Efficient Asymmetric Synthesis of a Novel Gastrin Receptor Antagonist AG-041R via Highly Stereoselective Alkylation of Oxindole Enolates

Takashi Emura,[*,†] Toru Esaki,[†] Kazutaka Tachibana,[†] and Makoto Shimizu[‡]

Chemistry Research Dept. 1 Chugai Pharmaceutical Co., LTD., 1-135 Komakado, Gotemba, Shizuoka 412-8513, Japan, and

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, 1577 Kurimamachiya-cho, Tsu, Mie 514-8507, Japan.

emuratks@chugai-pharm.co.jp

Supporting Information

Table of Contents

General Methods

All reactions were performed under nitrogen atmosphere. All commercially available reagents and solvents were used without further purification unless otherwise noted. Column chromatography was performed with silica gel (0.040–0.100 mm). The combined organic layers were dried over Na_2SO_4. Solvents were evaporated under reduced pressure. All yields given refer to an isolated yield. Diastereomeric ratios were determined by ^{1}H NMR spectra or HPLC analysis using YMC-Pack CN column (4.6 × 300) with a mobile phase of *n*-Hexane/*i*-PrOH = 99:1, and flow rate 0.9 mL/min. NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are reported in ppm. Coupling constants (*J* values) are reported in Hertz. HRMS experiments were performed on a high resolution magnetic sector mass spectrometer.

Experimental and Spectral Data

[(R)-2-Oxo-1-(2-oxo-ethyl)-3-(3-*p*-tolyl-ureido)-2,3-dihydro-1*H*-indol-3-yl]-acetic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (11). To a solution of **9** (210 mg, 0.386 mmol) in acetone (10 mL) and water (10 mL) was added 2 N HCl (0.5 mL). The mixture was refluxed for 14 h. To the reaction mixture was added saturated $NaHCO_3$ solution, followed by removal of solvent in vacuo. The mixture was extracted with diethyl ether (20 ml × 2). The combined organic layers were dried over $MgSO_4$ and then concentrated under vacuum. The crude mixture was purified by silica gel chromatography to give title compound **11** as a white amorphous powder (142 mg, 78% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.30 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.25 (ddd, *J* = 7.8, 7.8, 1.2 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.06–6.94 (m, 5H), 6.71 (d, *J* = 7.8 Hz, 1H), 4.64 (d, *J* = 18.6 Hz, 1H), 4.63 (dd, *J* = 11.0, 6.6 Hz, 1H), 4.48 (d, *J* = 18.3 Hz, 1H), 2.95 (d, *J* = 15.4 Hz, 1H), 2.60 (d, *J* = 15.4 Hz, 1H), 2.26 (s, 3H), 1.91–1.82 (m, 1H), 1.70–1.56 (m, 3H), 1.52–1.32 (m, 1H), 1.31–1.18 (m, 1H), 1.08–0.74 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 176.1, 169.4, 153.9, 141.8, 135.2, 133.1, 129.4, 129.3, 129.1, 123.2, 123.0, 120.7, 108.5, 75.6, 59.3, 49.9, 46.7, 41.1, 40.8, 34.1, 31.5, 26.1, 23.3, 22.1, 20.9, 20.8, 16.2. HRMS m/z $[M + H]^+$ calcd for $C_{30}H_{38}N_3O_5$, 520.2811; found, 520.2806.

[(R)-1-(2-Hydroxy-ethyl)-2-oxo-3-(3-*p*-tolyl-ureido)-2,3-dihydro-1*H*-indol-3-yl]-acetic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (12). To a solution of **11** (448 mg, 0.862 mmol) in MeOH (5.0 mL) was added sodium borohydride (16.3 mg, 0.431 mmol). After stirring at rt for 1 h, water was added and then extracted with methylene chloride (20 ml × 2). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The crude mixture was purified by silica gel chromatography to give the title compound **12** as a white crystal (443 mg, 94% yield): mp 155–157 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 7.09–6.96 (m, 5H), 6.92 (d, J = 7.5 Hz, 1H), 6.89 (s, 1H), 6.84 (s, 1H), 4.62 (ddd, J = 10.8, 10.8, 4.4 Hz, 1H), 4.26–4.15 (m, 1H), 4.04–3.85 (m, 3H), 3.80–3.69 (m, 1H), 3.03 (d, J = 15.4 Hz, 1H), 2.68 (d, J = 15.3 Hz, 1H), 2.24 (s, 3H), 1.89–1.80 (m, 1H), 1.71 (s, 1H), 1.70–1.52 (m, 3H), 1.51–1.34 (m, 1H), 1.28–1.16 (m, 1H), 1.06–0.72 (m, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 7.0Hz, 3H) 0.60 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 169.5, 153.9, 142.8, 134.9, 133.4, 129.4, 129.22, 129.17, 123.1, 122.7, 120.9, 109.1, 75.6, 59.05, 58.96, 46.8, 43.3, 40.8, 40.7, 34.1, 31.4, 26.1, 23.3, 22.1, 20.9, 20.8, 16.2. HRMS m/z $[M + H]^+$ calcd for $C_{30}H_{40}N_3O_5$, 522.2968; found, 522.2968. The crystal for X-ray analysis was obtained by recrystallization from ethyl acetate and hexane.

General procedure for the asymmetric alkylation. To a solution of oxindole derivatives (0.10 mmol) in THF (0.40 mL) was added LiHMDS (0.10 mmol) at 0 ^oC followed by the addition of bromoacetic acid ester (0.110 mmol). After stirring for 5 h, aqueous NH_4Cl was added and extracted with methylene chloride (20 ml × 2). The combined organic layers were dried over Na_2SO_4 and then concentrated in vacuo. The crude mixture was purified by silica gel chromatography to give the title compound.

1-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-3-*p*-tolyl-urea (14a). To a solution of oxime 1-methyl-1H-indole-2,3-dione, 3-(O-methyloxime) (511 mg, 2.69 mmol) in acetonitrile was added 5% palladium on carbon (50 mg). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 2 h. After removal of the palladium on carbon, *p*-tolyl isocyanate (358 mg, 2.69 mmol) was added at ambient temperature. The mixture was stirred for 1 h during which time a solid was

generated. The cake was collected and washed with acetonitrile and then dried under reduced pressure to give the title compound **14a** as a white crystal (690 mg, 87% yield): mp 260 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.30–7.21 (m, 4H), 7.04–6.89 (m, 5H), 5.02 (d, J = 7.6 Hz, 1H), 3.11 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 174.3, 154.2, 143.5, 137.2, 129.8, 128.7, 128.0, 127.8, 122.9, 121.7, 117.6, 108.0, 52.5, 26.1, 20.2. HRMS m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$, 296.1399; found, 296.1393.

(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-carbamic acid *tert*-butyl ester (14b). To a solution of 1-methyl-1H-indole-2,3-dione, 3-(O-methyloxime) (310 mg, 1.63 mmol) and BOC_2O (391 mg, 1.79 mmol) in acetonitrile was added 5% palladium on carbon (20 mg). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 2 h. After removal of the palladium on carbon, the solvent was removed under reduced pressure. The mixture was purified by a silica gel column to give the title product **14b**. (394 mg, 92% yield): mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1H), 7.31 (dd, J = 7.9, 7.8 Hz, 1H), 7.07 (ddd, J = 7.8, 7.3, 1.1 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.20–5.00 (m, 2H), 3.22 (s, 3H), 1.45 (brs, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 155.7, 143.4, 128.9, 126.7, 124.3, 122.7, 108.1, 80.4, 53.6, 28.3, 26.5. HRMS m/z $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_3$, 263.1396; found, 263.1390.

(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-carbamic acid (14c). To a solution of 1-methyl-1H-indole-2,3-dione, 3-(O-methyloxime) (511 mg, 2.69 mmol) in acetonitrile (30 mL) was added 5% palladium on carbon (50 mg). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 2 h. After removal of the palladium carbon by filtration, N,N-dimethylaniline (391 mg, 3.22 mmol) and methyl chloroformate (305 mg, 3.22 mmol) were added successively at ambient temperature. The mixture was stirred for 0.5 h. The mixture was extracted with AcOEt. The organic layer was washed with 2 N HCl, saturated NaCl, and saturated $NaHCO_3$ successively. After removal of the solvent in vacuo, a crystalline product was obtained. The crystalline mixture was washed with 1:1 AcOEt/hexane, affording the title product **14c**. (295 mg, 50% yield): mp 158–159 °C; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 2H), 7.04 (ddd, J = 7.5, 7.5, 0.2 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 5.76 (br, 1H), 5.00 (d, J = 7.9 Hz, 1H), 3.67 (s, 3H), 3.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 156.7, 143.4, 129.1, 126.2, 124.1, 122.8, 108.1, 53.8, 52.6, 26.5. HRMS m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_3$, 221.0926; found, 221.0917.

(3-Methoxycarbonylamino-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (15c + 16c). General procedure was followed with **14c**. The diastereomeric ratio was determined to be 72:28 by comparison of one of geminal protons in ^{1}H NMR analysis of the crude product (-CH_2CO_2*l*-Menthyl, major δ 2.55 ppm, minor δ 2.50 ppm). The title compounds **15c** and **16c** was obtained in 58% yield as an inseparable mixture of diastereomers as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (m, 2H), 7.06–6.98 (m, 1H), 6.88–6.80 (m, 1.3 H), 6.61 (brs, 0.7H), 4.80–4.62 (m, 1H), 3.55 (s, 3H), 3.27 (s, 3H), 3.00 (d, J = 15.3 Hz, 0.7H), 2.97 (d, J = 15.3 Hz, 0.3H), 2.55 (d, J = 15.3 Hz, 0.7H), 2.50 (d, J = 15.3 Hz, 0.3H), 1.96–1.87 (m, 1H), 1.78–1.56 (m, 3H), 1.55–1.36 (m, 1H), 1.35–1.21 (m, 1H), 1.12–0.8 (m, 3H), 0.90 (d, J = 6.6 Hz, 0.9H), 0.89 (d, J = 6.4 Hz, 2.1H), 0.85 (d, J = 7.0 Hz, 2.1H), 0.79 (d, J = 6.9 Hz, 0.9H), 0.73 (d, J = 6.9 Hz, 0.9H), 0.69 (d, J = 7.0 Hz, 2.1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 169.3, 155.0, 143.4, 129.4, 128.7, 123.3, 123.0, 122.7, 122.6, 108.3, 75.7, 75.6, 59.1, 52.4, 46.8, 46.7, 40.8, 40.7, 40.6, 34.1, 31.45, 31.40, 26.7, 26.2, 25.9, 23.3, 22.0, 20.7, 16.3, 16.1. HRMS m/z $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_5$, 417.2389; found, 417.2390.

***N*-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-benzamide (14d).** To a solution of 1-methyl-1H-indole-2,3-dione, 3-(O-methyloxime) (419 mg, 2.20 mmol) in acetonitrile (25 mL) was added 5% palladium on carbon (23 mg). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 1.5 h. After removal of the palladium carbon by filtration, N,N-dimethylaniline (319 mg, 2.64 mmol) and benzoyl chloride (340 mg, 2.42 mmol) were added successively at ambient temperature. The mixture was stirred for 0.5 h. The mixture was extracted with AcOEt. The organic layer was washed with 2 N HCl, saturated NaCl, and saturated $NaHCO_3$, successively. After removal of

the solvent in vacuo, a crystalline product was obtained. The crystalline mixture was washed with 1:1 AcOEt:Hexane, affording the title product **14d**. (577 mg, 98%): mp 190–191 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 2H), 7.52 (dddd, *J* = 7.5, 6.9, 1.5, 1.4 Hz, 1H), 7.47–7.38 (m, 3H), 7.34 (dddd, *J* = 7.7, 7.6, 1.2, 0.7 Hz, 1H), 7.08 (ddd, *J* = 7.6, 7.3, 1.1 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 7.0 Hz, 1H), 5.57 (d, *J* = 7.3 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 167.3, 143.5, 132.8, 131.7, 129.0, 128.3, 127.1, 126.5, 124.4, 123.0, 108.2, 53.2, 26.6. HRMS m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$, 267.1134; found, 267.1124.

