-(p-Methoxy-phenyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (**Entry **5**, table 1**)**; ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamers) 7.21-7.05 (m, 2H), 6.94-6.70 (m, 2H), 4.33-4.17 (m, 1H), 4.15-3.90 (m, 1H), 3.82-3.62 (m, 6H), 2.98-2.80 (m, 1H), 2.45-2.25 (m, 1H), 2.24-1.95 (m, 3H), 1.94-1.75 (m, 2H), 1.75-1.28 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (rotamers) 174.5, 174.2, 157.0, 154.4, 153.5, 134.9, 134.8, 127.3, 127.1, 126.9, 121.0, 120.8, 110.6, 80.3, 80.1, 59.9, 59.3, 58.6, 58.1, 55.7, 52.6, 52.4, 37.0, 36.4, 34.7, 34.4, 34.2, 34.1, 33.0, 32.2, 28.8, 28.7, 27.4, 27.3, 26.5; $[\alpha]_D$ -25.0° (c 1.35, $CHCl_3$); HRMS for $C_{22}H_{31}NO_5$ calculated (H^+) 389.220223, found 389.222015.

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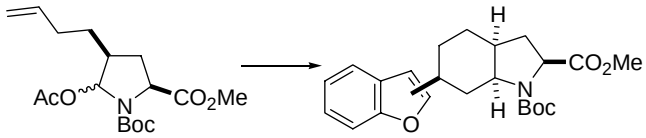

(2S,3aS,6S,7aS)-6-(2/3-Benzofuranyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **6**, table 1**)**. Same procedure as for **5**, except that the reaction was done in benzofuran at –25°C (50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.63-7.05 (m, 4H), 6.82-6.68 (m, 1H), 4.38-4.19 (m, 1H), 4.18-4.05 (m, 1H), 3.91-3.66 (m, 3H), 2.65-2.52 (m, 1H), 2.50-2.28 (m, 2H), 2.28-2.02 (m, 2H), 2.01-1.30 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.4, 174.2, 154.3, 153.3, 145.6, 145.5, 144.9, 144.8, 139.8, 124.8, 124.7, 124.0, 121.8, 119.6, 119.3, 119.1, 111.5, 111.4, 109.6, 106.9, 106.7, 105.2, 80.2, 59.8, 59.3, 58.4, 58.1, 52.6, 52.4, 39.6, 39.5, 36.3, 36.2, 36.1, 34.7, 32.9, 32.2, 28.8, 28.7, 28.0, 27.7, 26.5, 26.3, 19.8; HRMS for $C_{23}H_{29}NO_5$ calculated (M^+) 399.204573, found 399.205404.

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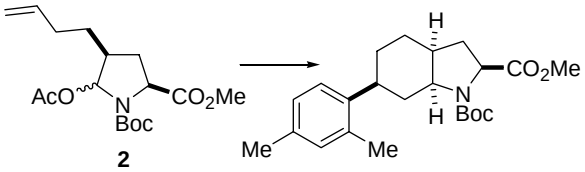

(2S,3aS,6S,7aS)-6-(2,4-Dimethyl-phenyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **7**, table 1**)**. Same procedure as for **5**, except that the reaction was done in *m*-xylene at –45°C (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 7.17-7.05 (m, 1H), 7.02-1.95 (m, 2H), 4.36-4.18 (m, 1H), 4.07-3.88 (m, 1H), 3.80-3.65 (m, 3H), 2.98-2.86 (m, 0.4H), 2.68-2.58 (m, 0.6H), 2.50-1.98 (m, 11H), 1.93-1.77 (m, 2H), 1.70-1.30 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 174.5, 174.2, 154.3, 153.5, 141.6, 136.5, 135.7, 135.5, 135.4, 131.6, 131.5, 127.3, 127.1, 126.3, 126.1, 125.7, 80.2, 80.1, 59.8, 59.3, 58.6, 58.2, 52.6, 52.4, 39.1, 38.8, 37.4, 37.2,

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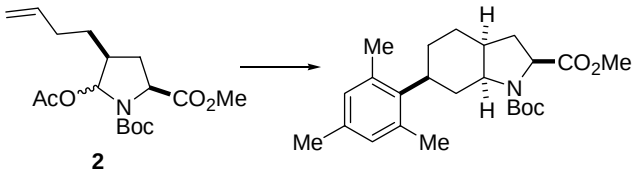
36.9, 36.4, 36.3, 35.1, 34.9, 33.0, 32.2, 28.8, 28.7, 28.0, 26.6, 21.3, 19.7, 19.5; $[\alpha]_D$ -22° (c 1.2, $CHCl_3$); HRMS for $C_{23}H_{34}NO_4$ calculated (M + H^+) 388.248784, found 388.247364.



2

(2S,3aS,6S,7aS)-6-(2,4,6-Trimethyl-phenyl)-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (Entry **8**, table 1**)**. Same procedure as for **5**, except that the reaction was done in mesitylene at –40°C (78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ (rotamers) 6.84-6.78 (m, 2H), 4.35-4.23 (m, 1H), 4.08-3.80 (m, 1H), 3.79 (s, 1.5H), 3.76 (s, 1.5H), 2.96-2.85 (m, 1H), 2.44-1.91 (m, 15H), 1.87-1.79 (m, 2H), 1.53-1.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (rotamers) 174.5, 174.2, 154.3, 153.5, 139.1, 139.0, 135.6, 135.4, 80.2, 80.1, 59.8, 59.3, 58.6, 58.2, 52.6, 52.4, 38.7, 38.4, 37.1, 36.4, 33.2, 32.4, 32.0, 31.4, 28.8, 28.7, 27.2, 27.1, 25.0, 24.8, 21.0; $[\alpha]_D$ -31.7° (c 1.06, $CHCl_3$); HRMS for $C_{24}H_{35}NO_4$ calculated (M^+) 401.256609, found 401.257421.

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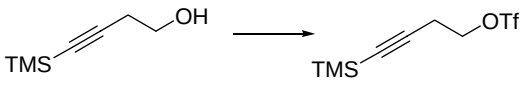

10

Trifluoro-methanesulfonic acid 4-trimethylsilanyl-but-3-ynyl ester (10). To a solution of pyridine (5.63 mL, 69.7 mmol) in CH_2Cl_2 (70 mL) at –78°C, was added Tf_2O (9.78 mL, 58.1 mmol), the mixture was stirred for 15 min. and the alcohol (8.26 g, 58.1 mmol) was added dropwise. After stirring for 20 min., the mixture was diluted with CH_2Cl_2, washed with ice cooled HCl 1N (40 mL), water and dried over Na_2SO_4. The solvent was removed under vacuum (without heating) and the resulting oil was purified on a small pad of silica gel (Hexanes/Et_2O 5:1) to give the corresponding triflate **10** (11.7 g, 74%) as a light brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (t, 2H, *J*=6.8 Hz),

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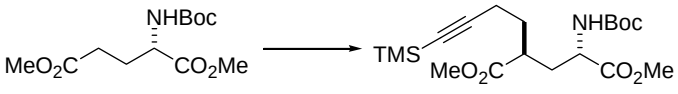
2.76 (t, 2H, *J*=6.8 Hz), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.6, 116.3, 98.4, 88.6, 73.6, 21.0, -0.4.



1 **11**

(2S,4S)-2-*tert*-Butoxycarbonylamino-4-(4-trimethylsilanyl-but-3-ynyl)-pentanedioic acid dimethyl ester (11). To a solution of *N*-Boc-glutamic acid dimethylester **1** (4.72 g, 17,1 mmol) in THF (100 mL) at –78°C, was added LiHMDS (36.0 mL, 1.0 N in THF), stirred for 45 min. and a solution of the triflate **10** (9.32 g, 34 mmol) in THF (35 mL) at –78°C was added dropwise *via canula*. After stirring for 20 min., the solution was quenched with NH_4Cl (2N), warmed up to RT and concentrated under vacuum. The resulting aqueous solution was extracted with CH_2Cl_2, the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 1:9 to 15:85) to give **11** (4.44 g, 65%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00-4.88 (m, 1H), 4.30-4.20 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 2.58-2.47 (m, 1H), 2.16 (t, 2H, *J*=7.3 Hz), 2.00-1.85 (m, 2H), 1.83-1.75 (m, 1H), 1.75-1.61 (m, 1H), 1.39 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 173.1, 155.7, 106.0, 85.7, 80.4, 52.8, 52.5, 52.2, 41.6, 34.4, 31.5, 28.6, 18.1, 0.4; $[\alpha]_D$ +3.2° (c 1.5, $CHCl_3$); FAB/MS for $C_{19}H_{34}NO_6Si$ calculated (M + H^+) 400.2, found 400.2.

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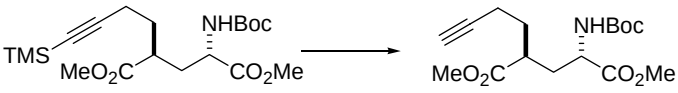

11

(2S,4S)-2-*tert*-Butoxycarbonylamino-4-but-3-ynyl-pentanedioic acid dimethyl ester. To a solution of the TMS derivative **11** (4.00 g, 10.0 mmol) in THF (50 mL), was added AcOH (0.63 mL, 11.0 mmol) and a solution of TBAF (11.0 mL, 1.0 M in THF). After stirring at RT for 45 min., the solution was concentrated under vacuum and the

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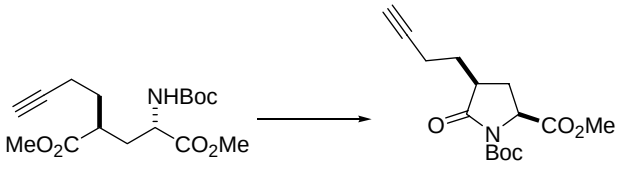
resulting residue was purified by flash chromatography (EtOAc/Hexanes 25:75) to give the corresponding terminal alkyne (2.88 g, 88%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (d, 1H, *J*=8.7 Hz), 4.35-4.30 (m, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.65-2.61 (m, 1H), 2.22-2.15 (m, 2H), 2.02-1.90 (m, 3H), 1.88-1.78 (m, 1H), 1.77-1.68 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 172.5, 155.1, 82.7, 79.9, 69.0, 52.2, 51.9, 51.7, 40.8, 34.0, 30.7, 28.1, 16.1; $[\alpha]_D$ +7.9^o (c 0.90, $CHCl_3$); FAB/MS for $C_{16}H_{26}NO_6$ calculated (M + H^+) 328.2, found 328.2.



12

(2S,4S)-4-But-3-ynyl-5-oxo-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (12). To a solution of the of *N*-Boc-glutamic acid dimethylester derivative (2.50 g, 7.64 mmol) in CH_2Cl_2 (30 mL), was added TFA (5.6 mL). After stirring at RT until no trace of starting material, the solution was concentrated under vacuum, the resulting oil was dissolved in toluene (100 mL), heated at reflux for 1.5h and the solution was concentrated under vacuum. To a solution of the lactams obtained in CH_2Cl_2 (30 mL), was added successively Et_3N (3.20 mL, 22.9 mmol), Boc_2O (2.50 g, 11.5 mmol) followed by DMAP (cat.). After stirring overnight, the solution was quenched with NH_4Cl (2N), the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 15:85 to 30:70) to give compounds **12** (1.80 g, 80%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (t, 1H, *J*=8.2 Hz), 3.74 (s, 3H), 2.75-2.65 (m, 1H), 2.60-2.50 (m, 1H), 2.42-2.31 (m, 1H), 2.28-2.18 (m, 1H), 2.13-2.04 (m, 1H), 1.94 (t, 1H, *J*=2.6 Hz), 1.70-1.50 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 172.3, 149.6, 84.1, 83.2, 69.9, 57.7, 52.9, 41.8, 30.1, 28.2, 16.7; $[\alpha]_D$ -10.7^o (c 1.00, $CHCl_3$); HRMS for $C_{15}H_{22}NO_5$ calculated (M + H^+) 296.149798, found 296.151085.

