

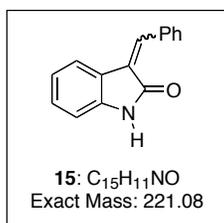
## A New Asymmetric Synthesis of Pyrrolidinoindolines. Application for the Practical Total Synthesis of (-)-Phenserine.

Audris Huang, Jeremy J. Kodanko, and Larry E. Overman\*

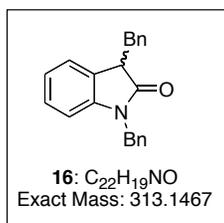
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### Supporting Information<sup>1</sup>

Experimental procedures for the preparation of **15–17**, **19–22**, **24–26**, **28a–c**, **29a–c**, **30a–c**, **31a–c**, **33a–c**, **34a–c**, **35a–c**, **37**, **39**, **41–44**, **46–63**, **65–69**; copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for **21**, **22**, **28b–c**, **29a–c**, **30a–c**, **31a–c**, **32b–c**, **33a–c**, **34a–c**, **35a–c**, **36b–c**, **37**, **41–44**, **46**, **47**, **49–57**, **59**, **62**, **63**, **65–67**, **69**; HPLC traces used to determine the enantiopurity of **48**, **66**, and **67**.



**3-Benzylidene-1,3-dihydroindol-2-one (15).** Benzaldehyde (16.8 mL, 165 mmol) and piperidine (2.97 mL, 300 mmol) were added to a suspension of oxindole **14** (20.0 g, 150 mmol) in ethanol (132 mL). The solution was heated at 80 °C for 1.5 h. The reaction was allowed to cool to room temperature. The precipitate was filtered, washed with ethanol and dried to afford the product as a yellow solid (26.5 g, 80%). The spectral data was consistent with that previously reported.<sup>2</sup>

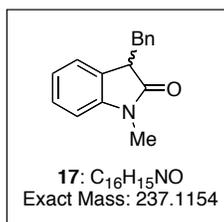


**1,3-Dibenzyl-1,3-dihydroindol-2-one (16).** A 60% dispersion of NaH (3.98 g, 99.4 mmol) was added to a solution of **15** (20.0 g, 90.4 mmol) in DMF (200 mL) at room temperature. The reaction was stirred for 15 min, then benzyl bromide (filtered through basic alumina, 11.8 mL, 99.4 mmol) was added. After 3 h, the reaction was quenched with H<sub>2</sub>O (200 mL) and diluted with MTBE (2 × 200 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford an orange residue (28.1 g, quant.), which was carried forward without further purification.

<sup>1</sup> General experimental details have been described: Ando, S.; Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379–6387. HPLC analyses to determine isomeric purity were calibrated with samples of the corresponding racemate.

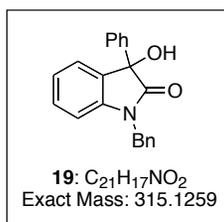
<sup>2</sup> Villemin, D.; Martin, B. *Synth. Commun.* **1998**, *28*, 3201–3208.

Zinc dust (40 g) and concentrated HCl (0.40 mL) were added to a solution of the orange residue (28.1 g, 90.4 mmol) in acetic acid (150 mL). The reaction was stirred overnight, then filtered through Celite. The filter cake was washed with EtOAc (300 mL). A solution of saturated aqueous NaHCO<sub>3</sub> (300 mL) was added to the filtrate and the layers were separated. The organic layer was washed with saturated aqueous NaHCO<sub>3</sub> (2 × 300 mL) and brine (1 × 300 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a thick brown-green residue. Crystallization of the product was induced by adding 90 mL of 2:1 EtOAc:hexanes to this residue. The resulting precipitate was filtered to yield the product as a yellow-green solid (17.7 g, 63%). The spectral data was consistent with that previously reported.<sup>3</sup>



**3-Benzyl-1-methyl-1,3-dihydroindol-2-one (17).** A 60% dispersion of NaH (398 mg, 9.94 mmol) was added to a solution of **15** (2.00 g, 9.04 mmol) in DMF (20 mL) at room temperature. After 20 min, MeI (0.62 mL, 9.9 mmol) was added. After stirring the reaction overnight, H<sub>2</sub>O (100 mL) was added and the resulting aqueous solution was extracted with ether (3 × 100 mL). The combined organic layers were washed with H<sub>2</sub>O (3 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and dried further under high vacuum. Purification of the crude product by silica gel chromatography (eluant 15–50% EtOAc/hexanes) afforded a yellow residue (2.06 g, 97%).

Zn dust (3.80 g) and HCl (0.038 mL) were added to the yellow residue (2.03 g, 8.63 mmol) in glacial acetic acid (14.3 mL). The reaction was stirred at room temperature overnight, then filtered through Celite. The filter cake was rinsed with CH<sub>2</sub>Cl<sub>2</sub>, and the filtrate was concentrated (required azeotrope with heptane). Purification of the crude product by silica gel chromatography (eluant 30–40% EtOAc/hexanes) afforded a yellow solid (1.77 g, 87%). The spectral data was consistent with that previously reported.<sup>4</sup>

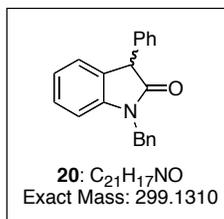


**1-Benzyl-3-hydroxy-3-phenyl-1,3-dihydroindol-2-one (19).** Phenylmagnesium chloride (2 M solution in THF, 24.0 mL, 47.2 mmol) was added dropwise to a solution of **18** (8.00 g, 33.7 mmol) in THF (170 mL) cooled to 0 °C. After 1 h, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (200 mL). The aqueous solution was extracted with EtOAc (3 × 200

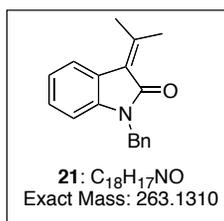
<sup>3</sup> Fujii, K.; Kawabata, T.; Ohmori, T.; Shang, M.; Node, M. *Heterocycles* **1998**, *47*, 951–964.

<sup>4</sup> Munusamy, R.; Dhathathreyan, K. S.; Balasubramanian, K. K.; Venkatachalam, C. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, *7*, 1154–1166.

mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow solid, which was further dried under high vacuum. Recrystallization from hot toluene afforded yellow crystals (9.32 g, 88%). The spectral data was consistent with that previously reported.<sup>5</sup>



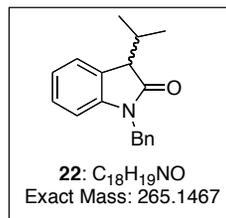
**1-Benzyl-3-phenyl-1,3-dihydroindol-2-one (20).**  $\text{BF}_3 \cdot \text{OEt}_2$  (0.16 mL, 1.3 mmol) was added to a solution of **19** (200 mg, 0.635 mmol) and triethylsilane (0.20 mL, 1.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) cooled to 0 °C. After 15 min, the reaction was allowed to warm to room temperature. After stirring the reaction overnight, saturated aqueous  $\text{Na}_2\text{CO}_3$  (1 mL) was added and the layers were separated. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 1–10% EtOAc/toluene) afforded a white solid (127 mg, 67%): mp 116–118 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.15 (m, 12H), 7.02 (ddd, 1H,  $J = 7.5, 7.5, 1.0$  Hz), 6.78 (d, 1H,  $J = 7.9$  Hz), 4.99 (d, 1H,  $J = 15.6$  Hz), 4.90 (d, 1H,  $J = 15.6$  Hz), 4.70 (s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  176.0, 143.5, 136.7, 135.9, 128.9, 128.8, 128.7, 128.4, 128.3, 127.6 (2), 127.3, 125.1, 122.7, 109.1, 52.0, 43.9; IR (thin film) 3087, 3060, 2923, 1710, 1611, 1488, 1345, 1183, 751, 695  $\text{cm}^{-1}$ ; HRMS (CI/ $\text{NH}_3$ )  $m/z$  calcd for  $\text{C}_{21}\text{H}_{17}\text{NO}$  ( $\text{M}^+$ ) 299.1310, found 299.1307; Anal. Calcd for  $\text{C}_{21}\text{H}_{17}\text{NO}$ : C, 84.25; H 5.72; N, 4.68. Found: C, 83.98; H, 5.74; N, 4.62.



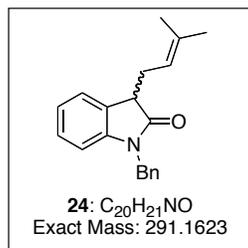
**1-Benzyl-3-isopropylidene-1,3-dihydroindol-2-one (21).** *n*-Butyllithium (0.52 mL, 1.14 mmol) was added dropwise to a stirring mixture of isopropyltriphenylphosphonium iodide (549 mg, 1.27 mmol) in THF (17 mL). The reaction was stirred for 1 h, then a solution of *N*-benzylisatin **18** (100 mg, 0.422 mmol) in THF (11 mL) was cannulaed into the phosphonium iodide suspension over 5 min. After stirring at 23 °C for 12 h, the reaction was quenched with  $\text{H}_2\text{O}$  (40 mL). The aqueous slurry was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  40 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a greenish-black residue. The crude product was purified by silica gel chromatography (eluant 2–20% EtOAc/hexanes) to yield a pink solid (72.5 mg, 65%): mp 151–154 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (d, 1H,  $J = 7.7$  Hz), 7.25–7.18 (m, 5H), 7.10 (t, 1H,  $J = 7.6$  Hz), 6.96 (ddd, 1H,  $J = 7.6, 7.6, 1.0$  Hz), 6.98 (d, 1H,  $J = 7.8$  Hz), 4.94 (s, 2H), 2.64 (s, 3H), 2.37 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  167.8, 155.3, 141.2, 136.5, 128.6, 127.4, 127.3, 127.2, 123.7, 123.4, 122.5,

<sup>5</sup> Kafka, S.; Klasek, A.; Kosmrlj, J. *J. Org. Chem.* **2001**, *66*, 6394–6399.

121.6, 108.4, 43.1, 25.3, 23.3; IR (thin film) 3509, 2927, 1692, 1607, 1468, 1352, 1182, 742  $\text{cm}^{-1}$ ; HRMS (CI/ $\text{NH}_3$ )  $m/z$  calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}$  ( $\text{M}^+$ ) 263.1310, found 263.1309.

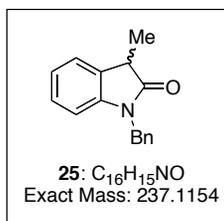


**1-Benzyl-3-isopropyl-1,3-dihydroindol-2-one (22).** A mixture of **21** (100 mg, 0.380 mmol) and 10% Pd/C (20 mg) in 1:1 MeOH/ $\text{CH}_2\text{Cl}_2$  (3.8 mL) was allowed to stir at 23 °C for 12 h under a  $\text{H}_2$  balloon. The reaction mixture was filtered through Celite and the filter cake was rinsed with  $\text{CH}_2\text{Cl}_2$  (30 mL). The filtrate was concentrated to afford a yellow residue, which was purified further by silica gel chromatography (eluant 10–20% EtOAc/hexanes) to yield the product as a clear residue (80 mg, 79%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27–7.20 (m, 6H), 7.12 (t, 1H,  $J = 7.7$  Hz), 6.97 (t, 1H,  $J = 7.5$  Hz), 6.68 (d, 1H,  $J = 7.8$  Hz), 4.99 (d, 1H,  $J = 15.6$  Hz), 4.76 (d, 1H,  $J = 15.6$  Hz), 3.43 (d, 1H,  $J = 3.4$  Hz), 2.53 (dddd, 1H,  $J = 14.1, 7.1, 7.1, 3.7$  Hz), 1.08 (d, 3H,  $J = 7.0$  Hz), 0.90 (d, 3H,  $J = 6.9$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  177.4, 143.9, 136.1, 128.7, 127.8, 127.7, 127.5, 127.3, 124.4, 122.1, 108.8, 51.5, 43.6, 30.9, 19.9, 18.2; IR (thin film) 3057, 2961, 1706, 1613, 1467, 1355, 1166, 749  $\text{cm}^{-1}$ ; HRMS (CI/ $\text{NH}_3$ )  $m/z$  calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}$  ( $\text{M}^+$ ) 265.1467, found 265.1468.



**1-Benzyl-3-(3-methylbut-2-enyl)-1,3-dihydroindol-2-one (24).** A solution of **23** (3.00 g, 13.4 mmol) in THF (67 mL) was cooled to  $-78$  °C and deoxygenated by vigorously sparging with argon for 30 min. A 1 M solution of LHMDS in THF (13.4 mL, 13.4 mmol) was added dropwise. After 55 min, 4-bromo-2-methyl-2-butene (1.95 mL, 16.8 mmol) was added dropwise. The reaction was stirred at  $-78$  °C for 2.5 h, then allowed to warm to  $-45$  °C and quenched with 3% AcOH in THF (30 mL). EtOAc (70 mL) and saturated aqueous  $\text{NaHCO}_3$  (70 mL) were added to the resulting solution, and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\times$  70 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield a brown residue. Purification of the crude product by silica gel chromatography (eluant 5–15% EtOAc/hexanes) afforded a yellow-orange liquid (2.45 g, 63%), which solidified upon storage at 0 °C. The spectral data was consistent with that previously reported.<sup>6</sup>

<sup>6</sup> Lakshmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699–1704.



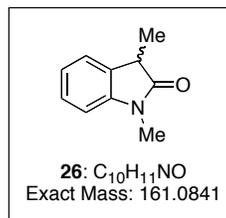
**1-Benzyl-3-methyl-1,3-dihydroindol-2-one (25).** A solution of freshly distilled sulfuryl chloride (12.9 mL, 161 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (162 mL) cooled to 0 °C was added to a solution of ethyl(methylthio)acetate (14.7 mL, 161 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (448 mL) by cannula over 5 min. The reaction mixture was maintained at -78 °C for 1.3 h. A solution of freshly distilled aniline (14.7 mL, 161 mmol) and 2,6-lutidine (18.9 mL, 161 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (136 mL) was added to the reaction mixture dropwise by an addition funnel over 1 h. After the addition was complete, the reaction mixture was maintained at -78 °C for 1 h. Et<sub>3</sub>N (22.5 mL, 161 mmol) was added, and the reaction mixture was allowed to warm to room temperature. Evaporation of the solvent yielded a yellow solid, which was taken up in Et<sub>2</sub>O (360 mL) and 1 N HCl (180 mL). The solution was stirred vigorously overnight. A solid precipitated and was filtered. A second crop was obtained by extracting the aqueous filtrate with ether (4 □ 200 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a solid, which was recrystallized from hot toluene. The combined crops yielded 18.5 g (64%) of 3-methylsulfanyl-1,3-dihydroindol-2-one as a solid. The spectral data was consistent with that previously reported.<sup>7</sup>

A 60% dispersion of NaH (1.10 g, 27.9 mmol) was added to a solution of 3-methylsulfanyl-1,3-dihydroindol-2-one (5.00 g, 27.9 mmol) in DMF (100 mL) at room temperature. After 40 min, MeI (1.7 mL, 27.9 mmol) was added, and the reaction was stirred overnight. Additional NaH (1.10 g, 27.9 mmol) was added. After 1.5 h, benzyl bromide (filtered through basic alumina, 3.3 mL, 28 mmol) was added. The reaction was allowed to stir for 7.5 h, then H<sub>2</sub>O (200 mL) was added and the resulting aqueous solution was extracted with ether (3 □ 250 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a red residue, which was further dried under high vacuum. Purification of the crude product by silica gel chromatography (eluant 15–60% EtOAc/hexanes) afforded 1-benzyl-3-methyl-3-methylsulfanyl-1,3-dihydroindol-2-one as a red residue (4.88 g, 62%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) □ 7.35 (dd, 1H, *J* = 7.4, 1.3, 0.51 Hz), 7.32–7.24 (m, 5H), 7.18 (ddd, 1H, *J* = 7.7, 7.7, 1.3 Hz), 7.07 (ddd, 1H, *J* = 7.6, 7.6, 1.0 Hz), 6.74 (d, 1H, *J* = 7.8 Hz), 5.01 (d, 1H, *J* = 15.6 Hz), 4.85 (d, 1H, *J* = 15.6 Hz), 1.96 (s, 3H), 1.72 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) □ 177.6, 141.8, 135.9, 131.2, 128.8, 128.7, 127.7, 127.3, 127.2, 123.7, 123.0, 109.1, 43.8, 21.7, 12.0; IR (thin film) 3505, 2974, 2927, 1715, 1607, 1491, 1352, 1182, 749 cm<sup>-1</sup>; HRMS (CI/NH<sub>3</sub>) *m/z* calcd for C<sub>17</sub>H<sub>17</sub>NOS (M<sup>+</sup>) 283.1031, found 283.1030.

A mixture of 1-benzyl-3-methyl-3-methylsulfanyl-1,3-dihydroindol-2-one (3.83 g, 13.5 mmol) and zinc dust (8.82 g, 135 mmol) in glacial acetic acid (112 mL) was heated at reflux for 6 h, then allowed to cool to room temperature. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (75 mL) and filtered through Celite. The filter cake was rinsed with additional CH<sub>2</sub>Cl<sub>2</sub> (200 mL). Evaporation of the solvent from the filtrate afforded a solid. Purification of the crude product by silica gel chromatography (eluant 2–8% EtOAc/toluene) and recrystallization of the resulting

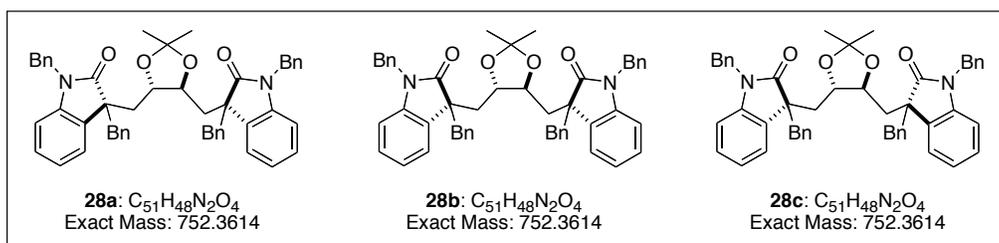
<sup>7</sup> Wright, S. W.; McClure, L. D.; Hageman, D. L. *Tetrahedron Lett.* **1996**, *37*, 4631–4634.

solid afforded the product as colorless crystals (2.60 g, 81%). The spectral data was consistent with that previously reported.<sup>8</sup>



**1,3-Dimethyl-1,3-dihydroindol-2-one (26).** A 60% dispersion of NaH (984 mg, 24.6 mmol) was added to a solution of 3-methylsulfanyl-1,3-dihydroindol-2-one (2.00 g, 11.2 mmol) in DMF (56 mL). After stirring the reaction at room temperature for 20 min, MeI (1.5 mL, 24.6 mmol) was added. Consumption of starting material required the addition of more NaH (492 mg, 12.3 mmol) and CH<sub>3</sub>I (0.77 mL, 12.3 mmol). The reaction was quenched with H<sub>2</sub>O (150 mL) and extracted with Et<sub>2</sub>O (3 × 200 mL). The combined organic layers were washed with H<sub>2</sub>O (3 × 150 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford 1,3-dimethyl-3-methylsulfanyl-1,3-dihydroindol-2-one as a yellow residue, which was used without further purification.

A mixture of 1,3-dimethyl-3-methylsulfanyl-1,3-dihydroindol-2-one (2.32g, 11.2 mmol) and zinc dust (732 mg, 112 mmol) in glacial acetic acid (93 mL) was heated at reflux overnight. Consumption of starting material required the addition of more zinc dust (732 mg, 112 mmol) and heating the reaction an additional 4 h. The reaction was allowed to cool to room temperature, then filtered through Celite. After the filter cake was rinsed with CH<sub>2</sub>Cl<sub>2</sub> (200 mL), the filtrate was concentrated. The crude product was purified by silica gel chromatography (eluant 30–50% EtOAc/hexanes) to afford **26** as a yellow solid (1.45 g, 81% over two steps). The spectral data was consistent with that previously reported.<sup>9</sup>



**C<sub>2</sub>- and C<sub>1</sub>-Symmetric products 28a, 28b, and 28c.** A solution of **16** (18.6 g, 59.6 mmol), DMPU (0.9 mL) and THF (400 mL) was cooled to –78 °C in a large dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 30 min. LHMDS (9.97 g, 59.6 mmol) was added. After 15 min, ditriflate **10** (11.5 g, 27.1 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) and concentrated. The resulting solid was dissolved in 500 mL of 1:1 benzene:EtOAc and the solution was extracted with brine (3 × 150 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a solid containing a mixture of three diastereomers **28a**, **28b**, and **28c**. Recrystallization from hot EtOH (700 mL, prolonged heating is required to solubilize the

<sup>8</sup> Giannangeli, M.; Baiocchi, L. *J. Heterocycl. Chem.* **1982**, *19*, 891–895.

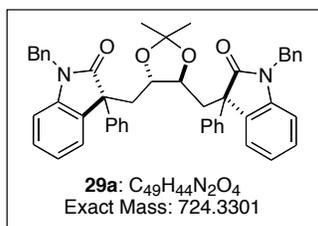
<sup>9</sup> Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553.

product) afforded the major  $C_2$ -symmetric product **28a** as a colorless solid (1.38 g, 64%). The mother liquor was concentrated and the residue was purified by silica gel chromatography (eluant 5–20% EtOAc/toluene) to afford a yellow solid. A portion of this solid was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23  $^{\circ}$ C, 85% MeOH in  $H_2O$  + 1%  $NH_4OH$ , flow rate 10 mL/min, UV detection at 254 nm,  $t_r$  = 42 min (major  $C_2$ ), 58 min ( $C_1$ ), 63 min (minor  $C_2$ )) to afford pure analytical samples of the  $C_1$ -symmetric product **28b** (27.6 mg) and the minor  $C_2$ -symmetric product **28c** (0.8 mg).

Major  $C_2$ -symmetric product, **28a**:  $[\alpha]_{589}^{27}$  -13,  $[\alpha]_{577}^{27}$  -16,  $[\alpha]_{546}^{27}$  -16,  $[\alpha]_{435}^{27}$  -27,  $[\alpha]_{405}^{27}$  -32 ( $c$  = 0.4,  $CHCl_3$ ); mp 128–131  $^{\circ}$ C;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.23–7.21 (m, 2H), 7.16–7.11 (m, 8H), 7.07–7.03 (m, 8H), 6.82–6.80 (m, 4H), 6.76–6.74 (m, 4H), 6.33–6.31 (m, 2H), 4.67 (d, 2H,  $J$  = 16.1 Hz), 4.52 (d, 2H,  $J$  = 16.2 Hz), 3.38 (dd, 2H,  $J$  = 5.4, 2.6 Hz), 3.17 (d, 2H,  $J$  = 12.8 Hz), 3.02 (d, 2H,  $J$  = 12.8 Hz), 2.24 (dd, 2H,  $J$  = 13.9, 9.5 Hz), 1.89 (dd, 2H,  $J$  = 14.0, 2.3 Hz), 1.08 (s, 6H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  178.5, 143.6, 135.7, 135.5, 130.2, 128.4, 128.0, 127.7, 127.0, 126.7, 126.5, 123.6, 121.8, 109.1, 108.8, 77.7, 52.8, 44.4, 43.6, 40.1, 26.9; IR (thin film) 3032, 1714, 1615, 1368  $cm^{-1}$ ; Anal. Calcd for  $C_{51}H_{48}N_2O_4$ : C, 81.35; H, 6.43; N, 3.72. Found: C, 81.32; H, 6.47; N, 3.66.

$C_1$ -Symmetric product, **28b**:  $[\alpha]_{589}^{27}$  -43.7,  $[\alpha]_{577}^{27}$  -46.3,  $[\alpha]_{546}^{27}$  -51.6,  $[\alpha]_{435}^{27}$  -88.1,  $[\alpha]_{405}^{27}$  -104.8 ( $c$  = 0.2,  $CH_2Cl_2$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.33 (m, 1H), 7.25 (m, 1H), 7.16–7.10 (m, 8H), 7.08–7.00 (m, 8H), 6.81 (m, 4H), 6.77 (m, 2H), 6.65 (d, 2H,  $J$  = 6.9 Hz), 6.38 (m, 1H), 6.30 (m, 1H), 4.95 (d, 1H,  $J$  = 16.0 Hz), 4.63 (d, 1H,  $J$  = 16.1 Hz), 4.53 (d, 1H,  $J$  = 16.1 Hz), 4.49 (d, 1H,  $J$  = 16.1 Hz), 3.57 (ddd, 1H,  $J$  = 8.0, 8.0, 3.3 Hz), 3.36 (ddd, 1H,  $J$  = 10.1, 7.8, 2.2 Hz), 3.31 (d, 1H,  $J$  = 13.1 Hz), 3.18 (d, 1H,  $J$  = 12.8 Hz), 3.15 (d, 1H,  $J$  = 13.2 Hz), 3.02 (d, 1H,  $J$  = 12.8 Hz), 2.25 (dd, 1H,  $J$  = 14.0, 10.4 Hz), 2.15 (dd, 1H,  $J$  = 14.3, 8.2 Hz), 2.02 (dd, 1H,  $J$  = 13.9, 2.3 Hz), 1.97 (dd, 1H,  $J$  = 14.2, 3.3 Hz), 1.17 (s, 3H), 1.00 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  178.9, 178.5, 143.5, 142.8, 135.9, 135.8, 135.5, 135.2, 130.5, 130.1, 130.0, 128.5, 128.4, 127.9 (2), 127.8, 127.6, 127.1, 126.9, 126.6 (2), 126.5, 124.6, 123.6, 122.1, 121.8, 109.1, 109.0, 108.8, 78.0, 77.9, 53.5, 52.9, 44.6, 44.0, 43.5, 40.0, 39.9, 26.9 (2); IR (thin film) 3053, 2985, 2929, 1711, 1611, 1368, 729  $cm^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $C_{51}H_{48}N_2O_4$  ( $M+Na$ ) $^+$  775.3512, found 775.3516.

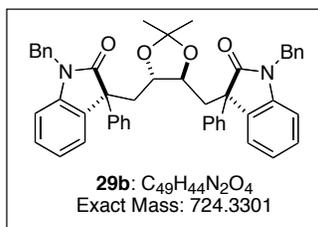
Minor  $C_2$ -symmetric product, **28c**:  $[\alpha]_{589}^{27}$  -46,  $[\alpha]_{577}^{27}$  -56,  $[\alpha]_{546}^{27}$  -59,  $[\alpha]_{435}^{27}$  -108,  $[\alpha]_{405}^{27}$  -133 ( $c$  = 0.1,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.37–7.35 (m, 2H), 7.15–7.08 (m, 8H), 7.06–6.99 (m, 8H), 6.82 (d, 4H,  $J$  = 7.6 Hz), 6.59 (d, 4H,  $J$  = 7.3 Hz), 6.34–6.33 (m, 2H), 4.82 (d, 2H,  $J$  = 16.0 Hz), 4.39 (d, 2H,  $J$  = 16.1 Hz), 3.70 (m, 2H), 3.37 (d, 2H,  $J$  = 13.1 Hz), 3.17 (d, 2H,  $J$  = 13.1 Hz), 2.16 (dd, 2H,  $J$  = 14.2, 8.4 Hz), 1.94 (dd, 2H,  $J$  = 14.2, 1.9 Hz), 1.15 (s, 6H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  178.7, 142.8, 136.1, 135.3, 130.6, 130.2, 128.5, 127.8, 127.7, 127.0, 126.6, 126.4, 124.7, 122.0, 109.0, 78.4, 53.4, 43.8, 43.3, 39.9, 27.1; IR (thin film) 2928, 1707, 1615  $cm^{-1}$ ; LRMS (ESI)  $m/z$  calcd for  $C_{51}H_{48}N_2O_4Na$  ( $M+Na$ ) $^+$  775.3, found: 775.3.



**Major  $C_2$ -symmetric product 29a.** A solution of **20** (500 mg, 1.67 mmol) and DMPU (0.22 mL) in THF (11 mL) was cooled to  $-78$   $^{\circ}$ C in a dry ice/*i*-PrOH bath and was deoxygenated

by vigorously sparging with argon for 30 min. A 1 M solution of LHMDS in THF (1.7 mL, 1.7 mmol) was added dropwise. After 15 min, ditriflate **10** (356 mg, 0.835 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (3 mL) and diluted with 16 mL of 1:1 benzene:EtOAc. After the layers were separated, the aqueous phase was extracted with EtOAc (3  $\times$  16 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 2–16% EtOAc/toluene) yielded a colorless residue consisting of a mixture of three diastereomers. A small amount of this diastereomeric mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu\text{m}$ , 250 x 21.2 mm, column temperature 23  $^\circ\text{C}$ , 80% MeOH in  $\text{H}_2\text{O}$ , flow rate 16 mL/min. UV detection at 254 nm,  $t_r$  = 58 min (major  $C_2$ ), 78 min (mixture of  $C_1$  and minor  $C_2$ )) to afford pure analytical samples of the major  $C_2$ -symmetric diastereomer **29a** (14.4 mg) and a mixture of the  $C_1$ -symmetric and minor  $C_2$ -symmetric diastereomers **29b** and **29c** (13.1 mg).