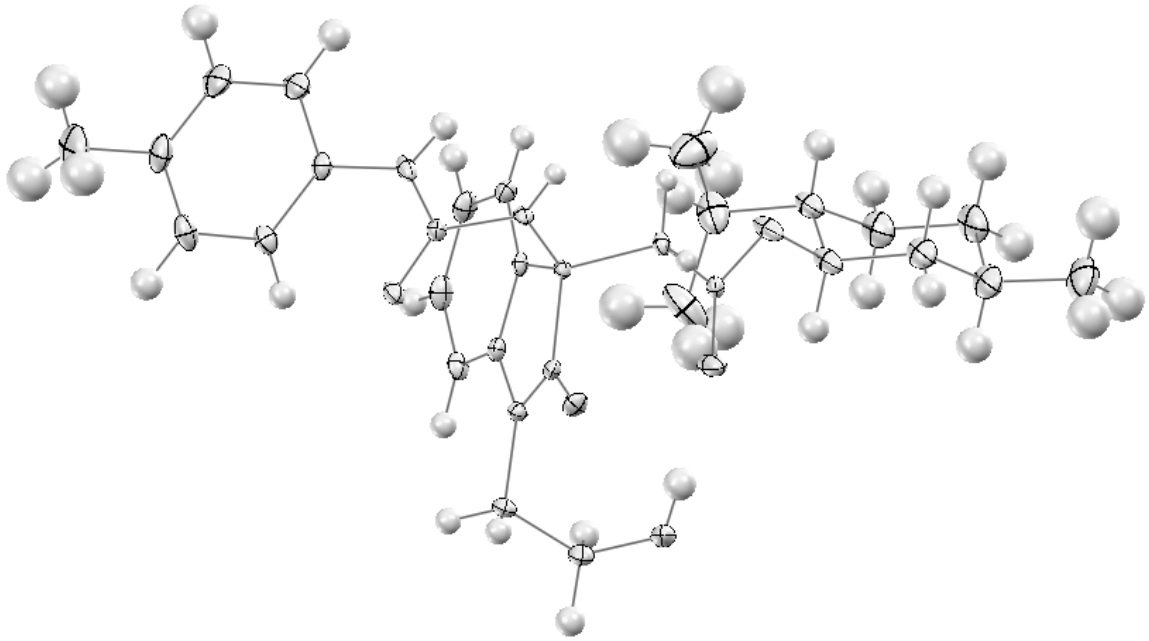
(3-Benzoylamino-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (15d + 16d). General procedure was followed with **14d**, 1.2 equivalent of base and 1.3 equivalent of *l*-menthyl bromoacetate. The diastereomeric ratio was determined to be 95:5 by comparison of one of geminal protons in ^{1}H NMR analysis of the crude product (-CH_2CO_2*l*-Menthyl, major δ 2.54 ppm, minor δ 2.51 ppm). The title compounds **15d** and **16d** was obtained in 82% yield as an inseparable mixture of diastereomers as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.85–7.78 (m, 2H), 7.52–7.45 (m, 1H), 7.44–7.36 (m, 2H), 7.32 (ddd, *J* = 7.8, 7.6, 1.2 Hz, 1H), 7.27–7.22 (m, 1H), 7.00 (ddd, *J* = 7.6, 7.5, 0.9 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 4.79 (ddd, *J* = 11.0, 10.8, 1.3 Hz, 1H), 3.33 (s, 3H), 3.12 (d, *J* = 15.3 Hz, 1H), 2.54 (d, *J* = 15.3 Hz, 1H), 2.07-1.98 (m, 1H), 1.86–1.62 (m, 3H), 1.60–1.42 (m, 1H), 1.40–1.28 (m, 1H), 1.14–0.80 (m, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 170.7, 165.5, 143.4, 132.6, 131.7, 129.3, 128.6, 128.3, 127.1, 122.6, 122.5, 108.4, 76.1, 59.2, 46.8, 40.9, 40.2, 34.1, 31.5, 26.9, 26.4, 23.5, 22.1, 20.7, 16.4. HRMS m/z $[M + H]^+$ calcd for $C_{28}H_{35}N_2O_4$, 463.2597; found, 463.2595.

***N*-(1-Methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetamide (14e).** To a solution of 1-methyl-1H-indole-2,3-dione, 3-(O-methyloxime) (406 mg, 2.13 mmol) in acetonitrile (25 mL) was added 5% palladium on carbon (50 mg). The mixture was stirred under hydrogen under atmospheric pressure at ambient temperature for 1.5 h. After removal of the palladium carbon by filtration, N,N-dimethylaniline (311 mg, 2.56 mmol) and acetic anhydride (234 mg, 2.34 mmol) were added successively at ambient

temperature. The mixture was stirred for 0.5 h. The mixture was extracted with AcOEt. The organic layer was washed with 2 N HCl, saturated NaCl and saturated $NaHCO_3$ successively. After removal of the solvent in vacuo, a crystalline product was obtained. The crystalline mixture was washed with 1:1 AcOEt/hexane, affording the title product **14e**. (242 mg, 56%): mp 205–207 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ8.65 (d, J = 8.2 Hz, 1H), 7.29 (dddd, J = 7.8, 7.6, 1.1, 1.1 Hz, 1H), 7.17 (d, J = 7.3 Hz, 1H), 7.01 (dd, J = 7.7, 7.3Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 5.15 (d, J = 8.1 Hz, 1H), 3.12 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ173.5, 169.0, 143.6, 128.3, 127.0, 123.1, 121.8, 108.1, 51.7, 26.1, 22.2. HRMS m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$, 205.0977; found, 205.0971.

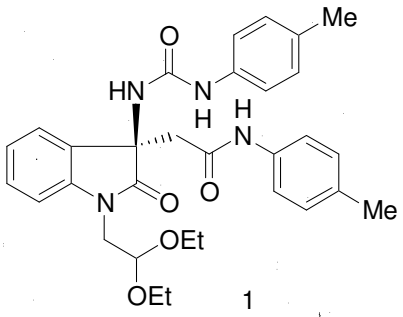
(3-Acetylamino-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetic acid (1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl ester (15e + 16e). General procedure was followed with **14e**, 1.2 equivalent of base and 1.3 equivalent of *l*-menthyl bromoacetate. The diastereomeric ratio was determined to be 84:16 by comparison of one of geminal protons in ^{1}H NMR analysis of the crude product (-CH_2CO_2*l*-Menthyl, major δ2.46 ppm, minor δ2.43 ppm). The title compound **15e** and **16e** was obtained in 69% yield as an inseparable mixture of diastereomers as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.51 (brs, 1H), 7.29 (ddd, J = 7.8, 7.6, 1.4 Hz, 1H), 7.23 (ddd, J = 7.9, 1.2, 0.5 Hz, 1H), 7.00 (ddd, J = 7.6, 7.5, 0.9 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 4.71 (ddd, J = 11.0, 10.8, 4.4 Hz, 1H), 3.26 (s, 3H), 2.98 (d, J = 15.3 Hz, 1H), 2.46 (d, J = 15.3 Hz, 1H), 1.95 (s, 3H), 2.00–1.90 (m, 1H), 1.80-1.58 (m, 3H), 1.56–1.39 (m, 1H), 1.36–1.22 (m, 1H), 1.12–0.76 (m, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ174.7, 170.0, 168.8, 143.4, 129.2, 128.5, 122.9, 122.5, 108.3, 75.9, 59.1, 46.9, 40.9, 40.2, 34.1, 31.5, 26.8, 26.3, 23.4, 22.8, 22.1, 20.8, 16.4. HRMS m/z $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_4$, 401.2440; found, 401.2443.

ORTEP Drawing for the X-ray Structure of 12.