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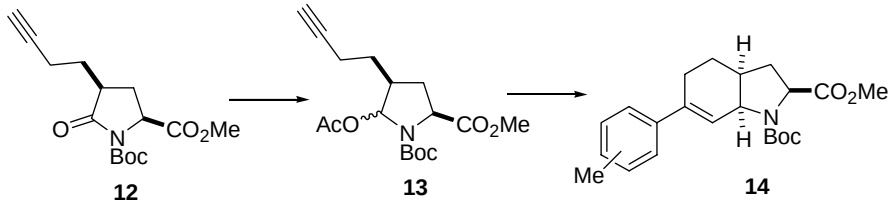

12 **13** **14**

(2S,3aS,7aS)-6-(o/p-Tolyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (14). Same procedure as **2** for reduction/acetylation (94%) and as compound **5** for cyclization (69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 7.35-7.00 (m, 4H), 6.21 (s, 0.25H), 6.08 (s, 0.25H), 5.78 (s, 0.25H), 5.65 (s, 0.25H), 4.60-4.50 (m, 0.5H), 4.48-4.40 (m, 0.5H), 4.38-4.20 (m, 1H), 3.77-3.62 (m, 3H), 2.60-2.43 (m, 1H), 2.40-1.80 (m, 9H), 1.56-1.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (mixture of regioisomers and rotamers) 174.0, 173.9, 154.6, 154.2, 154.0, 143.7, 138.9, 138.6, 135.5, 135.3, 130.5, 130.3, 129.4, 129.3, 128.7, 128.6, 128.3, 127.3, 127.2, 126.1, 126.0, 125.9, 125.5, 125.3, 123.1, 80.4, 59.6, 59.5, 59.1, 57.5, 57.1, 56.9, 52.5, 52.4, 52.3, 35.7, 35.1, 34.9, 32.3, 32.2, 31.5, 28.9, 28.7, 28.6, 25.3, 25.1, 23.2, 22.9, 20.0, 19.9; HRMS for $C_{22}H_{29}NO_4$ calculated (M^+) 372.217484, found 372.218648.

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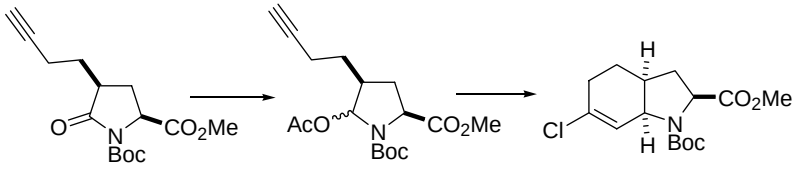

12 **13** **16a**

(2S,3aS,7aS)-6-Chloro-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (16a). Same procedure as **2** for reduction/acetylation (94%). To a solution of the hemiaminal derivative **13** (0.200 g, 0.589 mmol) in CH_2Cl_2 (5 mL) at –78^{o}C, was added a solution of $SnCl_4$ (0.77 mL, 1.0 M in CH_2Cl_2) dropwise. After stirring for 10 min., the solution was quenched with $NaHCO_3$ (sat.), warmed up to RT, filtered on a small celite pad, the filtrated was washed with brine, dried over Na_2SO_4 and

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concentrated under vacuum. The crude oil obtained was purified by flash chromatography (EtOAc/Hexanes 10:90 to 15:85) to give **16a** (0.106 g, 57%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 6.03 (broad s, 0.5H), 5.90 (broad s, 0.5H), 4.42 (broad s, 0.5), 4.33 (broad s, 0.5H), 4.30-4.10 (m, 1H), 3.70 (s, 3H), 2.50-2.27 (m, 2H), 2.26-2.08 (m, 2H), 1.97-1.70 (m, 3H), 1.46 (s, 4.5H), 1.39 (s, 4.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.6, 173.2, 154.3, 153.9, 132.9, 132.5, 124.4, 124.2, 80.8, 80.7, 59.4, 58.9, 57.8, 57.6, 52.6, 52.4, 35.2, 34.5, 32.0, 31.2, 28.8, 28.6, 28.3, 28.2, 28.1, 23.5, 23.4; $[\alpha]_D$ +31.8^{o} (c 1.08, $CHCl_3$); HRMS for $C_{15}H_{21}NO_4Cl$ calculated (M – H$^-$) 314.115911, found 314.116090.

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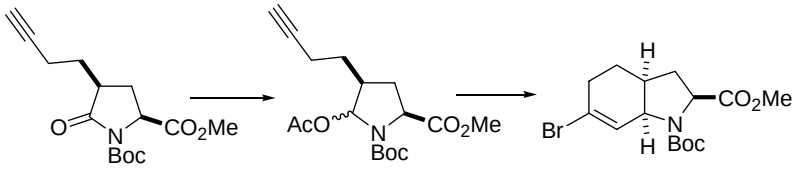

12 **13** **16b**

(2S,3aS,7aS)-6-Bromo-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (16b). Same procedure as **2** for reduction/acetylation (94%) and same procedure as **16a** for cyclization (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 6.26 (broad s, 0.5H), 6.13 (broad s, 0.5H), 2.41-4.33 (broad s, 0.5 H), 4.33-4.10 (m, 1.5H), 3.70 (s, 3H), 2.50-2.22 (m, 3H), 2.21-2.08 (m, 1H), 1.98-1.67 (m, 3H), 1.45 (s, 4.5H), 1.38 (s, 4.5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.6, 173.2, 154.2, 153.8, 128.5, 128.4, 123.2, 122.8, 80.9, 80.7, 59.4, 58.9, 58.6, 58.3, 57.6, 52.6, 52.5, 35.1, 34.5, 34.3, 32.0, 31.2, 30.6, 30.5, 28.8, 28.6, 28.3, 24.1, 24.0, 23.4; $[\alpha]_D$ +53.6^{o} (c 1.03, $CHCl_3$); HRMS for $C_{15}H_{21}NO_4Br$ calculated (M – H$^-$) 358.065395, found 358.064219.

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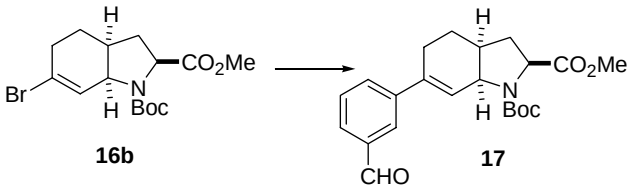

16b **17**

(2S,3aS,7aS)-6-(3-Formyl-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (17). Same procedure as **21** (70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 10.0 (s, 1H), 7.90-7.80 (m, 1H), 7.78-7.57 (m, 2H), 7.55-7.38 (m, 1H), 6.35 (s, 0.6H), 6.19 (s, 0.4H), 4.62-4.50 (m, 0.6H), 4.49-4.40 (m, 0.4H), 4.30 (t, 0.4H, *J*=8.2 Hz), 4.26 (t, 0.6H, *J*=8.2 Hz), 3.69-3.65 (m, 3H), 2.60-2.28 (m, 3H), 2.23-2.10 (m, 1H), 2.07-1.70 (m, 4H), 1.50 (s, 4.5H), 1.42 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 192.9, 173.9, 154.2, 142.9, 136.8, 135.3, 132.1, 131.8, 129.5, 129.3, 129.2, 128.8, 127.2, 127.0, 126.4, 125.6, 125.4, 80.6, 59.4, 58.9, 57.5, 57.4, 56.1, 52.5, 52.4, 35.7, 35.0, 32.2, 31.4, 28.9, 28.7, 22.9, 22.7; $[\alpha]_D$ +42.1^{o} (c 1.25, $CHCl_3$); FAB/MS for $C_{22}H_{28}NO_5$ calculated ($M + H^+$) 386.2, found 386.2.

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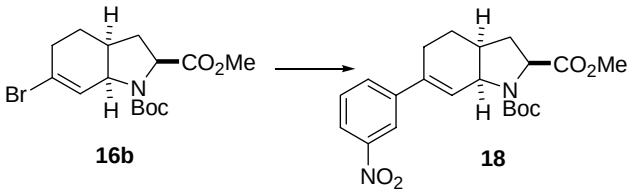

16b **18**

(2S,3aS,7aS)-6-(3-Nitro-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (18). Same procedure as **21** (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 8.20 (s, 1H), 8.10-8.03 (m, 1H), 7.78-7.63 (m, 1H), 7.48-7.39 (m, 1H), 6.38 (s, 0.6H), 6.22 (s, 0.4H), 4.60-4.52 (m, 0.6H), 4.50-4.41 (m, 0.4H), 4.31 (t, 0.4H, *J*=8.3 Hz), 4.25 (t, 0.6H, *J*=8.3 Hz), 3.67 (s, 3H), 2.60-2.30 (m, 3H), 2.27-2.17 (m, 1H), 2.02-1.75 (m, 3H), 1.50 (s, 4.5H), 1.43 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.9, 173.6, 154.2, 148.7, 143.7, 135.2, 134.5, 132.1, 131.6, 129.7, 129.5, 127.6, 126.7, 126.5, 122.3, 120.8, 80.7, 60.8, 59.4, 58.9, 57.4, 57.2, 56.2, 52.5, 52.4, 34.9, 32.1, 31.3, 28.9, 28.7, 22.9, 22.8; $[\alpha]_D$ +70.6^{o} (c 1.42, $CHCl_3$); HRMS for $C_{10}H_{26}N_2O_6$ calculated (M^+) 402.179087, found 402.179414.

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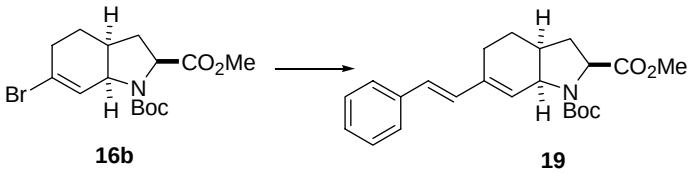

(2S,3aS,7aS)-6-(E-Styryl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (19). Same procedure as **21** (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 7.42-7.10 (m, 5H), 6.80 (s, 0.4H), 6.78 (s, 0.6H), 6.50-6.42 (m, 1H), 6.04 (s, 0.6H), 5.90 (s, 0.4H), 4.47-4.43 (m, 0.4H), 4.42-4.37 (m, 0.6H), 4.30 (t, 0.4H, *J*=8.5 Hz), 4.23 (t, 0.6H, *J*=8.5 Hz), 3.75-3.62 (m, 3H), 2.58-2.28 (m, 2H), 2.23-2.08 (m, 2H), 1.98-1.75 (m, 4H), 1.56-1.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.9, 146.9, 137.9, 135.4, 135.0, 132.2, 132.1, 129.8, 129.0, 128.7, 127.9, 127.6, 127.2, 80.8, 80.5, 59.6, 59.0, 57.6, 57.4, 56.2, 52.5, 52.4, 36.3, 35.5, 32.2, 31.5, 28.9, 28.7, 22.5, 19.8; $[\alpha]_D$ +48^{o} (c 0.75, $CHCl_3$); FAB/MS for $C_{23}H_{30}NO_4$ calculated (M + H^+) 384.2, found 384.2.