Major  $C_2$ -symmetric product, **29a**:  $[\alpha]_D^{27}$   $+100$ ,  $[\alpha]_D^{27}$   $+106$ ,  $[\alpha]_D^{27}$   $+120$ ,  $[\alpha]_D^{27}$   $+435$   $+240$ ,  $[\alpha]_D^{27}$   $+313$  ( $c$  = 0.14,  $\text{CH}_2\text{Cl}_2$ ); mp 115–117  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30–7.20 (m, 22H), 7.16 (t, 2H,  $J$  = 7.7 Hz), 7.06 (t, 2H,  $J$  = 7.5 Hz), 6.67 (d, 2H,  $J$  = 7.8 Hz), 4.87 (d, 2H,  $J$  = 15.9 Hz), 4.75 (d, 2H,  $J$  = 15.9 Hz), 3.35 (m, 2H), 2.60 (m, 2H), 2.16 (d, 2H,  $J$  = 13.0 Hz), 1.05 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  178.1, 143.7, 140.8, 136.0, 130.5, 128.6, 128.5, 128.4, 127.4, 127.2, 126.8, 125.2, 122.2, 109.5, 109.1, 77.9, 54.6, 44.3, 40.4, 26.8; IR (thin film) 3058, 2944, 1717, 1611, 1488, 1356, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{49}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  747.3199, found 747.3193.

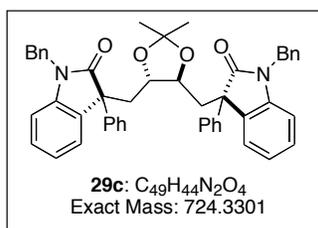


**$C_1$ -Symmetric product 29b.** *p*-Toluenesulfonic acid monohydrate (34.4 mg, 0.181 mmol) and  $\text{H}_2\text{O}$  (0.12 mL) were added to a stirring solution containing a mixture of **29b** and **29c** (34.4 mg, 0.0472 mmol) in MeOH (1.0 mL). The reaction was heated at reflux overnight, then allowed to cool to room temperature. Saturated aqueous  $\text{NaHCO}_3$  (5 mL) was added, and the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford colorless residue. Purification of the crude product by silica gel chromatography (eluant 30–60% EtOAc/hexanes) afforded pure analytical samples of the  $C_1$ -symmetric diol (15.4 mg, 48%) minor  $C_2$ -symmetric diol (1.7 mg, 5%).

$C_1$ -Symmetric diol:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36–7.21 (m, 22H), 7.17 (m, 2H), 7.09 (t, 1H,  $J$  = 7.5 Hz), 7.05 (t, 1H,  $J$  = 7.6 Hz), 6.76 (dd, 2H,  $J$  = 7.7, 2.4 Hz), 4.99 (d, 1H,  $J$  = 26.9 Hz), 4.96 (d, 1H,  $J$  = 27.0 Hz), 4.85 (d, 1H,  $J$  = 15.8 Hz), 4.74 (d, 1H,  $J$  = 15.7 Hz), 3.51 (m, 1H), 3.45 (br s, 1H), 3.19 (d, 1H,  $J$  = 9.8 Hz), 2.97 (dd, 1H,  $J$  = 14.2, 10.7 Hz), 2.59 (dd, 1H,  $J$  = 14.8, 2.4 Hz), 2.28 (m, 2H), 2.17 (br s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  179.9, 179.4, 143.7, 141.7, 141.2, 139.3, 136.0, 135.4, 133.0, 131.3, 128.9, 128.7, 128.5, 128.3, 128.2, 127.7, 127.5, 127.4, 127.3 (2), 127.1, 126.7, 126.6, 125.0, 124.5, 123.2, 122.4, 109.7, 109.6, 71.7, 71.4,

55.5, 54.7, 44.1, 43.9, 41.0 (2); IR 3462, 3061, 2922, 1702, 1610, 1351, 733  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{46}\text{H}_{40}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 707.2886, found 707.2879.

Camphorsulfonic acid (2.2 mg) was added to a solution of the  $\text{C}_1$ -symmetric diol (23 mg, 0.034 mmol) and 2,2-dimethoxypropane (0.5 mL) in acetone (1.0 mL). After 24 h, EtOAc (5 mL) and saturated aqueous  $\text{NaHCO}_3$  (5 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (2  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield a residue. Purification of the crude product by silica gel chromatography (eluant 15–50% EtOAc/hexanes) afforded a colorless film (24 mg, 99%):  $[\alpha]_{589}^{27} -33$ ,  $[\alpha]_{577}^{27} -35$ ,  $[\alpha]_{546}^{27} -38$ ,  $[\alpha]_{435}^{27} -51$ ,  $[\alpha]_{405}^{27} -50$  ( $c = 0.48$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37–7.16 (m, 24H), 7.11 (ddd, 1H,  $J = 7.6, 7.6, 1.0$  Hz), 7.01 (t, 1H,  $J = 7.1$  Hz), 6.74 (d, 1H,  $J = 7.7$  Hz), 6.69 (d, 1H,  $J = 7.7$  Hz), 4.94 (t, 2H,  $J = 16.3$  Hz), 4.74 (dd, 2H,  $J = 15.7, 5.6$  Hz), 3.49 (ddd, 1H,  $J = 7.5, 7.5, 3.7$  Hz), 3.32 (ddd, 1H,  $J = 9.8, 8.0, 1.9$  Hz), 2.67 (dd, 1H,  $J = 13.9, 10.1$  Hz), 2.57 (dd, 1H,  $J = 14.3, 3.7$  Hz), 2.42 (dd, 1H,  $J = 14.2, 7.4$  Hz), 2.36 (dd, 1H,  $J = 14.0, 2.0$  Hz), 1.02 (s, 3H), 0.87 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.4, 178.2, 143.8, 142.7, 141.2, 140.7, 136.2, 135.8, 131.7, 130.7, 128.7, 128.6, 128.6, 128.5, 128.2, 128.0, 127.6, 127.4, 127.3 (2), 127.2 (2), 126.8, 126.7, 125.9, 125.4, 122.4, 122.3, 109.4, 109.2, 108.9, 78.3, 78.0, 55.2, 54.8, 44.3, 43.9, 40.4, 40.1, 26.7, 26.6; IR (thin film) 3058, 1710, 1611, 1466, 1358, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{49}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ )<sup>+</sup> 725.3380, found 725.3408.

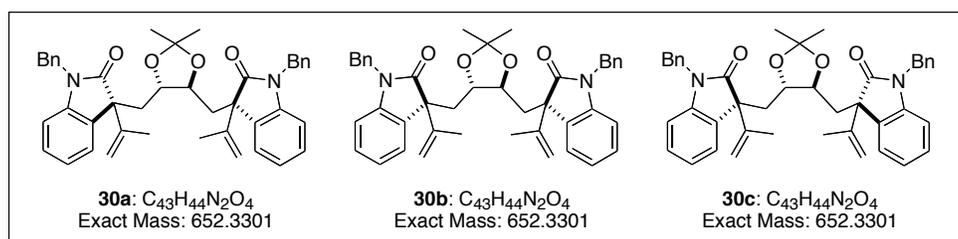


**Minor  $\text{C}_2$ -symmetric product 29c.** *p*-Toluenesulfonic acid monohydrate (34.4 mg, 0.181 mmol) and  $\text{H}_2\text{O}$  (0.12 mL) were added to a stirring solution containing a mixture of **29b** and **29c** (34.4 mg, 0.0472 mmol) in MeOH (1.0 mL). The reaction was heated at reflux overnight, then allowed to cool to room temperature. Saturated aqueous  $\text{NaHCO}_3$  (5 mL) was added, and the aqueous solution was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford colorless residue. Purification of the crude product by silica gel chromatography (eluant 30–60% EtOAc/hexanes) afforded pure analytical samples of the  $\text{C}_1$ -symmetric diol (15.4 mg, 48%) minor  $\text{C}_2$ -symmetric diol (1.7 mg, 5%).

Minor  $\text{C}_2$ -symmetric diol:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (m, 4H), 7.34–7.22 (m, 18H), 7.15 (ddd, 2H,  $J = 7.7, 7.7, 1.1$  Hz), 7.04 (ddd, 2H,  $J = 7.6, 7.6, 0.9$  Hz), 6.75 (d, 2H,  $J = 7.8$  Hz), 5.05 (d, 2H,  $J = 15.6$  Hz), 4.89 (d, 2H,  $J = 15.6$  Hz), 3.58 (m, 2H), 3.51 (d, 2H,  $J = 3.8$  Hz), 2.71 (dd, 2H,  $J = 14.8, 1.5$  Hz), 2.21 (dd, 2H,  $J = 15.0, 8.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  180.0, 141.7, 139.6, 135.6, 133.7, 128.9, 128.8, 128.1, 127.7, 127.4, 127.3, 126.8, 124.5, 123.1, 109.5, 71.3, 55.7, 44.0, 40.5; IR (thin film) 3405, 3061, 2926, 1683, 1610, 1370, 733  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{46}\text{H}_{40}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 707.2886, found 707.2899.

Camphorsulfonic acid (2.0 mg) was added to a solution of diol (5 mg, 0.007 mmol) and 2,2-dimethoxypropane (0.5 mL) in acetone (1.0 mL). After 24 h, EtOAc (5 mL) and saturated aqueous  $\text{NaHCO}_3$  (5 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (2  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ ,

filtered, and concentrated to yield a residue. Purification of the crude product by silica gel chromatography (eluant 15–50% EtOAc/hexanes) afforded a colorless film (4.7 mg, 89%):  $[\alpha]_{589}^{27} -74$ ,  $[\alpha]_{577}^{27} -76$ ,  $[\alpha]_{546}^{27} -85$ ,  $[\alpha]_{435}^{27} -158$ ,  $[\alpha]_{405}^{27} -194$  ( $c = 0.09$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39–7.36 (m, 4H), 7.31–7.19 (m, 18H), 7.15 (ddd, 2H,  $J = 7.7, 7.7, 1.3$  Hz), 7.00 (t, 2H,  $J = 7.5$  Hz), 6.72 (d, 2H,  $J = 7.8$  Hz), 4.94 (d, 2H,  $J = 15.6$  Hz), 4.86 (d, 2H,  $J = 15.7$  Hz), 3.50 (m, 2H), 2.69 (dd, 2H,  $J = 14.3, 1.9$  Hz), 2.34 (dd, 2H,  $J = 14.2, 8.3$  Hz), 0.71 (s, 6H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  178.2, 142.7, 140.6, 136.1, 132.3, 128.6, 128.5, 127.7, 127.4, 127.3 (2), 126.9, 125.9, 122.1, 109.0, 108.5, 78.3, 55.2, 43.9, 39.9, 26.4; IR (thin film) 3058, 2925, 1710, 1611, 1466, 1360, 697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{49}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  725.3380, found 725.3369.



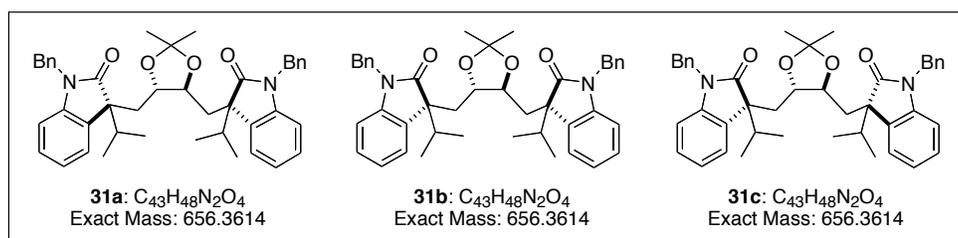
**$C_2$ - and  $C_1$ -Symmetric products 30a, 30b, and 30c.** A solution of **21** (400 mg, 1.52 mmol) and DMPU (0.20 mL) in THF (10.1 mL) was cooled to  $-78$  °C in a dry ice/*i*-PrOH and was deoxygenated by vigorously sparging with argon for 35 min. A 1 M solution of LHMDS in THF (1.5 mL, 1.5 mmol) was added dropwise. After 45 min, ditriflate **10** (295 mg, 0.691 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (10 mL) and diluted with EtOAc (9 mL). After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\times$  16 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford an orange solid. Purification of the crude product by silica gel chromatography (eluant 8–50% EtOAc/hexanes) yielded a residue consisting of a mixture of three diastereomers (365 mg, 81%). A small amount of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu\text{m}$ , 250 x 21.2 mm, column temperature 23 °C, 85% MeOH in  $\text{H}_2\text{O}$ , flow rate 5 mL/min, UV detection at 254 nm,  $t_r = 63$  min (major  $C_2$ ), 82 min ( $C_1$ ), 88 min (minor  $C_2$ )) to afford pure analytical samples of the major  $C_2$ -symmetric diastereomer **30a**, the  $C_1$ -symmetric diastereomer **30b**, and the minor  $C_2$ -symmetric diastereomer **30c**.

Major  $C_2$ -symmetric product, **30a**:  $[\alpha]_{589}^{28} -31$ ,  $[\alpha]_{577}^{28} -31$ ,  $[\alpha]_{546}^{28} -35$ ,  $[\alpha]_{435}^{28} -48$  ( $c = 0.25$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.23 (m, 10 H), 7.16 (ddd, 2H,  $J = 7.7, 7.7, 1.6$  Hz), 7.08–7.02 (m, 4H), 6.66 (d, 2H,  $J = 7.8$  Hz), 4.96 (m, 4H), 4.89 (d, 2H,  $J = 15.9$  Hz), 4.78 (d, 2H,  $J = 15.8$  Hz), 3.17 (m, 2H), 2.25 (m, 2H), 1.97 (m, 2H), 1.59 (s, 6H), 1.03 (s, 6H);  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 143.9 (2), 136.2, 130.5, 128.6, 128.2, 127.4, 127.3, 123.9, 122.2, 113.1, 109.2, 109.0, 77.9, 56.2, 44.3, 37.5, 26.9, 19.6; IR (thin film) 3056, 2919, 1717, 1611, 1490, 1355, 756  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  675.3199, found 675.3210.

$C_1$ -Symmetric product, **30b**:  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.33–7.22 (m, 10 H), 7.17–7.11 (m, 3H), 7.06 (m, 2H), 6.95 (t, 1H,  $J = 7.5$  Hz), 6.73 (d, 1H,  $J = 7.6$  Hz), 6.63 (d, 1H,  $J = 7.7$  Hz), 5.02–4.94 (m, 5H), 4.90 (d, 1H,  $J = 15.6$  Hz), 4.84 (s, 2H), 3.30 (ddd, 1H,  $J = 7.4, 7.4, 3.5$  Hz), 3.06 (ddd, 1H,  $J = 9.8, 7.9, 1.9$  Hz), 2.28 (m, 1H), 2.17 (m, 3H), 1.60 (s, 3H), 1.59 (s,

3H), 0.93 (s, 3H), 0.86 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  177.9, 177.8, 144.0, 143.9, 143.8, 142.9, 136.3, 136.0, 131.3, 130.6, 128.8, 128.6, 128.1, 127.8, 127.7, 127.4, 127.3, 124.8, 124.0, 122.3, 122.2, 113.1, 113.0, 109.1, 108.8, 108.7, 78.1, 77.8, 56.8, 56.3, 44.2, 43.9, 37.2, 36.8, 26.8, 26.5, 19.7, 19.6; IR (thin film) 3058, 2921, 1713, 1611, 1488, 1356, 1173, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  653.3380, found 653.3395.

Minor  $\text{C}_2$ -symmetric product, **30c**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  7.33–7.23 (m, 10H), 7.12–7.05 (m, 4H), 6.95 (m, 2H), 6.67 (d, 2H,  $J = 7.7$  Hz), 4.95 (m, 8H), 3.38 (m, 2H), 2.31 (dd, 2H,  $J = 14.1, 1.7$  Hz), 2.11 (m, 2H), 1.62 (s, 6H), 0.72 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  177.7, 143.9, 143.0, 136.2, 132.0, 128.7, 127.6, 127.5, 127.4, 124.7, 122.1, 113.1, 108.7, 108.3, 78.2, 56.7, 43.8, 36.8, 26.5, 19.7; IR (thin film) 3058, 2919, 1710, 1611, 1488, 1360, 1175, 745  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{44}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  653.3380, found 653.3398.



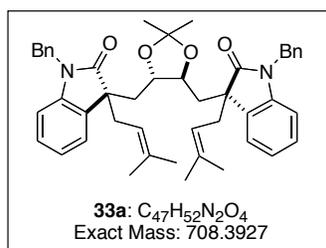
**$\text{C}_2$ - and  $\text{C}_1$ -Symmetric products 31a, 31b, and 31c.** A solution of **22** (239 mg, 0.903 mmol) and DMPU (0.62 mL) in THF (5.5 mL) was cooled to  $-78$   $^\circ\text{C}$  in a dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 40 min. A 1 M solution of LHMDS in THF (0.90 mL, 0.90 mmol) was added dropwise. After 50 min, ditriflate **10** (175 mg, 0.410 mmol) was added as a solid. The reaction was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (8 mL) and diluted with EtOAc (14 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2  $\square$  14 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 10–50% EtOAc/hexanes) yielded a residue consisting of a mixture of three diastereomers. A small portion of this residue was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\square$ m, 250 x 21.2 mm, column temperature 23  $^\circ\text{C}$ , 85% MeOH in  $\text{H}_2\text{O}$ , flow rate 16 mL/min, UV detection at 254 nm,  $t_r = 57$  min (major  $\text{C}_2$ ), 78 min ( $\text{C}_1$ ), 87 min (minor  $\text{C}_2$ )) to afford pure analytical samples of the major  $\text{C}_2$ -symmetric product **31a** (9.5 mg),  $\text{C}_1$ -symmetric product **31b** (2.1 mg) and the minor  $\text{C}_2$ -symmetric product **31c** (4.2 mg).

Major  $\text{C}_2$ -symmetric product, **31a**:  $[\alpha]_D^{26}$ <sub>589</sub>  $-77$ ,  $[\alpha]_D^{26}$ <sub>577</sub>  $-79$ ,  $[\alpha]_D^{26}$ <sub>546</sub>  $-89$ ,  $[\alpha]_D^{26}$ <sub>435</sub>  $-155$  ( $c = 0.16$ ,  $\text{CH}_2\text{Cl}_2$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  7.34–7.21 (m, 10H), 7.14 (ddd, 2H,  $J = 7.7, 7.7, 1.3$  Hz), 7.08 (dd, 2H,  $J = 7.4, 0.8$  Hz), 7.01 (ddd, 2H,  $J = 7.5, 7.5, 1.0$  Hz), 6.64 (d, 2H,  $J = 7.5$  Hz), 4.86 (d, 2H,  $J = 15.8$  Hz), 4.81 (d, 2H,  $J = 15.8$  Hz), 3.17 (m, 2H), 2.12–2.03 (m, 4H), 1.77 (dd, 2H,  $J = 13.8, 2.2$  Hz), 1.01 (s, 6H), 0.89 (d, 6H,  $J = 6.9$  Hz), 0.77 (d, 6H,  $J = 6.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.4, 144.1, 136.4, 130.3, 128.6, 127.7, 127.4, 127.3, 123.6, 121.7, 108.8, 108.5, 78.0, 54.0, 44.0, 37.9, 36.0, 26.8, 17.5, 17.0; IR (thin film) 2966, 2935, 1711, 1611, 1466, 1362, 1171, 755  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ ) $^+$  679.3512, found 679.3533.

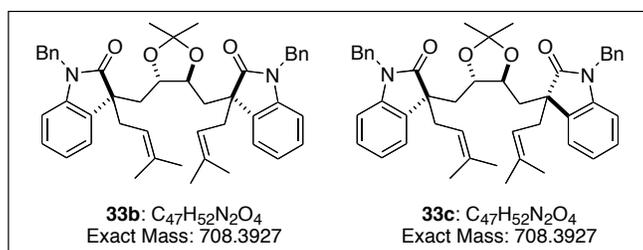
$\text{C}_1$ -Symmetric product, **31b**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  7.34–7.21 (m, 10H), 7.19–7.02 (m, 5H), 6.92 (t, 1H,  $J = 7.5$  Hz), 6.69 (d, 1H,  $J = 7.9$  Hz), 6.63 (d, 1H,  $J = 7.9$  Hz),

4.93 (d, 1H,  $J = 15.7$  Hz), 4.92 (s, 2H), 4.75 (d, 1H,  $J = 15.9$  Hz), 3.25 (ddd, 1H,  $J = 7.7, 7.7, 2.8$  Hz), 3.09 (ddd, 1H,  $J = 8.1, 8.1, 3.4$  Hz), 2.16–2.10 (m, 2H), 2.07–2.00 (m, 3H), 1.82 (dd, 1H,  $J = 14.4, 2.9$  Hz), 0.96 (s, 3H), 0.94 (d, 3H,  $J = 6.9$  Hz), 0.89 (d, 3H,  $J = 6.9$  Hz), 0.83 (s, 3H), 0.78 (d, 3H,  $J = 6.7$  Hz), 0.72 (d, 3H,  $J = 6.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.8, 179.5, 144.0, 143.3, 136.5, 136.2, 130.8, 130.3, 128.7, 128.5, 127.6, 127.5, 127.4 (2), 127.2, 124.7, 123.8, 121.8 (2), 108.7, 108.5, 78.4, 78.2, 54.8, 54.2, 43.9, 43.7, 37.8, 37.6, 36.0 (2), 26.8, 26.7, 17.5, 17.4, 17.2, 17.1; IR (thin film) 2966, 2931, 1708, 1611, 1466, 1364, 1173, 754  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_4(\text{M}+\text{Na})^+$  679.3512, found 679.3492.

Minor  $\text{C}_2$ -symmetric product, **31c**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  7.32–7.23 (m, 10H), 7.12 (d, 2H,  $J = 7.4$  Hz), 7.08 (ddd, 2H,  $J = 7.7, 7.7, 1.2$  Hz), 6.93 (ddd, 2H,  $J = 7.6, 7.6, 0.9$  Hz), 6.64 (d, 2H,  $J = 7.7$  Hz), 4.96 (d, 2H,  $J = 15.7$  Hz), 4.86 (d, 2H,  $J = 15.7$  Hz), 3.36 (m, 2H), 2.23–2.17 (m, 2H), 2.06 (dd, 2H,  $J = 14.3, 8.3$  Hz), 2.01 (dd, 2H,  $J = 14.3, 2.5$  Hz), 0.94 (d, 6H,  $J = 6.9$  Hz), 0.73 (d, 6H,  $J = 6.7$  Hz), 0.72 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.6, 143.3, 136.3, 131.4, 128.6, 127.3 (2), 127.1, 124.6, 121.6, 108.4, 108.2, 78.6, 54.6, 43.6, 37.6, 36.1, 26.6, 17.3 (2); IR (thin film) 2964, 2919, 1708, 1613, 1466, 1368, 1181, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{43}\text{H}_{48}\text{N}_2\text{O}_4(\text{M}+\text{Na})^+$  679.3512, found 679.3492.



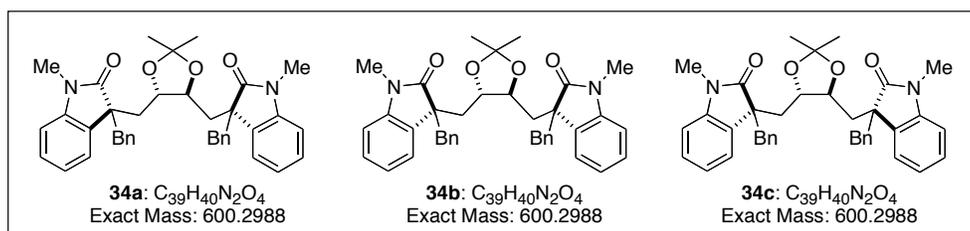
**Major  $\text{C}_2$ -symmetric product 33a.** A solution of **24** (400 mg, 1.37 mmol) and DMPU (0.19 mL) in THF (9.1 mL) was cooled to  $-78$   $^\circ\text{C}$  in a dry ice/*i*-PrOH and was deoxygenated by vigorously sparging with argon for 40 min. A 1 M solution of LHMDS in THF (1.4 mL, 1.4 mmol) was added dropwise. After 40 min, ditriflate **10** (266 mg, 0.623 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (9 mL) and diluted with EtOAc (10 mL). After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\square$  15 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 10–40 EtOAc/hexanes) yielded a residue consisting of a mixture of three diastereomers (389 mg, 88%). Recrystallization from MeOH (10 mL) afforded the major  $\text{C}_2$ -symmetric diastereomer **33a** as a colorless solid (181 mg, 41%):  $[\alpha]_{589}^{27} +22$ ,  $[\alpha]_{577}^{27} +22$ ,  $[\alpha]_{546}^{27} +27$ ,  $[\alpha]_{435}^{27} +60$  ( $c = 0.21$ ,  $\text{CH}_2\text{Cl}_2$ ); mp 130–131  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  7.28–7.21 (m, 10H), 7.12 (t, 4H,  $J = 7.3$  Hz), 7.00 (t, 2H,  $J = 7.4$  Hz), 6.58 (d, 2H,  $J = 8.2$  Hz), 4.95 (d, 2H,  $J = 15.8$  Hz), 4.75 (m, 2H), 4.71 (d, 2H,  $J = 15.9$  Hz), 3.26 (m, 2H), 2.57 (dd, 2H,  $J = 13.7, 8.2$  Hz), 2.39 (dd, 2H,  $J = 13.8, 6.5$  Hz), 2.05 (dd, 2H,  $J = 13.9, 9.3$  Hz), 1.76 (dd, 2H,  $J = 13.9, 1.6$  Hz), 1.55 (s, 6H), 1.49 (s, 6H), 1.05 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.4, 143.5, 136.3, 135.5, 131.1, 128.6, 127.7, 127.2, 127.1, 123.3, 121.8, 117.7, 108.9, 108.6, 77.7, 51.1, 43.8, 39.4, 37.1, 26.9, 25.9, 18.0; IR (thin film) 3058, 3031, 2929, 1715, 1613, 1490, 1368, 751  $\text{cm}^{-1}$ , HRMS (ESI)  $m/z$  calcd for  $\text{C}_{47}\text{H}_{52}\text{N}_2\text{O}_4(\text{M}+\text{H})^+$  709.4005, found 709.4021.



**C<sub>2</sub>- and C<sub>1</sub>-Symmetric products 33b and 33c.** A solution of **24** (200 mg, 0.687 mmol) in THF (4.6 mL) was cooled to 0 °C and deoxygenated by vigorously sparging with argon for 30 min. A 60% dispersion of NaH (27.5 mg, 0.687 mmol) was added to this solution. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) and diluted with EtOAc (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 10–40% EtOAc/hexanes) yielded a residue consisting of a mixture of three diastereomers. A small amount of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5 μm, 250 x 21.2 mm, column temperature 23 °C, 90% MeOH in H<sub>2</sub>O, flow rate 5 mL/min, UV detection at 254 nm, t<sub>r</sub> = 61 min (major C<sub>2</sub>), 76 min (C<sub>1</sub>), 80 min (minor C<sub>2</sub>)) to afford pure analytical samples of the C<sub>1</sub>-symmetric diastereomer **33b** (2 mg) and the minor C<sub>2</sub>-symmetric diastereomer **33c** (< 1 mg).