AG041R

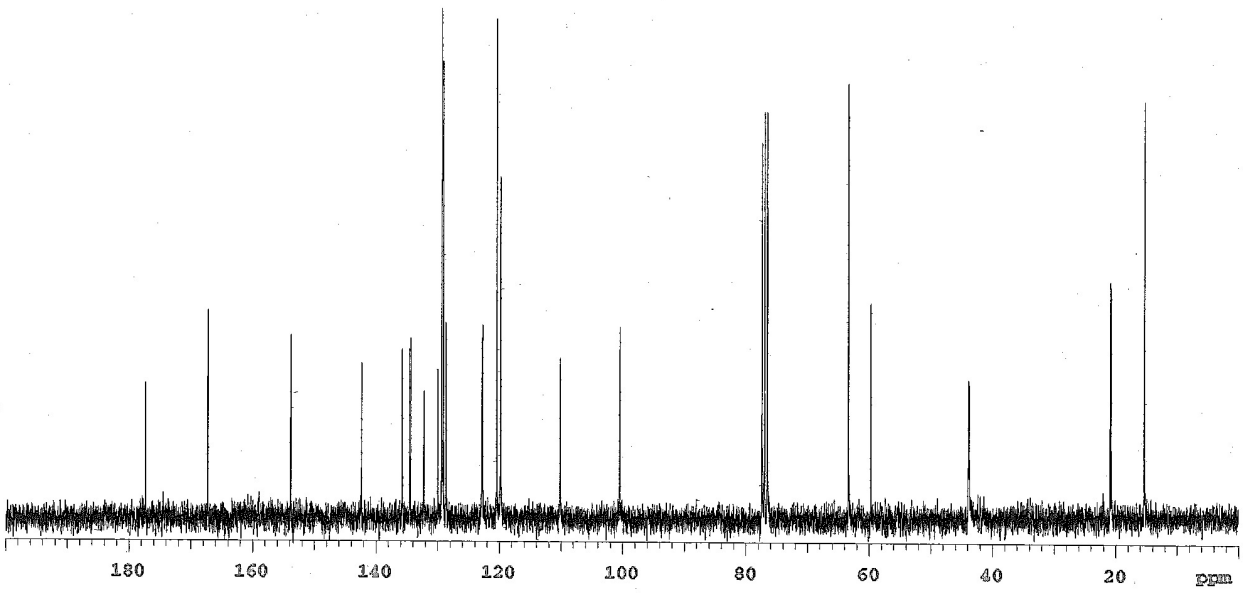
Pulse Sequence: s2pul

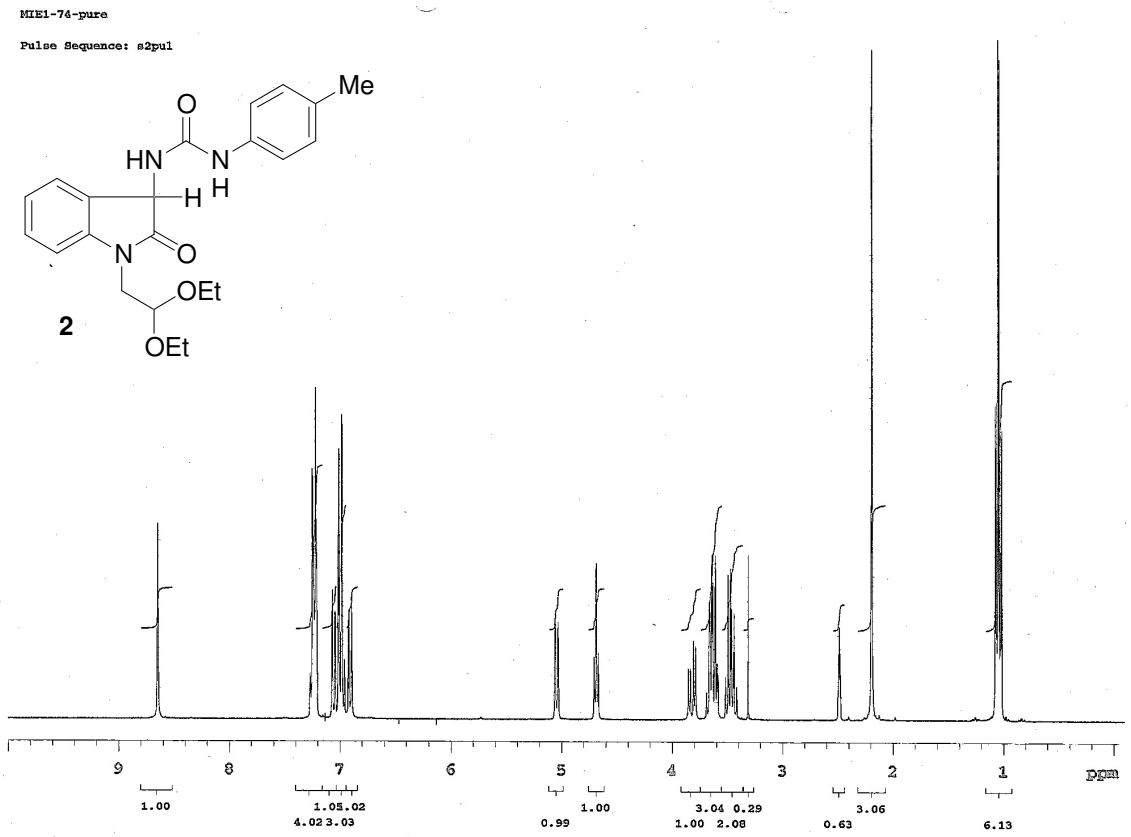


1

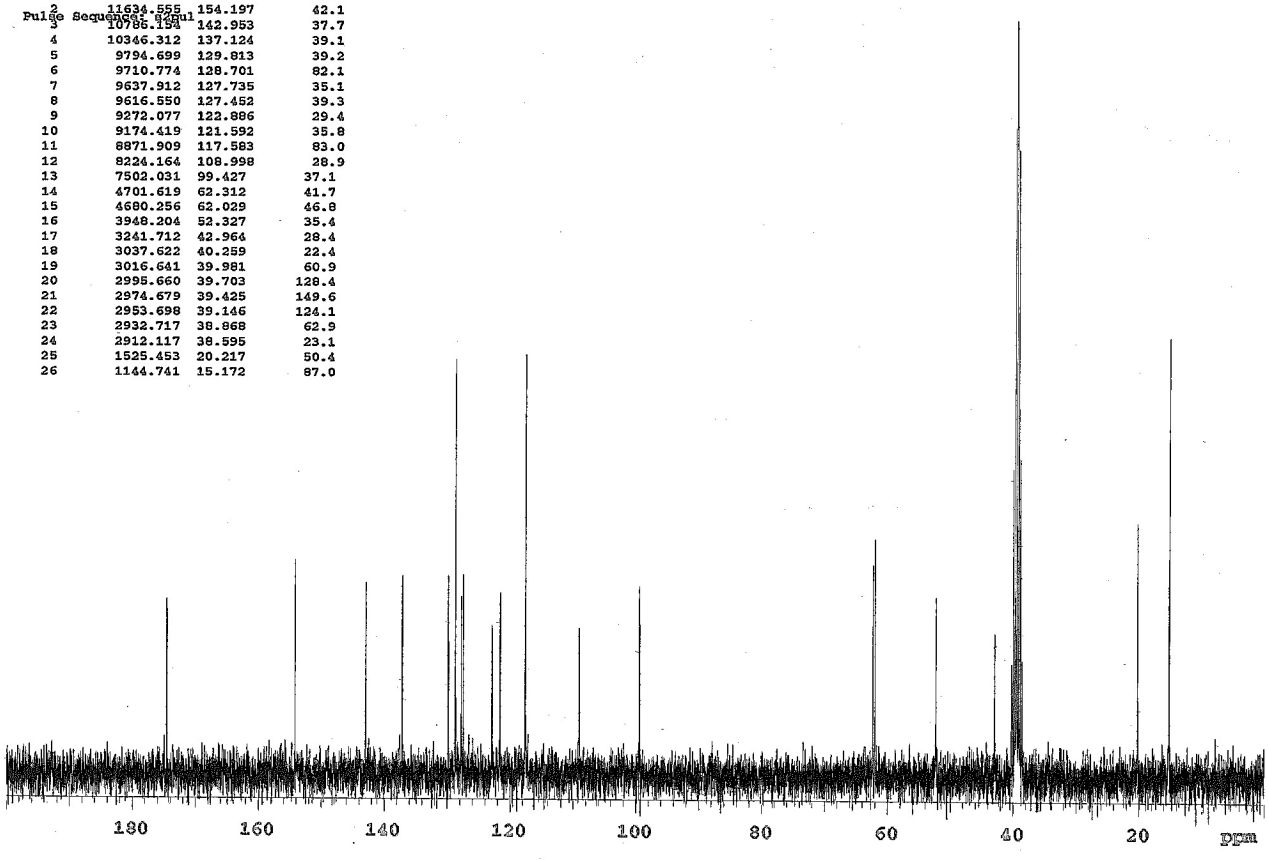
C13 STANDARD PARAMETER

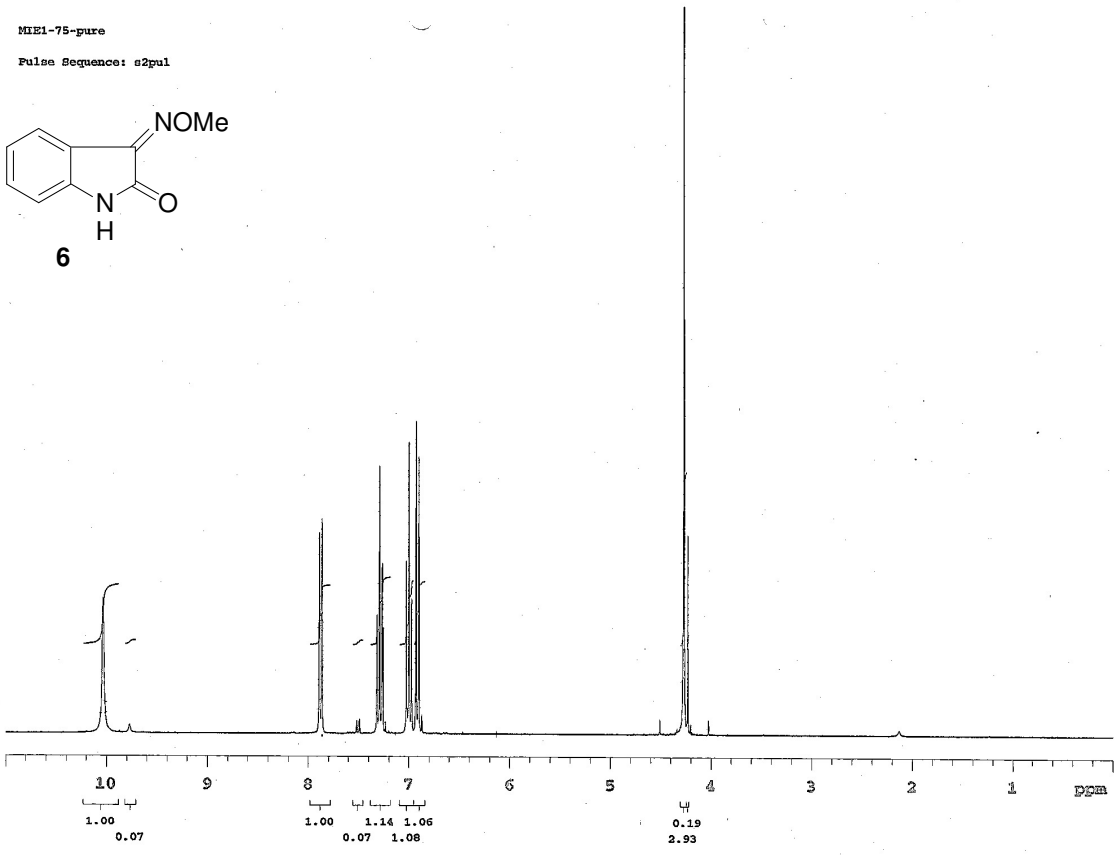
Pulse Sequence: s2pul

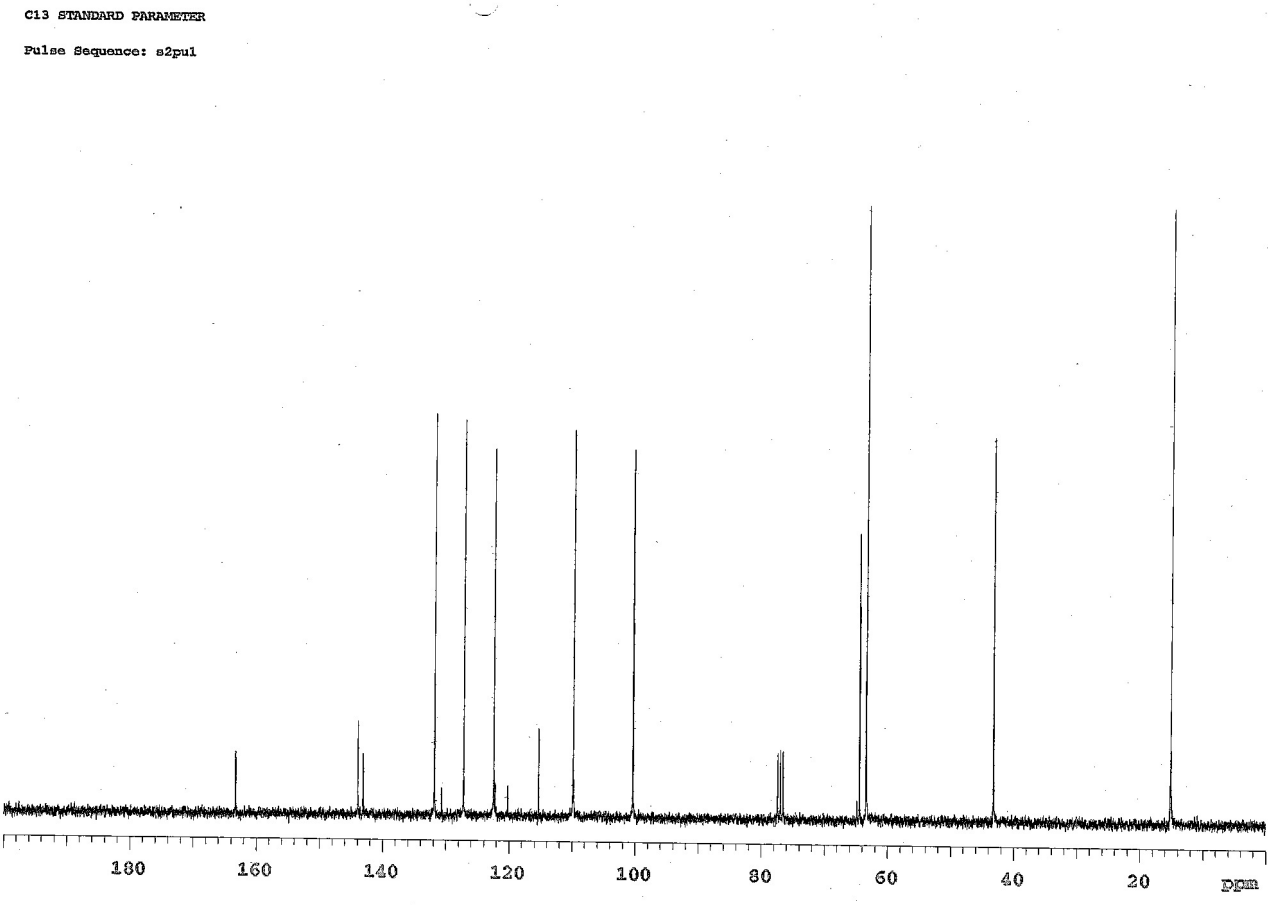




CT	INDEX	STANDARD PARAMETER	PPM	HEIGHT
	1	13171.520	174.567	34.3
	2	11634.555	154.197	42.1
Pulse Sequence: s2pul	3	10785.154	142.953	37.7
	4	10346.312	137.124	39.1
	5	9794.699	129.813	39.2
	6	9710.774	128.701	82.1
	7	9637.912	127.735	35.1
	8	9616.550	127.452	39.3
	9	9272.077	122.886	29.4
	10	9174.419	121.592	35.8
	11	8871.909	117.583	83.0
	12	8224.164	108.998	28.9
	13	7502.031	99.427	37.1
	14	4701.619	62.312	41.7
	15	4680.256	62.029	46.8
	16	3948.204	52.327	35.4
	17	3241.712	42.964	28.4
	18	3037.622	40.259	22.4
	19	3016.641	39.981	60.9
	20	2995.660	39.703	128.4
	21	2974.679	39.425	149.6
	22	2953.698	39.146	124.1
	23	2932.717	38.868	62.9
	24	2912.117	38.595	23.1
	25	1525.453	20.217	50.4
	26	1144.741	15.172	87.0

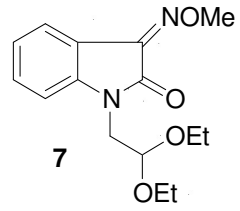



MIE1-75-pure
Pulse Sequence: s2pul
NOMe
N
H
O
6
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.07
1.00
0.07
1.14
1.08
1.06
0.19
2.93