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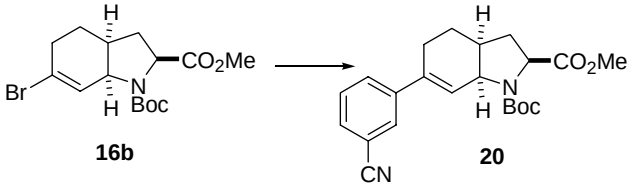

(2S,3aS,7aS)-6-(3-Cyano-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (20). Same procedure as **21** (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 7.63-7.58 (m, 2H), 7.55-7.45 (m, 1H), 7.44-7.32 (m, 1H), 6.30 (s, 0.6H), 6.10 (s, 0.4H), 4.58-4.48 (m, 0.6H), 4.47-4.38 (m, 0.4H), 4.32 (t, 0.4H, *J*=8.5 Hz), 4.25 (t, 0.6H, *J*=8.5 Hz), 3.68-3.66 (m, 3H), 2.60-2.27 (m, 3H), 2.26-2.10 (m, 1H), 2.00-1.72 (m, 3H), 1.53-1.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.9, 154.2, 143.1, 134.6, 131.1, 130.9, 130.5, 130.4, 129.9, 129.6, 129.4, 126.4, 126.2, 119.4, 112.7, 80.7, 59.3, 58.8, 57.4, 57.2, 52.5, 52.4, 35.6, 34.9, 32.1, 31.3, 28.9, 28.7, 22.8; $[\alpha]_D$ +44.4^{o} (c 1.11, $CHCl_3$); FAB/MS for $C_{22}H_{27}N_2O_4$ calculated (M + H^+) 383.2, found 383.2.

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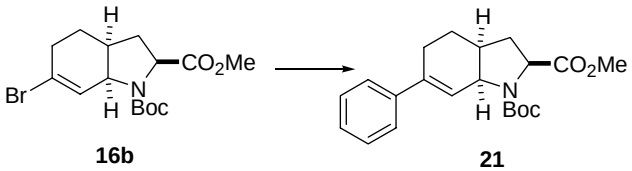

16b **21**

(2S,3aS,7aS)-6-Phenyl-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (21). To a solution of the bromide **16b** (0.080 g, 0.222 mmol) and phenylboronic acid (0.041 g, 0.333 mmol) in THF (2 mL), was added a solution of Cs_2CO_3 (0.88 mL, 1.0 M in H_2O) followed by $Pd(PPh_3)_4$ (cat.). After heating the solution at reflux for 4h, the mixture was concentrated under vacuum, the aqueous solution was extracted with CH_2Cl_2, the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 10:90) to give **21** (0.067 g, 84%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 6.45-6.15 (m, 4H), 6.25 (s, 0.5H), 6.10 (s, 0.5H), 4.58-4.52 (m, 0.5H), 4.50-4.40 (m, 0.5H), 4.33 (t, 0.5H, *J*=8.4 Hz), 4.25 (t, 0.5H, *J*=8.4 Hz), 3.75-3.61 (m, 3H), 2.57-2.29 (m, 3H), 2.28-2.12 (m, 1H), 2.08-1.75 (m, 4H), 1.56-1.30 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 128.2, 128.0, 127.1, 126.9, 125.5, 123.3, 79.9, 59.0, 56.9, 51.9, 34.5, 31.6, 28.4, 28.2, 22.4, 22.1; $[\alpha]_D$ +49.8^o (c 1.50, $CHCl_3$); FAB/MS for $C_{21}H_{28}NO_4$ calculated (M + H^+) 358.2, found 358.2.

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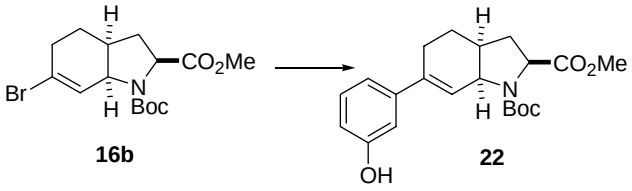

16b **22**

(2S,3aS,7aS)-6-(3-Hydroxy-phenyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (22). Same procedure as **21** (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 7.18-7.05 (m, 1H), 6.95-6.67 (m, 3H), 6.22 (s, 0.5H), 6.08 (s, 0.5H), 4.61-4.53 (m, 0.5H), 4.48-4.37 (m, 0.5H), 4.35 (t, 0.5H,

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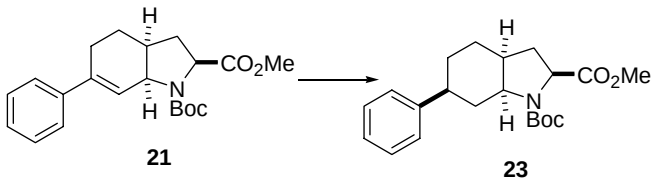
J=8.2 Hz), 4.25 (t, 0.5H, *J*=8.2 Hz), 3.68 (s, 1.5H), 3.66 (s, 1.5H), 2.58-2.10 (m, 4H), 2.03-1.68 (m, 3H), 1.50 (s, 4.5H), 1.43 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 174.1, 174.0, 157.3, 156.5, 154.9, 154.6, 143.4, 136.3, 130.3, 129.7, 129.6, 123.4, 119.0, 117.9, 114.9, 114.7, 113.0, 81.1, 80.9, 59.6, 58.9, 57.6, 52.7, 52.5, 35.2, 32.1, 31.4, 28.9, 28.8, 22.9, 22.5, 21.5; $[\alpha]_D$ +21.7^o (c 1.08, $CHCl_3$); HRMS for $C_{21}H_{27}NO_5$ calculated (M^+) 373.188923, found 373.188356.



21 **23**

(2S,3aS,6S,7aS)-6-phenyl-octahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (23). To a solution of **21** (0.050 g, 0.140 mmol) in EtOAc (2.5 mL), was added Pd/C 10% (cat.) and stirred under 1 atm. of H_2 for 24h. The catalyst was filtered through a celite pad, the filtrate was concentrated under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 0:100 to 10:90) to give **23** (0.035 g, 70%) as a white solid crystallizing in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 7.34-7.15 (m, 5H), 4.29 (dd, 0.6H, *J*=7.7 Hz, *J*=9.9 Hz), 4.24 (dd, 0.4H, *J*=7.7 Hz, *J*=9.9 Hz), 4.08-4.02 (m, 0.6H), 3.95-3.90 (m, 0.4H), 3.76 (s, 1.5H), 3.74 (s, 1.5H), 2.53-2.30 (m, 2H), 2.25-2.00 (m, 2H), 1.90-1.79 (m, 2H), 1.75-1.50 (m, 4H), 1.43 (s, 4.5H), 1.39 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.9, 153.0, 146.0, 128.3, 128.1, 126.7, 126.0, 125.8, 79.7, 59.3, 58.7, 57.8, 57.5, 52.0, 51.8, 41.6, 41.4, 36.3, 35.6, 35.1, 34.8, 32.4, 31.6, 28.6, 28.3, 28.1, 27.8, 25.9, 25.7; $[\alpha]_D$ -16.8^o (c 0.75, $CHCl_3$); m.p.: 100-103^{o}C ;HRMS for $C_{21}H_{30}NO_4$ calculated ($M+H^+$) 360.217484, found 360.217267.

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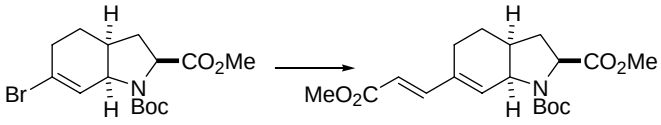
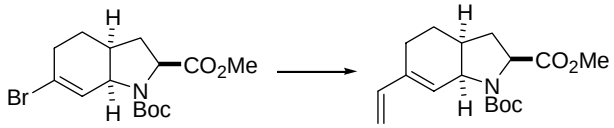


16b **24**

(2S,3aS,7aS)-6-(2-Methoxycarbonyl-vinyl)-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (24). To a solution of the bromide **16b** (0.072 g, 0.200 mmol), methyl acrylate (0.14 mL, 1.60 mmol) and Et_3N (0.11 mL, 0.800 mmol) in MeCN (3 mL), was added P(o-tolyl)$_3$ (0.009 g, 0.03 mmol) and $Pd(OAc)_2$ (0.003 g, 0.01 mmol). After heating the solution at reflux for 12h under argon, P(o-tolyl)$_3$ (0.009 g, 0.03 mmol) and $Pd(OAc)_2$ (0.003 g, 0.01 mmol) were added and the heating was continue for another 12h. Finally, the solution was cooled down to RT, H_2O was added, the aqueous solution was extracted with CH_2Cl_2, the combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 15:85) to give **24** (0.055 g, 75%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, 1H, *J*=15.9 Hz), 6.30 (s, 0.6H), 6.18 (s, 0.4H), 5.86-5.76 (m, 1H), 4.51-4.42 (m, 0.6H), 4.40-4.33 (m, 0.4H), 4.27 (t, 0.4H, *J*=8.4 Hz), 4.22 (t, 0.6H, *J*=8.4 Hz), 3.74 (s, 3H), 3.68 (s, 3H), 2.58-2.41 (m, 1H), 2.22-1.97 (m, 3H), 1.88-1.70 (m, 3H), 1.50 (s, 4.5H), 1.42 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.3, 167.9, 147.8, 135.9, 135.8, 134.1, 133.7, 117.2, 117.1, 80.8, 59.4, 58.9, 57.3, 57.1, 52.4, 51.9, 45.1, 36.0, 35.2, 32.1, 31.4, 28.9, 28.7, 22.2, 22.1, 19.5; $[\alpha]_D$ +141^o (c 0.750, $CHCl_3$); HRMS for $C_{19}H_{27}NO_6$ calculated (M^+) 365.183838, found 365.183716.



16b **25**

(2S,3aS,7aS)-6-Vinyl-2,3,3a,4,5,7a-hexahydro-indole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (25). To a solution of the **16b** (0.080 g, 0.222 mmol) and tributylvinyltin (71 μL, 0.244 mmol) in toluene (2.5 mL), was added $Pd(PPh_3)_4$ (cat.). After heating the solution at 100^{o}C for 8h, the mixture was concentrated under vacuum and the resulting oil was purified by flash chromatography (EtOAc/Hexanes 10:90) to give **25** (0.048 g, 71%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (rotamers) 6.40-

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6.33 (m, 1H), 5.91 (s, 0.6H), 5.78 (m, 0.4H), 5.17-5.10 (m, 1H), 5.03-4.96 (m, 1H), 4.48-4.41 (m, 0.6H), 4.38-4.30 (m, 0.4H), 4.28 (t, 0.4H, *J*=8.3 Hz), 4.23 (t, 0.6H, *J*=8.3 Hz), 3.67 (s, 3H), 2.50-2.35 (m, 1H), 2.22-2.08 (m, 2H), 2.07-1.90 (m, 1H), 1.87-1.70 (m, 3H), 1.48 (s, 4.5H), 1.41 (s, 4.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamers) 173.9, 154.2, 140.0, 135.6, 135.2, 128.1, 112.7, 112.4, 80.5, 59.5, 58.9, 57.4, 57.2, 52.5, 52.3, 36.3, 35.5, 32.2, 31.4, 28.9, 28.7, 22.3, 19.0; $[\alpha]_D$ +131^o (c 1.00, $CHCl_3$); HRMS for $C_{17}H_{25}NO_4$ calculated (M^+) 307.178359, found 307.179443.