C<sub>1</sub>-Symmetric product, **33b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31–7.21 (m, 10H), 7.16 (d, 2H, *J* = 7.4 Hz), 7.11 (ddd, 2H, *J* = 7.7, 7.7, 1.1 Hz), 6.99 (t, 1H, *J* = 7.4 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 6.63 (d, 1H, *J* = 7.7 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 5.16 (d, 1H, *J* = 15.9 Hz), 4.91 (d, 1H, *J* = 15.9 Hz), 4.76–4.66 (m, 4H), 3.42 (ddd, 1H, *J* = 7.9, 7.9, 3.3 Hz), 3.24 (m, 1H), 2.64–2.54 (m, 3H), 2.41 (m, 1H), 2.07 (m, 1H), 1.99 (dd, 1H, *J* = 13.9, 8.0 Hz), 1.90 (dd, 1H, *J* = 14.0, 1.9 Hz), 1.84 (dd, 1H, *J* = 14.0, 3.4 Hz), 1.54 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H), 1.47 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 179.7, 179.5, 143.5, 142.7, 136.4, 136.0, 135.5, 135.3, 131.5, 131.0, 128.7, 128.5, 127.6, 127.5, 127.4, 127.1 (3), 124.2, 123.3, 122.1, 121.8, 118.0, 117.7, 108.8, 108.7, 108.6, 78.0 (2), 51.8, 51.2, 43.7, 43.6, 39.3, 39.0, 37.3, 36.9, 26.9, 26.8, 25.8 (2), 18.0 (2); IR (thin film) 3056, 2927, 1713, 1613, 1490, 1380, 1187, 751 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>47</sub>H<sub>52</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 731.3825, found 731.3849.

Minor C<sub>2</sub>-symmetric product, **33c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.30–7.21 (m, 10H), 7.18 (d, 2H, *J* = 7.3 Hz), 7.09 (t, 2H, *J* = 7.7 Hz), 6.96 (t, 2H, *J* = 7.4 Hz), 6.59 (d, 2H, *J* = 7.6 Hz), 5.04 (d, 2H, *J* = 15.6 Hz), 4.67 (m, 2H), 4.60 (d, 2H, *J* = 15.8 Hz), 3.52 (m, 2H), 2.66 (dd, 2H, *J* = 14.2, 6.7 Hz), 2.58 (dd, 2H, *J* = 14.2, 8.5 Hz), 1.99 (dd, 2H, *J* = 14.2, 8.2 Hz), 1.84 (dd, 2H, *J* = 14.2, 2.0 Hz), 1.50 (s, 6H), 1.49 (s, 6H), 1.03 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 179.6, 142.8, 136.1, 135.2, 131.7, 128.6, 127.5, 127.3, 127.1, 124.2, 121.9, 118.1, 108.7 (2), 78.3, 51.6, 43.5, 39.1, 36.8, 27.0, 25.8, 18.1; IR (thin film) 3056, 2927, 1711, 1613, 1466, 1368, 1171, 751 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>47</sub>H<sub>52</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 731.3825, found 731.3819.



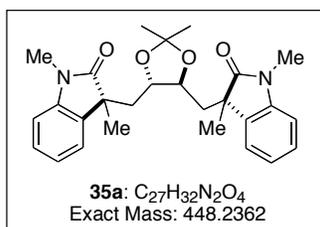
**C<sub>2</sub>- and C<sub>1</sub>-Symmetric products 34a, 34b, and 34c.** A solution of **17** (385 mg, 1.62 mmol) and DMPU (0.22 mL) in THF (10.6 mL) was cooled to  $-78\text{ }^{\circ}\text{C}$  in a dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 30 min. A 1 M solution of LHMDS in THF was added dropwise (1.6 mL, 1.6 mmol). After 30 min, ditriflate **10** (315 mg, 0.738 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (11 mL) and diluted with 16 mL of 1:1 benzene:EtOAc. After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\times$  16 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 30–70% EtOAc/toluene) yielded a residue consisting of a mixture of three diastereomers. A small portion of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23  $^{\circ}\text{C}$ , 75% MeOH in H<sub>2</sub>O, flow rate 16 mL/min, UV detection at 254 nm,  $t_r$  = 36 min (major C<sub>2</sub>), 45 min (C<sub>1</sub>)) to afford pure analytical samples of the major C<sub>2</sub>-symmetric diastereomer **34a** and C<sub>1</sub>-symmetric diastereomer **34b**. The reaction was repeated under less selective conditions,<sup>10</sup> and a small amount of the resulting mixture of diastereomers was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23  $^{\circ}\text{C}$ , 75% MeOH in H<sub>2</sub>O, flow rate 16 mL/min, UV detection at 254 nm,  $t_r$  = 49 min (minor C<sub>2</sub>)) to afford a pure analytical sample of the minor C<sub>2</sub>-symmetric diastereomer **34c**.

Major C<sub>2</sub>-symmetric product, **34a**: [ $\delta$ ]<sup>27</sup><sub>589</sub> +67, [ $\delta$ ]<sup>27</sup><sub>577</sub> +71, [ $\delta$ ]<sup>27</sup><sub>546</sub> +81, [ $\delta$ ]<sup>27</sup><sub>435</sub> +153, [ $\delta$ ]<sup>27</sup><sub>405</sub> +190 ( $c$  = 0.24, CH<sub>2</sub>Cl<sub>2</sub>); mp 183–185  $^{\circ}\text{C}$ ; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.18 (m, 2H), 7.10 (d, 2H,  $J$  = 6.7 Hz), 7.04–6.99 (m, 8H), 6.78 (m, 4H), 6.54 (d, 2H,  $J$  = 7.7 Hz), 3.27 (m, 2H), 3.08 (d, 2H,  $J$  = 12.9 Hz), 2.93 (d, 2H,  $J$  = 12.9 Hz), 2.88 (s, 6H), 2.10 (dd, 2H,  $J$  = 14.0, 9.1 Hz), 1.79 (dd, 2H,  $J$  = 13.9, 1.9 Hz), 1.01 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  178.8, 144.1, 135.6, 130.3, 130.0, 127.9, 127.4, 126.4, 123.8, 121.6, 108.2, 107.6, 77.5, 52.5, 43.9, 39.3, 26.7, 25.9; IR (thin film) 3058, 2917, 1708, 1613, 1495, 1378, 1090, 753 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 623.2886, found 623.2890.

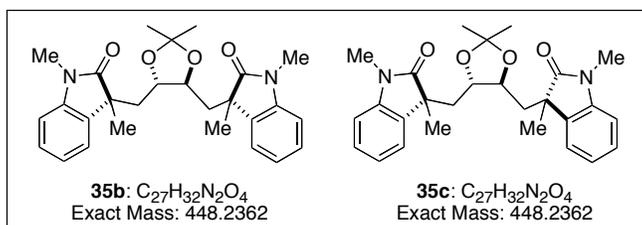
C<sub>1</sub>-Symmetric product, **34b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.23 (m, 1H), 7.19–7.14 (m, 3H), 7.05–6.96 (m, 8H), 6.78 (m, 2H), 6.74 (m, 2H), 6.55 (m, 2H), 3.45 (ddd, 1H,  $J$  = 7.7, 7.7, 4.0 Hz), 3.30 (ddd, 1H,  $J$  = 10.3, 7.8, 2.6), 3.17 (d, 1H,  $J$  = 13.1 Hz), 3.06 (dd, 2H,  $J$  = 15.1, 13.0 Hz), 2.94 (d, 1H,  $J$  = 6.7 Hz), 2.94 (s, 3H), 2.88 (s, 3H), 2.10 (dd, 1H,  $J$  = 14.0, 2.5 Hz), 2.09 (d, 1H,  $J$  = 14.2 Hz), 1.90 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  178.9, 178.8, 144.1, 143.4, 135.6, 135.5, 130.2, 130.1, 129.9, 129.7, 127.8 (2), 127.3, 127.2, 126.3, 124.6, 123.8, 121.9, 121.5, 108.3, 107.6, 107.4, 78.0, 77.7, 53.2, 52.5, 44.3, 43.9, 39.2, 38.6, 26.7 (2), 25.8, 25.7; IR (thin film) 3060, 2933, 1711, 1613, 1495, 1378, 753 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 623.2886, found 623.2899.

Minor C<sub>2</sub>-symmetric product, **34c**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.22 (d, 2H,  $J$  = 7.4 Hz), 7.15 (ddd, 2H,  $J$  = 7.8, 7.8, 1.1 Hz), 7.03–6.94 (m, 8H), 6.74 (m, 4H), 6.51 (d, 2H,  $J$  = 7.8 Hz), 3.61 (m, 2H), 3.20 (d, 2H,  $J$  = 13.1 Hz), 3.07 (d, 2H,  $J$  = 12.9 Hz), 2.86 (s, 6H), 2.07 (dd, 2H,  $J$  = 14.2, 7.7 Hz), 1.92 (dd, 2H,  $J$  = 14.3, 2.6 Hz), 1.13 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  178.9, 143.5, 135.8, 130.5, 129.8, 127.8, 127.3, 126.2, 124.8, 121.8, 108.8, 107.6, 78.3, 53.2, 44.2, 38.6, 27.0, 25.7; IR (thin film) 3058, 2927, 1710, 1613, 1470, 1378, 700 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 623.2886, found 623.2877.

<sup>10</sup> Less selective conditions employed 2.2 equiv NaH, 2.2 equiv oxindole substrate, and 1.0 equiv ditriflate **10**. These reactions were conducted at 23  $^{\circ}\text{C}$ .



**Major C<sub>2</sub>-symmetric product 35a.** A 60% dispersion of NaH (18.8 mg, 0.471 mmol) was added to a solution of **56** (90.0 mg, 0.214 mmol) in DMF (0.5 mL). After 1 h, additional NaH (19.1 mg, 0.469 mmol) and MeI (24.7  $\mu$ L, 0.397 mmol) were added and the reaction was heated for 5 min at 60 °C, then allowed to cool to room temperature. Addition of H<sub>2</sub>O (10 mL) caused a colorless solid to precipitate. The solid was collected and dried. The aqueous filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated, and further dried under high vacuum to afford a solid. The crude solid was combined with the previously filtered colorless solid. Purification of the crude product by silica gel chromatography (eluant 50–90% EtOAc/hexanes) afforded a colorless film (79.6 mg, 83%): [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>589</sub> –5.1, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>577</sub> –4.7, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>546</sub> –3.4, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>435</sub> +18, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>405</sub> +38 (*c* = 0.25, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.27–7.24 (m, 2H), 7.14 (dd, 2H, *J* = 7.3, 0.7 Hz), 7.03 (ddd, 2H, *J* = 7.5, 7.5, 0.9 Hz), 6.79 (d, 2H, *J* = 7.7 Hz), 3.15 (m, 2H), 3.13 (s, 6H), 1.93 (m, 2H), 1.66 (dd, 2H, *J* = 13.3, 2.3 Hz), 1.32 (s, 6H), 1.01 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  180.4, 143.6, 133.2, 127.9, 122.9, 122.0, 108.1, 107.8, 77.5, 46.5, 40.4, 26.7, 26.2, 23.9; IR (thin film) 3056, 2983, 2931, 1713, 1613, 1378, 755 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 471.2260, found 471.2274.

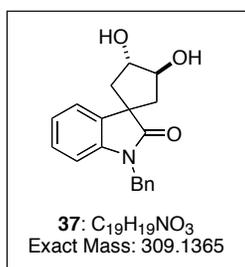


**C<sub>2</sub>- and C<sub>1</sub>-Symmetric products 35b and 35c.** A solution of **26** (261 mg, 1.62 mmol) and DMPU (0.22 mL) in THF (10.7 mL) was cooled to –78 °C in a dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 1 h. A 1 M solution of LHMDS in THF (1.6 mL, 1.6 mmol) was added dropwise. After 40 min, ditriflate **10** (304 mg, 0.714 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (6 mL) and diluted with 7 mL of 1:1 benzene:EtOAc. After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\times$  7 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a residue. Purification of the crude product by silica gel chromatography (eluant 2–16% EtOAc/toluene) yielded a residue consisting of a mixture of three diastereomers (285 mg, 89%). A small amount of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23 °C, 70% MeOH in H<sub>2</sub>O, flow rate 16 mL/min, UV detection at 254 nm, *t*<sub>r</sub> = 17 min (major C<sub>2</sub>), 21 min (C<sub>1</sub>)) to afford pure analytical samples of the major C<sub>2</sub>-symmetric diastereomer **35a** and C<sub>1</sub>-symmetric diastereomer **35b**. The reaction was repeated under less selective conditions,<sup>26</sup> and a small amount of the resulting mixture of diastereomers was purified further by HPLC

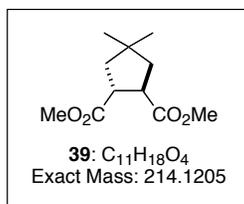
(Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23 °C, 70% MeOH/H<sub>2</sub>O, flow rate 16 mL/min, UV detection at 254 nm,  $t_r$  = 24 min (minor C<sub>2</sub>)) to afford a pure analytical sample of the minor C<sub>2</sub>-symmetric diastereomer **35c**.

C<sub>1</sub>-Symmetric product, **35b**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.27–7.22 (m, 2H), 7.17 (d, 1H,  $J$  = 7.4 Hz), 7.14 (d, 1H,  $J$  = 7.3 Hz), 7.01 (m, 2H), 6.83 (d, 1H,  $J$  = 7.7 Hz), 6.78 (d, 1H,  $J$  = 7.7 Hz), 3.34 (ddd, 1H,  $J$  = 7.9, 7.9, 3.1 Hz), 3.21 (s, 3H), 3.16 (ddd, 1H,  $J$  = 9.9, 7.9, 2.0 Hz), 3.12 (s, 3H), 1.91 (m, 2H), 1.71 (m, 2H), 1.35 (s, 3H), 1.31 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  180.6, 180.5, 143.6, 142.9, 133.3, 133.1, 127.8, 127.7, 123.7, 122.9, 122.4, 122.0, 108.3, 107.9, 107.7, 78.1, 77.7, 47.1, 46.5, 40.4, 39.4, 26.8, 26.7, 26.2, 24.1, 24.0; IR (thin film) 3056, 2983, 2931, 1710, 1613, 1493, 1376, 1121, 753 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 471.2260, found 471.2279.

Minor C<sub>2</sub>-symmetric product, **35c**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (m, 2H), 7.16 (d, 2H,  $J$  = 7.4 Hz), 7.01 (app t, 2H,  $J$  = 7.5 Hz), 6.80 (d, 2H,  $J$  = 7.7 Hz), 3.47 (m, 2H), 3.15 (s, 6H), 1.88 (dd, 2H,  $J$  = 14.0, 8.0 Hz), 1.69 (d, 2H,  $J$  = 14.3, 1.8 Hz), 1.35 (s, 6H), 1.11 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  180.6, 142.9, 133.4, 127.7, 123.8, 122.2, 108.7, 107.9, 78.2, 47.0, 39.2, 27.0, 26.1, 24.0; IR (thin film) 3054, 2981, 2931, 1708, 1613, 1453, 1376, 753 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub> (M+Na)<sup>+</sup> 471.2260, found 471.2274.

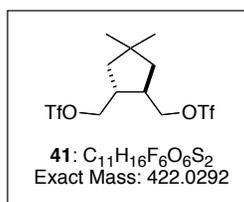


**Oxindole diol 37.** A solution of **23** (400 mg, 1.79 mmol), and DMPU (0.24 mL) in THF (12 mL) was cooled to -78 °C in a dry ice/*i*-PrOH bath and was deoxygenated by vigorously sparging with argon for 40 min. A 1 M solution of LHMDS in THF (1.8 mL, 1.8 mmol) was added dropwise. After 30 min, ditriflate **10** (347 mg, 0.815 mmol) was added as a solid. The reaction flask was covered with aluminum foil and allowed to warm slowly to room temperature overnight. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (9 mL) and diluted with EtOAc (9 mL). After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\times$  9 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a residue. Purification of the crude product by silica gel chromatography (eluant 20% EtOAc/hexanes–100% EtOAc) yielded a colorless residue (133 mg, 53%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.38 (d, 1H,  $J$  = 7.4 Hz), 7.34–7.31 (m, 2H), 7.29–7.27 (m, 3H), 7.16 (m, 1H), 7.08 (m, 1H), 6.75 (d, 1H,  $J$  = 7.8 Hz), 4.92 (J<sub>AB</sub>, 2H,  $J$  = 15.6 Hz), 4.51 (d, 1H,  $J$  = 4.8 Hz), 4.24 (br s, 1H), 2.70 (dd, 1H,  $J$  = 14.8, 5.0 Hz), 2.57 (dd, 1H,  $J$  = 14.3, 4.5 Hz), 2.12 (d, 1H,  $J$  = 14.3 Hz), 1.99 (d, 1H,  $J$  = 14.7 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  184.2, 142.1, 135.5, 135.1, 128.9, 127.8, 127.2, 123.7, 123.5, 109.2, 79.8, 79.7, 53.2, 44.4, 44.1, 43.1; IR (thin film) 3382, 3058, 2937, 1681, 1611, 1455, 1353, 1079, 753 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub> (M+Na)<sup>+</sup> 332.1263, found 332.1267.



**4,4-Dimethylcyclopentane-1,2-dicarboxylic acid dimethyl ester (39).** Following a procedure of Paquette,<sup>11</sup> bromine (2.8 mL, 54.8 mmol) was added dropwise over 1 h with a syringe pump to a solution of 4,4-dimethyl-2-carbomethoxycyclohexanone (8.0 g, 43.5 mmol) in ether cooled to –21 °C in a salt ice bath. The reaction was stirred at –21 °C for 1 h, then poured into an ice bath containing NaHCO<sub>3</sub> (6.9 g). Ether (150 mL) was added, and the layers were separated. The aqueous phase was extracted with ether (1 × 150 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 5–8% EtOAc/hexanes) afforded 6-bromo-4,4-dimethyl-2-carbomethoxycyclohexanone as a pale yellow liquid (8.86 g, 78%).

6-Bromo-4,4-dimethyl-2-carbomethoxycyclohexanone (5.0 g, 19.1 mmol) was added dropwise to a stirring solution of sodium metal (~1.7 g) dissolved in MeOH (39 mL). The reaction was heated at reflux for 13 h, then allowed to cool to room temperature. The reaction mixture was poured into a solution of dilute HCl (100 mL), and the resulting aqueous solution was extracted with Et<sub>2</sub>O (3 × 125 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow biphasic liquid. The crude product was purified by silica gel chromatography (eluant 8–16% EtOAc/hexanes). Product-containing fractions were identified by GC, then combined and concentrated to afford **39** as a clear liquid (1.80 g, 44%). The spectral data was consistent with that previously reported.<sup>12</sup>



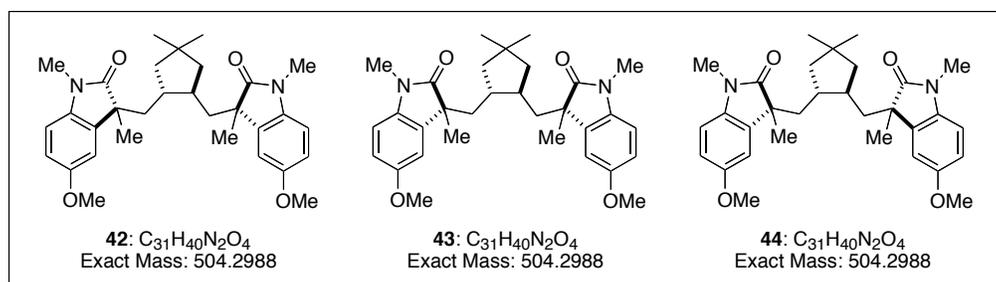
**Trifluoromethanesulfonic acid 4,4-dimethyl-2-trifluoromethanesulfonyloxymethylcyclopentylmethyl ester (41).** A 1 M solution of LiAlH<sub>4</sub> (11.0 mL, 11.0 mmol) was added dropwise to a stirring solution of **39** (1.57 g, 7.33 mmol) cooled to 0 °C. The reaction was allowed to warm to room temperature and stirred overnight, then quenched with H<sub>2</sub>O (1.7 mL), followed by 15% NaOH (1.7 mL), and H<sub>2</sub>O (1.7 mL). A solid precipitated and was filtered. After washing the filter cake with EtOAc (40 mL), the layers in the filtrate were separated. The aqueous phase was extracted with EtOAc (2 × 40 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield a liquid. Purification of the crude product by silica gel chromatography (eluant 50–70% EtOAc/hexanes) afforded (2-hydroxymethyl-4,4-dimethylcyclopentyl)methanol as a clear liquid (1.03 g, 90%).

Trifluoromethanesulfonyl anhydride (1.3 mL, 7.70 mmol) was added to a stirring solution of (2-hydroxymethyl-4,4-dimethylcyclopentyl)methanol (495 mg, 3.13 mmol) and diisopropylethylamine (1.5 mL, 8.40 mmol) in Et<sub>2</sub>O (15.2 mL) cooled to 0 °C. The reaction was

<sup>11</sup> Paquette, L. A.; Farkas, E.; Galemno, R. *J. Org. Chem.* **1981**, *46*, 5434–5436.

<sup>12</sup> Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183–5197.

allowed to stir at 0 °C for 10 min, then allowed to warm to room temperature and stirred for 2 h. The reaction mixture was filtered through Celite, and the filter cake was washed with Et<sub>2</sub>O. The filtrate was concentrated to afford a brown oil. Purification of the crude product by silica gel chromatography (eluant 10–20% ether/petroleum ether) afforded a pale yellow liquid (1.16 g, 88%), which solidifies upon storage at 0 °C: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.55–4.49 (m, 4H), 2.39–2.35 (m, 2H), 1.82 (dd, 2H, *J* = 13.2, 7.8 Hz), 1.41 (dd, 2H, *J* = 13.2, 8.4 Hz), 1.08 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  122.4, 119.9, 117.4, 114.8, 78.8, 43.6, 41.4, 38.1, 29.6; IR (thin film) 2962, 2873, 1410, 1245, 1142, 926, 834 cm<sup>-1</sup>.



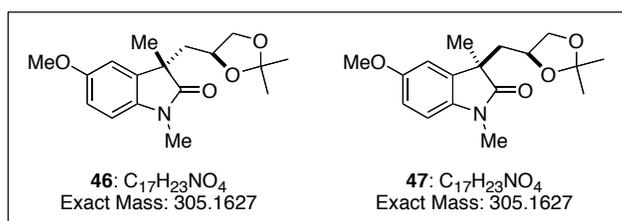
**C<sub>2</sub>- and C<sub>1</sub>-Symmetric products 42, 43, and 44.** A solution of **27** (200 mg, 1.05 mmol) and DMPU (0.14 mL) in THF (6 mL) was cooled to -78 °C in a dry ice/*i*-PrOH and was deoxygenated by vigorously sparging with argon for 35 min. A 1 M solution of LHMDS in THF (1.05 mL, 1.05 mmol) was added dropwise. After 50 min, ditriflate **41** (201 mg, 0.477 mmol) in THF (0.5 mL) was added dropwise. The syringe was rinsed with THF (0.5 mL) into the flask. The reaction flask was covered with aluminum foil and allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (10 mL) and diluted with EtOAc (10 mL). After the layers were separated, the aqueous phase was extracted with EtOAc (2  $\times$  15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 30–80% EtOAc/hexanes) yielded the major C<sub>2</sub>-symmetric diastereomer **42** as a colorless foam (154 mg, 64%) and a mixture of C<sub>1</sub>-symmetric and minor C<sub>2</sub>-symmetric diastereomers **43** and **44** (87 mg, 36%). A small amount of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\mu$ m, 250 x 21.2 mm, column temperature 23 °C, 80% MeOH/H<sub>2</sub>O, flow rate 6 mL/min, UV detection at 254 nm, *t<sub>r</sub>* = 27 min (major C<sub>2</sub>), 32 min (minor C<sub>2</sub>), 34 min (C<sub>1</sub>)) to afford pure analytical samples of the C<sub>1</sub> diastereomer **43** (17 mg) and the minor C<sub>2</sub>-diastereomer **44** (3 mg).

Major C<sub>2</sub>-symmetric product, **42**: mp 153–155 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.80 (dd, 2H, *J* = 8.4, 2.5 Hz), 6.76 (d, 2H, *J* = 2.4 Hz), 6.72 (d, 2H, *J* = 8.4 Hz), 3.84 (s, 6H), 3.13 (s, 6H), 1.81 (dd, 2H, *J* = 13.7, 0.9 Hz), 1.61 (dd, 2H, *J* = 13.7, 9.6 Hz), 1.31 (6H), 0.94 (m, 2H), 0.87 (m, 2H), 0.79 (m, 2H), 0.63 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  180.6, 156.1, 136.8, 135.2, 111.5, 110.4, 108.1, 55.8, 48.4, 46.4, 42.6, 42.4, 37.4, 30.8, 26.3, 25.2; IR (thin film) 3056, 2950, 1700, 1598, 1493, 1289, 1036, 803, 735 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>31</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub> (M+H)<sup>+</sup> 505.3066, found 505.3067.

C<sub>1</sub>-Symmetric product, **43**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.85 (d, 1H, *J* = 2.5 Hz), 6.79 (dd, 1H, *J* = 8.4, 2.5 Hz), 6.76 (dd, 1H, *J* = 8.4, 2.5 Hz), 6.71 (d, 2H, *J* = 8.0 Hz), 6.69 (d, 1H, *J* = 2.7 Hz), 3.84 (s, 3H), 3.76 (s, 3H), 3.19 (s, 3H), 3.13 (s, 3H), 1.99 (dd, 1H, *J* = 13.9, 1.8 Hz), 1.96 (dd, 1H, *J* = 13.7, 1.8 Hz), 1.75 (dd, 1H, *J* = 13.9, 10.4 Hz), 1.33 (m, 4H), 1.29 (s, 3H), 1.03 (m, 1H), 0.99 (m, 1H), 0.87 (dd, 1H, *J* = 12.7, 9.4 Hz), 0.78 (m, 1H), 0.62 (s, 3H), 0.57 (s, 3H),

0.53 (dd, 1H,  $J = 12.9, 7.7$  Hz), 0.37 (dd, 1H,  $J = 12.9, 9.9$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  180.7, 180.1, 156.0, 155.7, 136.9 (2), 135.8, 135.4, 112.2, 111.8, 110.9, 109.9, 108.0, 107.9, 55.9, 48.9, 48.7, 48.1, 46.3, 43.3, 43.1, 42.8, 42.7, 37.8, 30.7, 30.5, 26.2 (2), 25.0, 24.7; IR (thin film) 3056, 2950, 1702, 1493, 1289, 1036, 803, 735  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  505.3066, found 505.3060.

Minor  $C_2$ -symmetric product, **44**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  6.77–6.74 (m, 4H), 6.68 (m, 2H), 3.78 (s, 6H), 3.18 (s, 6H), 2.22 (d, 2H,  $J = 12.9$  Hz), 1.51 (dd, 2H,  $J = 13.8, 10.3$  Hz), 1.33 (s, 6H), 1.13 (m, 2H), 0.53 (s, 6H), 0.50 (dd, 2H,  $J = 13.0, 7.1$  Hz), 0.38 (dd, 2H,  $J = 12.9, 9.6$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  180.2, 155.8, 136.8, 136.4, 111.8, 110.8, 107.9, 55.9, 48.9, 47.4, 43.6, 42.7, 37.3, 30.8, 26.1, 25.0; IR (thin film) 3058, 2948, 1706, 1600, 1495, 1289, 1036, 807  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  505.3066, found 505.3060.

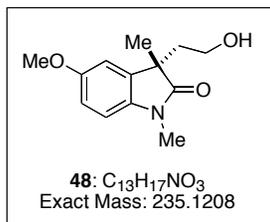


**Major and minor diastereomers 46 and 47.** A solution of **27** (200 mg, 1.05 mmol) and DMPU (0.14 mL) in THF (7 mL) was cooled to  $-78$   $^\circ\text{C}$  in a dry ice/*i*-PrOH and was deoxygenated by vigorously sparging with argon for 30 min. KHMDS (209 mg, 1.05 mmol) was added as a solid. After 75 min, freshly prepared triflate **45** (264 mg, 1.00 mmol) was added dropwise. The reaction flask was covered with aluminum foil and towels. After 3h, the reaction was quenched with 3% AcOH in THF (2 mL) and allowed to warm to room temperature. Saturated aqueous  $\text{NaHCO}_3$  (10 mL) was added to the resulting solution and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\square$  15 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 20–40% EtOAc/toluene) yielded a residue consisting of a mixture of two diastereomers (207 mg, 68%). A small amount of this mixture was purified further by HPLC (Phenomenex, Luna C-18 (2), 5  $\square$  m, 250 x 21.2 mm, column temperature 23  $^\circ\text{C}$ , 60% MeOH in  $\text{H}_2\text{O}$ , flow rate 10 mL/min, UV detection at 254 nm,  $t_r = 24$  min (major), 27 min (minor)) to afford pure analytical samples of the major diastereomer **46** (2.8 mg) and the minor diastereomer **47** (0.8 mg).