C13 STANDARD PARAMETER
Pulse Sequence: s2pul
180
160
140
120
100
80
60
40
20
ppm

NOMe-OEt

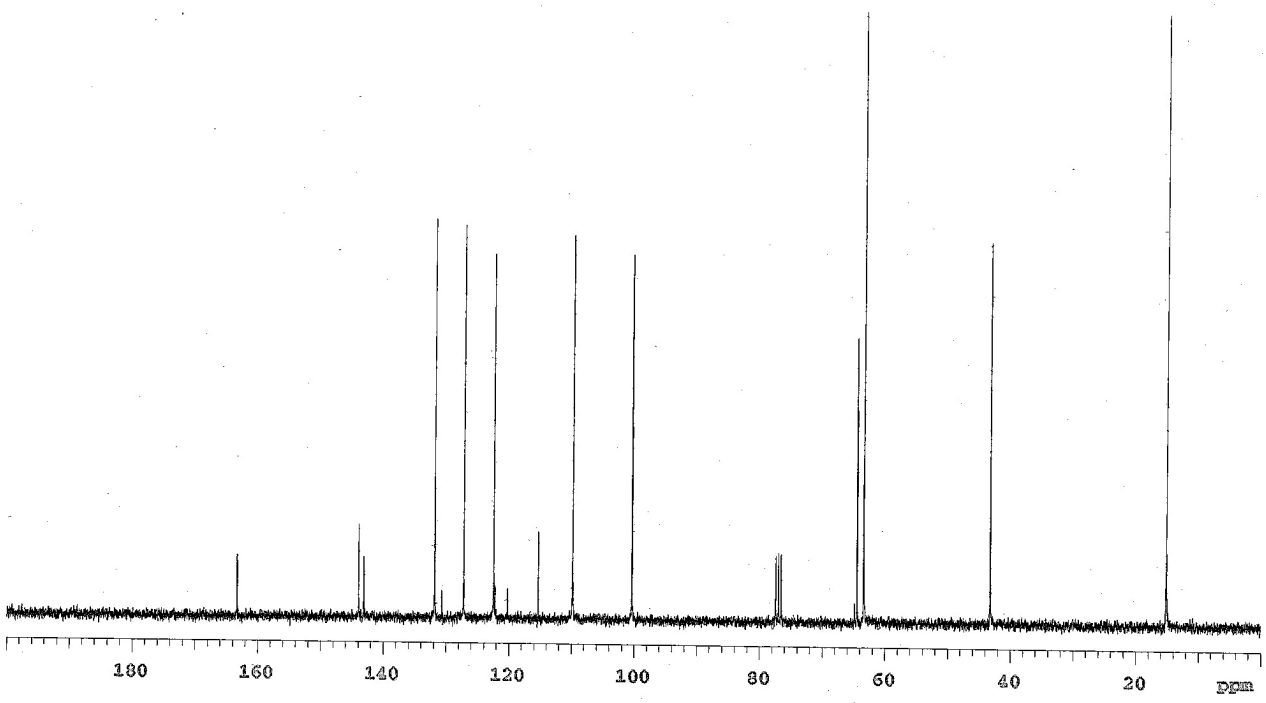
Pulse Sequence: s2pul



7

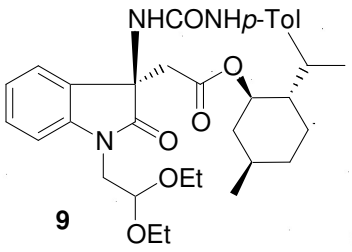
C13 STANDARD PARAMETER

Pulse Sequence: s2pul



urea-menthyl-pure

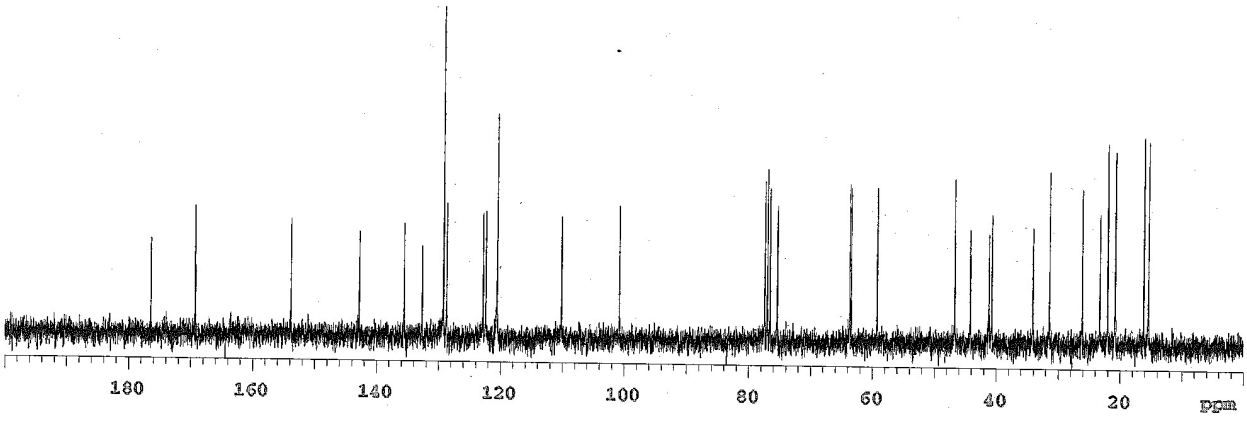
Pulse Sequence: s2pul

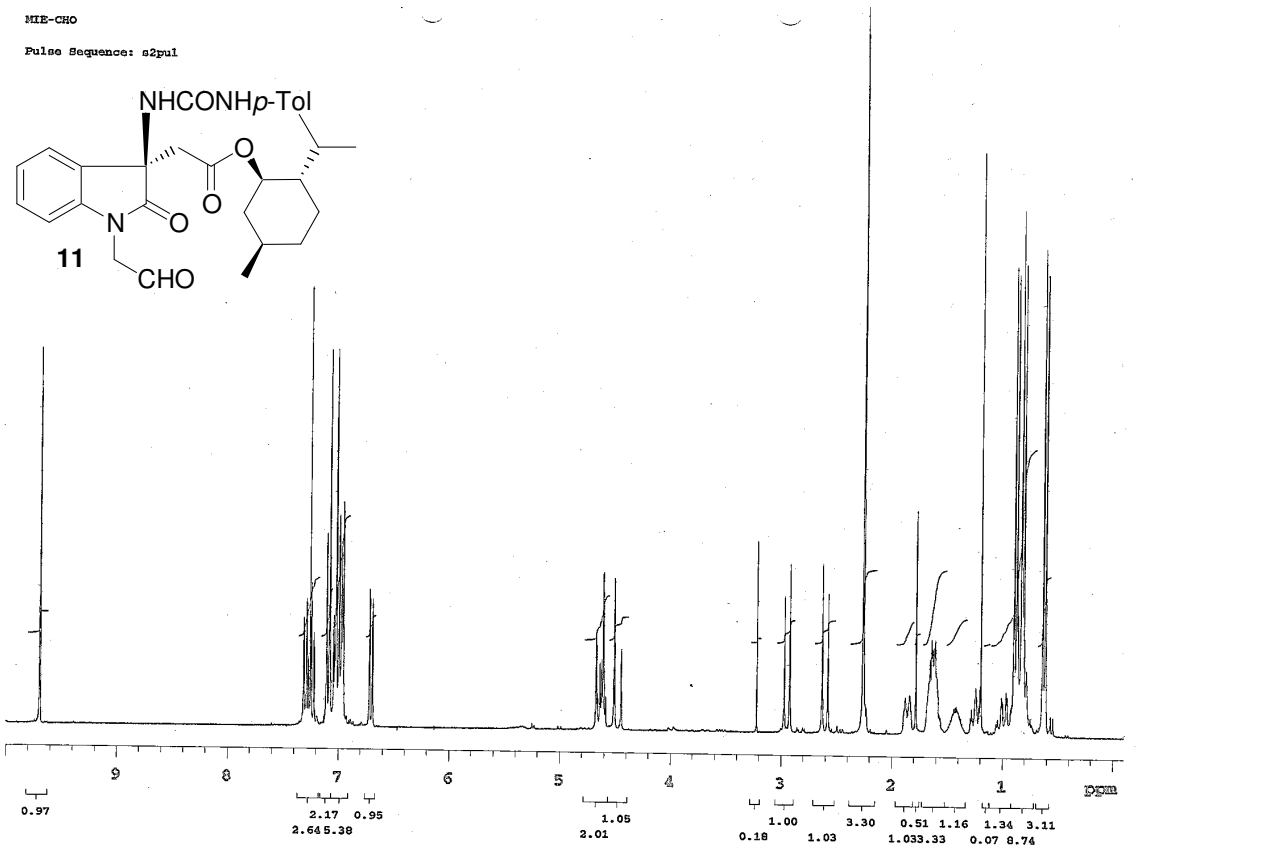


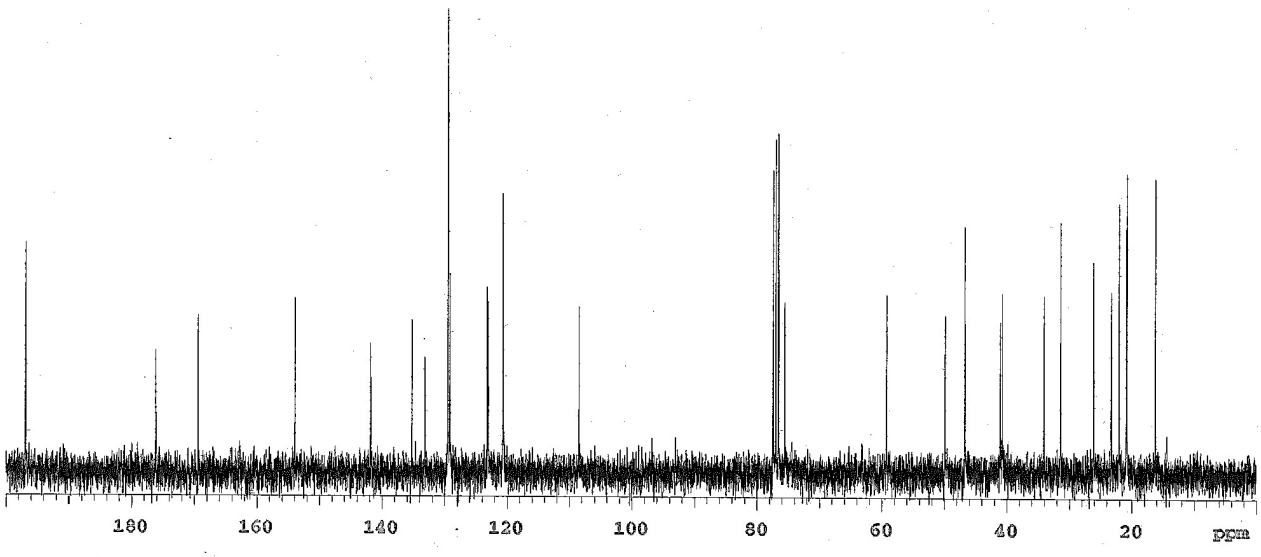
9

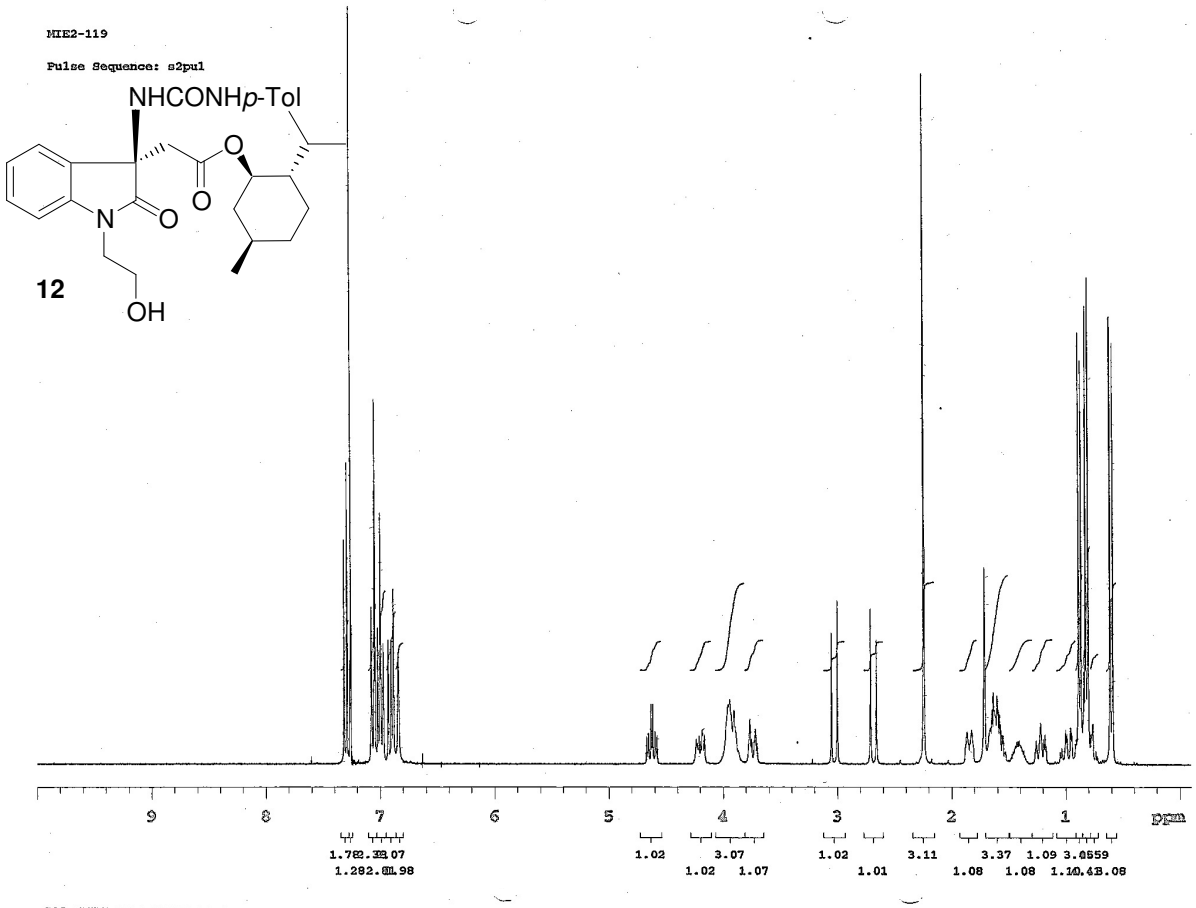
C13 STANDARD PARAMETER

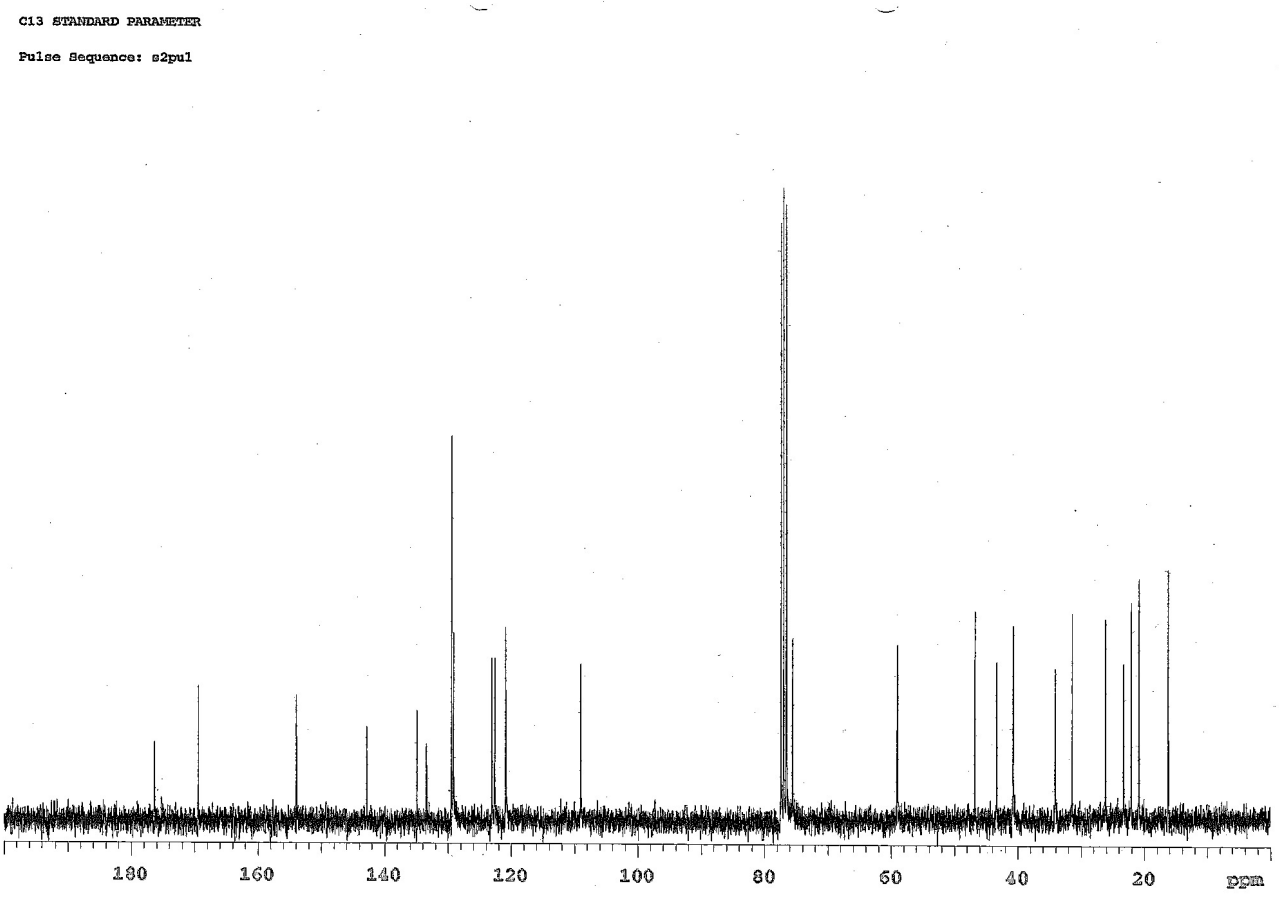
Pulse Sequence: s2pul




MIE-CHO
Pulse Sequence: s2pul
NHCONHp-Tol
O
O
N
O
11
CHO
9
8
7
6
5
4
3
2
1
ppm
0.97
2.17
0.95
2.64
5.38
1.05
2.01
1.00
0.18
1.03
3.30
0.51
1.16
1.34
3.11
1.03
3.33
0.07
8.74