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

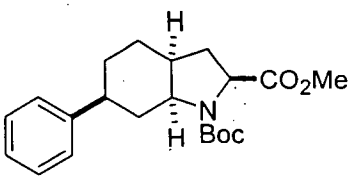
C21 H29 N O4 COMPOUND (HAN403)

Friday, September 03, 2004

Equipe Hanessian

Département de chimie, Université de Montréal,

C.P. 6128, Succ. Centre-Ville, Montréal, Québec, H3C 3J7 (Canada)



Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C21 H29 N O4.

Identification code	HAN403
Empirical formula	C21 H29 N O4
Formula weight	359.45
Temperature	293(2)K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.467(3) Å α = 90° b = 10.980(5) Å β = 90° c = 29.081(17) Å γ = 90°
Volume	2065.0(18)Å^3
Z	4
Density (calculated)	1.156 Mg/m^3
Absorption coefficient	0.638 mm^{-1}
F(000)	776
Crystal size	0.50 x 0.15 x 0.12 mm
Theta range for data collection	3.04 to 70.05°
Index ranges	$-7 \leq h \leq 7$, $-13 \leq k \leq 13$, $-35 \leq \lambda \leq 35$
Reflections collected	16270
Independent reflections	3915 [R_{int} = 0.070]
Absorption correction	None
Max. and min. transmission	0.9300 and 0.7400
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3915 / 0 / 240
Goodness-of-fit on F^2	0.738
Final R indices [I>2sigma(I)]	R_1 = 0.0426, wR_2 = 0.0858
R indices (all data)	R_1 = 0.0822, wR_2 = 0.0976
Absolute structure parameter	-0.5(3)

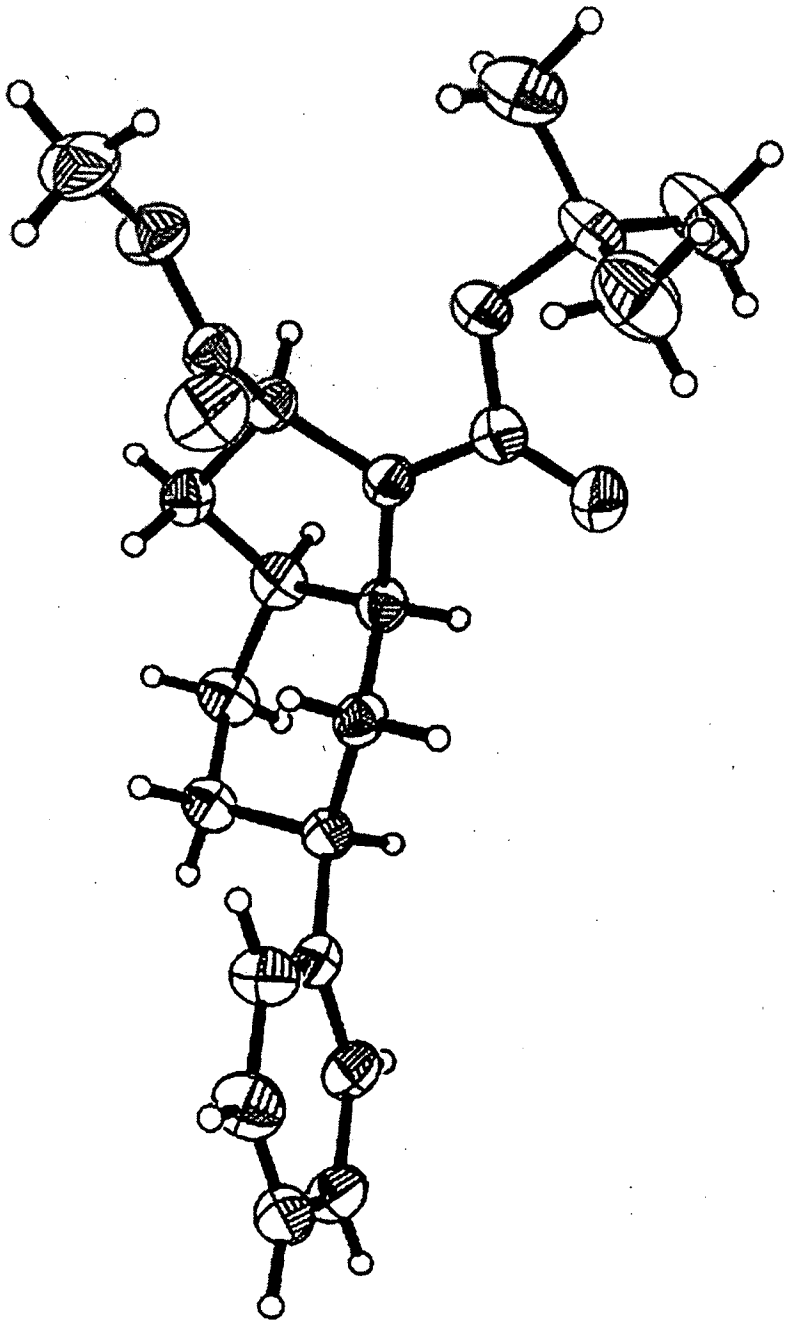
Extinction coefficient	0.00322(19)
Largest diff. peak and hole	0.124 and -0.141 e/Å^3

Table 5. Bond lengths [Å] and angles [°] for C21 H29 N O4

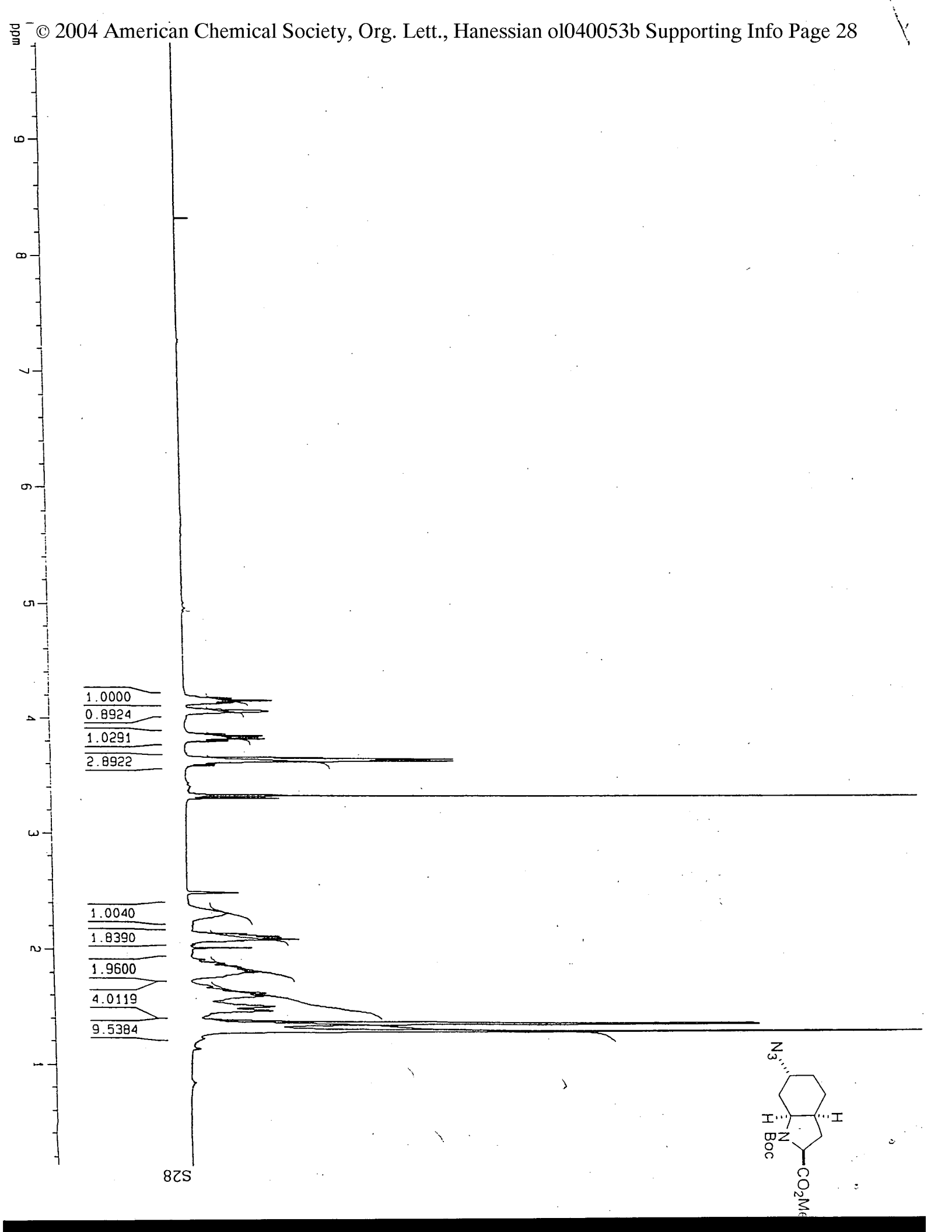
O(1)-C(9)	1.212(3)	C(14)-C(1)-C(2)	112.3(2)
O(2)-C(9)	1.338(3)	C(3)-C(2)-C(1)	103.5(2)
O(2)-C(10)	1.481(3)	C(8)-C(3)-C(2)	103.6(2)
O(3)-C(14)	1.192(3)	C(8)-C(3)-C(4)	114.9(2)
O(4)-C(14)	1.321(3)	C(2)-C(3)-C(4)	116.9(3)
O(4)-C(15)	1.445(4)	C(5)-C(4)-C(3)	113.1(2)
N(1)-C(9)	1.354(4)	C(6)-C(5)-C(4)	111.2(2)
N(1)-C(8)	1.468(3)	C(16)-C(6)-C(7)	114.9(2)
N(1)-C(1)	1.469(3)	C(16)-C(6)-C(5)	111.0(2)
C(1)-C(14)	1.496(4)	C(7)-C(6)-C(5)	108.1(2)
C(1)-C(2)	1.539(4)	C(6)-C(7)-C(8)	111.1(2)
C(2)-C(3)	1.519(3)	N(1)-C(8)-C(3)	101.8(2)
C(3)-C(8)	1.512(4)	N(1)-C(8)-C(7)	112.4(2)
C(3)-C(4)	1.528(4)	C(3)-C(8)-C(7)	113.1(2)
C(4)-C(5)	1.526(3)	O(1)-C(9)-O(2)	127.0(3)
C(5)-C(6)	1.522(3)	O(1)-C(9)-N(1)	123.4(3)
C(6)-C(16)	1.507(4)	O(2)-C(9)-N(1)	109.6(3)
C(6)-C(7)	1.517(3)	O(2)-C(10)-C(13)	109.1(3)
C(7)-C(8)	1.529(3)	O(2)-C(10)-C(12)	110.8(3)
C(10)-C(13)	1.486(5)	C(13)-C(10)-C(12)	111.8(4)
C(10)-C(12)	1.495(4)	O(2)-C(10)-C(11)	101.5(3)
C(10)-C(11)	1.501(5)	C(13)-C(10)-C(11)	111.5(4)
C(16)-C(17)	1.380(4)	C(12)-C(10)-C(11)	111.7(3)
C(16)-C(21)	1.386(4)	O(3)-C(14)-O(4)	124.0(3)
C(17)-C(18)	1.377(4)	O(3)-C(14)-C(1)	125.1(3)
C(18)-C(19)	1.363(4)	O(4)-C(14)-C(1)	110.6(3)
C(19)-C(20)	1.371(4)	C(17)-C(16)-C(21)	116.4(3)
C(20)-C(21)	1.380(4)	C(17)-C(16)-C(6)	123.7(3)
		C(21)-C(16)-C(6)	119.8(3)
C(9)-O(2)-C(10)	120.8(3)	C(18)-C(17)-C(16)	121.3(3)
C(14)-O(4)-C(15)	116.3(3)	C(19)-C(18)-C(17)	121.4(3)
C(9)-N(1)-C(8)	122.5(2)	C(18)-C(19)-C(20)	118.6(3)
C(9)-N(1)-C(1)	123.8(3)	C(19)-C(20)-C(21)	120.0(3)
C(8)-N(1)-C(1)	113.3(2)	C(20)-C(21)-C(16)	122.3(3)
N(1)-C(1)-C(14)	112.6(2)		
N(1)-C(1)-C(2)	102.1(2)		