Major product, **46**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  6.82 (d, 1H,  $J = 2.5$  Hz), 6.80 (dd, 1H,  $J = 8.4, 2.6$  Hz), 6.74 (d, 1H,  $J = 8.3$  Hz), 3.80 (s, 3H), 3.78 (m, 1H), 3.49 (dd, 1H,  $J = 8.1, 5.7$  Hz), 3.21 (t, 1H,  $J = 8.0$  Hz), 3.17 (s, 3H), 2.34 (dd, 1H,  $J = 13.8, 6.9$  Hz), 1.89 (dd, 1H,  $J = 13.8, 6.2$  Hz), 1.38 (s, 3H), 1.31 (s, 3H), 1.18 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.7, 155.9, 136.9, 134.7, 112.0, 110.7, 108.3 (2), 72.8, 69.7, 55.8, 46.8, 42.0, 26.7, 26.3, 25.8, 24.1; IR (thin film) 2927, 1706, 1600, 1495, 1370, 1291, 1214, 1052, 803  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_4$  ( $\text{M}^+$ ) 305.1627, found 305.1627.

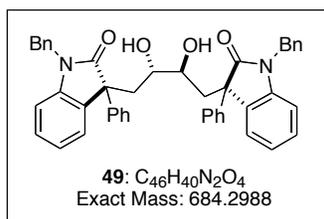
Minor product, **47**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\square$  6.86 (d, 1H,  $J = 2.5$  Hz), 6.80 (dd, 1H,  $J = 8.4, 2.5$  Hz), 6.75 (d, 1H,  $J = 8.4$  Hz), 3.81 (s, 3H), 3.70 (dd, 1H,  $J = 7.9, 5.6$  Hz), 3.64 (m, 1H), 3.46 (t, 1H,  $J = 7.9$  Hz), 3.19 (s, 3H), 2.24 (dd, 1H,  $J = 13.8, 4.9$  Hz), 2.10 (dd, 1H,  $J = 13.9, 7.9$  Hz), 1.39 (s, 3H), 1.30 (s, 3H), 1.21 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\square$  179.8, 156.2, 136.4, 134.5, 112.1, 110.7, 108.4, 108.2, 72.9, 69.5, 55.8, 47.1, 41.3, 26.7, 26.3, 25.9,

24.8; IR (thin film) 2933, 1706, 1600, 1497, 1370, 1291, 1219, 1059, 857, 807  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{23}\text{NO}_4$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 328.1525, found 328.1522.



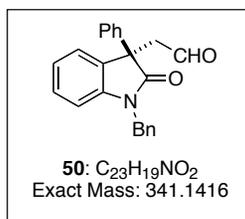
**(S)-3-(2-Hydroxyethyl)-5-methoxy-1,3-dimethyl-1,3-dihydroindol-2-one (48).**

Sodium borohydride (3.6 mg, 0.094 mmol) was added to a solution of **8** (10 mg, 0.043 mmol) in EtOH (1.6 mL) at room temperature. After 12 h, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (4 mL) and  $\text{H}_2\text{O}$  (3 mL). The aqueous solution was diluted with EtOAc (10 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\times$  10 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a residue. Purification of the crude product by silica gel chromatography (eluant 70% EtOAc/hexanes–100%EtOAc) afforded a colorless residue (9.2 mg, 91%): HPLC (Daicel Chiracel OD–H column, column temperature 23  $^\circ\text{C}$ , 90% *n*-hexane/isopropanol, flow rate 0.8 mL/min, 18.2 min (minor enantiomer), 20.3 min (major enantiomer). The spectral data was consistent with that previously reported.<sup>13</sup>

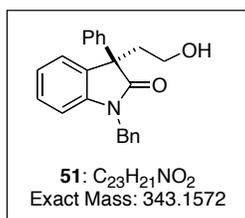


**Major  $\text{C}_2$ -symmetric diol 49.** *p*-Toluenesulfonic acid monohydrate (20.1 mg, 0.106 mmol) and  $\text{H}_2\text{O}$  (0.04 mL) were added to a solution of **29a** (20 mg, 0.0276 mmol) in MeOH (0.66 mL). The reaction was heated at 79  $^\circ\text{C}$  for 4.5 h, then allowed to cool to room temperature. Evaporation of the solvent afforded a thin film, which was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) and extracted with saturated aqueous  $\text{NaHCO}_3$  (5 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  5 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield a solid. Purification of the crude product by silica gel chromatography (eluant 25–80% EtOAc/hexanes) afforded a colorless film (17.3 mg, 92%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (m, 4H), 7.28–7.18 (m, 18H), 7.15 (d, 2H,  $J = 6.9$  Hz), 7.05 (t, 2H,  $J = 7.5$  Hz), 6.75 (d, 2H,  $J = 7.8$  Hz), 4.91 (d, 2H,  $J = 15.7$  Hz), 4.82 (d, 2H,  $J = 15.7$  Hz), 3.17 (d, 2H,  $J = 9.5$  Hz), 2.83 (dd, 2H,  $J = 14.2, 10.4$  Hz), 2.25 (dd, 2H,  $J = 14.1, 1.7$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  179.4, 143.4, 140.9, 135.9, 131.1, 128.7, 128.6, 128.3, 127.5, 127.3, 126.7, 124.9, 122.5, 109.7, 72.1, 54.7, 44.2, 41.1; IR (thin film) 3482, 3061, 1695, 1610, 1351, 733  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{46}\text{H}_{40}\text{N}_2\text{O}_4$  ( $\text{M}+\text{Na}$ )<sup>+</sup> 707.2886, found 707.2881.

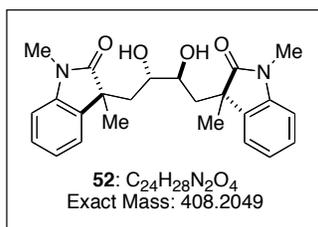
<sup>13</sup> Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500–6503.



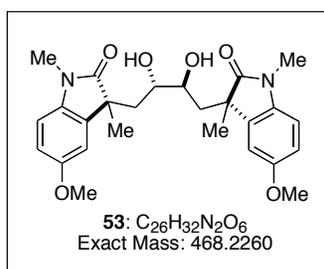
**(R)-1-Benzyl-2-oxo-3-phenyl-2,3-dihydro-1H-indol-3-yl)-acetaldehyde (50).** A mixture of **49** (15.9 mg, 0.0232 mmol) and NaIO<sub>4</sub> (74.1 mg, 0.346 mmol) in THF (0.25 mL) and H<sub>2</sub>O (0.13 mL) was stirred at room temperature overnight. The reaction mixture was diluted with H<sub>2</sub>O (2 mL) and the aqueous solution was extracted with EtOAc (2 × 2 mL), then CH<sub>2</sub>Cl<sub>2</sub> (1 × 2 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 25–80% EtOAc/hexanes) afforded a colorless film (12.3 mg, 78%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.53 (br s, 1H), 7.31–7.17 (m, 12H), 7.03 (t, 1H, *J* = 7.4 Hz), 6.77 (d, 1H, *J* = 7.8 Hz), 4.95 (d, 1H, *J* = 15.7 Hz), 4.89 (d, 1H, *J* = 15.7 Hz), 3.50 (dd, 1H, *J* = 17.4, 1.0 Hz), 3.42 (dd, 1H, *J* = 17.4, 1.9 Hz); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  198.4, 177.7, 143.0, 138.8, 135.7, 131.1, 128.9, 128.8, 128.7, 127.8, 127.6, 127.2, 126.5, 124.5, 122.9, 109.8, 52.6, 50.5, 44.2; IR (thin film) 3089, 3060, 2925, 2833, 2734, 1711, 1611, 1488, 1358, 751, 697 cm<sup>-1</sup>; HRMS (CI/NH<sub>3</sub>) *m/z* calcd for C<sub>23</sub>H<sub>19</sub>NO<sub>2</sub> (M<sup>+</sup>) 341.1416, found 341.1419.



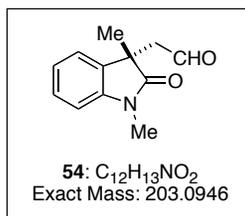
**(R)-1-Benzyl-3-(2-hydroxyethyl)-3-phenyl-1,3-dihydroindol-2-one (51).** Sodium borohydride (3.0 mg, 0.079 mmol) was added to a solution of **50** (12.3 mg, 0.036 mmol) in EtOH (2 mL) at room temperature. After 5.5 h, the reaction was quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) and H<sub>2</sub>O (2 mL). The aqueous solution was diluted with EtOAc (10 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 25–50% EtOAc/hexanes) afforded a colorless solid (12.3 mg, 100%): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.39–7.37 (m, 2H), 7.34–7.24 (m, 9H), 7.21 (ddd, 1H, *J* = 7.8, 7.8, 1.3 Hz), 7.08 (ddd, 1H, *J* = 7.6, 7.6, 1.0 Hz), 4.94 (m, 2H), 3.61–3.50 (m, 2H), 2.85 (m, 1H), 2.46 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  179.2, 142.7, 140.0, 135.8, 131.9, 128.8, 128.7, 128.3, 127.6, 127.4, 127.3, 126.7, 124.7, 122.8, 109.6, 59.5, 55.0, 44.1, 40.0; IR (thin film) 3423, 3058, 2927, 1702, 1611, 1488, 1349, 1169, 1030, 697 cm<sup>-1</sup>; HRMS (CI/NH<sub>3</sub>) *m/z* calcd for C<sub>23</sub>H<sub>21</sub>NO<sub>2</sub> (M<sup>+</sup>) 343.1572, found 343.1573.



**Major C<sub>2</sub>-symmetric diol 52.** *p*-Toluenesulfonic acid monohydrate (116 mg, 0.6.9 mmol) and H<sub>2</sub>O (0.23 mL) were added to a solution of **35a** (71.3 mg, 0.159 mmol) in MeOH (1.9 mL). The reaction was heated at reflux for 7.5 h, then allowed to cool to room temperature. The reaction was quenched with saturated aqueous NaHCO<sub>3</sub> (5 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield a colorless foam. Purification of the crude product by silica gel chromatography (eluant 100% EtOAc, 2–12% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded a colorless solid (49 mg, 72%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.25 (ddd, 2H, *J* = 8.8, 7.7, 1.2 Hz), 7.09 (dd, 2H, *J* = 1.0 Hz), 7.03 (t, 2H, *J* = 7.4 Hz), 6.82 (d, 2H, *J* = 7.8 Hz), 3.15 (s, 6H), 2.89 (d, 2H, *J* = 9.8 Hz), 2.63 (br s, 2H), 2.24 (dd, 2H, *J* = 14.1, 11.1 Hz), 1.77 (d, 2H, *J* = 14.3 Hz), 1.29 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 181.6, 143.4, 133.3, 127.8, 122.5, 122.3, 108.2, 72.0, 46.5, 41.4, 26.3, 25.2; IR (thin film) 3450, 3054, 2927, 1690, 1611, 1493, 1380, 1125, 755 cm<sup>-1</sup>; HRMS (CI/NH<sub>3</sub>) *m/z* calcd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup>) 408.2049, found 408.2047.

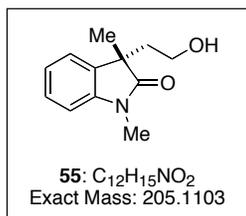


**Major C<sub>2</sub>-symmetric diol 53.** *p*-Toluenesulfonic acid monohydrate (2.9 g, 15.1 mmol) and H<sub>2</sub>O (5.7 mL) were added to a solution of **36a** (2.00 g, 3.93 mmol) in MeOH (46 mL). The reaction was heated at 79 °C overnight, then allowed to cool to room temperature. The solvent was evaporated to afford a solid, which was dissolved in EtOAc (30 mL) and partitioned with saturated aqueous NaHCO<sub>3</sub> (2 × 30 mL). After the aqueous layers were combined and extracted with EtOAc (6 × 60 mL), the organic layers were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a colorless solid. The solid was recrystallized from hot EtOH (19 mL / 2 g) to afford colorless crystals (1.66 g, 90%): mp 228–229 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.78 (dd, 2H, *J* = 8.5, 2.4 Hz), 6.72 (m, 4H), 3.79 (s, 6H), 3.15 (s, 6H), 2.94 (d, 2H, *J* = 10.7 Hz), 2.18 (dd, 2H, *J* = 14.0, 10.3 Hz), 1.77 (dd, 2H, *J* = 14.6, 1.2 Hz), 1.31 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 181.2, 155.9, 137.0, 134.8, 111.6, 110.4, 108.4, 72.0, 55.8, 47.0, 41.4, 26.4, 25.3; IR (thin film) 3458, 3056, 2929, 1690, 1600, 1495, 1291, 1036, 697 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub> (M+Na)<sup>+</sup> 491.2158, found 491.2166.

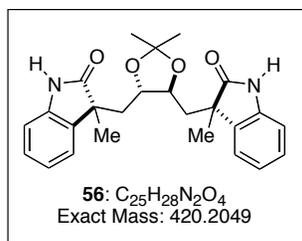


**(S)-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetaldehyde (54).** A mixture of **52** (48.3 mg, 0.118 mmol) and NaIO<sub>4</sub> (377 mg, 1.76 mmol) in THF (1.3 mL) and H<sub>2</sub>O (0.66 mL) was stirred at room temperature overnight. The reaction was diluted with H<sub>2</sub>O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant

50–90% EtOAc/hexanes) afforded a colorless film (41.4 mg, 86%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.51 (br s, 1H), 7.28 (ddd, 1H,  $J = 7.7, 7.7, 1.3$  Hz), 7.18 (ddd, 1H,  $J = 7.4, 1.3, 0.6$  Hz), 7.05 (ddd, 1H,  $J = 7.6, 7.6, 1.0$  Hz), 6.88 (d, 1H,  $J = 7.8$  Hz), 3.26 (s, 3H), 3.02–2.92 (m, 2H), 1.41 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  198.7, 179.5, 143.1, 132.7, 128.3, 122.7, 122.4, 108.4, 50.5, 44.9, 26.4, 23.9; IR (thin film) 3056, 2929, 1711, 1613, 1472, 1380, 1127, 756  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{NO}_2$  ( $\text{M}+\text{Na}$ ) $^+$  226.0844, found 226.0853.

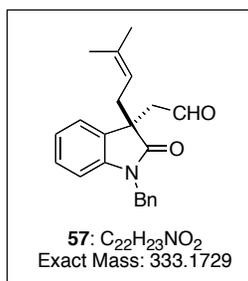


**(S)-3-(2-Hydroxyethyl)-1,3-dimethyl-1,3-dihydroindol-2-one (55).** Sodium borohydride (5.00 mg, 0.132 mmol) was added to a solution of **54** (12.2 mg, 0.0601 mmol) in EtOH (2 mL). After 1 h, the reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The aqueous solution was diluted with EtOAc (10 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\times$  10 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 25–50% EtOAc/hexanes) yielded a colorless film (10 mg, 81%):  $[\alpha]_D^{27}$   $-17$ ,  $[\alpha]_D^{28}$   $-17$ ,  $[\alpha]_D^{28}$   $-19$ ,  $[\alpha]_D^{28}$   $-37$  ( $c$  0.2,  $\text{CHCl}_3$ ); %:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28 (ddd, 1H,  $J = 7.7, 7.7, 1.3$  Hz), 7.18–7.16 (m, 1H), 7.08 (ddd, 1H,  $J = 7.6, 7.6, 1.0$  Hz), 6.86 (d, 1H,  $J = 7.8$  Hz), 3.66 (ddd, 1H,  $J = 12.3, 7.0, 5.3$  Hz), 3.46 (m, 1H), 3.22 (s, 3H), 2.15 (ddd, 1H,  $J = 14.3, 6.6, 5.3$  Hz), 1.98 (ddd, 1H,  $J = 14.3, 7.0, 5.5$  Hz), 1.41 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  181.5, 142.9, 134.1, 128.0, 122.8, 122.4, 108.3, 59.4, 47.0, 40.1, 26.3, 23.5; IR (thin film) 3417, 3056, 2927, 1692, 1613, 1470, 1380, 1042, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{15}\text{NO}_2$  ( $\text{M}+\text{Na}$ ) $^+$  228.1001, found 228.1111.

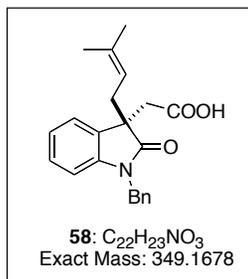


**$\text{C}_2$ -Symmetric product 56.** A 2-necked roundbottom flask fitted with a liquid  $\text{NH}_3$  condenser was charged with Na metal (86 mg) under a positive flow of  $\text{N}_2$ . The reaction flask and condenser were cooled to  $-78$   $^\circ\text{C}$ . A separate 3-necked roundbottom flask attached to a bubbler was cooled to  $-78$   $^\circ\text{C}$  and  $\text{NH}_3$  (25 mL) was condensed directly from the tank into this flask. The  $\text{NH}_3$  was redistilled from the 3-necked roundbottom flask into the reaction vessel through a cannula to create a dark blue solution. A solution of **32a** (200 mg, 0.333 mmol) in THF (2.4 mL, 0.14 M) was added via syringe to the dark blue solution. After 10 min, MeOH (10 mL) was added dropwise to the reaction and the solution became clear. The solution was allowed to warm slowly to room temperature by replacing the dry ice/acetone bath with a water bath. The  $\text{NH}_3$  condenser was removed, thus allowing evaporation of  $\text{NH}_3$ . After the evolution of gas ceased, the solution was partitioned between EtOAc (10 mL) and saturated aqueous

$\text{NH}_4\text{Cl}$  (20 mL). The layers were separated, and the aqueous layer was extracted with  $\text{CHCl}_3$  (saturated with  $\text{NH}_3$ , 3  $\times$  20 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 50–100% EtOAc/hexanes) afforded a colorless film (101 mg, 72%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (br s, 2H), 7.19 (ddd, 2H,  $J = 7.7, 7.7, 1.3$  Hz), 7.15 (m, 2H), 7.03 (ddd, 2H,  $J = 7.5, 7.5, 1.0$  Hz), 6.84 (d, 2H,  $J = 7.6$  Hz), 3.32 (m, 2H), 1.99 (dd, 2H,  $J = 14.2, 9.2$  Hz), 1.72 (dd, 2H,  $J = 14.2, 2.1$  Hz), 1.35 (s, 6H), 1.08 (s, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  183.3, 140.7, 133.7, 127.8, 123.2, 122.0, 109.9, 108.6, 77.6, 47.1, 40.1, 26.8, 24.4; IR (thin film) 3211, 3093, 2929, 1706, 1621, 1472, 1225, 754  $\text{cm}^{-1}$ ; HRMS (CI/ $\text{NH}_3$ )  $m/z$  calcd for  $\text{C}_{25}\text{H}_{38}\text{N}_2\text{O}_4$  ( $\text{M}^+$ ) 420.2049, found 420.2045.

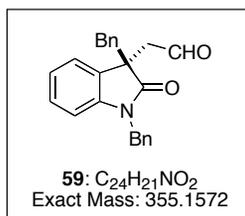


**(S)-[1-Benzyl-3-(3-methyl-but-2-enyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-acetaldehyde (57).** A suspension of diol ah026 (69.1 mg, 0.103 mmol) and  $\text{NaIO}_4$  (329 mg, 1.54 mmol) in THF (1.1 mL) and  $\text{H}_2\text{O}$  (0.58 mL) was stirred at room temperature overnight. The reaction was diluted with  $\text{H}_2\text{O}$  (2 mL) and the resulting solution was extracted with EtOAc (3  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 40% EtOAc/hexanes) afforded a colorless liquid (53.3 mg, 78%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.45 (s, 1H), 7.27–7.23 (m, 4H), 7.19 (m, 1H), 7.12 (dd, 1H,  $J = 7.4, 0.7$  Hz), 7.08 (ddd, 1H,  $J = 7.7, 7.7, 1.1$  Hz), 6.93 (ddd, 1H,  $J = 7.4, 7.4, 0.7$  Hz), 6.64 (d, 1H,  $J = 7.8$  Hz), 5.08 (d, 1H,  $J = 15.8$  Hz), 4.79 (m, 1H), 4.72 (d, 1H,  $J = 15.8$  Hz), 3.00 (m, 2H), 2.52 (m, 2H), 1.53 (s, 3H), 1.46 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  198.6, 178.8, 142.9, 136.4, 135.8, 130.8, 128.6, 128.1, 127.4, 127.1, 122.8, 122.3, 116.8, 109.1, 49.6, 49.1, 43.8, 36.4, 25.8, 18.0; IR (thin film) 3058, 2916, 1710, 1611, 1466, 1355, 1171, 753  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{22}\text{H}_{23}\text{NO}_2$  ( $\text{M}+\text{Na}$ ) $^+$  356.1627, found 356.1636.



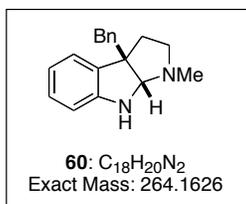
**(S)-[1-Benzyl-3-(3-methyl-but-2-enyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-acetic acid (58).** A solution of sodium chlorite (7.4 mg, 0.082 mmol) and potassium phosphate monobasic (12.2 mg, 0.090 mmol) in  $\text{H}_2\text{O}$  (0.20 mL) was added to a stirring solution of **57** (24.9 mg, 0.075 mmol) in *tert*-butanol (1.2 mL) and 2-methyl-2-butene (0.30 mL) at room temperature. After 1 h, additional sodium chlorite (3.7 mg, 0.041 mmol) and potassium phosphate monobasic (6.1

mg, 0.045 mmol) were added and the reaction was stirred for 1 h, then diluted with EtOAc (15 mL) and H<sub>2</sub>O (6 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a residue. Purification of the crude product by silica gel chromatography (eluant 60–80% EtOAc/hexanes) afforded a colorless residue (11.4 mg, 44%). The spectral data was consistent with that previously reported.<sup>6</sup>



**(S)-(1,3-Dibenzyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetaldehyde (59).** *p*-Toluenesulfonic acid monohydrate (15 g, 78.9 mmol) was added to a suspension of **28a** (15.5 g, 20.6 mmol) in a solution of benzene (80 mL), MeOH (120 mL) and H<sub>2</sub>O (15 mL). The mixture was refluxed in a 500 mL roundbottom flask fitted with a distillation head. After 100 mL of distillate was collected, additional benzene (40 mL) and MeOH (80 mL) were added. After an additional 100 mL of distillate was collected (6 h total) the mixture was cooled to room temperature and combined with benzene (250 mL) and EtOAc (250 mL) and the organic phase was washed with NaHCO<sub>3</sub> (3 × 150 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford a solid. Sequential recrystallizations of the crude product from hot ethanol yielded the major C<sub>2</sub>-symmetric diol as a colorless solid (2 crops, 11.5 g total, 85%): [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>589</sub> +4, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>577</sub> +3, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>546</sub> +4, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>435</sub> +8, [ $\alpha$ ]<sub>D</sub><sup>27</sup><sub>405</sub> +12 (*c* = 0.6, benzene); mp 107–109 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.20–7.14 (m, 10H), 7.09–7.02 (m, 8H), 6.82 (d, 4H, *J* = 7.2 Hz), 6.71 (d, 4H, *J* = 7.5 Hz), 6.38 (d, 2H, *J* = 8.0 Hz), 4.84 (d, 2H, *J* = 16.1 Hz), 4.49 (d, 2H, *J* = 16.1 Hz), 3.20 (d, 2H, *J* = 12.8 Hz), 3.07 (d, 2H, *J* = 12.8 Hz), 2.65 (d, 2H, *J* = 6.6 Hz), 2.51–2.47 (m, 2H), 2.05 (d, 2H, *J* = 14.2 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  180.2, 143.7, 135.8, 135.7, 130.7, 130.5, 128.7, 128.2, 128.0, 127.3, 127.0, 126.8, 123.6, 122.3, 109.6, 72.2, 58.6, 53.1, 45.3, 44.0, 41.3, 18.7; IR (film) 3444, 1693, 1612, 1467 cm<sup>-1</sup>; LRMS (ESI) *m/z* calcd for C<sub>48</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na)<sup>+</sup>: 735.3, found: 735.3; Anal. Calcd for C<sub>48</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>: C, 80.87; H, 6.22; N, 3.93. Found: C, 80.35; H, 6.29; N, 3.93.

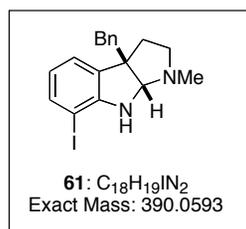
A mixture of the major C<sub>2</sub>-symmetric diol (16.9 g, 24.1 mmol) and NaIO<sub>4</sub> (77 g, 360 mmol) in THF (260 mL) and H<sub>2</sub>O (130 mL) was stirred at room temperature for 18 h. The mixture was combined with EtOAc (500 mL) and H<sub>2</sub>O (500 mL). The layers were separated and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 200 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford a clear viscous oil (16.9 g, 100%) that was used without further purification: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.54 (br s, 1H), 7.23–7.21 (m, 1H), 7.19–7.16 (m, 4H), 7.10–7.06 (m, 3H), 7.03 (ddd, 1H, *J* = 7.4, 7.4, 1.1 Hz), 6.86–6.84 (m, 2H), 6.80–6.78 (m, 2H), 6.43 (d, 1H, *J* = 7.3 Hz), 4.90 (d, 1H, *J* = 16.0 Hz), 4.62 (d, 1H, *J* = 16.0 Hz), 3.25–3.13 (m, 4H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  198.2, 178.0, 143.1, 135.3, 134.6, 130.2, 129.9, 128.5, 128.4, 127.9, 127.1, 126.9, 126.7, 123.2, 122.3, 109.4, 50.6, 50.3, 43.7, 43.6; IR (thin film) 3087, 3060, 2919, 1708, 1613, 1490, 1366, 1173, 753 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>21</sub>NO<sub>2</sub> (M+Na)<sup>+</sup> 378.1470, found 378.1462.



**(3a*S*,8a*S*)-3a-Benzyl-1-methyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole (60).**

Triethylamine (42.2 mL, 300 mmol) was added to a stirring mixture of **59** (10.7 g, 30.2 mmol), methylamine hydrochloride (20.4 g, 300 mmol), and MgSO<sub>4</sub> (20.2 g) in THF (400 mL) at room temperature. After 48 h, LiAlH<sub>4</sub> (11.4 g, 300 mmol) was added in four portions (caution: exotherm with rapid gas evolution occurs). After the addition was complete, the mixture was heated to reflux for 1.5 h, then cooled to 0 °C. Excess hydride was decomposed by the dropwise addition of EtOAc (125 mL) followed by isopropyl alcohol (125 mL). The mixture was filtered and the filter cake was washed with EtOAc (3 × 50 mL). The filtrate was combined with saturated aqueous NaHCO<sub>3</sub> (300 mL) and the layers were separated. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (2 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow oil. Purification of **68** by silica gel chromatography (eluant 75:25:2 hexanes: EtOAc: Et<sub>3</sub>N) yielded a clear oil (6.15 g, 58%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26–7.20 (m, 6H), 7.06–7.00 (m, 4H), 6.96–6.93 (m, 2H), 6.72 (t, 1H, *J* = 6.5 Hz), 6.22 (d, 1H, *J* = 7.8 Hz), 4.38 (s, 1H), 4.28 (d, 1H, *J* = 16.5 Hz), 4.19 (d, 1H, *J* = 16.5 Hz), 3.44 (d, 1H, *J* = 13.4 Hz), 2.94 (d, 1H, *J* = 13.4 Hz), 2.78–2.72 (m, 1H), 2.69–2.63 (m, 1H), 2.33–2.27 (m, 1H), 2.22 (s, 3H), 2.15–2.09 (m, 1H).