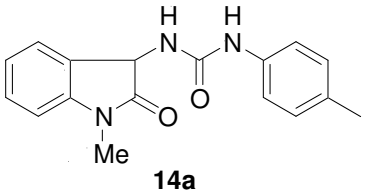

180
160
140
120
100
80
60
40
20
ppm


MIE2-119
Pulse Sequence: s2pul
NHCONHp-Tol
O
O
N
O
12
OH
9
8
7
6
5
4
3
2
1
ppm
1.02
3.07
1.02
1.07
1.02
1.01
3.11
3.37
1.09
1.08
1.08


C13 STANDARD PARAMETER
Pulse Sequence: s2pul
180
160
140
120
100
80
60
40
20
ppm

MIE1-66-pure

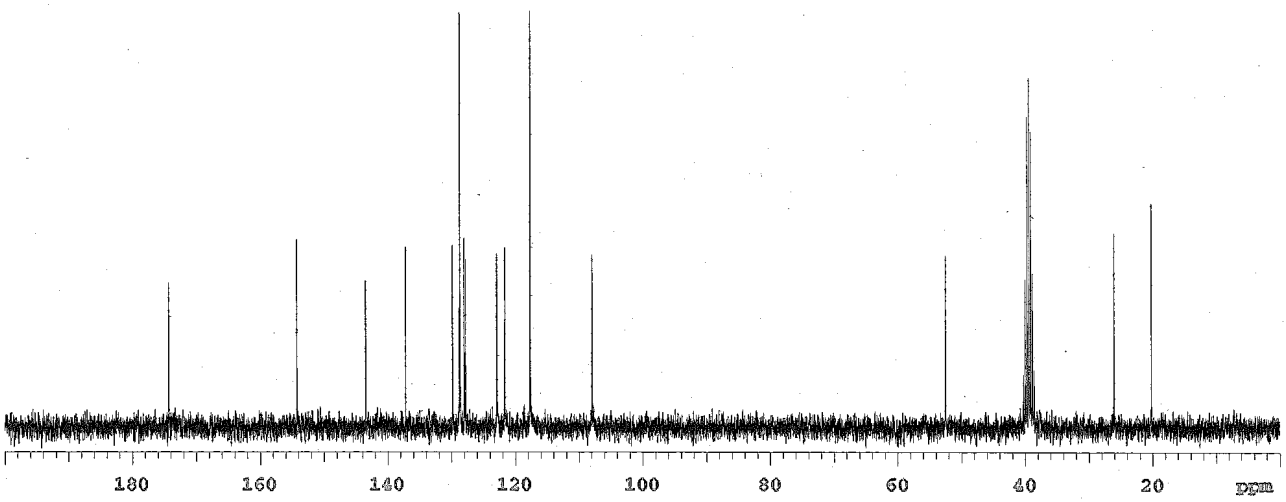
Pulse Sequence: s2pul

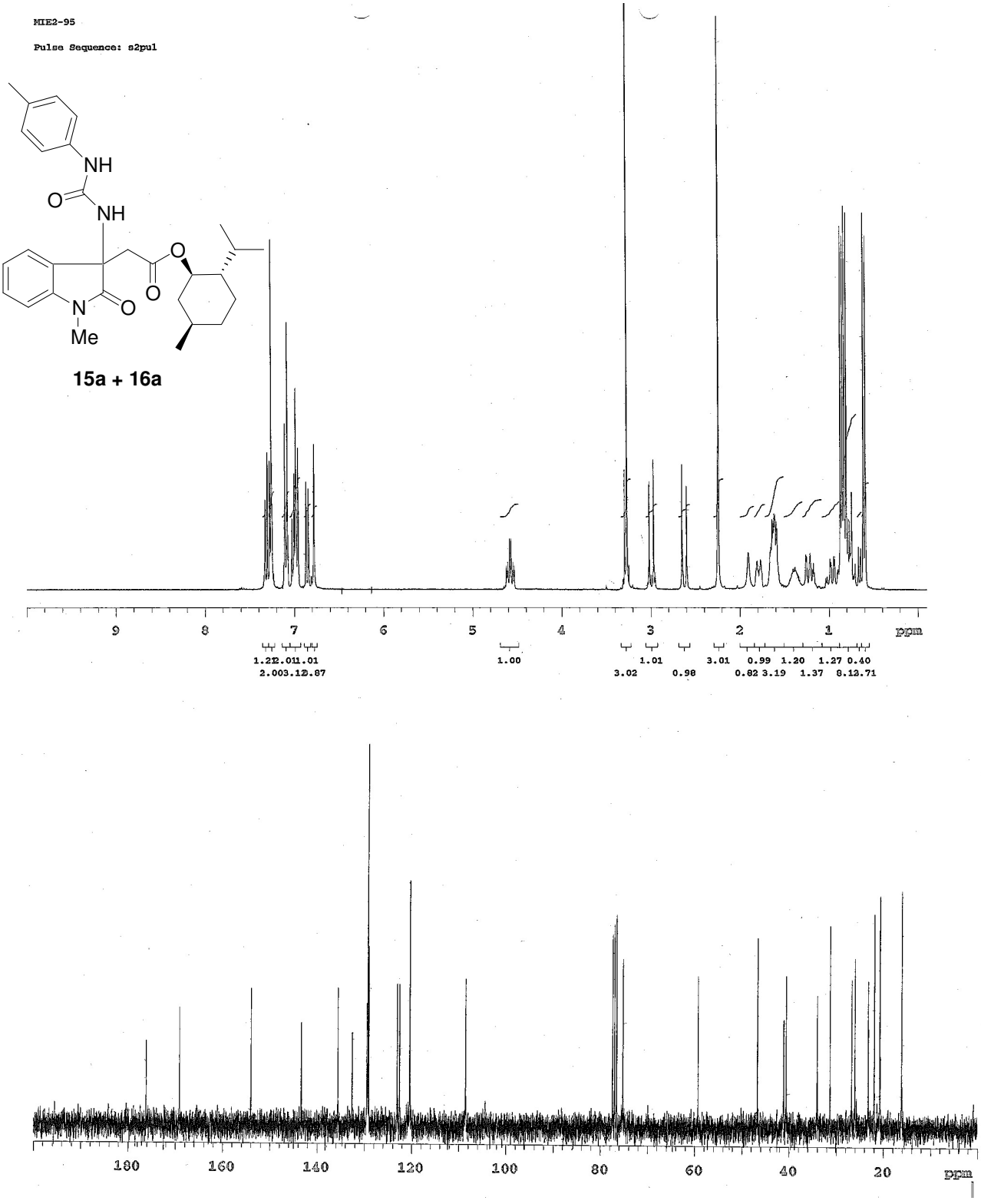


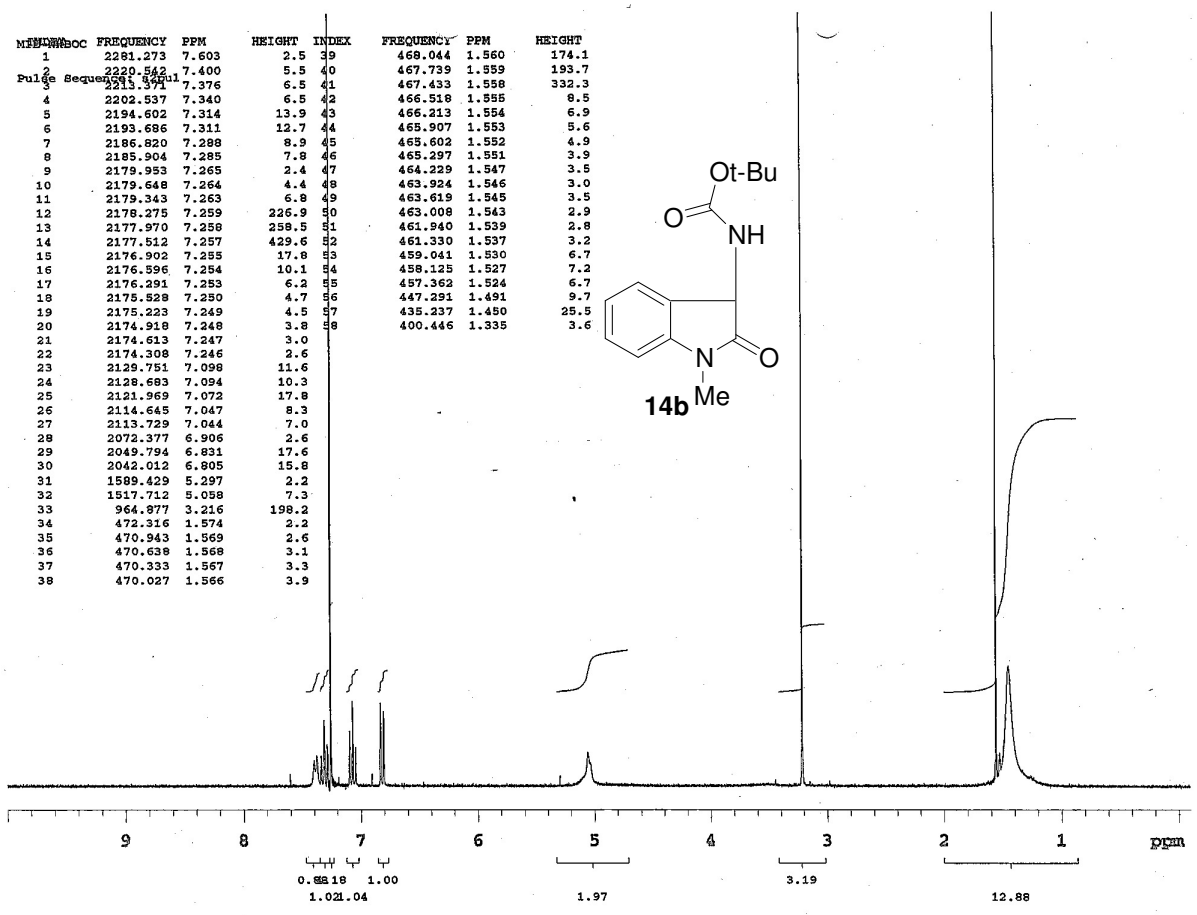
14a

C13 STANDARD PARAMETER

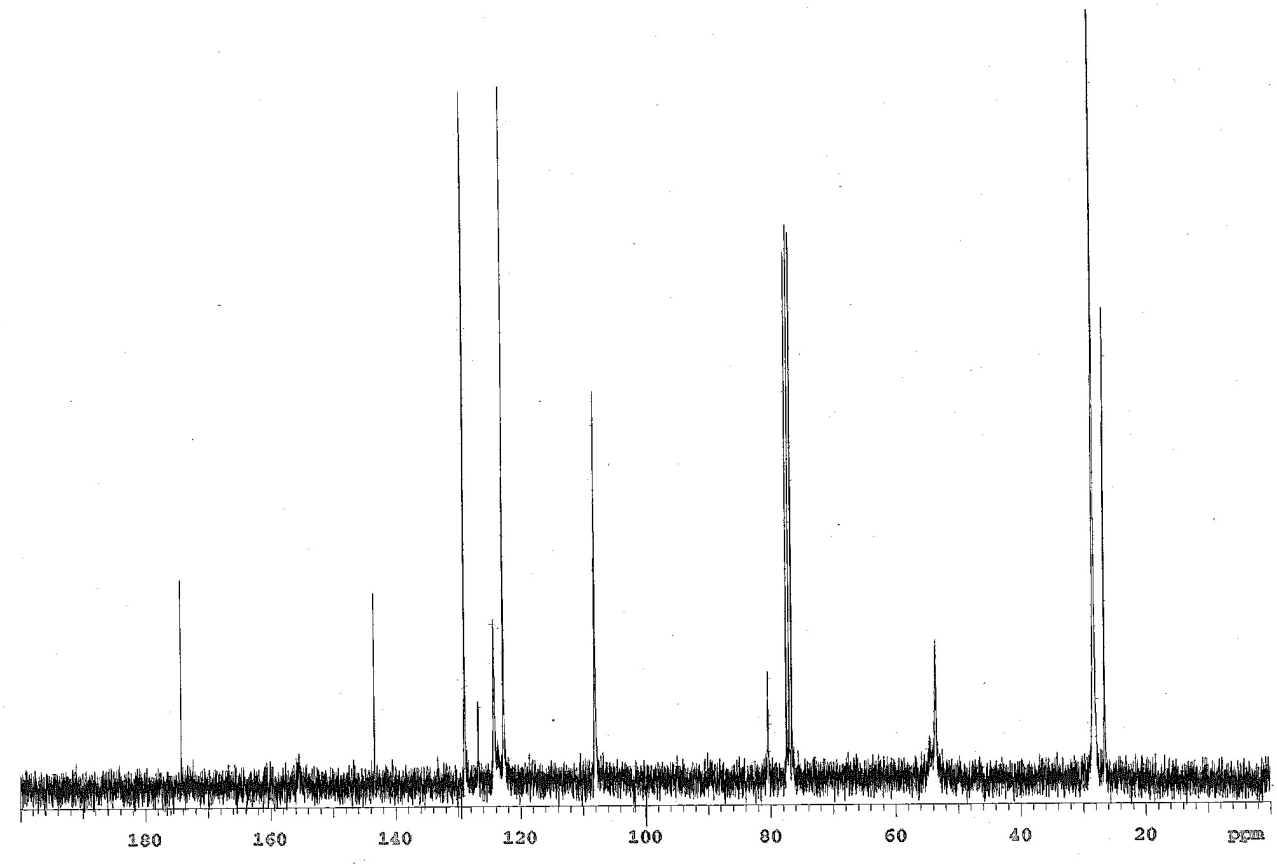
Pulse Sequence: s2pul

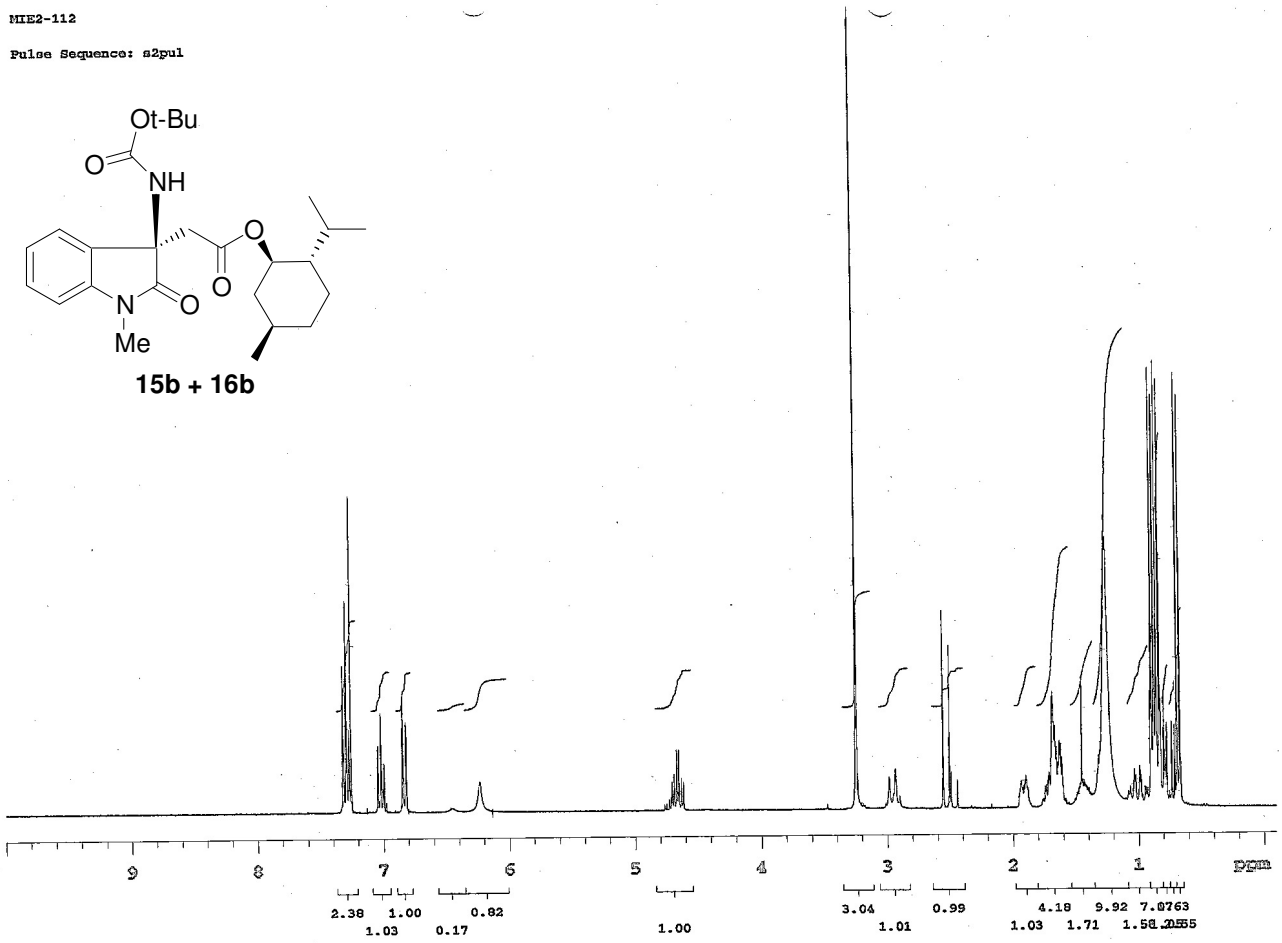


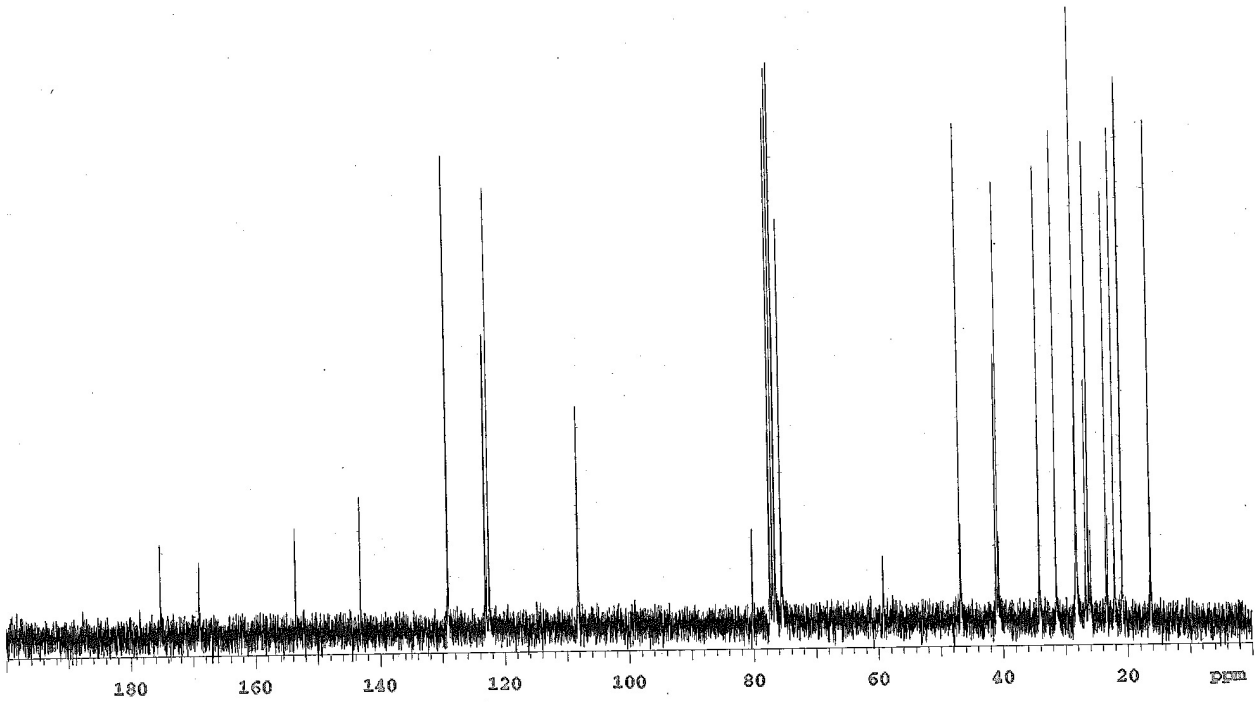

MIE2-95
Pulse Sequence: s2pul
NH
O
NH
O
O
O
N
O
Me
15a + 16a
9
8
7
6
5
4
3
2
1
ppm
1.22 2.00 1.01 1.01
2.00 3.12 8.87
1.00
1.01
3.02
0.98
3.01
0.99 1.20 1.27 0.40
0.82 3.19 1.37 8.12 7.71
180
160
140
120
100
80
60
40
20
ppm



INDEX	FREQUENCY	PPM	HEIGHT	INDEX	FREQUENCY	PPM	HEIGHT
1	2281.273	7.603	2.5	39	468.044	1.560	174.1
2	2220.542	7.400	5.5	40	467.739	1.559	193.7
3	2213.371	7.376	6.5	41	467.433	1.558	332.3
4	2202.537	7.340	6.5	42	466.518	1.555	8.5
5	2194.602	7.314	13.9	43	466.213	1.554	6.9
6	2193.686	7.311	12.7	44	465.907	1.553	5.6
7	2186.820	7.288	8.9	45	465.602	1.552	4.9