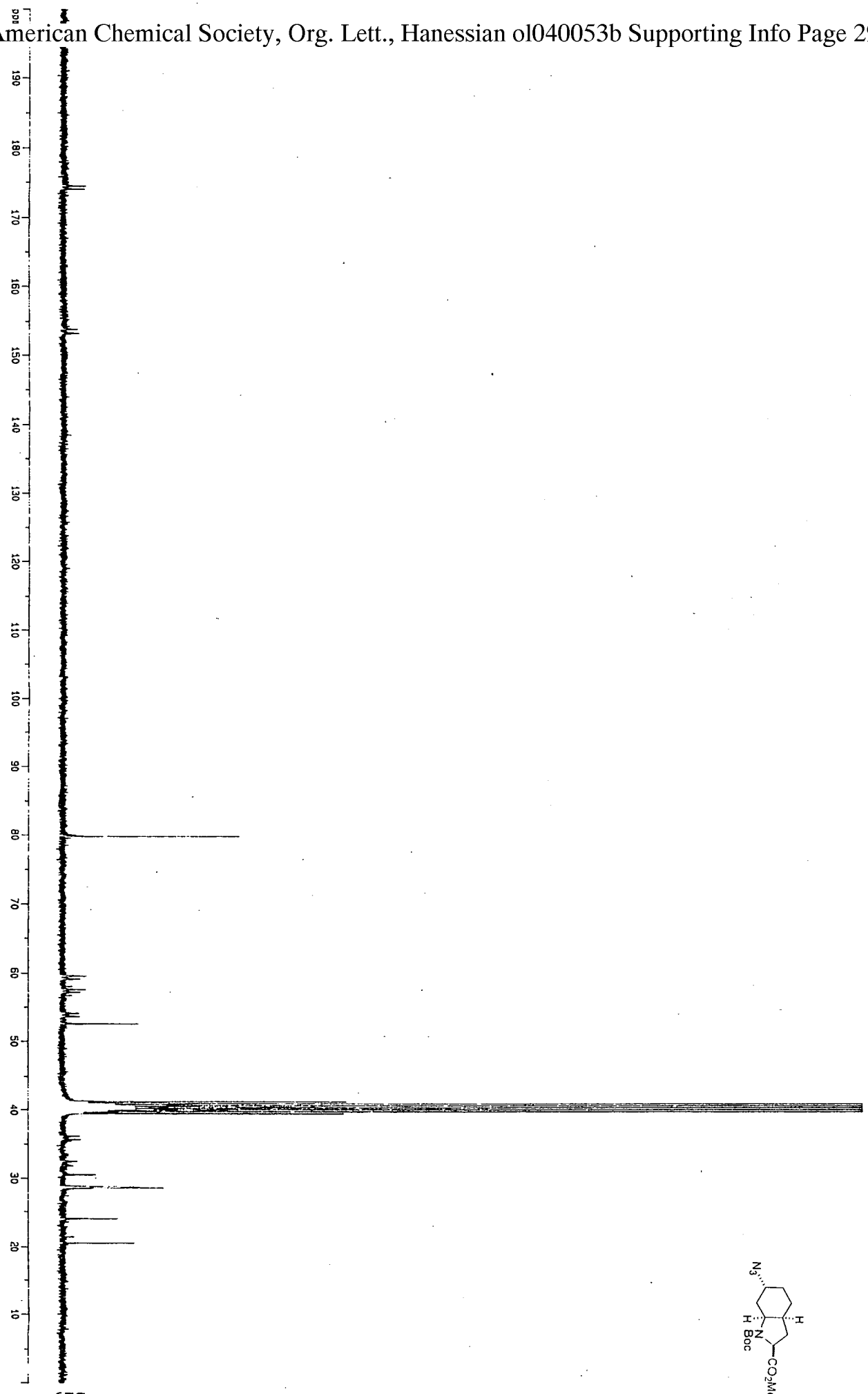
Table 6. Torsion angles [°] for C21 H29 N O4.

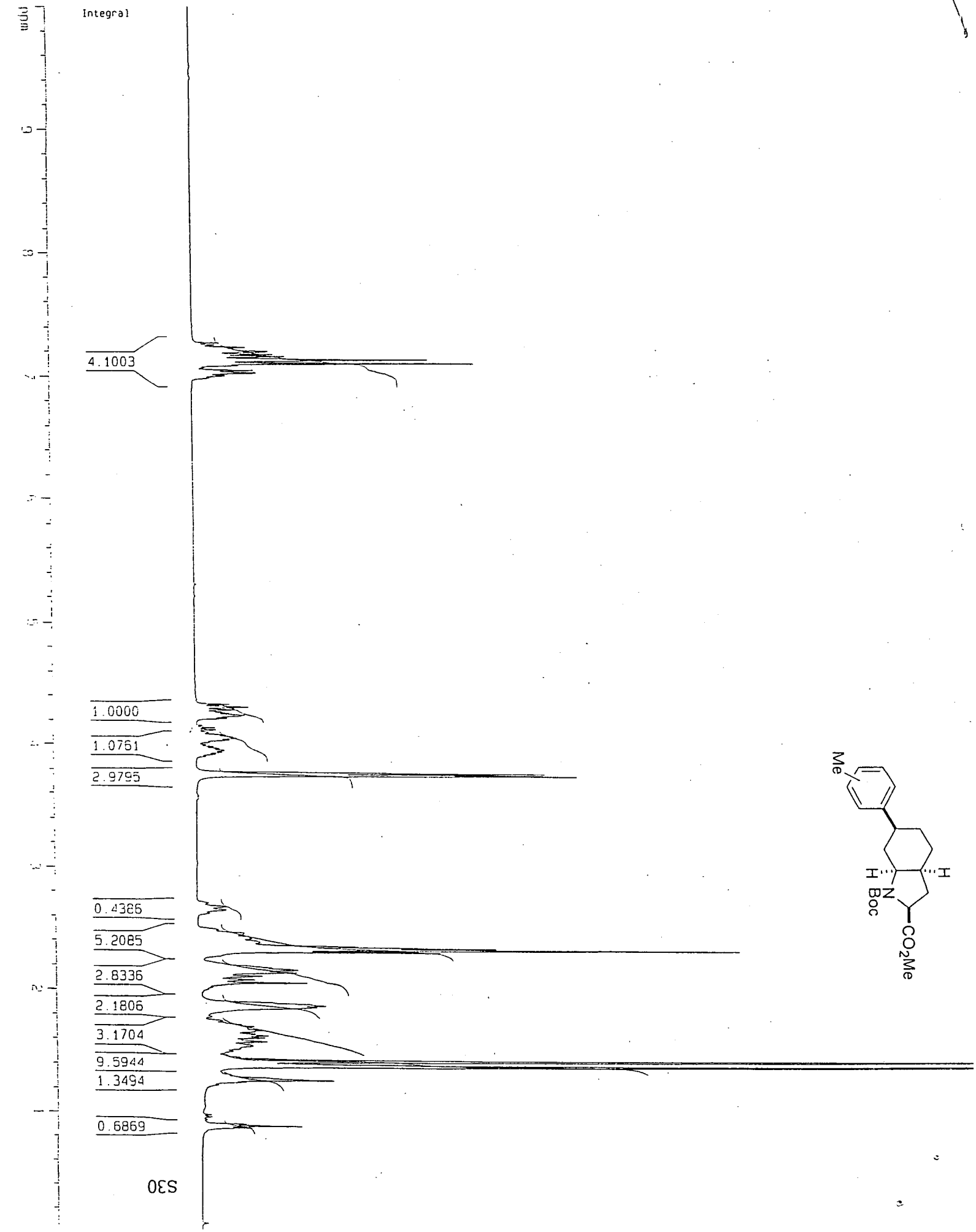
C(9)-N(1)-C(1)-C(14)	-60.5(4)	C(8)-N(1)-C(9)-O(1)	-5.3(5)
C(8)-N(1)-C(1)-C(14)	126.9(3)	C(1)-N(1)-C(9)-O(1)	-177.2(3)
C(9)-N(1)-C(1)-C(2)	178.8(3)	C(8)-N(1)-C(9)-O(2)	174.0(2)
C(8)-N(1)-C(1)-C(2)	6.2(3)	C(1)-N(1)-C(9)-O(2)	2.1(4)
N(1)-C(1)-C(2)-C(3)	-27.9(3)	C(9)-O(2)-C(10)-C(13)	-60.1(4)
C(14)-C(1)-C(2)-C(3)	-148.8(2)	C(9)-O(2)-C(10)-C(12)	63.4(4)
C(1)-C(2)-C(3)-C(8)	39.8(3)	C(9)-O(2)-C(10)-C(11)	-177.9(3)
C(1)-C(2)-C(3)-C(4)	167.3(2)	C(15)-O(4)-C(14)-O(3)	3.6(5)
C(8)-C(3)-C(4)-C(5)	42.4(4)	C(15)-O(4)-C(14)-C(1)	177.9(3)
C(2)-C(3)-C(4)-C(5)	-79.4(3)	N(1)-C(1)-C(14)-O(3)	-37.5(4)
C(3)-C(4)-C(5)-C(6)	-52.0(3)	C(2)-C(1)-C(14)-O(3)	77.1(4)
C(4)-C(5)-C(6)-C(16)	-171.5(2)	N(1)-C(1)-C(14)-O(4)	148.3(2)
C(4)-C(5)-C(6)-C(7)	61.7(3)	C(2)-C(1)-C(14)-O(4)	-97.0(3)
C(16)-C(6)-C(7)-C(8)	173.4(2)	C(7)-C(6)-C(16)-C(17)	36.3(4)
C(5)-C(6)-C(7)-C(8)	-62.1(3)	C(5)-C(6)-C(16)-C(17)	-86.6(3)
C(9)-N(1)-C(8)-C(3)	-154.7(3)	C(7)-C(6)-C(16)-C(21)	-147.4(3)
C(1)-N(1)-C(8)-C(3)	18.0(3)	C(5)-C(6)-C(16)-C(21)	89.7(3)
C(9)-N(1)-C(8)-C(7)	84.0(3)	C(21)-C(16)-C(17)-C(18)	-0.3(4)
C(1)-N(1)-C(8)-C(7)	-103.3(3)	C(6)-C(16)-C(17)-C(18)	176.1(3)
C(2)-C(3)-C(8)-N(1)	-34.9(3)	C(16)-C(17)-C(18)-C(19)	-0.3(5)
C(4)-C(3)-C(8)-N(1)	-163.6(2)	C(17)-C(18)-C(19)-C(20)	0.6(5)
C(2)-C(3)-C(8)-C(7)	85.9(3)	C(18)-C(19)-C(20)-C(21)	-0.2(5)
C(4)-C(3)-C(8)-C(7)	-42.8(3)	C(19)-C(20)-C(21)-C(16)	-0.5(5)
C(6)-C(7)-C(8)-N(1)	167.8(2)	C(17)-C(16)-C(21)-C(20)	0.7(4)
C(6)-C(7)-C(8)-C(3)	53.2(3)	C(6)-C(16)-C(21)-C(20)	-175.8(3)
C(10)-O(2)-C(9)-O(1)	-4.0(5)		
C(10)-O(2)-C(9)-N(1)	176.8(3)		



ORTEP view of the C21 H29 N O4 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogens represented by sphere of arbitrary size.