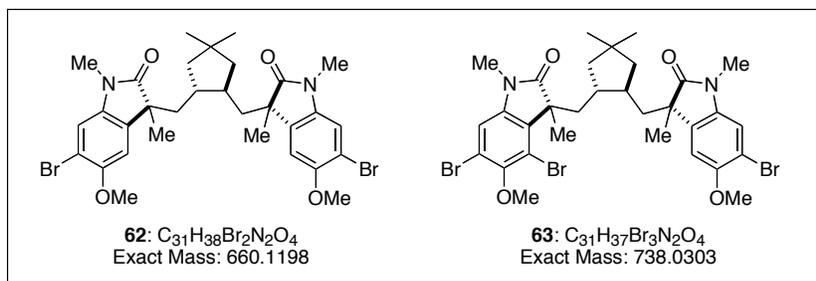
A solution of **68** (1.23 g, 3.47 mmol) in THF (5 mL) was added dropwise to a blue solution of Na (320 mg, 13.9 mmol) and NH<sub>3</sub> (100 mL) at –78 °C. After 15 min, a solution of diphenyl ether (2.9 g) in THF (5 mL) was added resulting in a light yellow solution that was subsequently treated with IPA (10 mL) resulting in a clear solution. After warming to room temperature, the solution was concentrated and combined with CHCl<sub>3</sub> saturated with NH<sub>3</sub> (100 mL) and NaHCO<sub>3</sub> (100 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to yield a residue. Purification of the crude product by silica gel chromatography (eluant 100% EtOAc–50% CHCl<sub>3</sub>:IPA) afforded a colorless solid **60** (790 mg, 86%). A small amount of this solid was recrystallized from hexanes/EtOAc to yield a pure analytical sample: [α]<sub>D</sub><sup>27</sup><sub>405</sub> –288, [α]<sub>D</sub><sup>27</sup><sub>435</sub> –207, [α]<sub>D</sub><sup>27</sup><sub>546</sub> –95, [α]<sub>D</sub><sup>27</sup><sub>577</sub> –81, [α]<sub>D</sub><sup>27</sup><sub>589</sub> –77 (*c* = 1.0, CHCl<sub>3</sub>); mp = 77–78 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.22–7.19 (m, 3H), 7.06–6.98 (m, 3H), 6.77 (t, 1H, *J* = 7.4 Hz), 6.54 (d, 1H, *J* = 7.8 Hz), 4.47 (s, 1H), 3.99 (br s, 1H), 3.24 (d, 1H, *J* = 13.5 Hz), 2.96 (d, 1H, *J* = 13.5 Hz), 2.76–2.62 (m, 2H), 2.42 (s, 3H), 2.31–2.26 (m, 1H), 2.11–2.07 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.6, 138.6, 135.0, 130.5, 128.1, 128.0, 126.5, 124.2, 118.9, 109.6, 86.4, 58.9, 52.6, 45.8, 39.7, 37.4; IR (thin film) 3158, 2924, 1607, 1487, 1246 cm<sup>-1</sup>; LRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>21</sub>N<sub>2</sub> (M+H)<sup>+</sup> 265.1, found: 265.1; Anal. Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>2</sub>: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.56; H, 7.68; N, 10.61.



**(3a*S*,8a*S*)-3a-Benzyl-7-iodo-1-methyl-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole (61).** A 1 M solution of NaHMDS in THF (7.50 mL, 7.52 mmol) was added dropwise to a stirring solution of **60** (705 mg, 2.64 mmol) in THF (25 mL) cooled to  $-78\text{ }^{\circ}\text{C}$ . After 15 min, a solution of  $\text{Boc}_2\text{O}$  (820 mg, 3.76 mmol) and THF (3 mL) was added. The reaction was removed from the cooling bath and allowed to warm to room temperature. After 15 min at room temperature, the reaction was quenched with saturated aqueous  $\text{NaHCO}_3$  (5 mL). The resulting solution was combined with EtOAc (150 mL) and  $\text{NaHCO}_3$  (100 mL). The organic phase was separated, washed with saturated aqueous  $\text{NaHCO}_3$  (2  $\times$  50 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield a yellow oil. Purification of the crude product by silica gel chromatography (30–50% EtOAc: petroleum ether) afforded the N-Boc-pyrrolidinoindoline (772 mg, 79%) as a clear oil: LRMS (ESI)  $m/z$  calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_2\text{O}_2$  ( $\text{M}+\text{H}$ ) $^+$  364.2, found: 364.2.

A 1.1 M solution of *sec*-BuLi in cyclohexane (filtered prior to use, 3.60 mL, 3.95 mmol) was added dropwise to a stirring solution of N-Boc-pyrrolidinoindoline (575 mg, 1.58 mmol) and TMEDA (714  $\mu\text{L}$ , 4.74 mmol) in  $\text{Et}_2\text{O}$  (16 mL) cooled to  $-78\text{ }^{\circ}\text{C}$ . After 30 min, a solution of diiodoethane (2.22 g, 7.90 mmol) and  $\text{Et}_2\text{O}$  (7.9 mL) was added in one portion, then submerged in a  $0\text{ }^{\circ}\text{C}$  bath and stirred vigorously for 30 min. The reaction mixture was diluted with EtOAc (100 mL), saturated aqueous  $\text{NaHCO}_3$  (50 mL), and saturated aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (50 mL). The organic phase was separated, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Purification of the crude product by silica gel chromatography (40% EtOAc: petroleum ether) afforded a clear oil (685 mg, 89%):  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d, 1H,  $J = 7.9$  Hz), 7.22–7.18 (m, 3H), 7.03–7.00 (m, 3H), 6.83 (t, 1H,  $J = 7.6$  Hz), 4.99 (s, 1H), 3.20 (d, 1H,  $J = 13.5$  Hz), 2.96 (d, 1H,  $J = 13.5$  Hz), 2.60–2.45 (m, 5H), 2.41 (s, 3H), 2.28–2.22 (m, 1H), 2.03–1.97 (m, 1H), 1.50 (s, 1H).

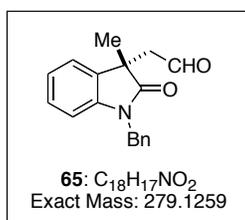
TMSOTf (400  $\mu\text{L}$ ) was added to a solution of N-Boc-iodo-pyrrolidinoindoline (860 mg, 1.75 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL). After consumption of the starting material by TLC, the reaction was quenched with MeOH (5 mL) and concentrated. Purification of the crude product by silica gel chromatography (3–10% MeOH in  $\text{CH}_2\text{Cl}_2$  + 0.5%  $\text{NH}_4\text{OH}$ ) afforded a colorless solid (690 mg, 97%). X-ray quality crystals were obtained by vapor diffusion with  $\text{Et}_2\text{O}$ :pentane:  $[\alpha]_{405}^{27} -310$ ,  $[\alpha]_{435}^{27} -224$ ,  $[\alpha]_{546}^{27} -103$ ,  $[\alpha]_{577}^{27} -89$ ,  $[\alpha]_{589}^{27} -88$  ( $c = 0.7$ ,  $\text{CHCl}_3$ ); mp =  $108\text{--}110\text{ }^{\circ}\text{C}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.35 (d, 1H,  $J = 7.8$  Hz), 7.21–7.20 (m, 3H), 7.02–7.00 (m, 2H), 6.82 (d, 1H,  $J = 7.2$  Hz), 6.45 (t, 1H,  $J = 7.6$  Hz), 4.50 (s, 1H), 4.20 (s, 1H), 3.15 (d, 1H,  $J = 13.5$  Hz), 2.93 (d, 1H,  $J = 13.5$  Hz), 2.61–2.59 (m, 2H), 2.41 (s, 3H), 2.30–2.25 (m, 1H), 2.02–1.97 (m, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  152.0, 138.1, 136.3, 134.8, 13.0.5, 128.2, 126.7, 124.1, 120.2, 85.2, 75.0, 60.8, 52.5, 45.6, 39.6, 37.2; IR (thin film) 3398, 2928, 1599, 1464  $\text{cm}^{-1}$ ; LRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{20}\text{IN}_2$  ( $\text{M}+\text{H}$ ) $^+$  391.1, found: 391.1; Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{IN}_2$ : C, 55.40; H, 4.91; N, 7.18. Found: C, 55.36; H, 4.95; N, 7.06.



**Major and minor products 62 and 63.** A solution of bromine (19.7  $\mu$ L, 0.384 mmol) in acetic acid (0.58 mL) was added to a stirring solution of **42** (58.7 mg, 0.116 mmol) in acetic acid (1.4 mL). After 18 h, the reaction mixture was poured into a mixture of crushed ice (19 g) and sodium metabisulfite (36.7 mg, 0.193 mmol). A solid precipitated and was filtered. The collected solid was dissolved in  $\text{CH}_2\text{Cl}_2$  (15 mL) and partitioned with an aqueous 5%  $\text{Na}_2\text{CO}_3$  solution. After the layers were separated, the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (2  $\times$  15 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to afford a residue. Purification of the crude product by silica gel chromatography (eluant 30–70% EtOAc/hexanes) yielded a colorless residue consisting of a mixture of **62** and **63** (58 mg, 76%). A small amount of this mixture was purified further by HPLC (Phenomenex C-18 (2), 5  $\mu$ m, 250  $\times$  21.2 mm, column temperature 23  $^\circ\text{C}$ , 90% MeOH in  $\text{H}_2\text{O}$ , flow rate 16 mL/min, UV detection at 254 nm,  $t_r$  = 8 min (**62**), 13 min (**63**)) to afford pure analytical samples of **62** (9.9 mg) and **63** (1.6 mg).

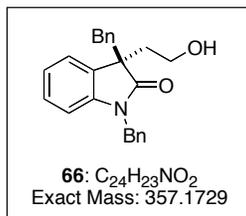
Major product, **62**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.02 (s, 2H), 6.76 (s, 2H), 3.90 (s, 6H), 3.13 (s, 6H), 1.82 (d, 2H,  $J$  = 13.5 Hz), 1.63 (dd, 2H,  $J$  = 13.9, 9.5 Hz), 1.32 (s, 6H), 1.02–0.95 (m, 4H), 0.84–0.78 (m, 2H), 0.68 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  180.2, 152.2, 137.6, 134.0, 112.9, 110.6, 108.5, 57.3, 48.5, 46.6, 42.5, 42.4, 37.5, 30.9, 26.3, 24.9; IR (thin film) 3056, 2929, 1710, 1493, 1407, 1235, 1042, 706  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{38}\text{Br}_2\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  661.1277, found 661.1295.

Minor product, **63**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.03 (s, 1H), 6.75 (s, 1H), 6.68 (s, 1H), 3.90 (d, 6H,  $J$  = 3.1 Hz), 3.54 (s, 3H), 3.13 (s, 3H), 1.79 (d, 2H,  $J$  = 13.6 Hz), 1.67–1.57 (m, 2H), 1.33 (s, 3H), 1.32 (s, 3H), 1.09–1.03 (m, 2H), 1.02–0.96 (m, 2H), 0.90–0.80 (m, 2H), 0.72 (s, 3H), 0.70 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  181.3, 180.7, 153.8, 152.7, 138.1, 136.6, 136.4, 134.5, 116.2, 113.4, 111.1, 108.9, 107.7, 107.1, 57.8 (2), 48.9, 48.7, 47.1, 47.0, 43.3, 42.9 (2), 42.8, 38.1, 31.4, 30.9, 30.2, 26.8, 25.6, 25.3; IR (thin film) 3064, 2923, 1713, 1465, 1227, 1048, 708  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{31}\text{H}_{37}\text{Br}_3\text{N}_2\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$  739.0381, found 739.0383.

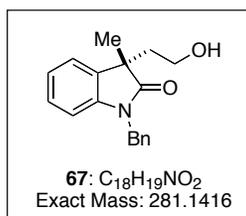


**(S)-(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-acetaldehyde (65).** A mixture of diol ah017 (530 mg, 0.946 mmol) and  $\text{NaIO}_4$  (3.02 g, 14.1 mmol) in THF (10.4 mL) and  $\text{H}_2\text{O}$  (5.3 mL) was stirred at room temperature overnight. The reaction was diluted with  $\text{H}_2\text{O}$  (10 mL) and extracted with EtOAc (3  $\times$  15 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated to yield a residue. Purification of the crude product by silica gel chromatography (eluant 50% EtOAc/hexanes) afforded a colorless film (481 mg, 91%): HPLC (Daicel Chiracel OD-H column) column temperature 23  $^\circ\text{C}$ , 98% *n*-hexane/isopropanol, flow rate 0.4 mL/min, 112.1 min (major enantiomer), 123.3 min (minor enantiomer);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.47 (s, 1H), 7.39 (d, 2H,  $J$  = 7.4 Hz), 7.30 (t, 2H,  $J$  = 7.5 Hz), 7.22 (t, 1H,  $J$  = 7.3 Hz), 7.18 (d, 1H,  $J$  = 7.4 Hz), 7.11 (t, 1H,  $J$  = 7.7 Hz), 6.98 (t, 1H,  $J$  = 7.5 Hz), 6.76 (d, 1H,  $J$  = 7.8 Hz), 4.96 (AB<sub>q</sub>, 2H,  $J_{\text{AB}}$  = 15.8 Hz), 3.02 (s, 2H), 1.43 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  198.1, 179.0, 141.7, 135.5, 132.3, 128.2, 127.5, 127.0, 126.7, 122.0, 121.8, 108.8, 49.8,

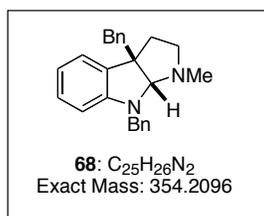
44.2, 43.1, 24.0; IR (thin film) 3060, 2970, 1706, 1613, 1490, 1356, 1179, 755  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{17}\text{NO}_2$  ( $\text{M}^+$ ) 279.1259, found 279.1251.



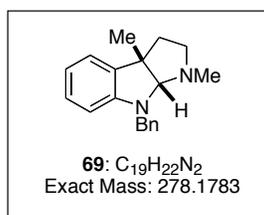
**(S)-1,3-Dibenzyl-3-(2-hydroxyethyl)-1,3-dihydroindol-2-one (66).** Sodium borohydride (3.9 mg, 0.10 mmol) was added to a solution of **59** (17 mg, 0.047 mmol) in EtOH (1.8 mL). The reaction was allowed to stir at room temperature overnight, then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The resulting aqueous solution was diluted with EtOAc (4 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\times$  4 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 30 and 60% EtOAc/hexanes) afforded a colorless film (15.9 mg, 94%): HPLC (Daicel Chiracel OD-H column) column temperature 23  $^\circ\text{C}$ , 98% *n*-hexane/isopropanol, flow rate 0.8 mL/min, 67.9 min (major enantiomer), 99.5 min (minor enantiomer);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.25–7.24 (m, 1H), 7.18–7.12 (m, 4H), 7.09–7.04 (m, 4H), 6.84 (m, 2H), 6.89 (m, 2H), 6.41–6.40 (m, 1H), 4.87 (d, 1H,  $J = 16.0$  Hz), 4.54 (d, 1H,  $J = 16.0$  Hz), 3.65 (dddd, 1H,  $J = 6.0, 6.0, 6.0, 6.0$  Hz), 3.48 (m, 1H), 3.31 (d, 1H,  $J = 12.9$  Hz), 3.12 (d, 1H,  $J = 12.9$  Hz), 2.45 (m, 1H), 2.21 (ddd, 1H,  $J = 14.0, 6.0, 6.0$  Hz), 1.92 (br s, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  179.7, 142.9, 135.4, 135.3, 130.9, 130.1, 128.5, 128.1, 127.8, 127.1, 126.7, 126.6, 123.4, 122.3, 109.3, 59.3, 53.0, 43.8, 43.6, 40.1; IR (thin film) 3419, 3060, 2919, 1708, 1694, 1611, 1466, 1356, 1171, 699  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{23}\text{NO}_2$  ( $\text{M}+\text{H}^+$ ) 358.1807, found 358.1798.



**(S)-1-Benzyl-3-(2-hydroxyethyl)-3-methyl-1,3-dihydroindol-2-one (67).** Sodium borohydride (7.7 mg, 0.203 mmol) was added to a solution of **65** (25.8 mg, 0.0924 mmol) in EtOH (2 mL). The reaction was allowed to stir at room temperature overnight, then quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (2 mL). The resulting solution was diluted with EtOAc (5 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (2  $\times$  5 mL). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. Purification of the crude product by silica gel chromatography (eluant 50 and 70% EtOAc/hexanes) afforded a colorless film (25.9 mg, 100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30–7.19 (m, 5H), 7.15–7.10 (m, 2H), 7.00 (m, 1H), 6.70 (d, 1H,  $J = 9.7$  Hz), 4.88 (AB<sub>q</sub>, 2H,  $J_{\text{AB}} = 19.6$  Hz), 3.63 (m, 1H), 3.46 (m, 1H), 2.20 (m, 1H), 2.01 (m, 1H), 1.43 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  181.5, 141.9, 135.8, 133.9, 128.8, 127.8, 127.6, 127.2, 122.7, 122.5, 109.3, 59.3, 46.9, 43.8, 40.1, 24.0; IR (thin film) 3413, 3060, 2925, 1694, 1611, 1488, 1382, 1177, 1061, 753  $\text{cm}^{-1}$ ; HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{19}\text{NO}_2$  ( $\text{M}^+$ ) 281.1416, found 281.1410.

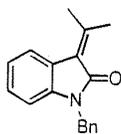


**(3a*S*,8a*R*)-3a,8-Dibenzyl-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (68).** Triethylamine (42.2 mL, 300 mmol) was added to a stirring mixture of **59** (10.7 g, 30.2 mmol), methylamine hydrochloride (20.4 g, 300 mmol), and MgSO<sub>4</sub> (20.2 g) in THF (400 mL) at room temperature. After 48 h, LiAlH<sub>4</sub> (11.4 g, 300 mmol) was added in four portions (caution: exotherm with rapid gas evolution occurs). After the addition was complete, the mixture was heated to reflux for 1.5 h, then cooled to 0 °C. Excess hydride was decomposed by the dropwise addition of EtOAc (125 mL) followed by isopropyl alcohol (125 mL). The mixture was filtered and the filter cake was washed with EtOAc (3 × 50 mL). The filtrate was combined with saturated aqueous NaHCO<sub>3</sub> (300 mL) and the layers were separated. The organic phase was washed with saturated aqueous NaHCO<sub>3</sub> (2 × 100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow oil. Purification of the crude product by silica gel chromatography (eluant 75:25:2 hexanes: EtOAc: Et<sub>3</sub>N) yielded N-Bn-pyrrolidinoindoline as a clear oil (6.15 g, 58%): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.26–7.20 (m, 6H), 7.06–7.00 (m, 4H), 6.96–6.93 (m, 2H), 6.72 (t, 1H, *J* = 6.5 Hz), 6.22 (d, 1H, *J* = 7.8 Hz), 4.38 (s, 1H), 4.28 (d, 1H, *J* = 16.5 Hz), 4.19 (d, 1H, *J* = 16.5 Hz), 3.44 (d, 1H, *J* = 13.4 Hz), 2.94 (d, 1H, *J* = 13.4 Hz), 2.78–2.72 (m, 1H), 2.69–2.63 (m, 1H), 2.33–2.27 (m, 1H), 2.22 (s, 3H), 2.15–2.09 (m, 1H).

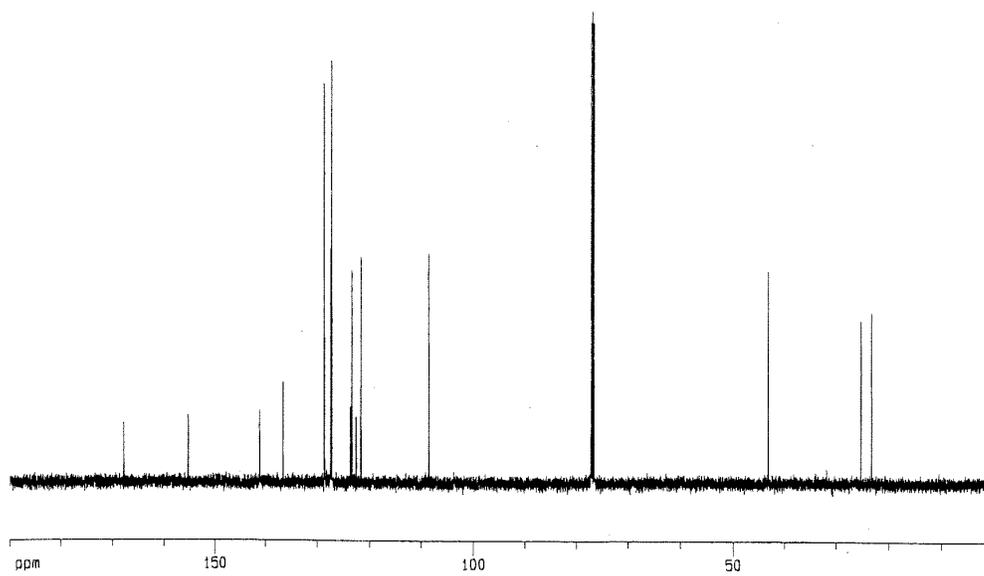
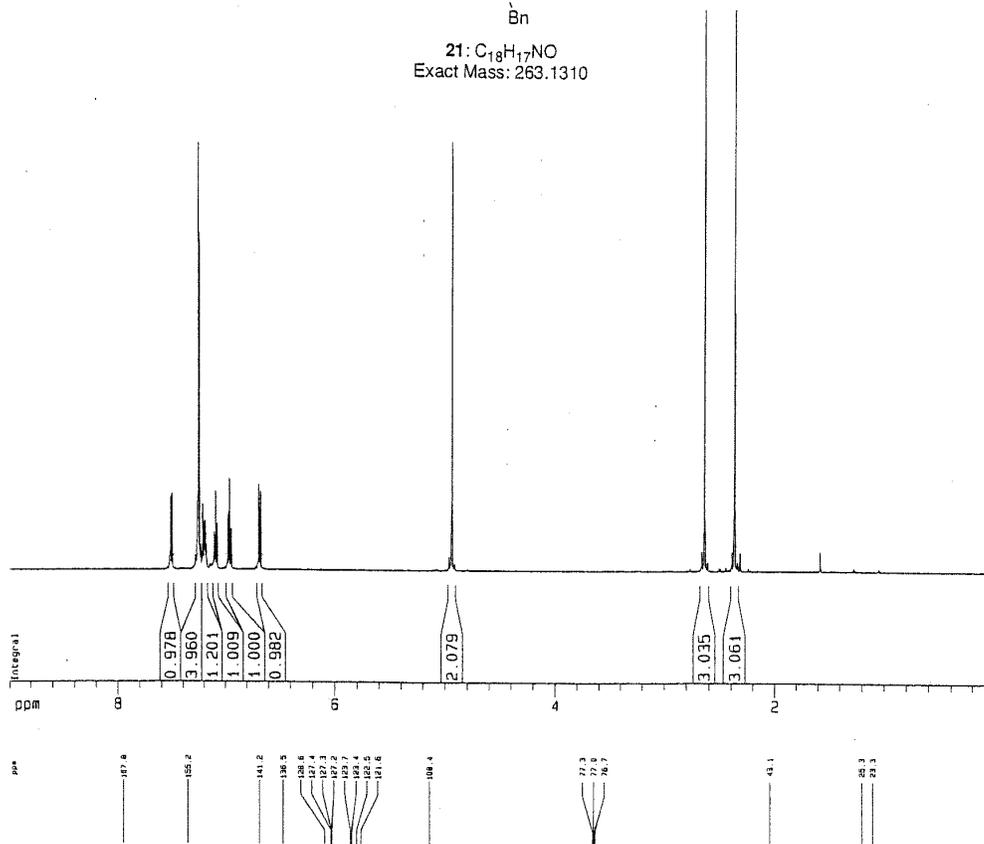


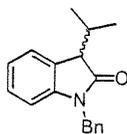
**(3a*S*,8a*R*)-8-Benzyl-1,3a-dimethyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (69).** Triethylamine (2.20 mL, 16.0 mmol) was added to a mixture of **65** (446 mg, 1.60 mmol), methylamine hydrochloride (1.08 g, 16.0 mmol), and MgSO<sub>4</sub> (1.09 g) in THF (39 mL) at room temperature. After 14 h, a 1 M solution of LiAlH<sub>4</sub> in THF (16.0 mL, 16.0 mmol) was added dropwise over 10 min to the mixture stirring at room temperature. After the evolution of gas ceased, the reaction was heated at 65 °C for 2 h, then allowed to cool to room temperature. Excess hydride was decomposed by adding EtOAc (40 mL). After 30 min, saturated aqueous NaHCO<sub>3</sub> (25 mL) was added dropwise. The mixture was filtered, and the filter cake was washed with EtOAc (25 mL). Water (50 mL) was added to the filtrate, and the layers were separated. The aqueous phase was extracted with EtOAc (1 × 150 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated to afford a yellow residue. Purification of the crude product by silica gel chromatography (eluant 2.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> + 1% NH<sub>4</sub>OH, 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> + 1% NH<sub>4</sub>OH) afforded an orange oil (409 mg, 92%): [α]<sub>D</sub><sup>28</sup><sub>589</sub> –82, [α]<sub>D</sub><sup>28</sup><sub>577</sub> –86, [α]<sub>D</sub><sup>28</sup><sub>546</sub> –100, [α]<sub>D</sub><sup>28</sup><sub>435</sub> –183 (*c* = 0.21, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.28–7.24 (m, 4H), 7.20 (m, 1H), 6.99 (m, 1H), 6.96 (m, 1H), 6.64 (t, 1H, *J* = 7.6 Hz), 6.26 (d, 1H, *J* = 7.9 Hz), 4.53 (d, 1H, *J* = 16.6 Hz), 4.39 (d, 1H, *J* = 16.6 Hz), 4.25 (s, 1H), 2.69 (m, 2H), 2.40 (s, 3H), 1.97 (m,

2H), 1.40 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  151.2, 139.1, 136.8, 128.4, 127.6, 127.0, 126.7, 122.3, 117.7, 106.9, 96.0, 53.1, 53.0, 52.8, 40.8, 38.6, 27.3; IR (thin film) 3025, 2958, 2865, 2794, 1603, 1490, 1451, 1351, 1034, 739, 699  $\text{cm}^{-1}$ ; HRMS (CI/ $\text{NH}_3$ )  $m/z$  calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_2$  ( $\text{M}^+$ ) 278.1783, found 278.1788.