8	2185.904	7.285	7.8	46	465.297	1.551	3.9
9	2179.953	7.265	2.4	47	464.229	1.547	3.5
10	2179.648	7.264	4.4	48	463.924	1.546	3.0
11	2179.343	7.263	6.8	49	463.619	1.545	3.5
12	2178.275	7.259	226.9	50	463.008	1.543	2.9
13	2177.970	7.258	258.5	51	461.940	1.539	2.8
14	2177.512	7.257	429.6	52	461.330	1.537	3.2
15	2176.902	7.255	17.8	53	459.041	1.530	6.7
16	2176.596	7.254	10.1	54	458.125	1.527	7.2
17	2176.291	7.253	6.2	55	457.362	1.524	6.7
18	2175.528	7.250	4.7	56	447.291	1.491	9.7
19	2175.223	7.249	4.5	57	435.237	1.450	25.5
20	2174.918	7.248	3.8	58	400.446	1.335	3.6
21	2174.613	7.247	3.0				
22	2174.308	7.246	2.6				
23	2129.751	7.098	11.6				
24	2128.683	7.094	10.3				
25	2121.969	7.072	17.8				
26	2114.645	7.047	8.3				
27	2113.729	7.044	7.0				
28	2072.377	6.906	2.6				
29	2049.794	6.831	17.6				
30	2042.012	6.805	15.8				
31	1589.429	5.297	2.2				
32	1517.712	5.058	7.3				
33	964.877	3.216	198.2				
34	472.316	1.574	2.2				
35	470.943	1.569	2.6				
36	470.638	1.568	3.1				
37	470.333	1.567	3.3				
38	470.027	1.566	3.9				

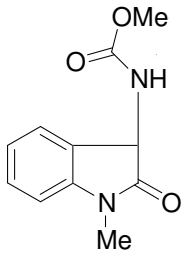



MIE2-112
Pulse Sequence: s2pul
Ot-Bu
O
NH
O
O
N
O
Me
15b + 16b
9
8
7
6
5
4
3
2
1
ppm
2.38
1.00
1.03
0.82
0.17
1.00
3.04
1.01
0.99
4.18
9.92
7.0763
1.03
1.71