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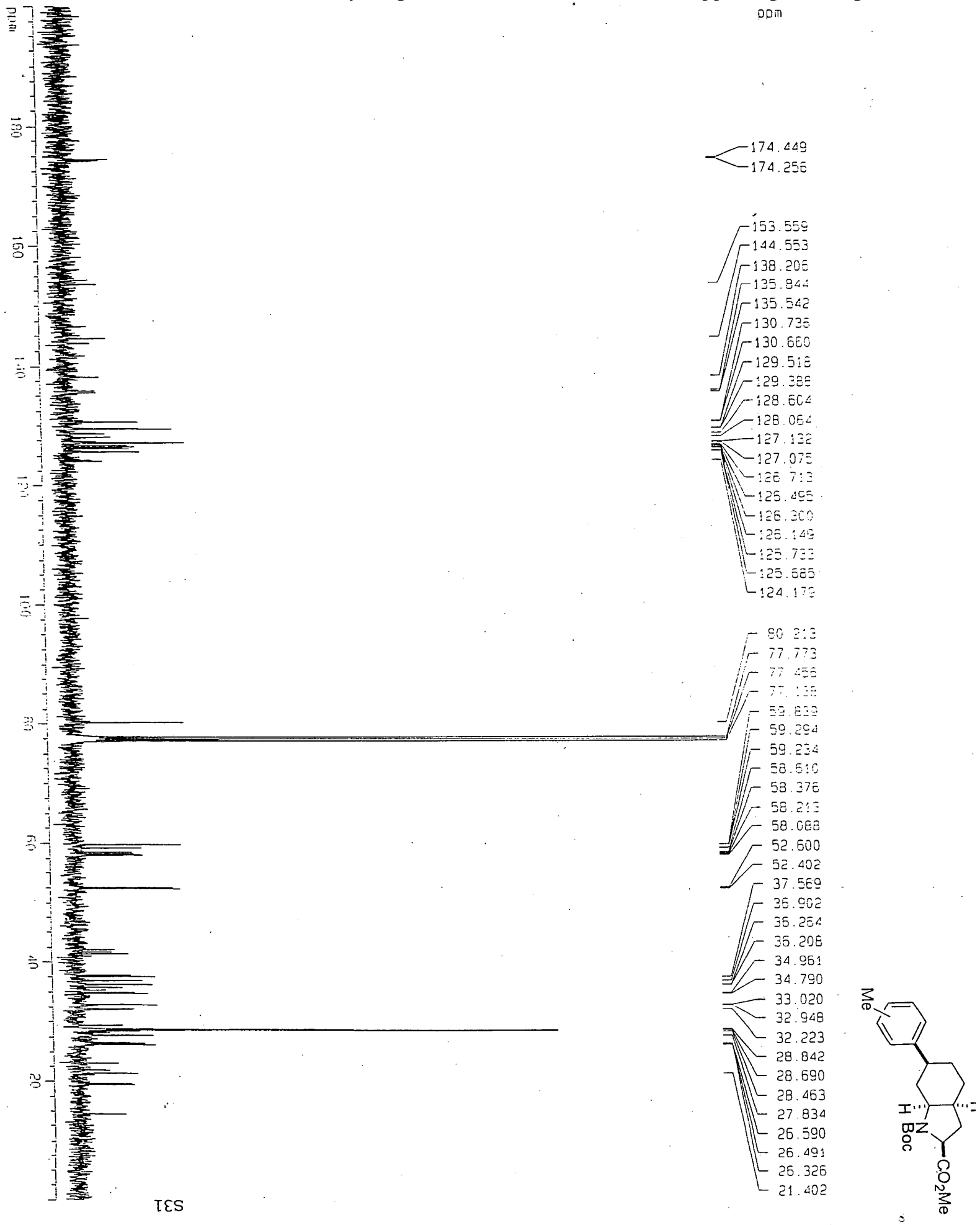
H
N
Boc
CO2Me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126.149
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Me
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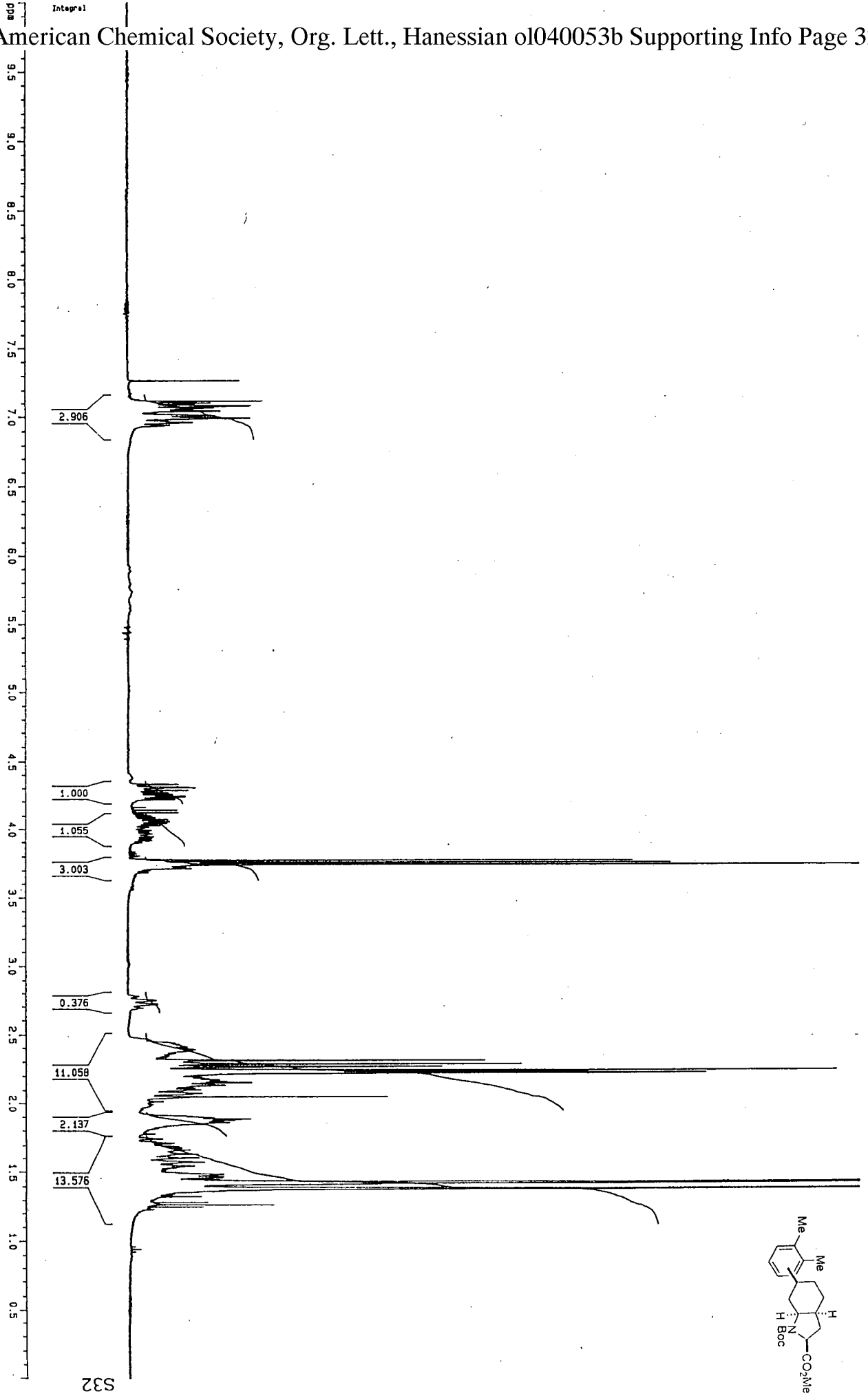
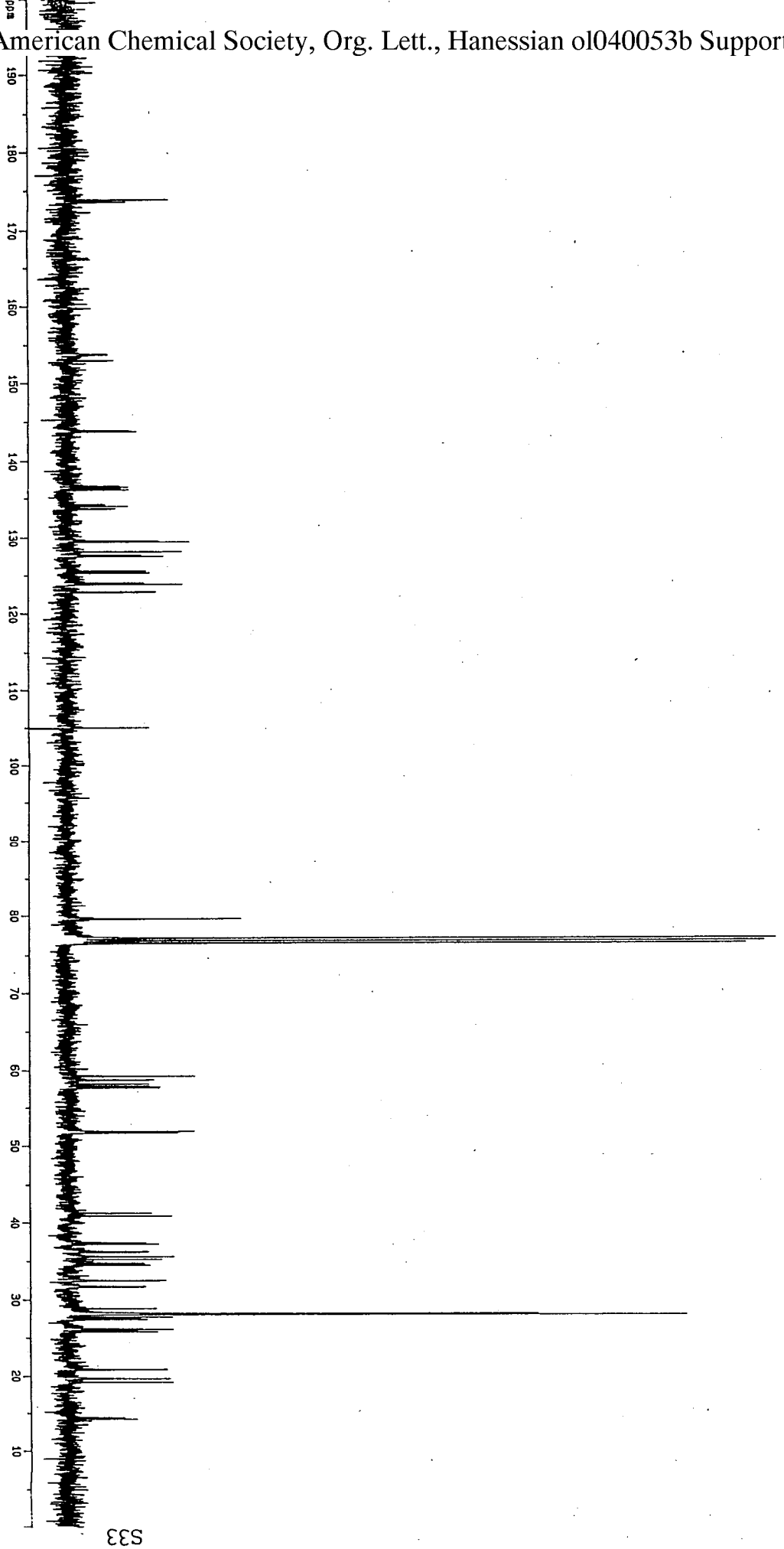
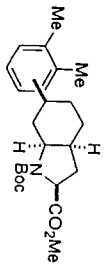
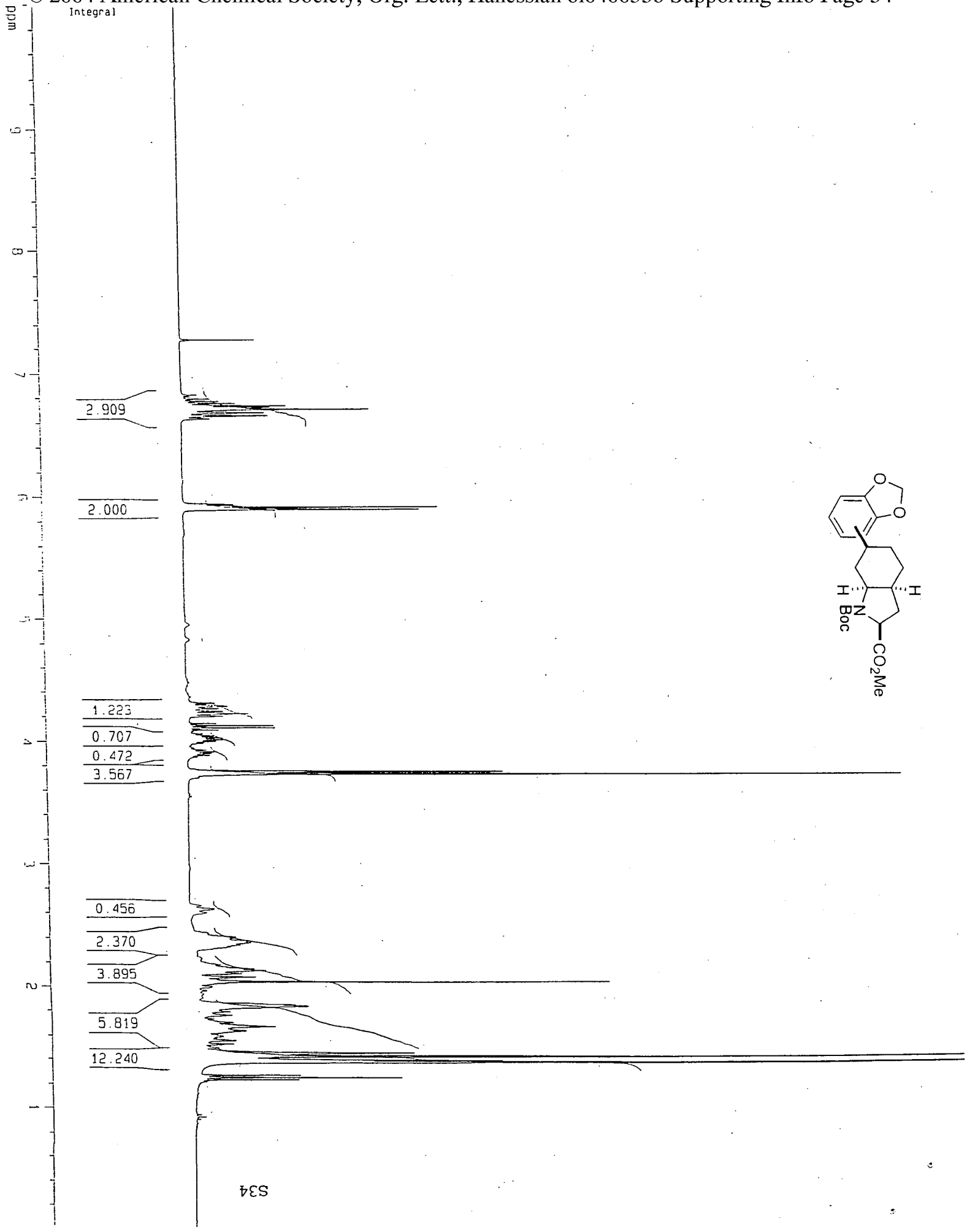
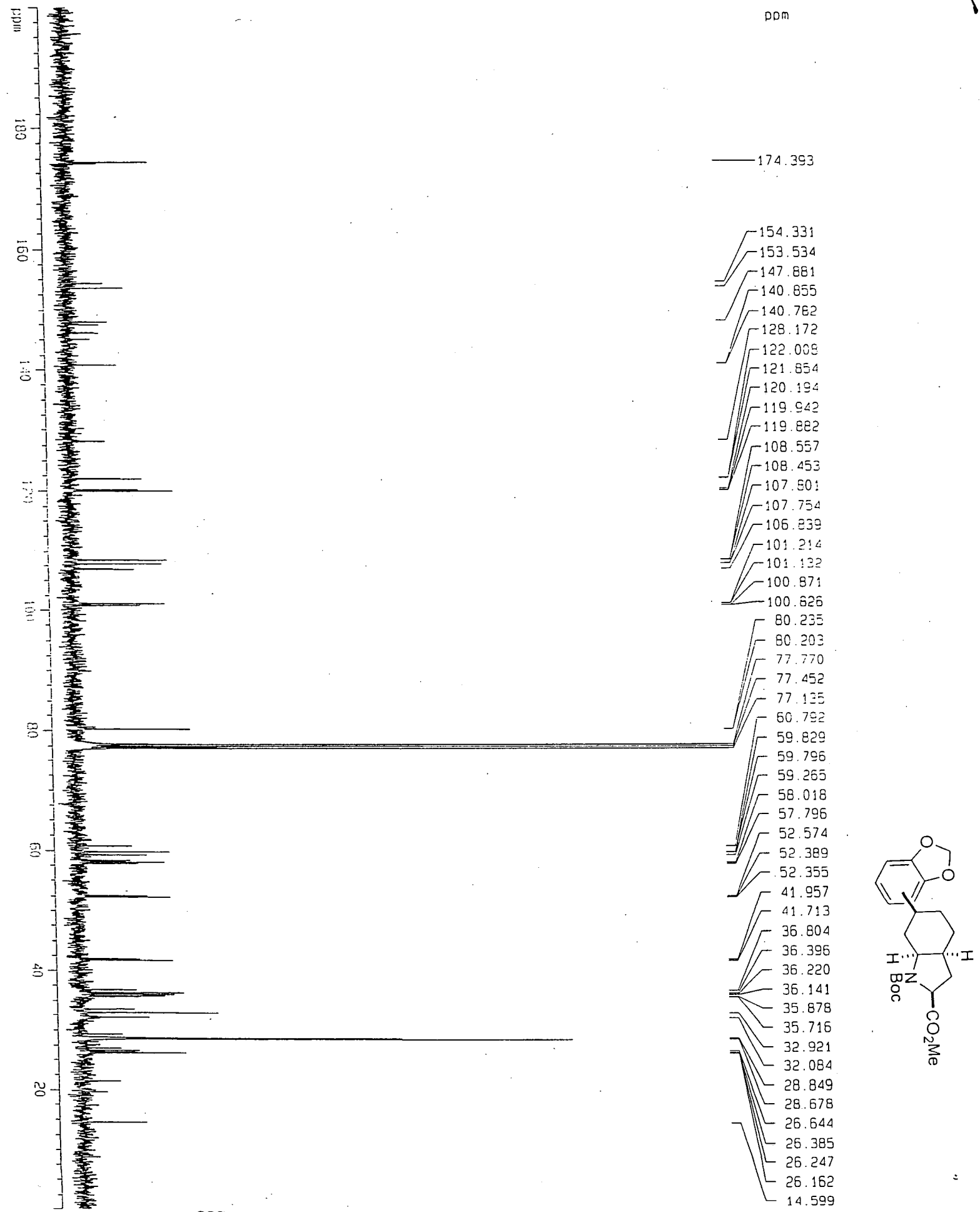
N
Boc
CO2Me