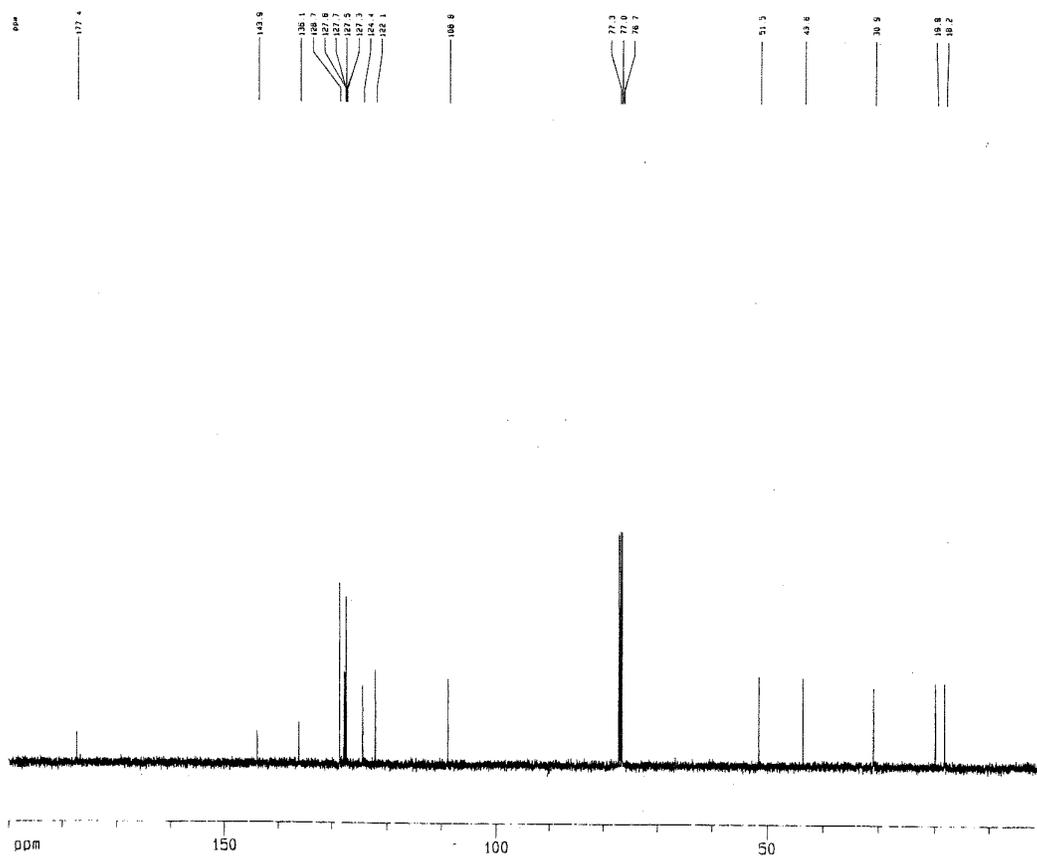
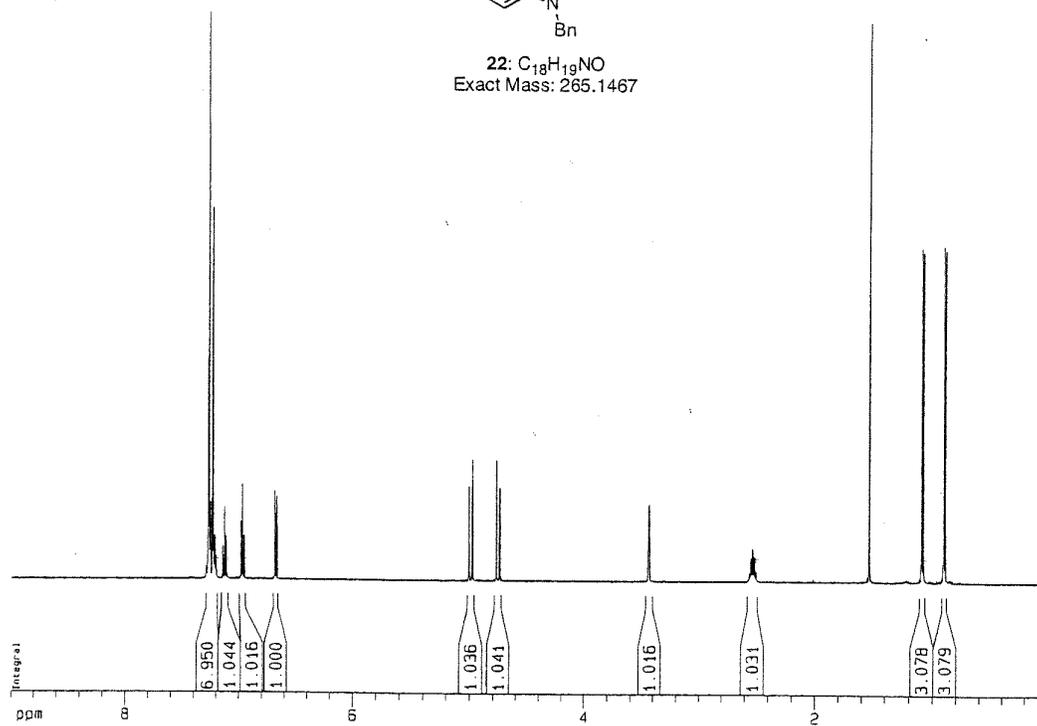


21: C<sub>18</sub>H<sub>17</sub>NO  
Exact Mass: 263.1310

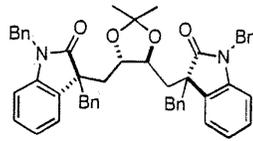




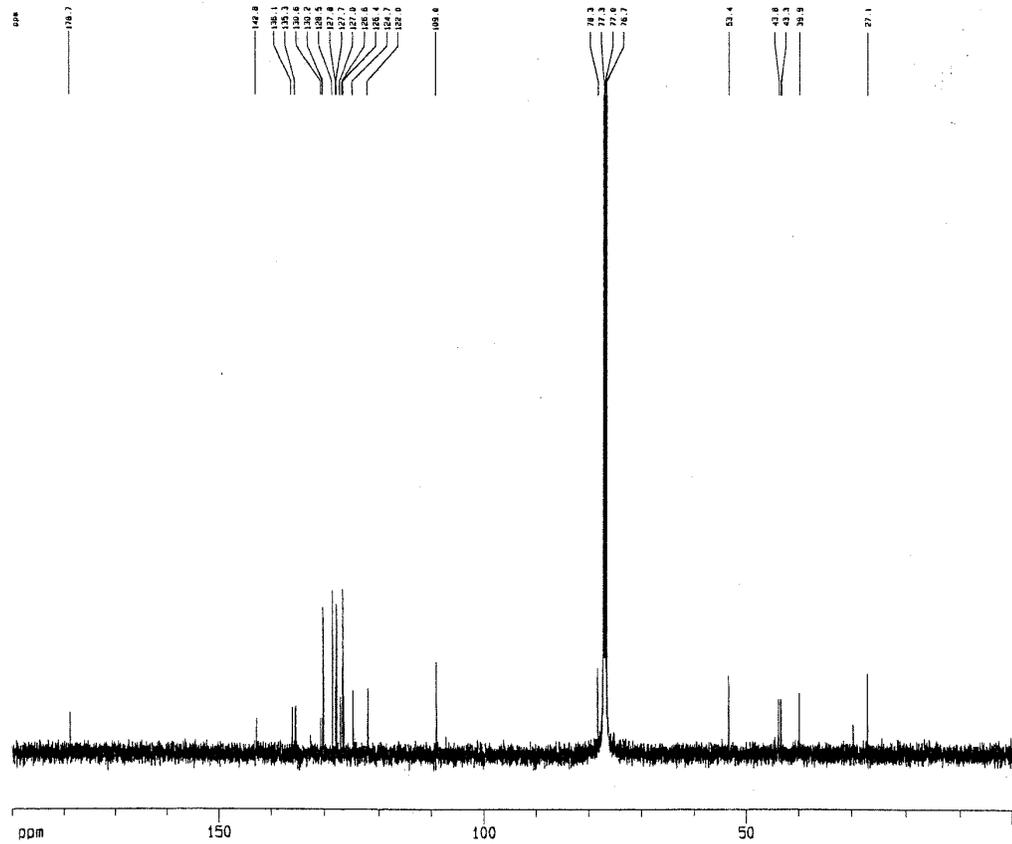
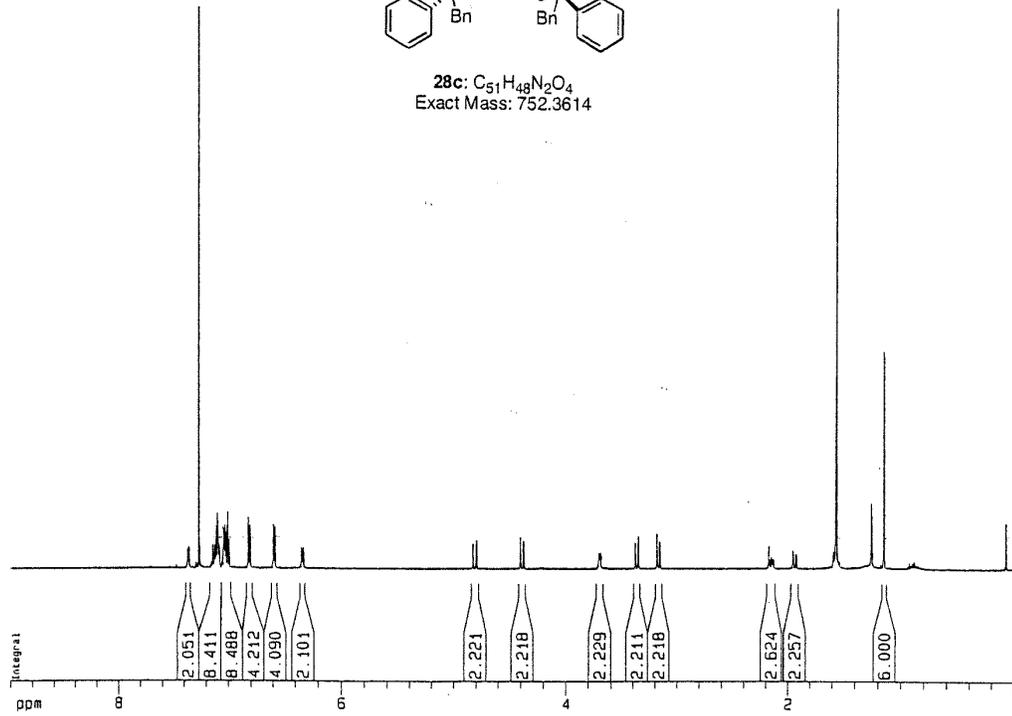
22: C<sub>18</sub>H<sub>19</sub>NO  
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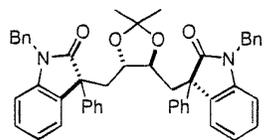




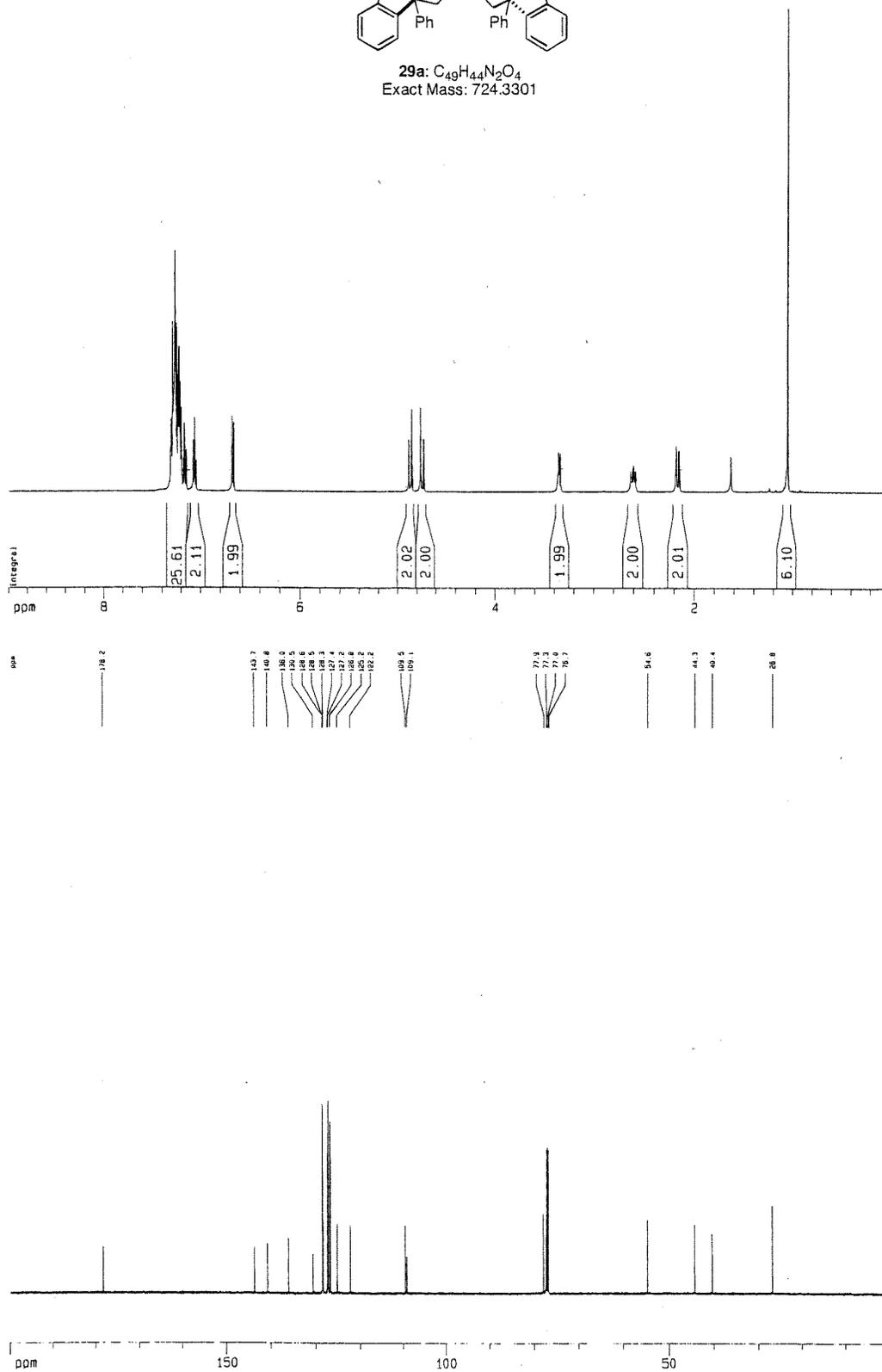


**28c:** C<sub>51</sub>H<sub>48</sub>N<sub>2</sub>O<sub>4</sub>  
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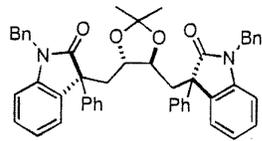




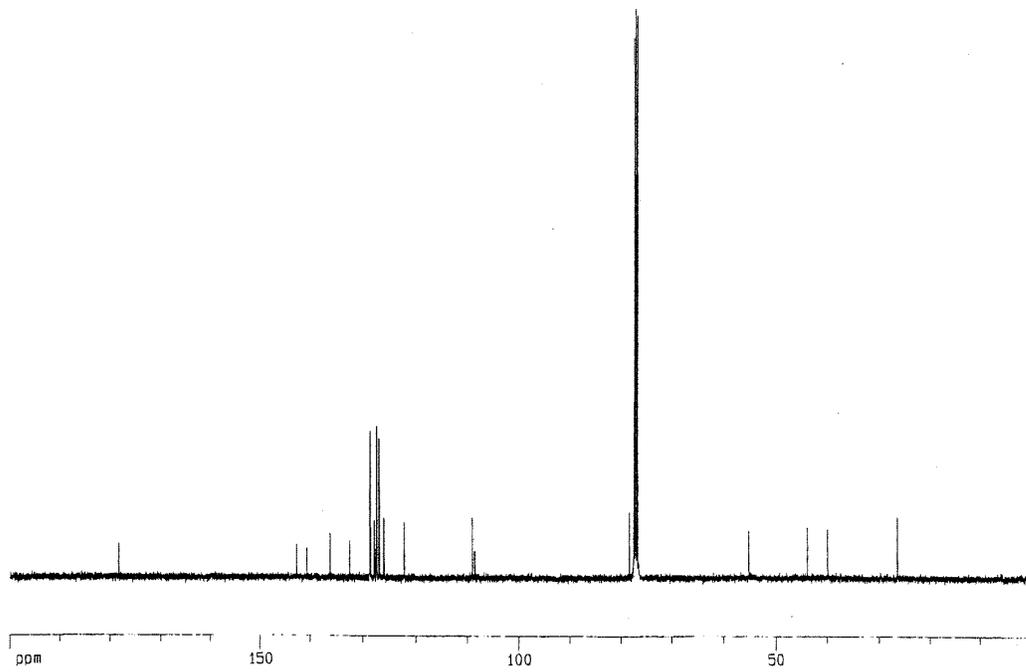
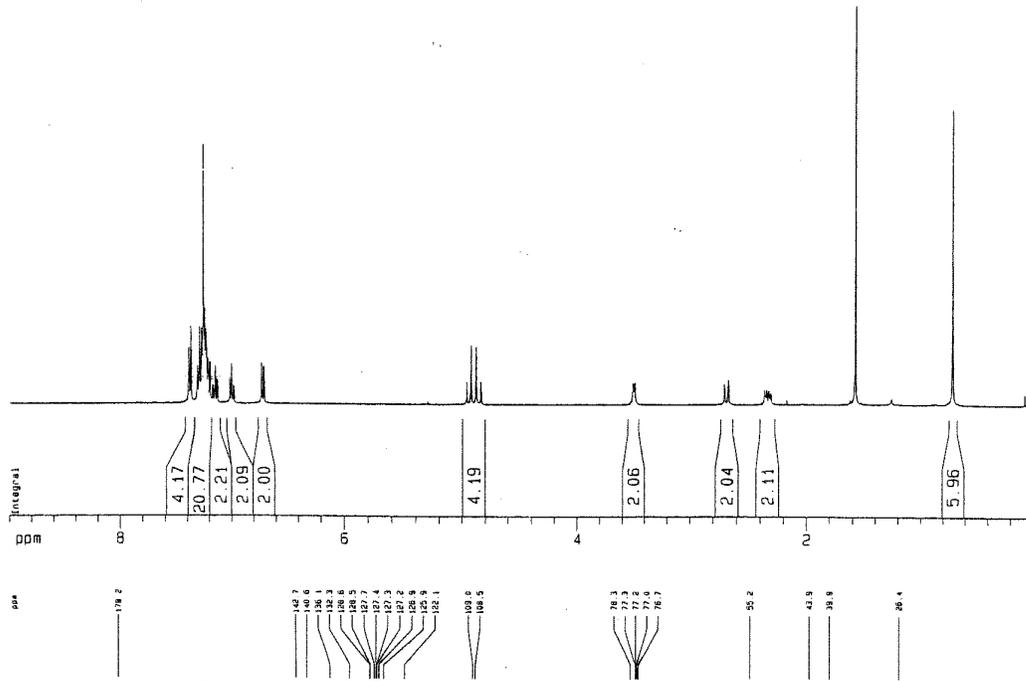
**29a**: C<sub>49</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 724.3301

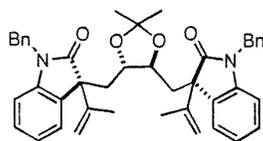




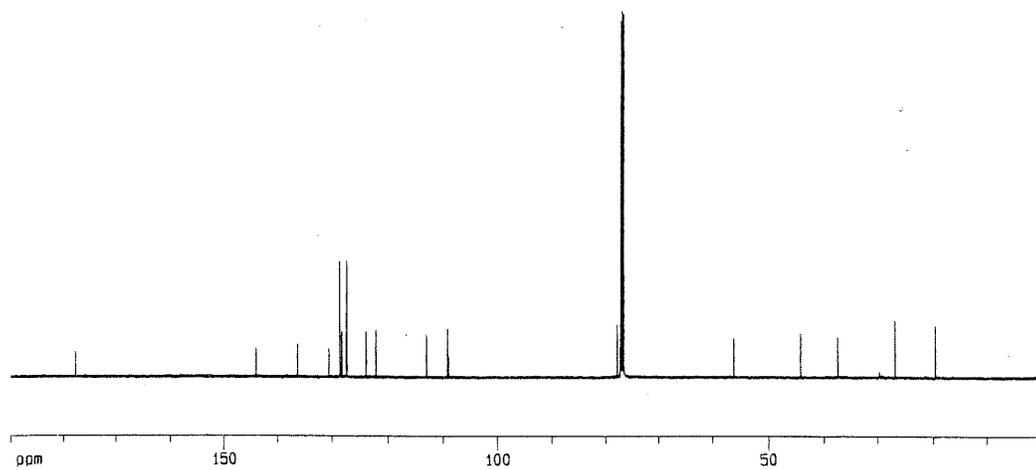
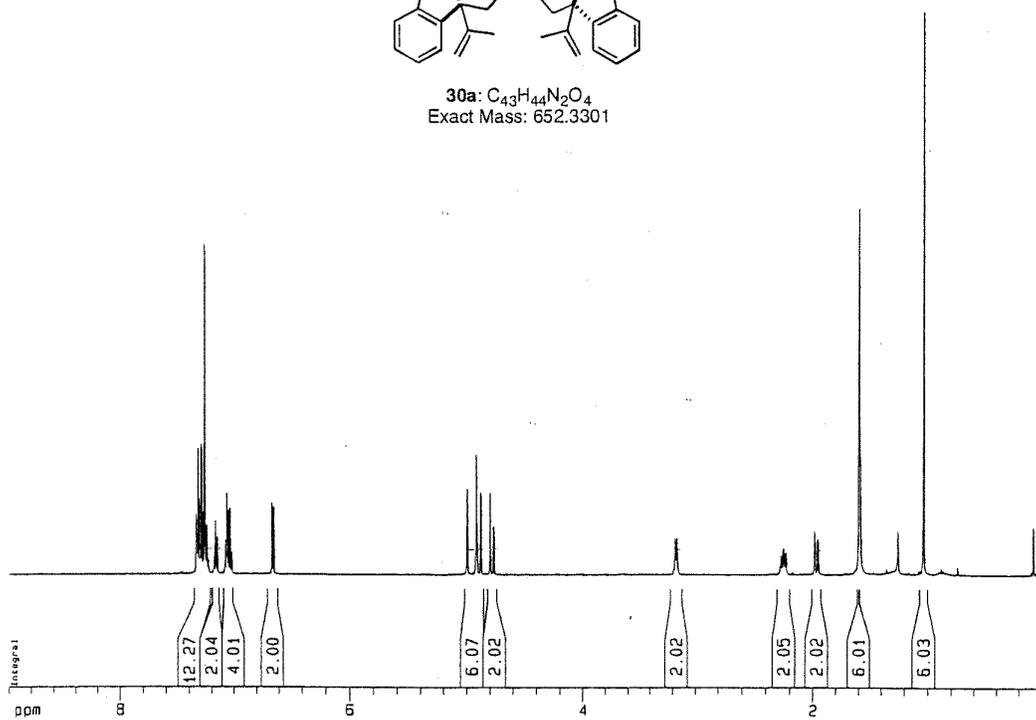


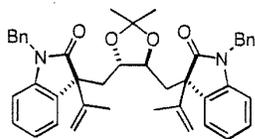
**29c:** C<sub>49</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 724.3301



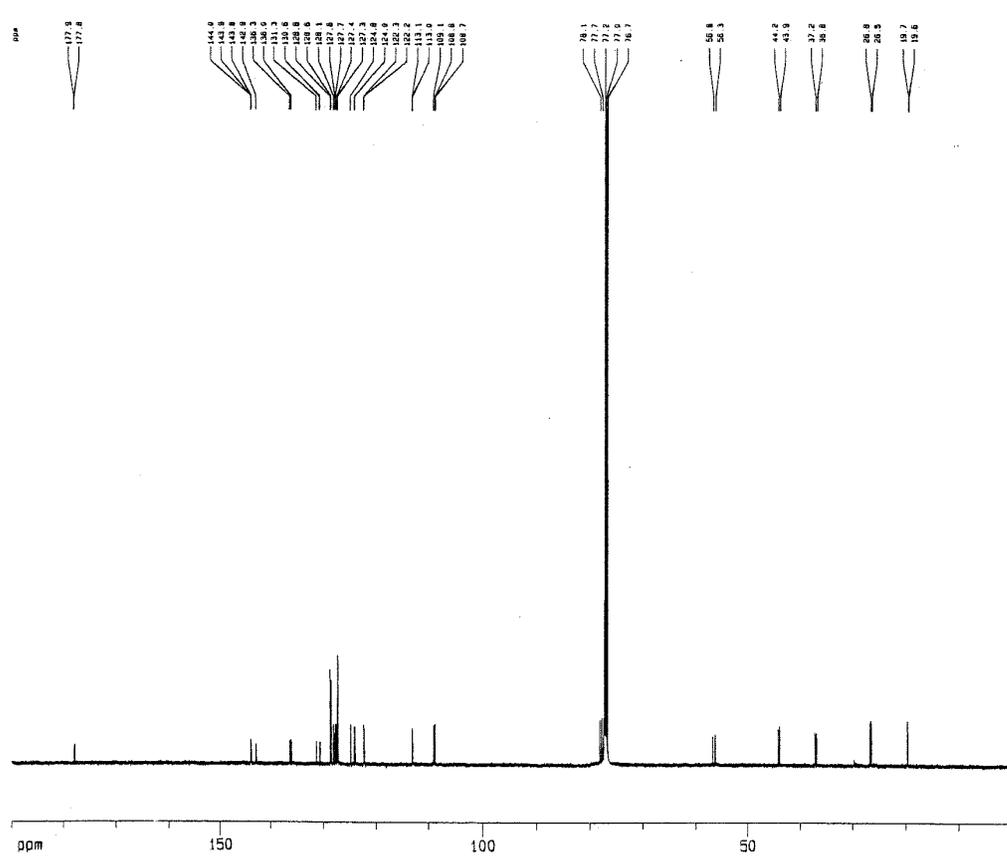
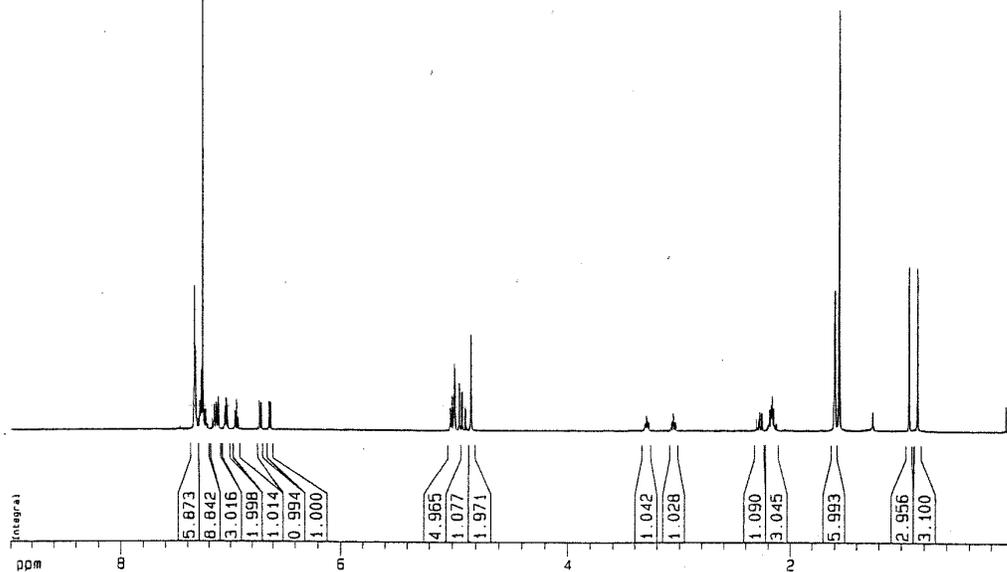


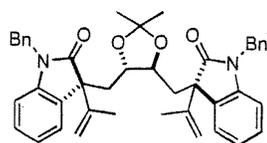
**30a:** C<sub>43</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 652.3301



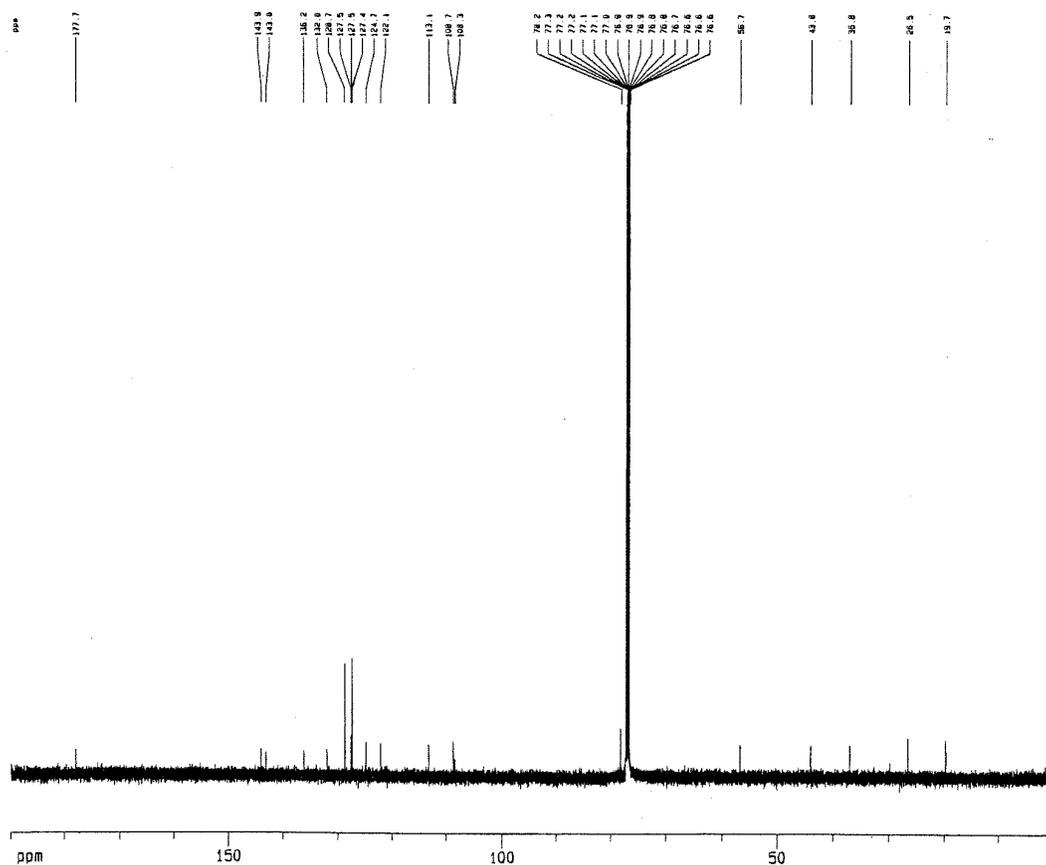
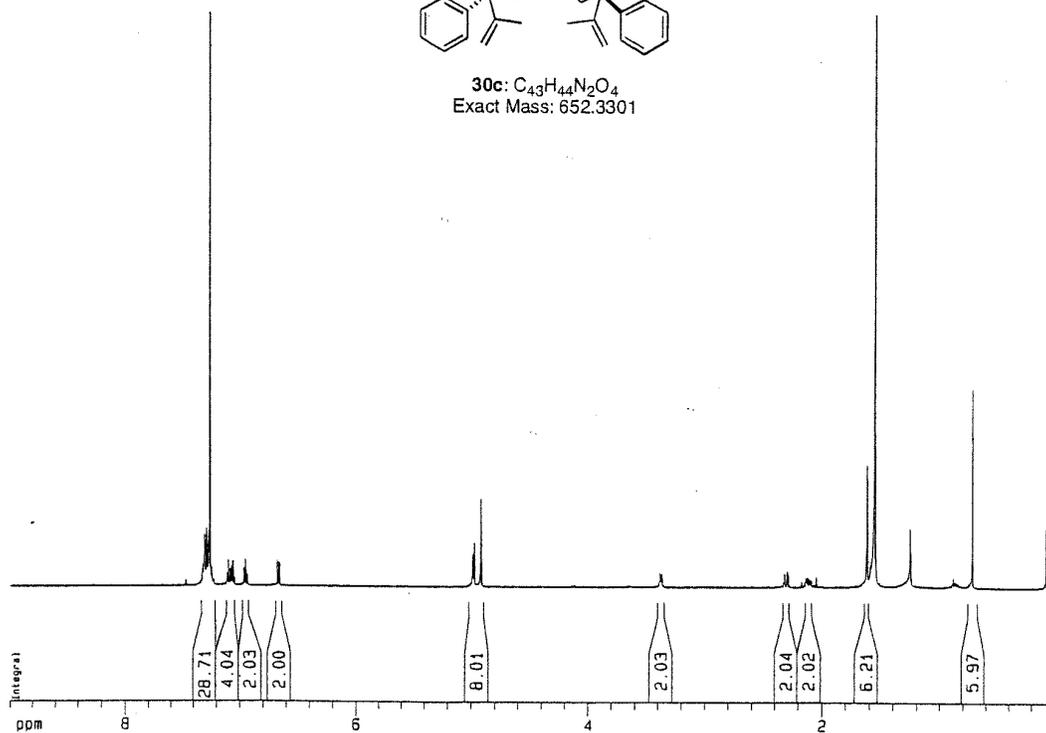