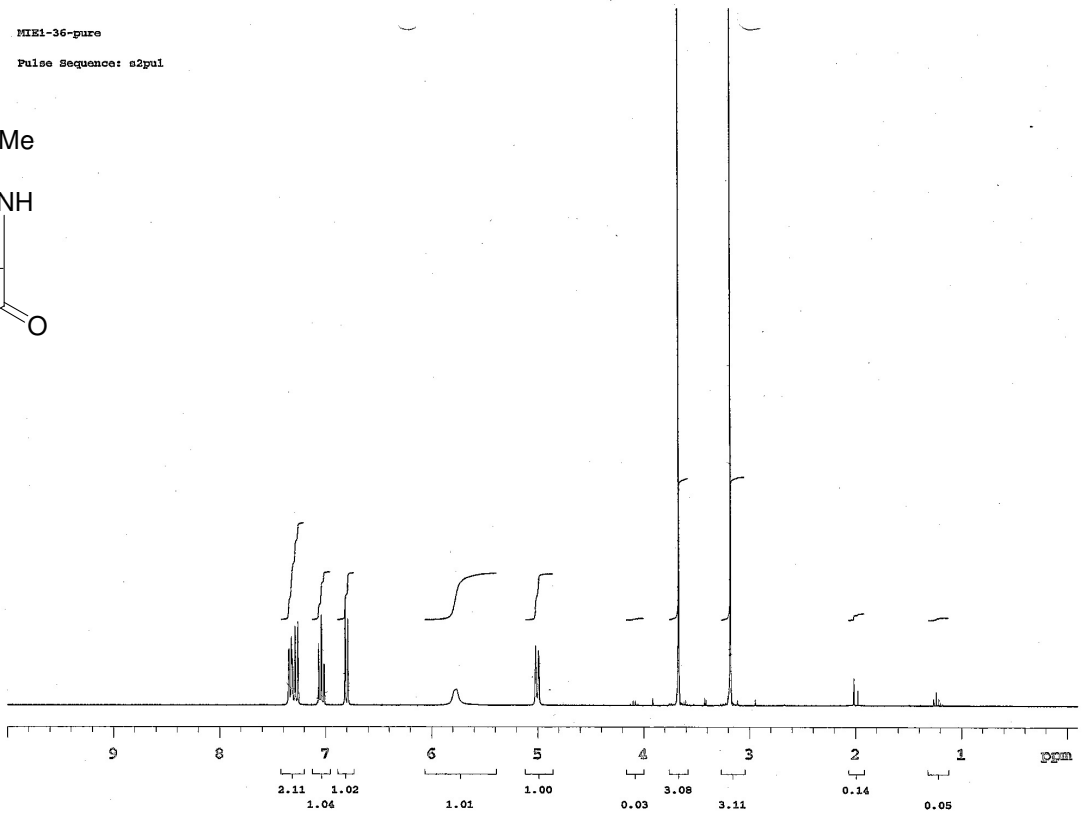

180
160
140
120
100
80
60
40
20
ppm

MIE1-36-pure

Pulse Sequence: s2pul

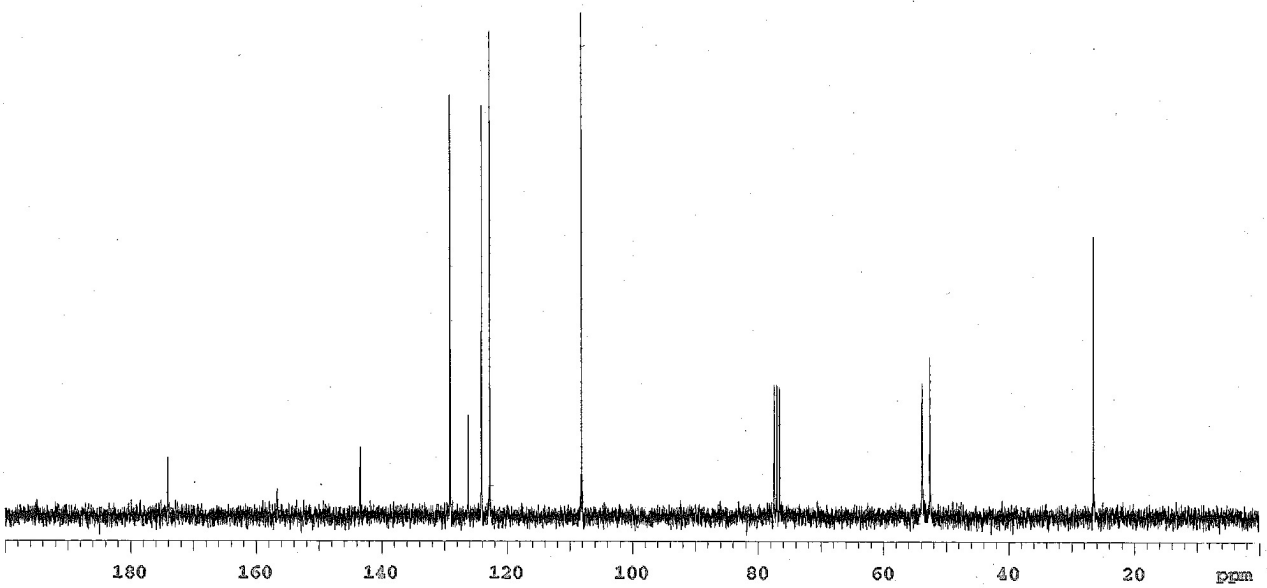


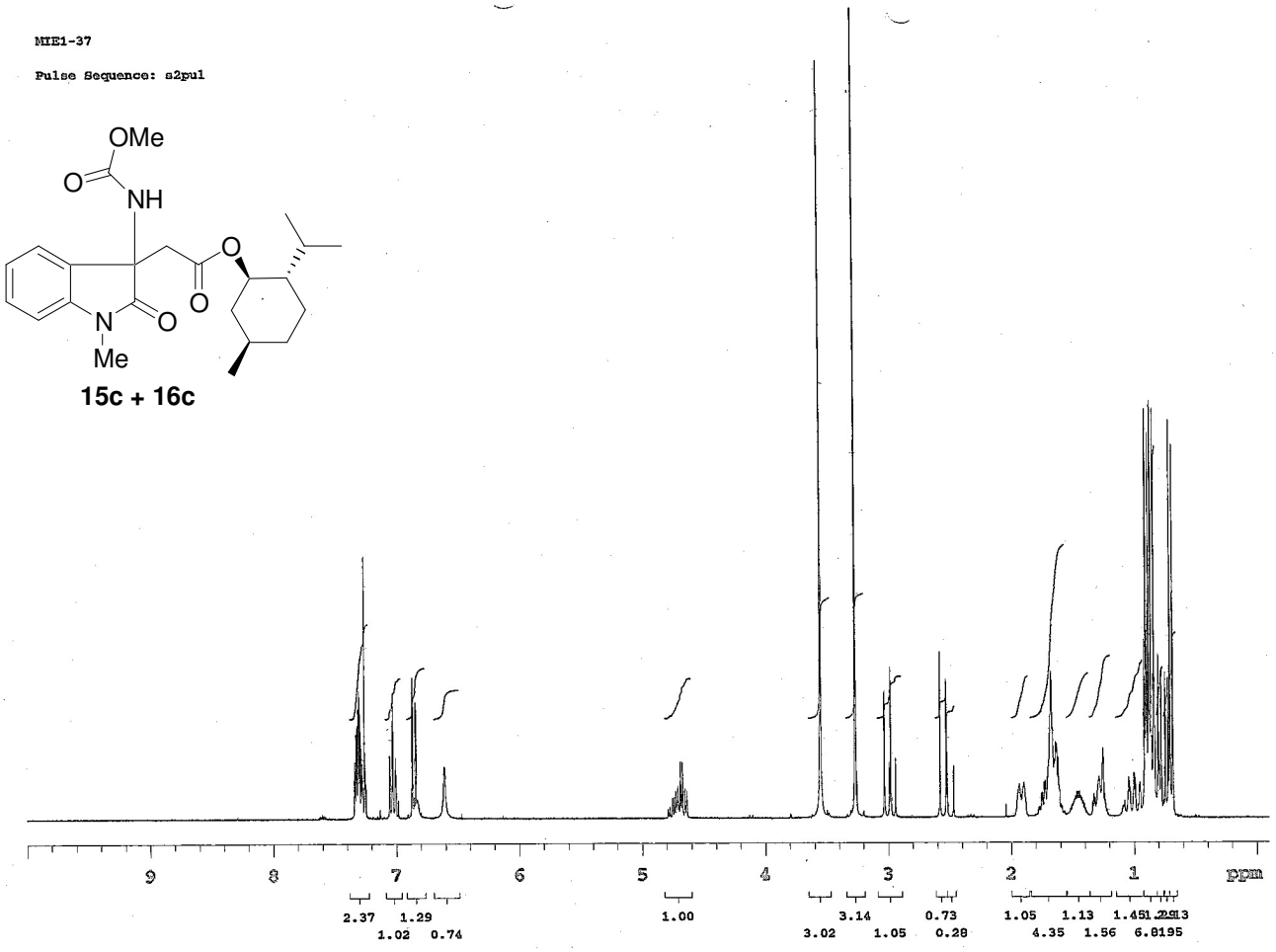
14c

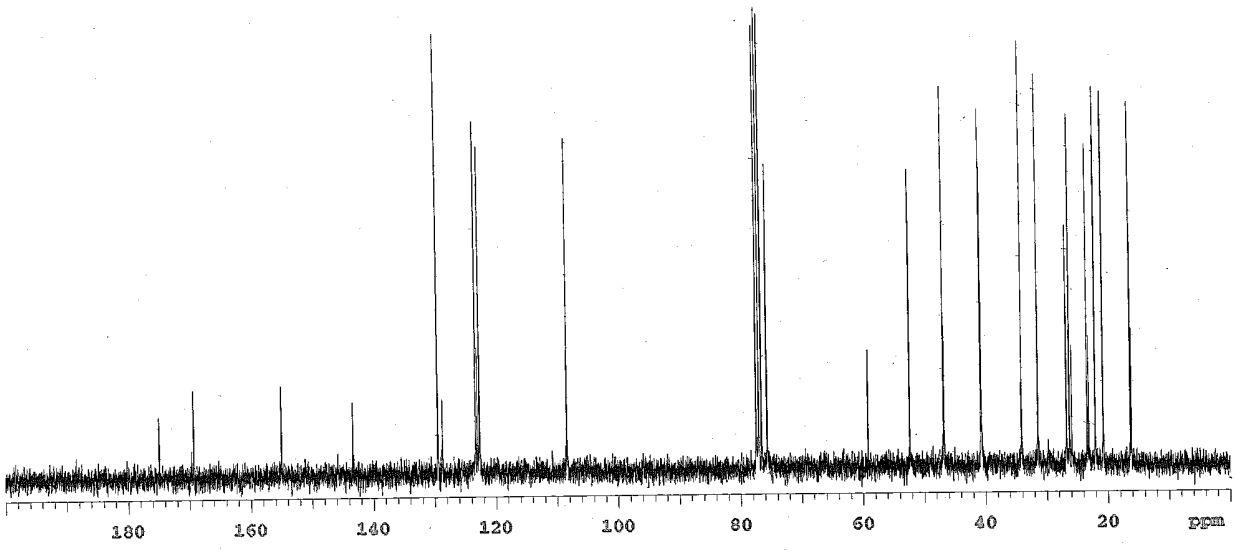


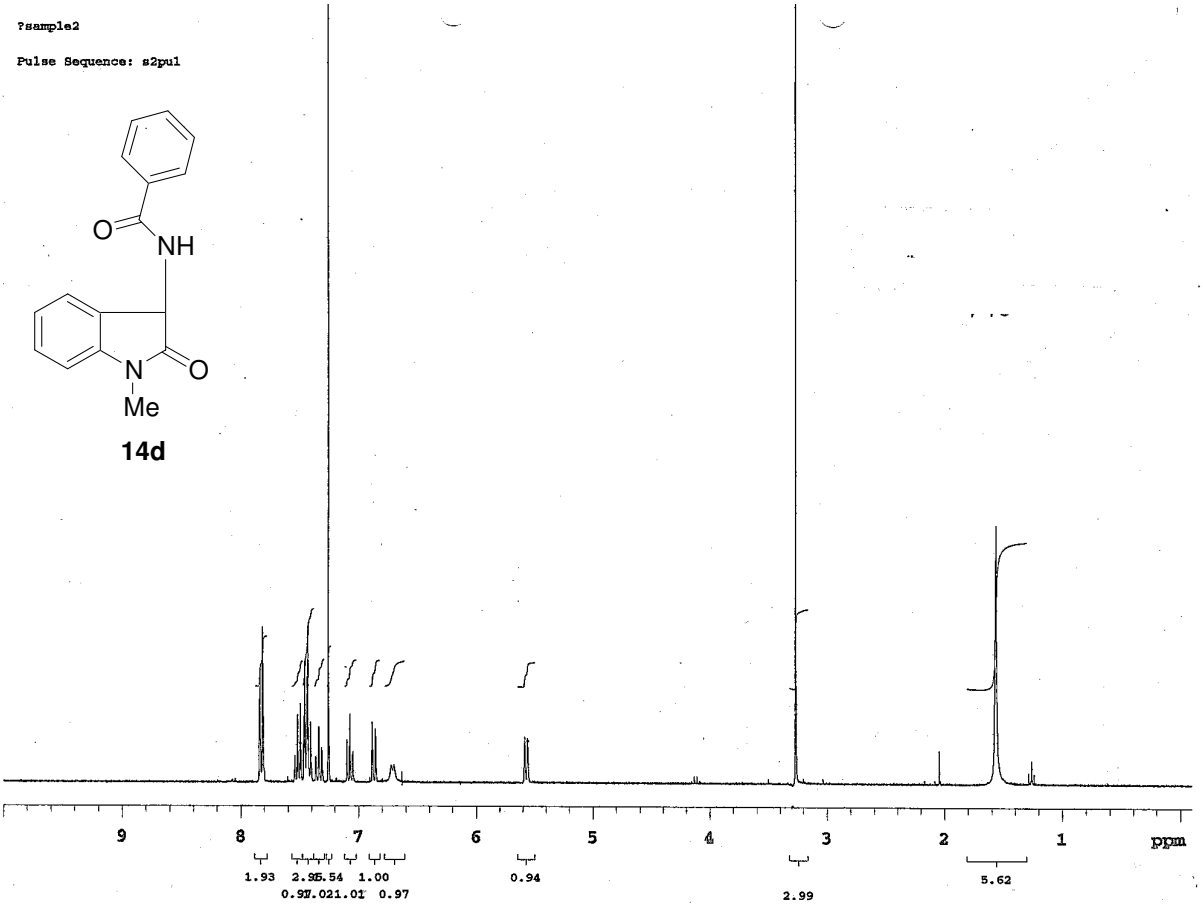
C13 STANDARD PARAMETER

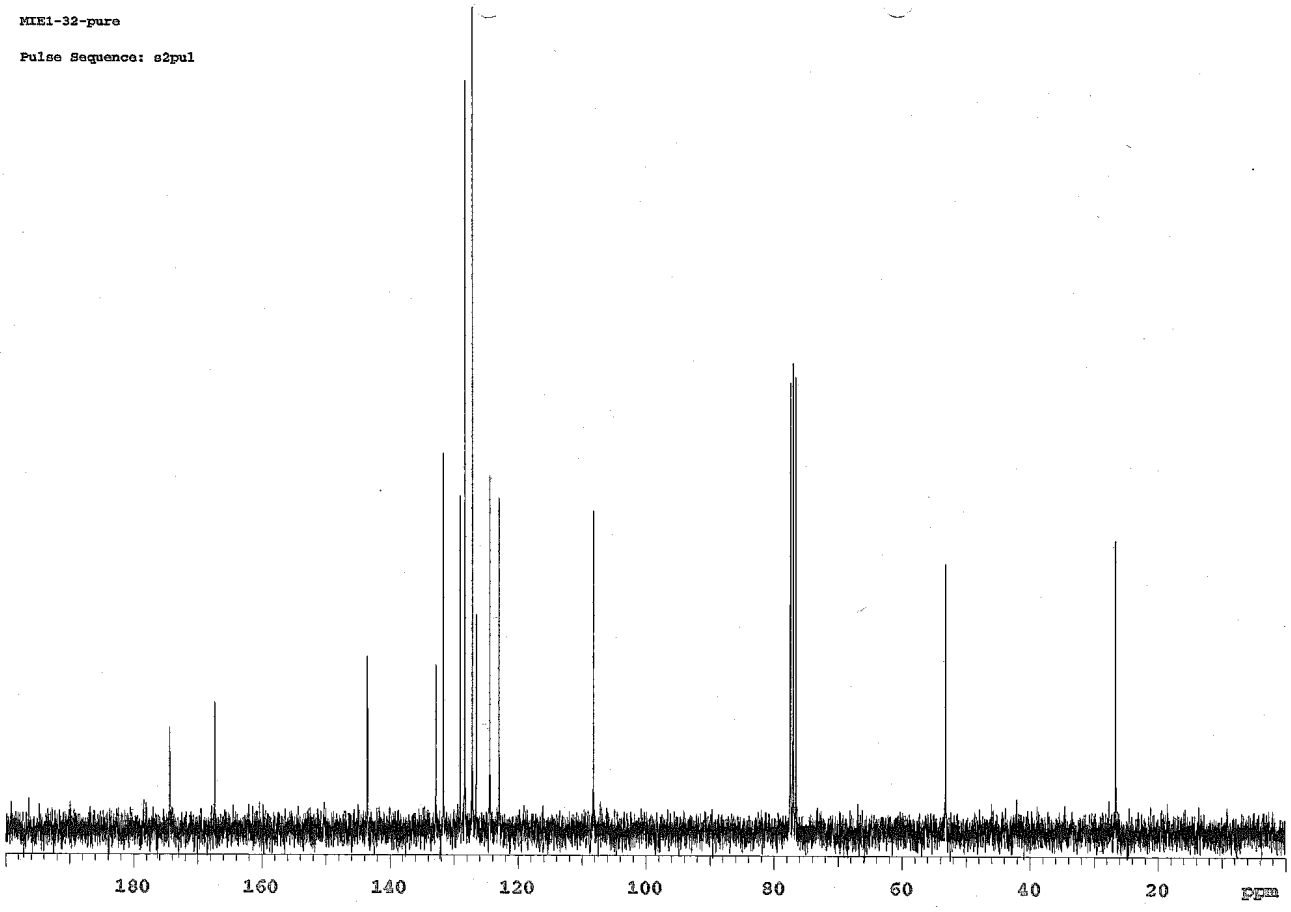
Pulse Sequence: s2pul

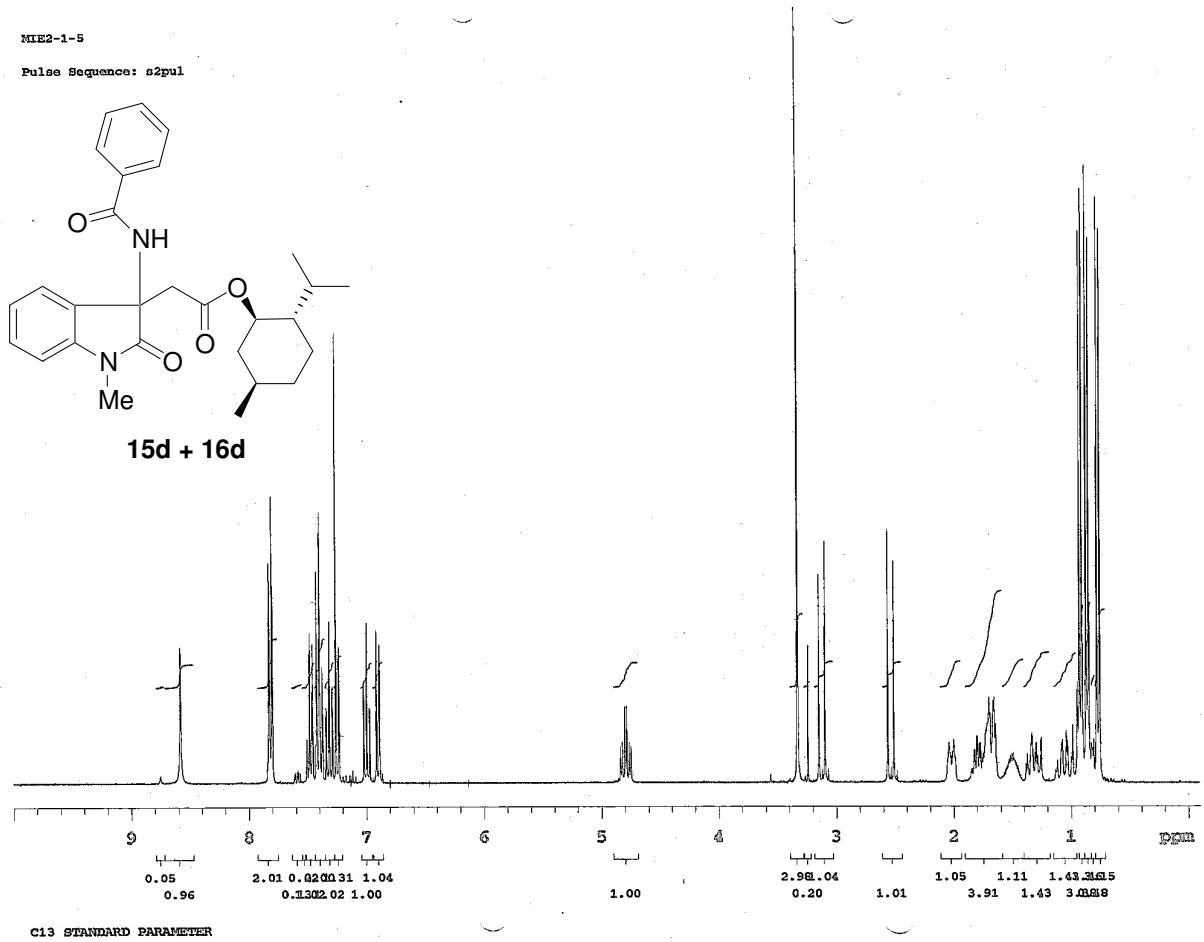


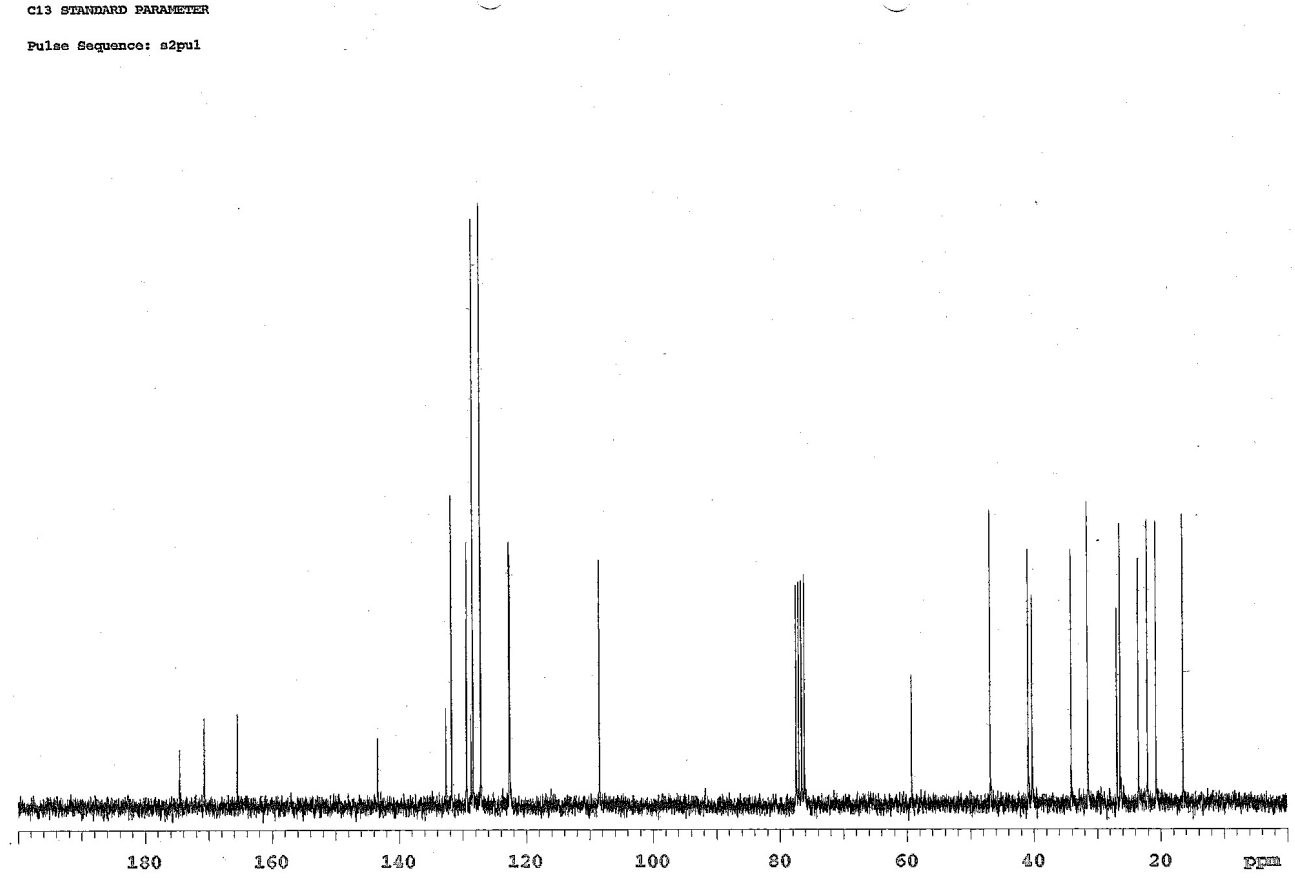

MIE1-37
Pulse Sequence: s2pul
OMe
O
NH
O
O
N
O
Me
15c + 16c
9
8
7
6
5
4
3
2
1
ppm
2.37
1.29
1.02
0.74
1.00
3.14
3.02
1.05
0.73
0.28
1.05
1.13
4.35
1.56

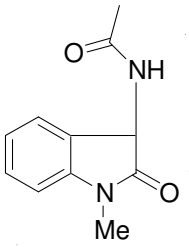