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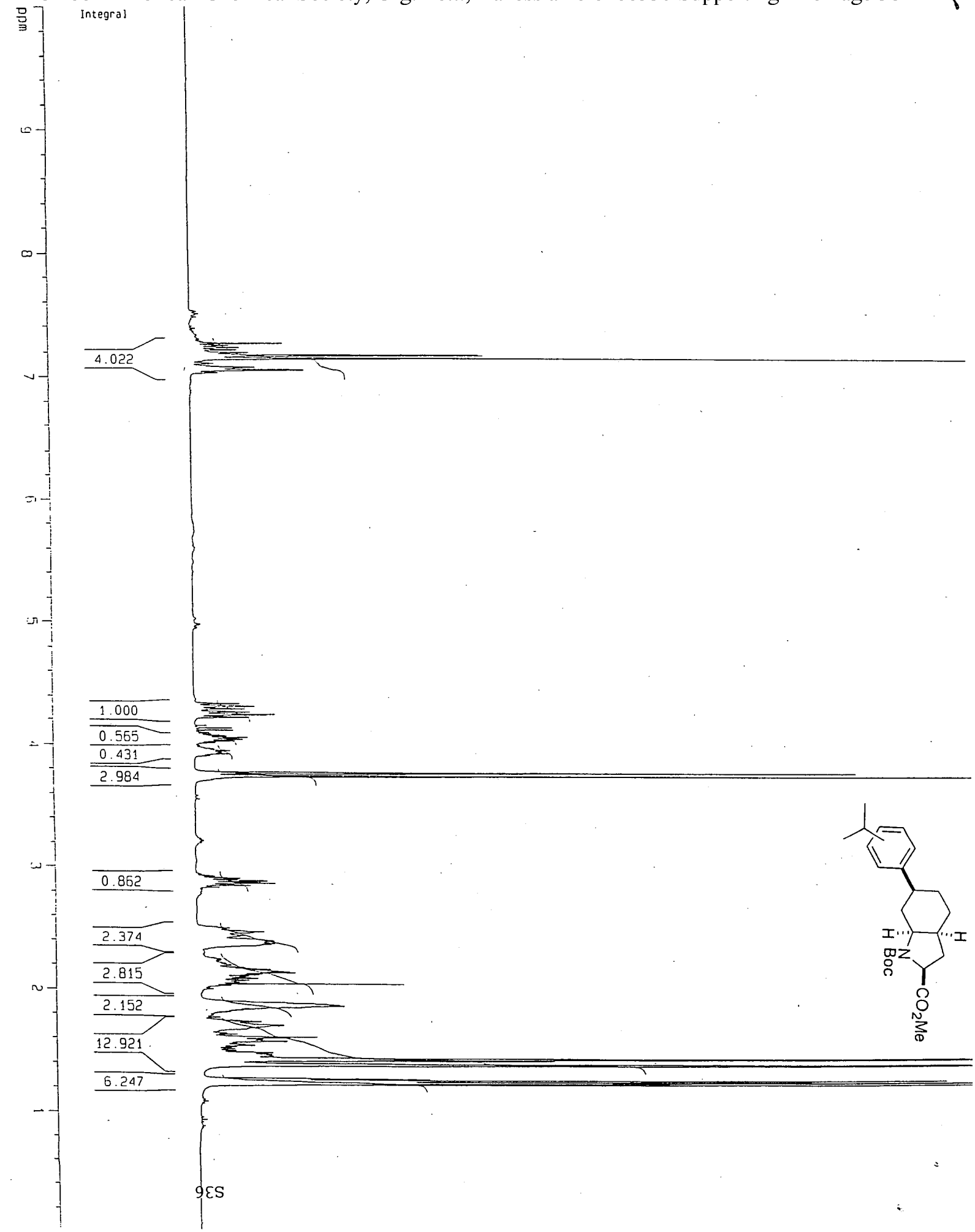
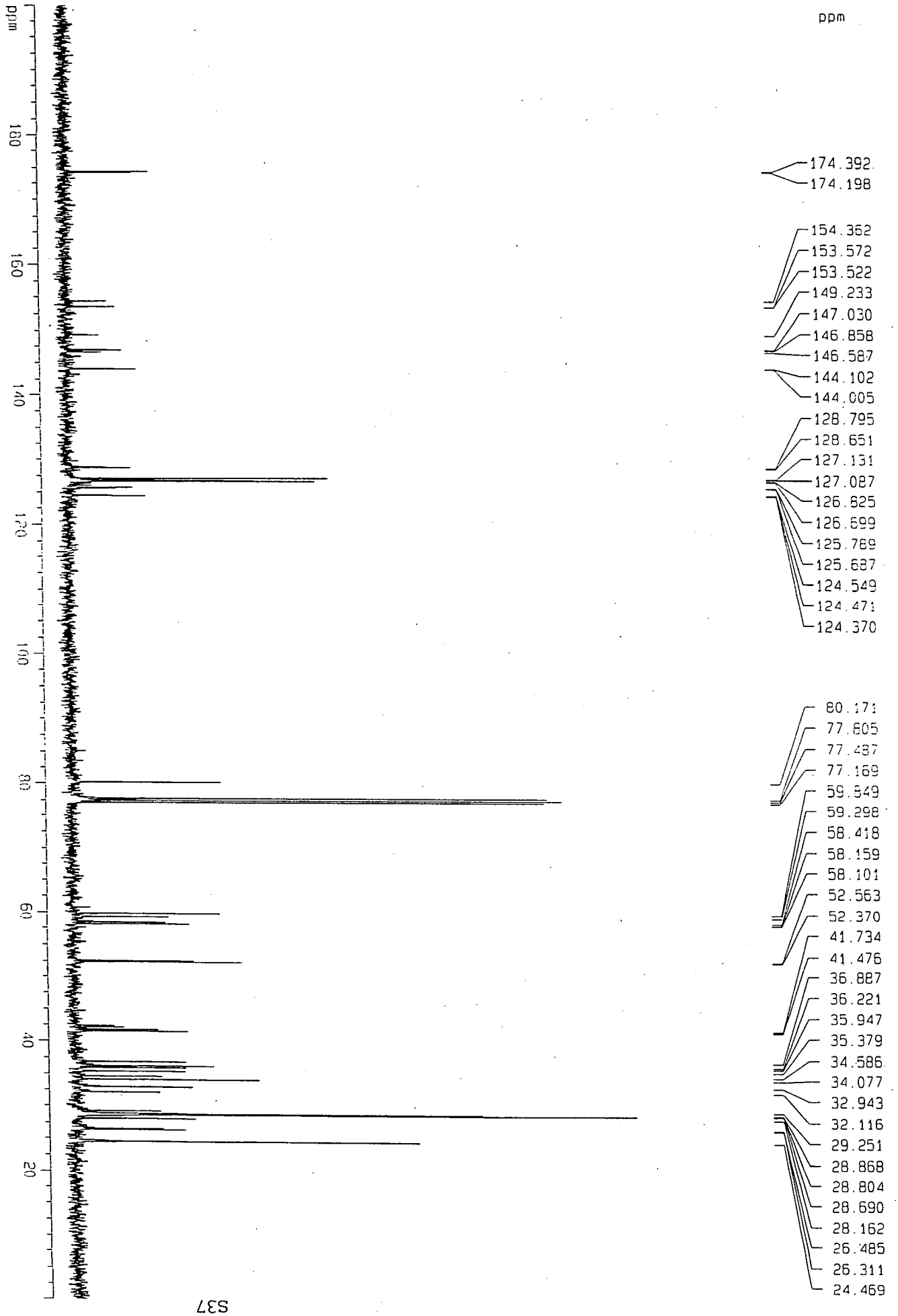
H
N
Boc
CO2Me