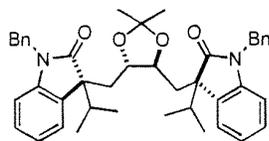
**30b**: C<sub>43</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 652.3301



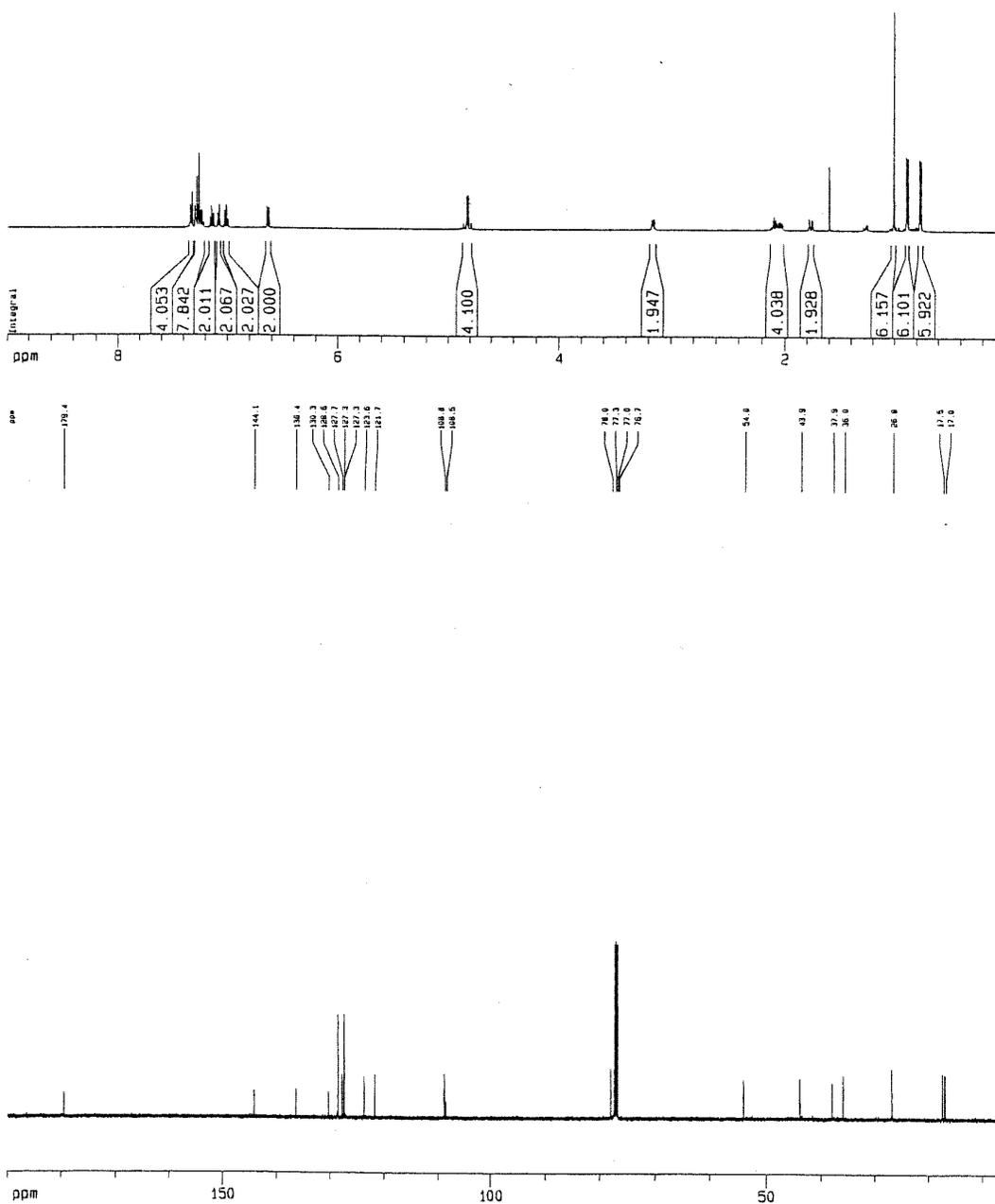


**30c:** C<sub>43</sub>H<sub>44</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 652.3301

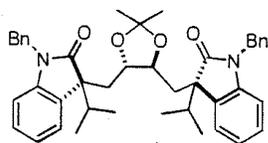




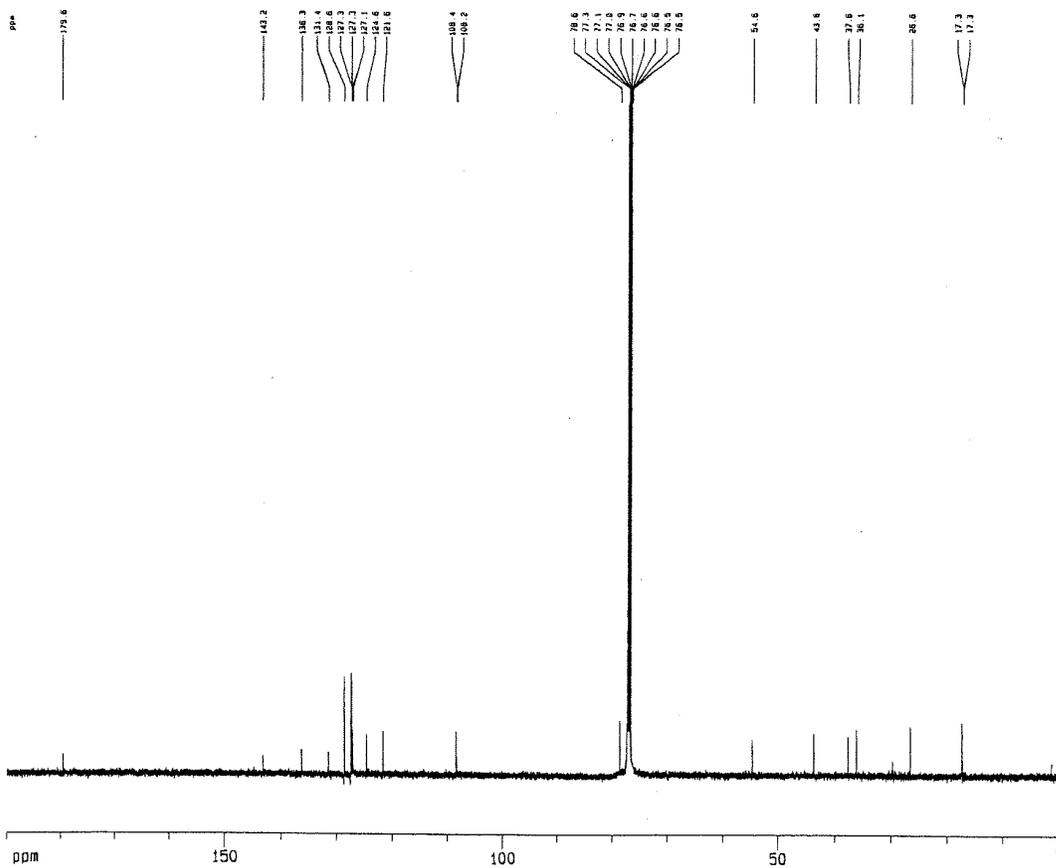
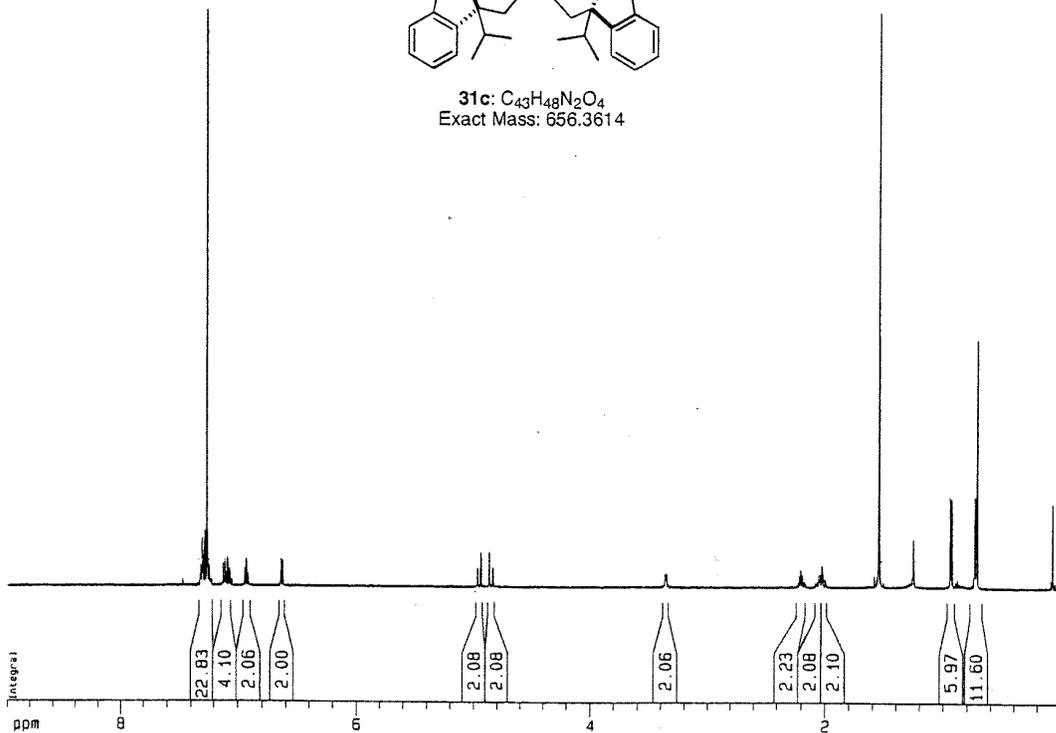
31a: C<sub>43</sub>H<sub>48</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 656.3614

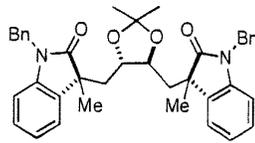




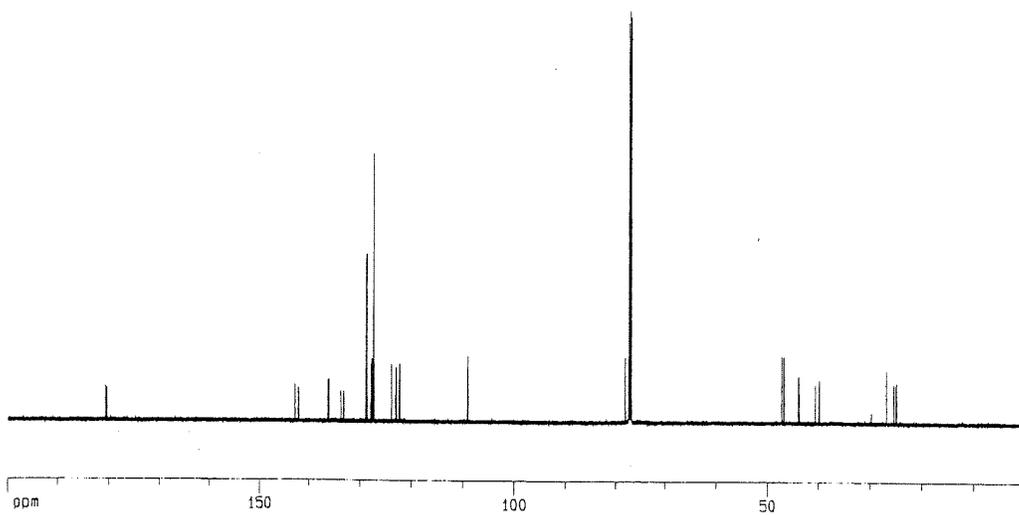
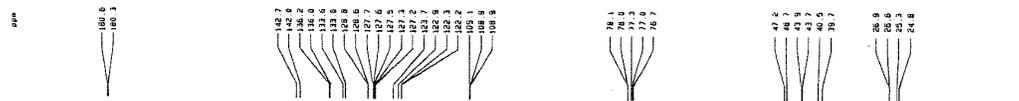
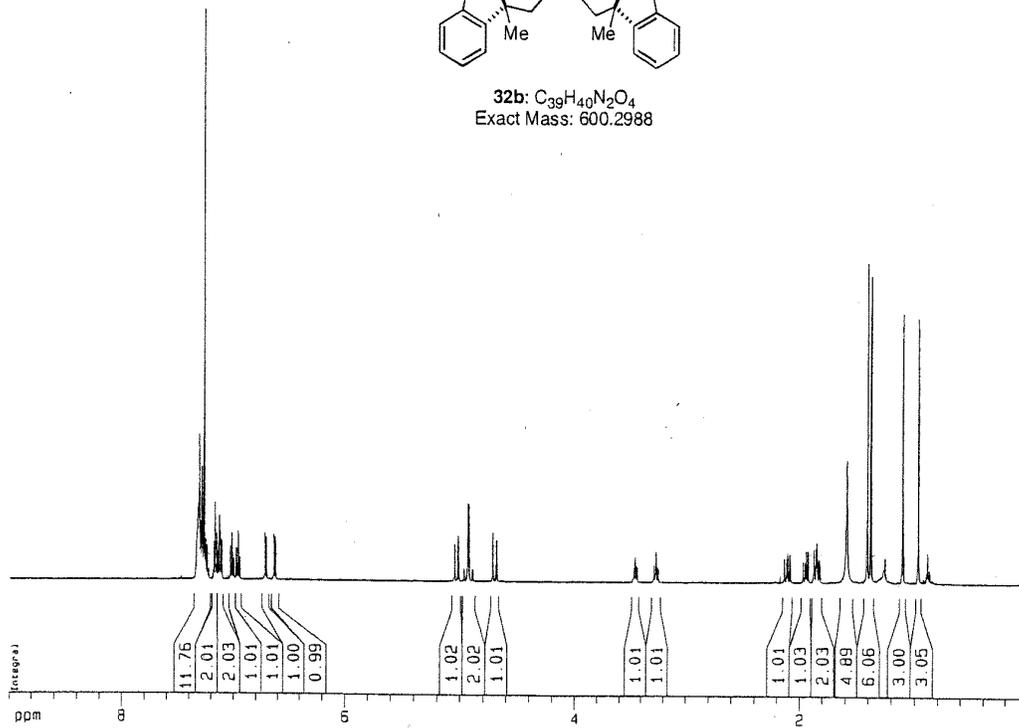


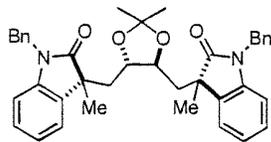
31c: C<sub>43</sub>H<sub>48</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 656.3614



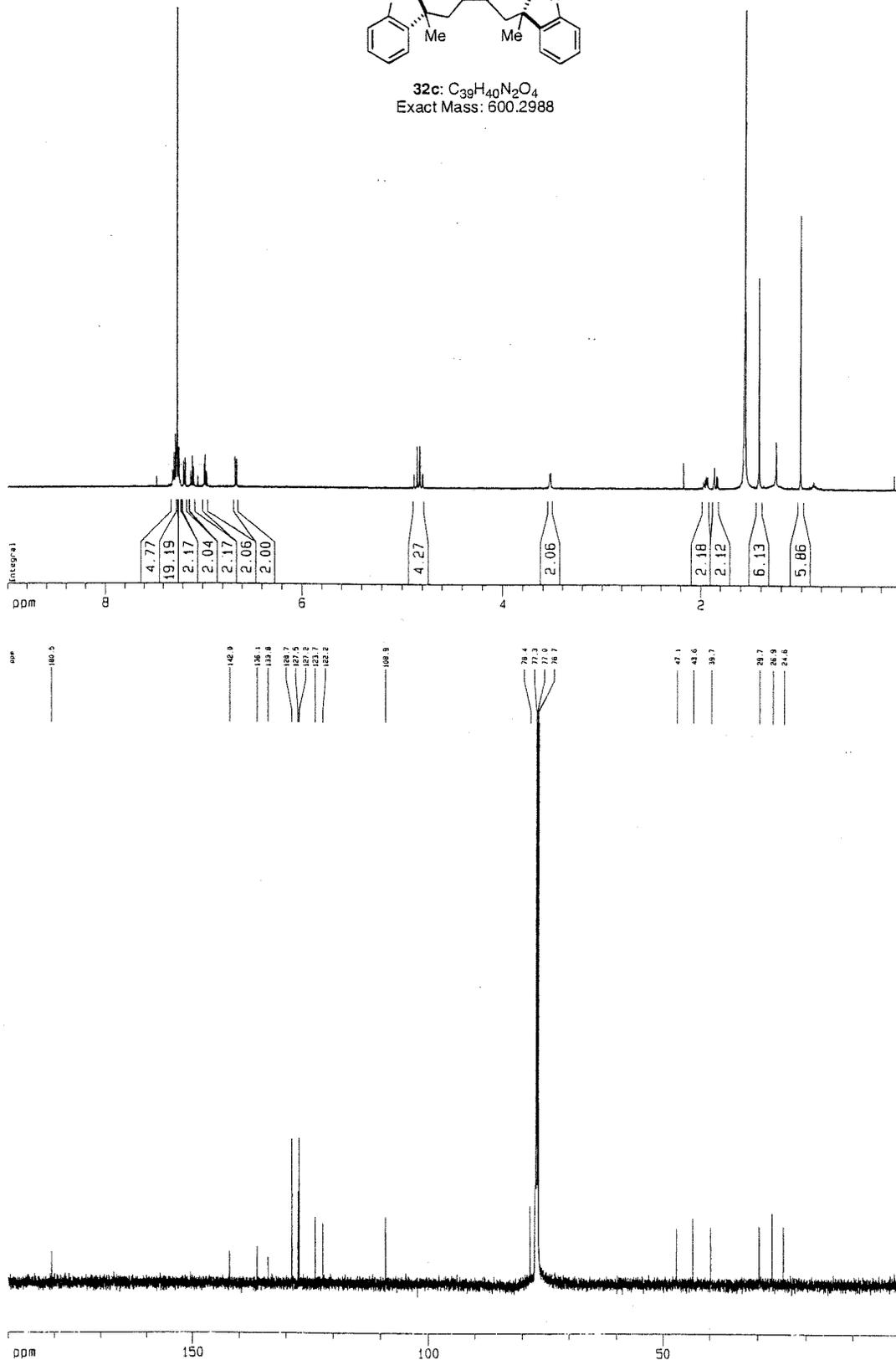


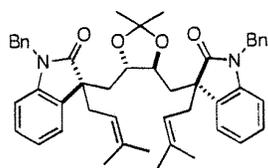
32b: C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 600.2988



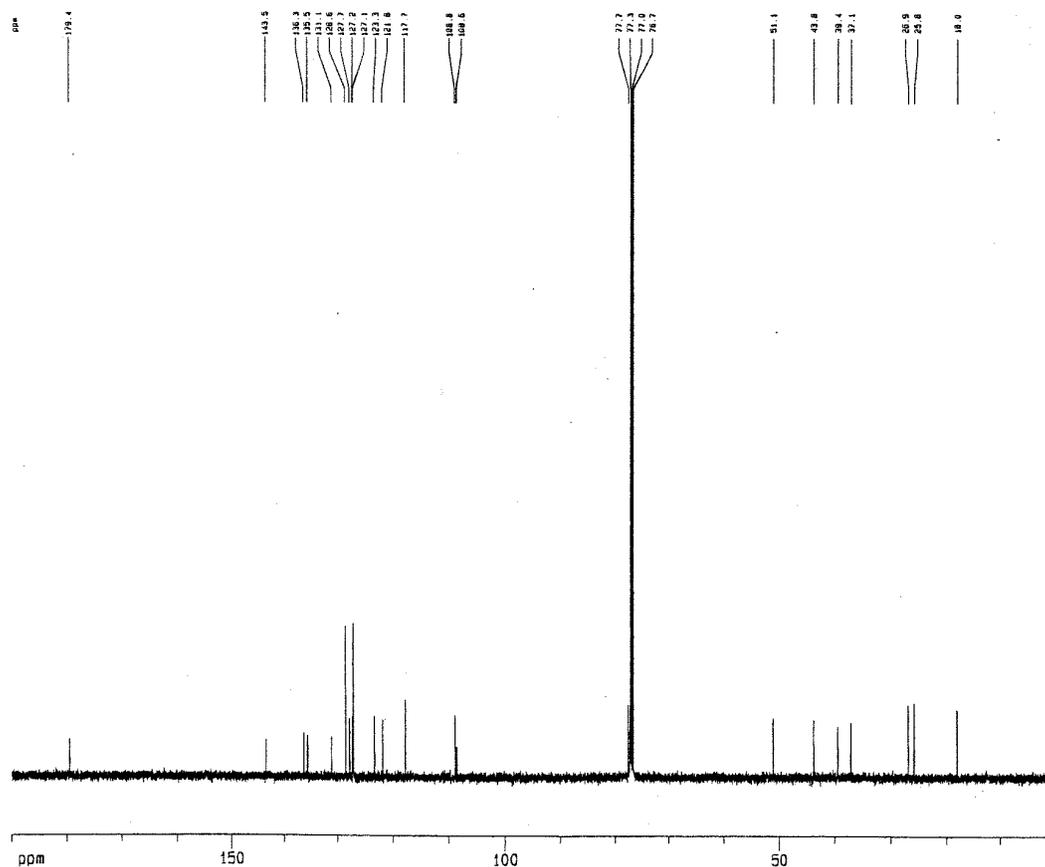
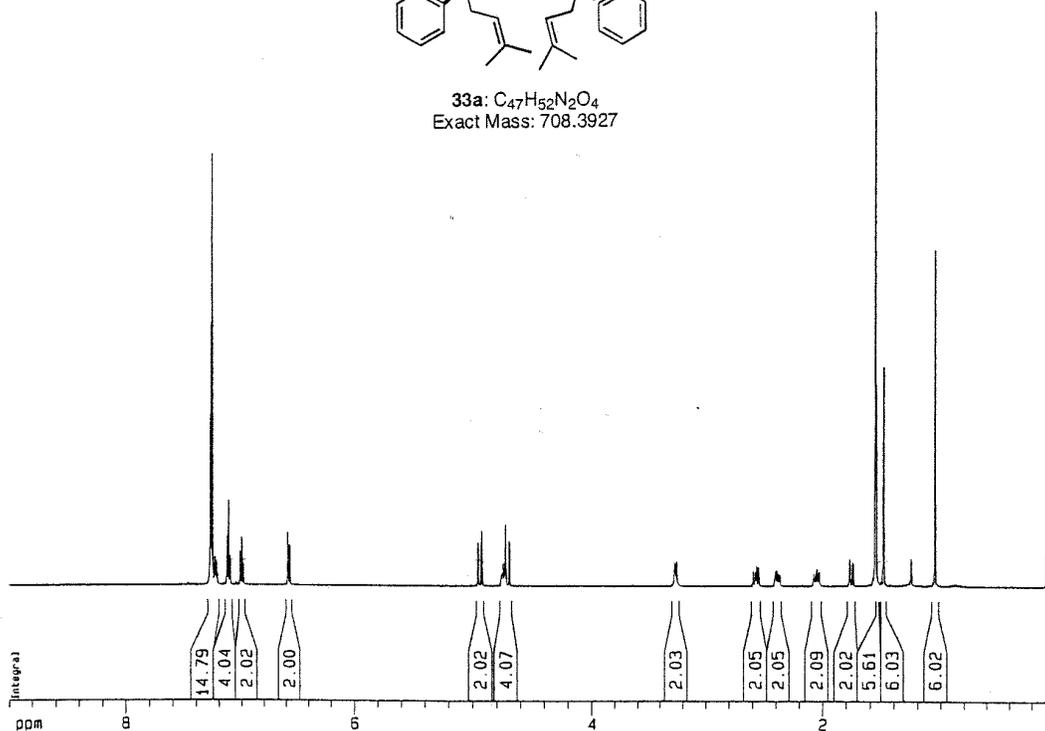


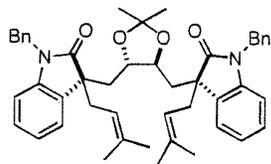
32c: C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 600.2988