180
160
140
120
100
80
60
40
20
ppm


?sample2
Pulse Sequence: s2pul
O
NH
N
O
Me
14d
9
8
7
6
5
4
3
2
1
ppm
1.93
2.95.54
1.00
0.97
0.94
2.99
5.62


MIE1-32-pure
Pulse Sequence: s2pul
180
160
140
120
100
80
60
40
20
ppm


MIE2-1-5
Pulse Sequence: s2pul
O
NH
O
O
N
O
Me
15d + 16d
9
8
7
6
5
4
3
2
1
ppm
0.05
2.01
1.04
1.00
2.98
1.04
1.05
1.11
0.96
1.00
0.20
1.01
3.91
1.43

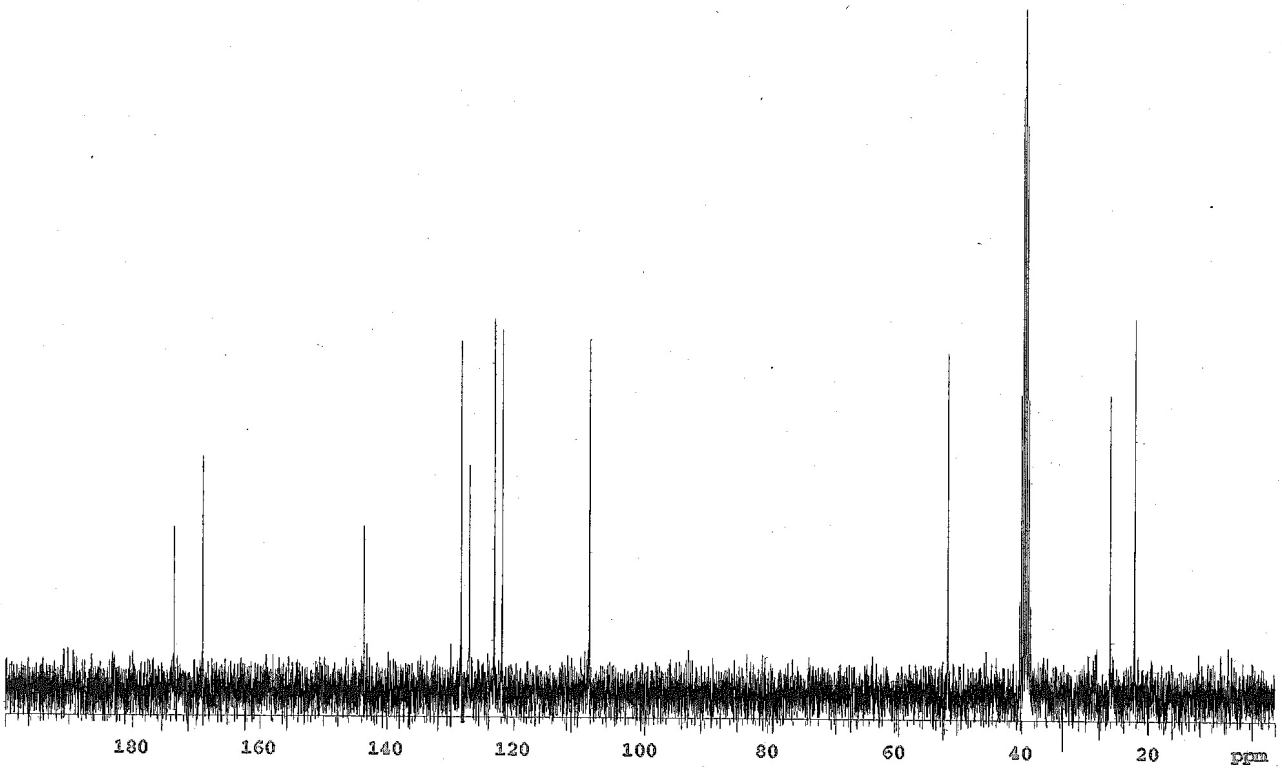

C13 STANDARD PARAMETER
Pulse Sequence: s2pul
180
160
140
120
100
80
60
40
20
ppm



14e

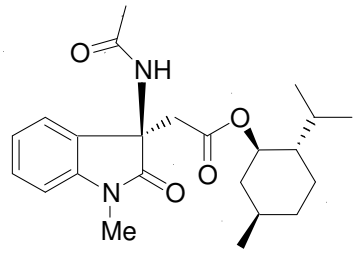
MIE1-33-pure

Pulse Sequence: s2pul



MIE2-106

Pulse Sequence: s2pul



15e + 16e