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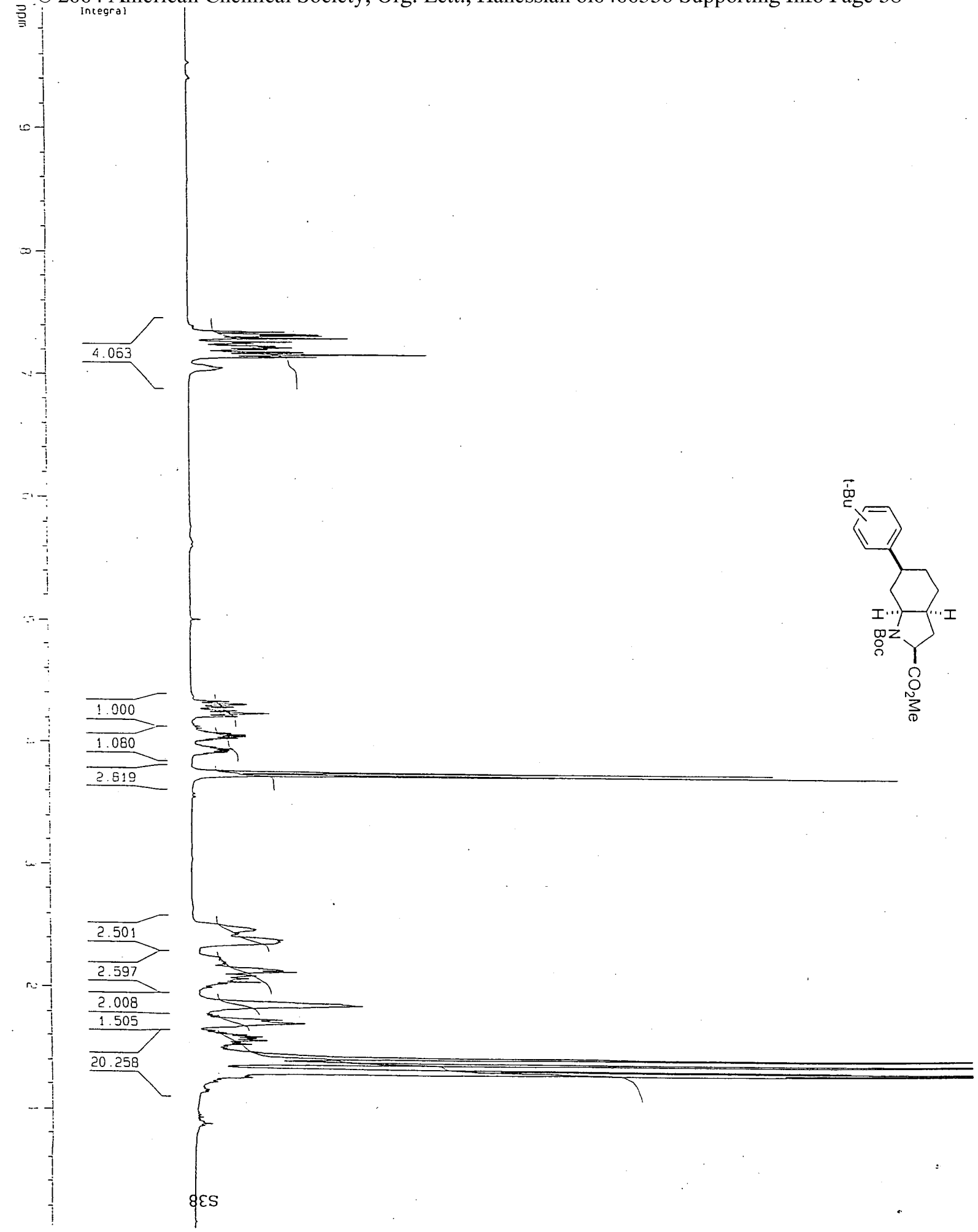
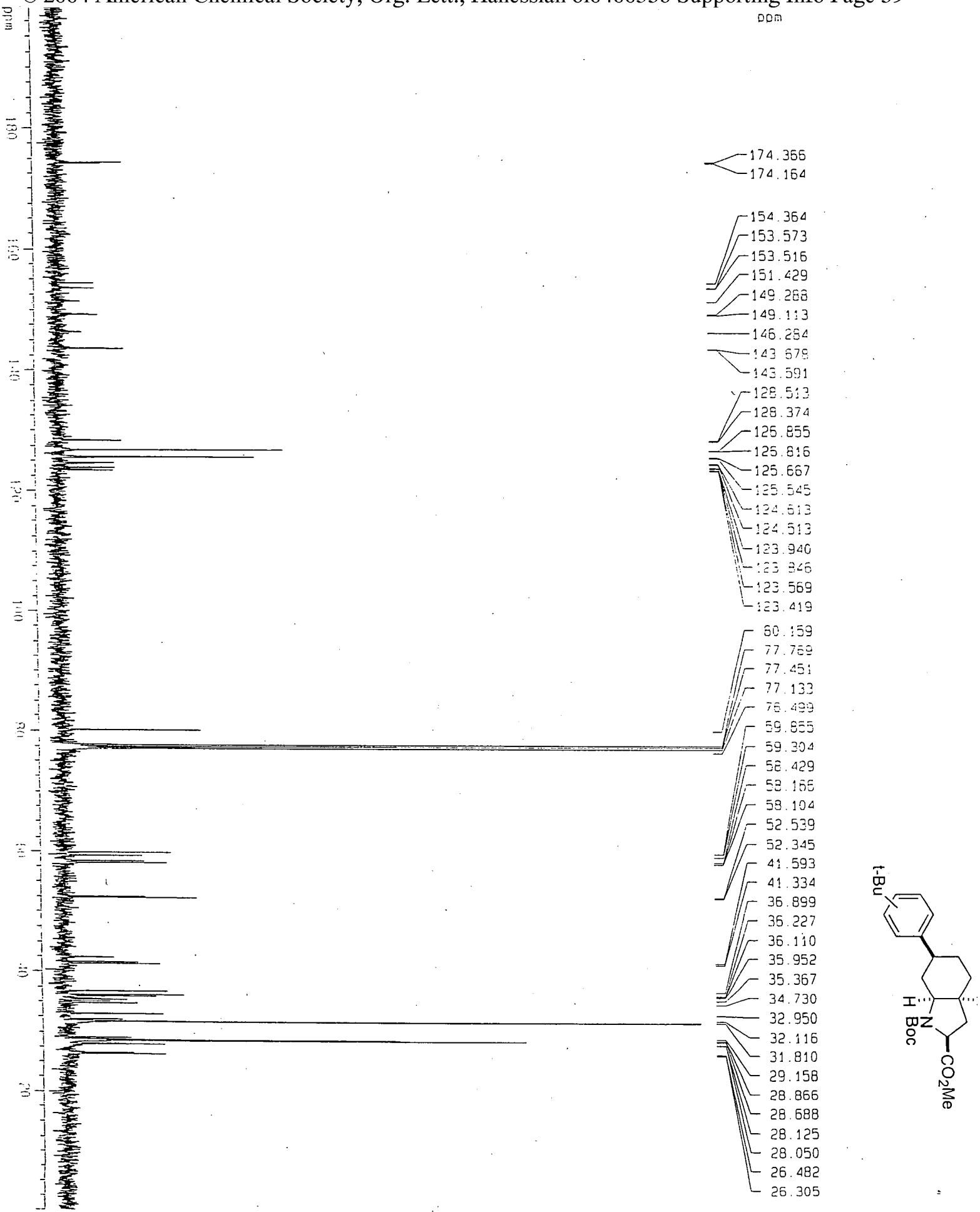
Boc
CO2Me

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t-Bu
H
N
Boc
CO2Me