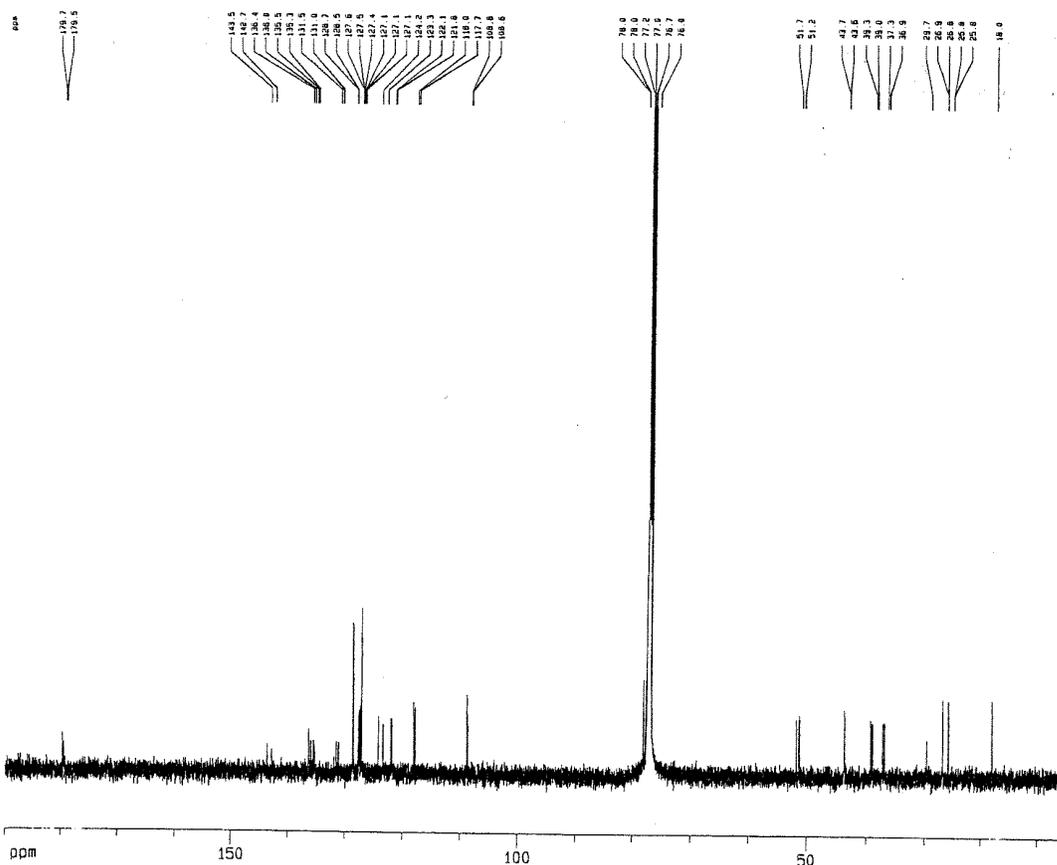
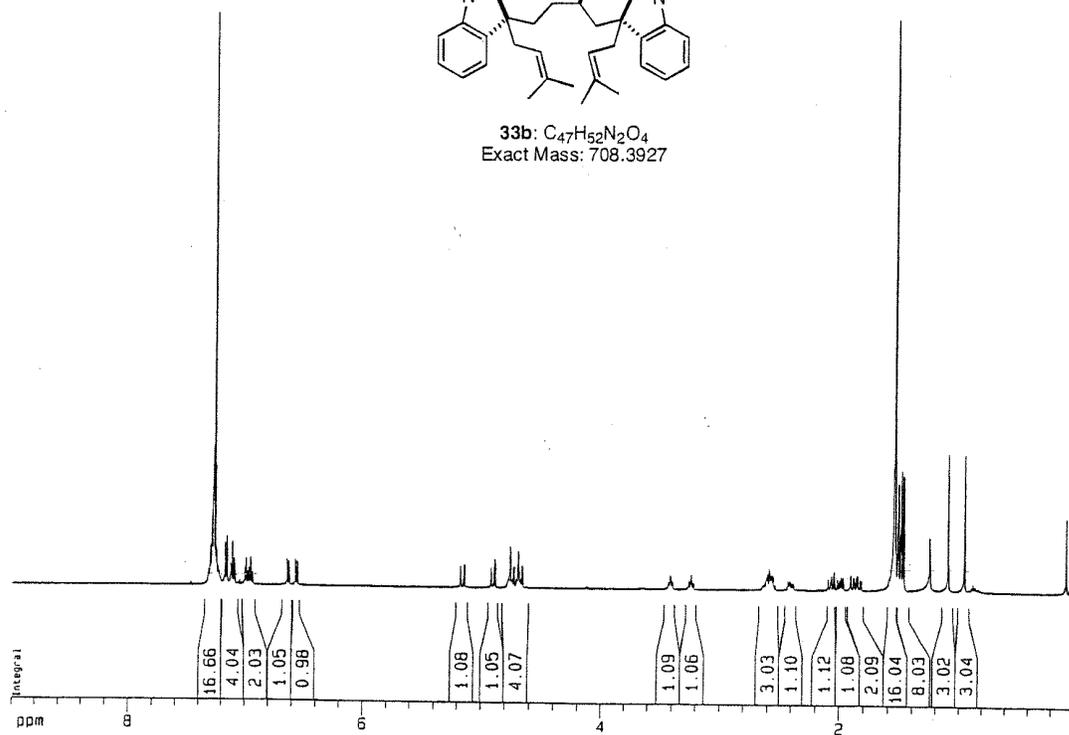


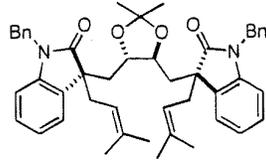
33a: C<sub>47</sub>H<sub>52</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 708.3927





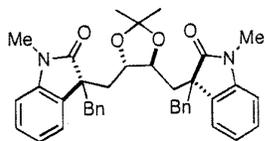
33b: C<sub>47</sub>H<sub>52</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 708.3927



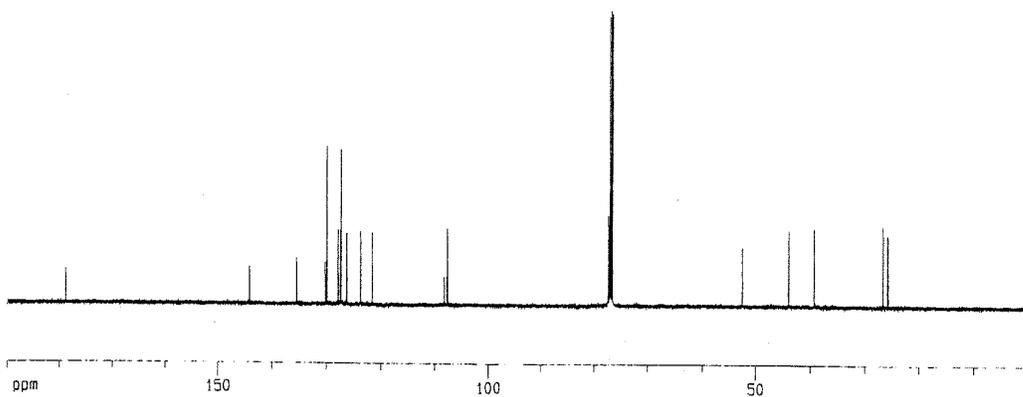
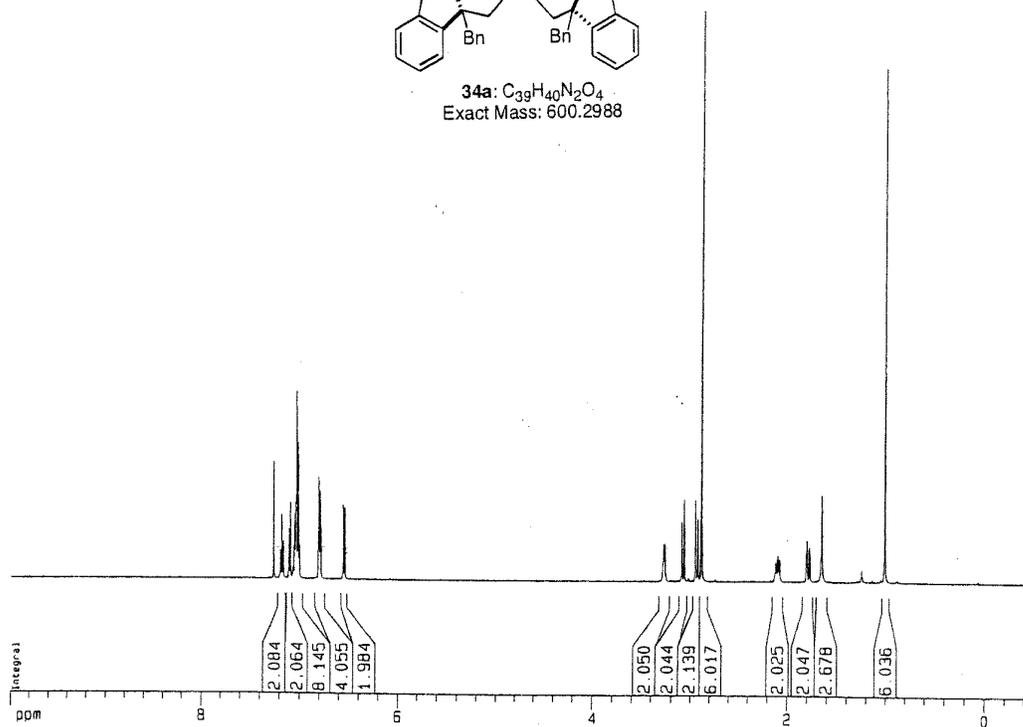


33c: C<sub>47</sub>H<sub>52</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 708.3927

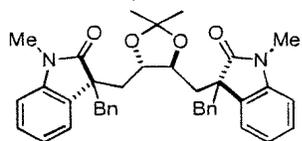




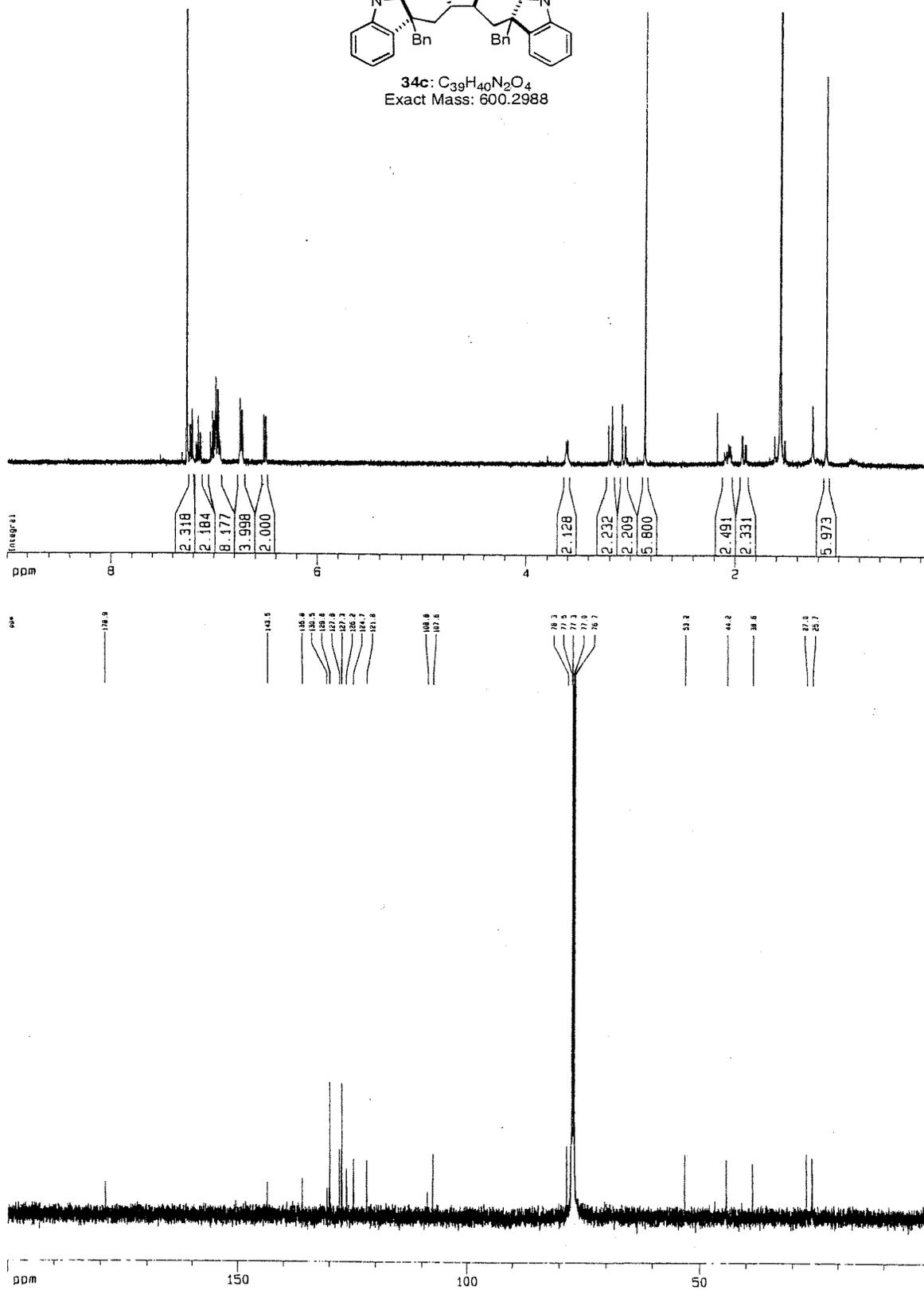
**34a:** C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 600.2988

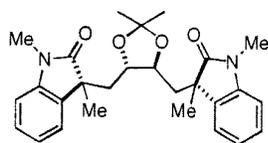




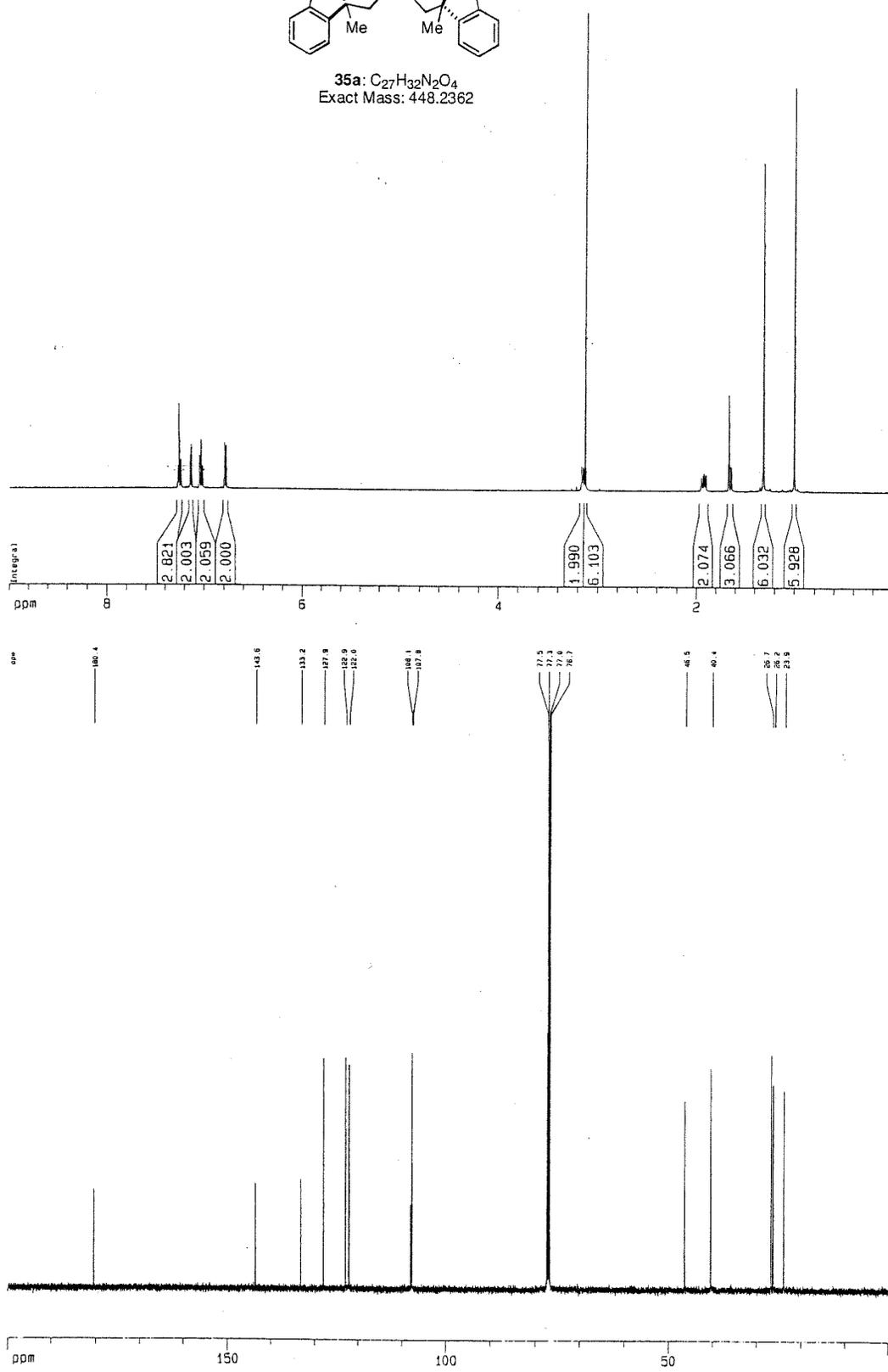


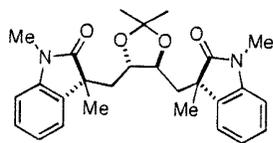
**34c**: C<sub>39</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 600.2988



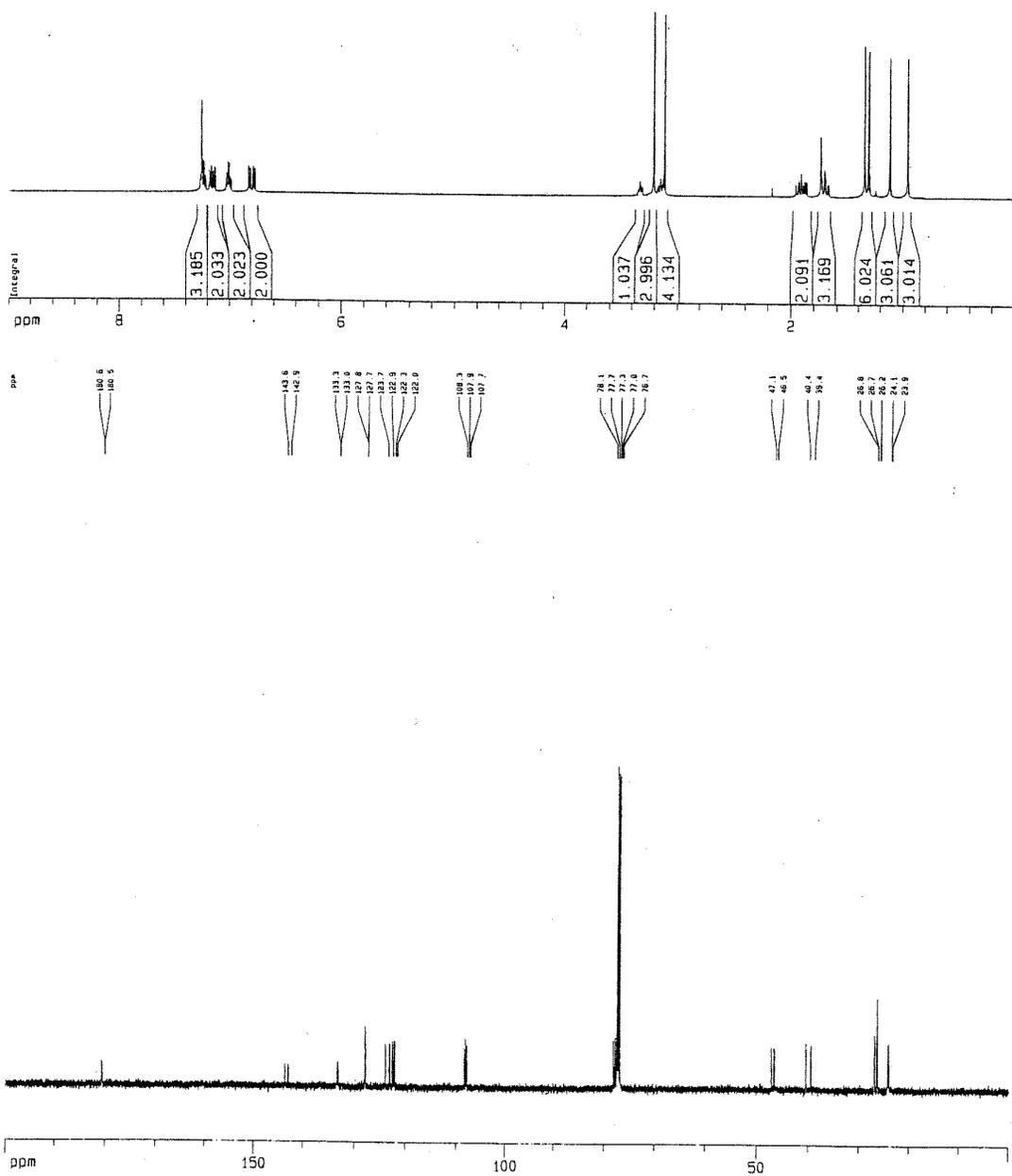


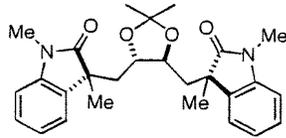
35a: C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 448.2362



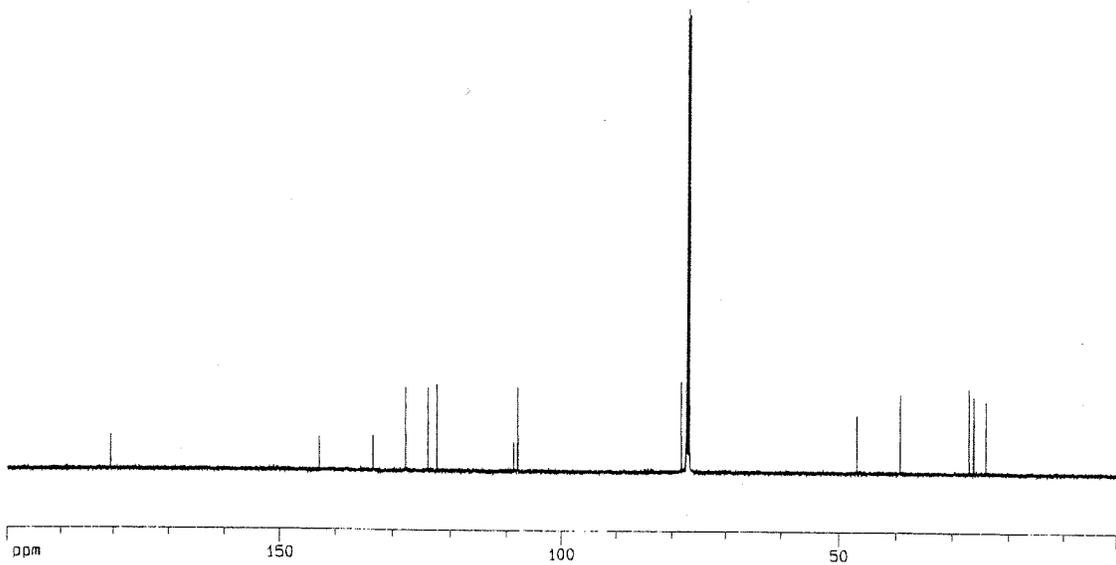
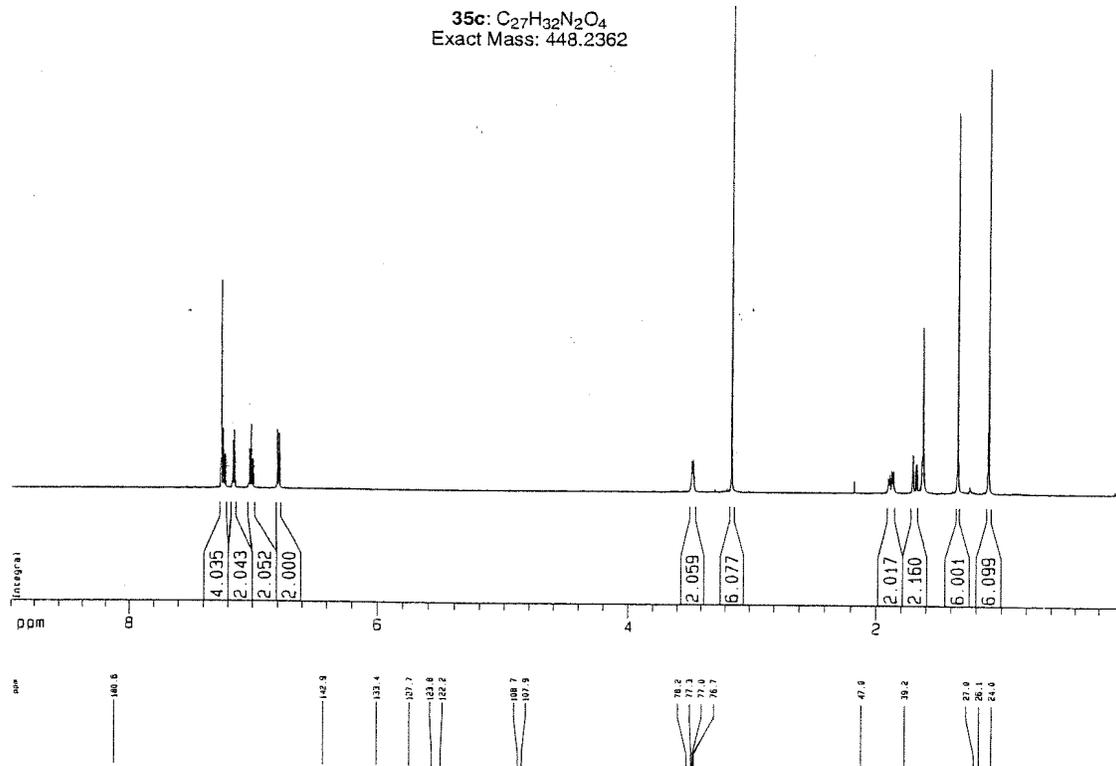


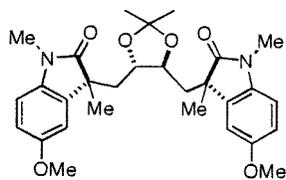
**35b:** C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 448.2362



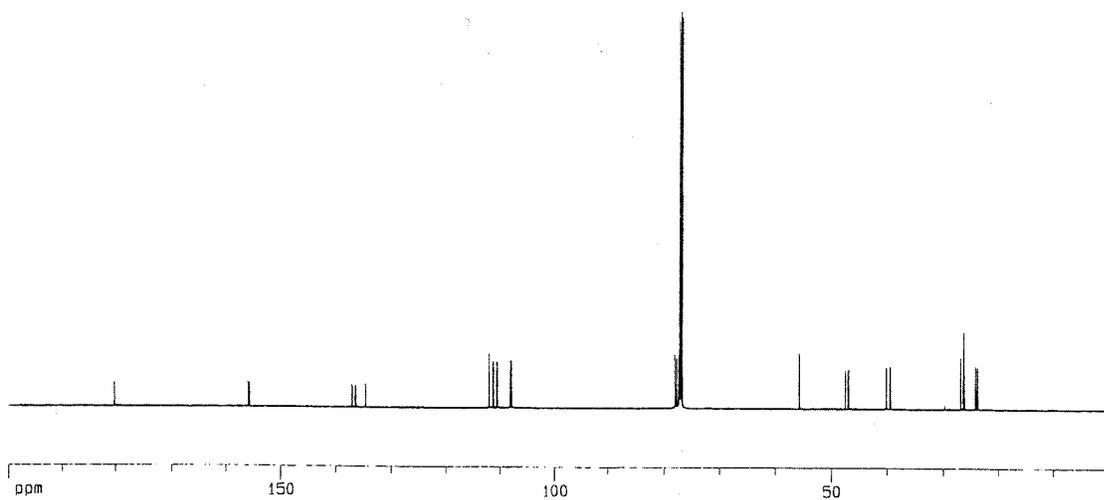
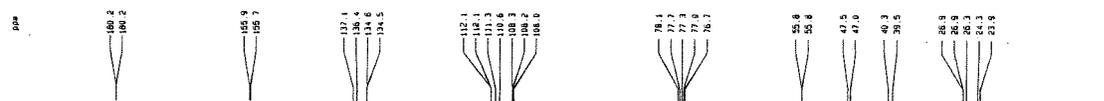
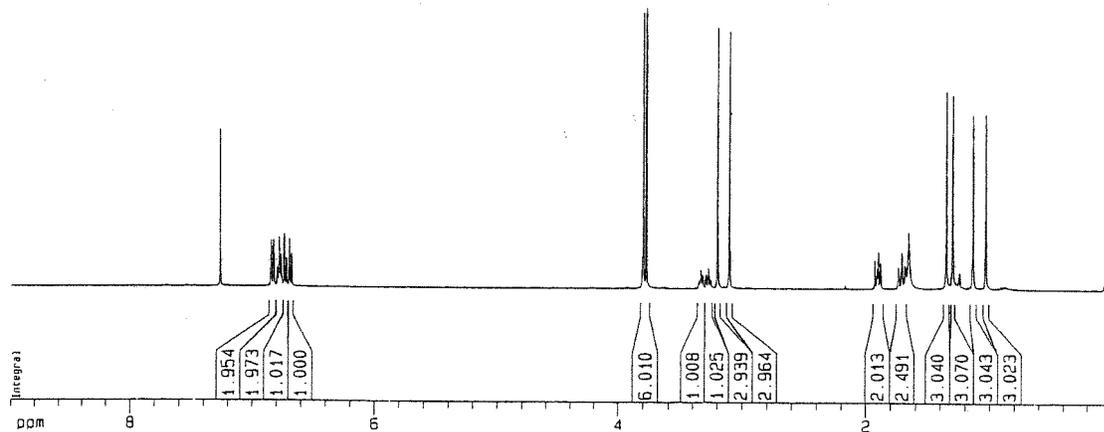


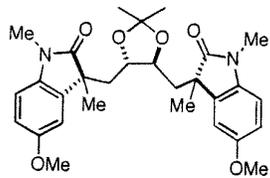
**35c:** C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 448.2362





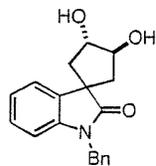
**36b:** C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>  
Exact Mass: 508.2573



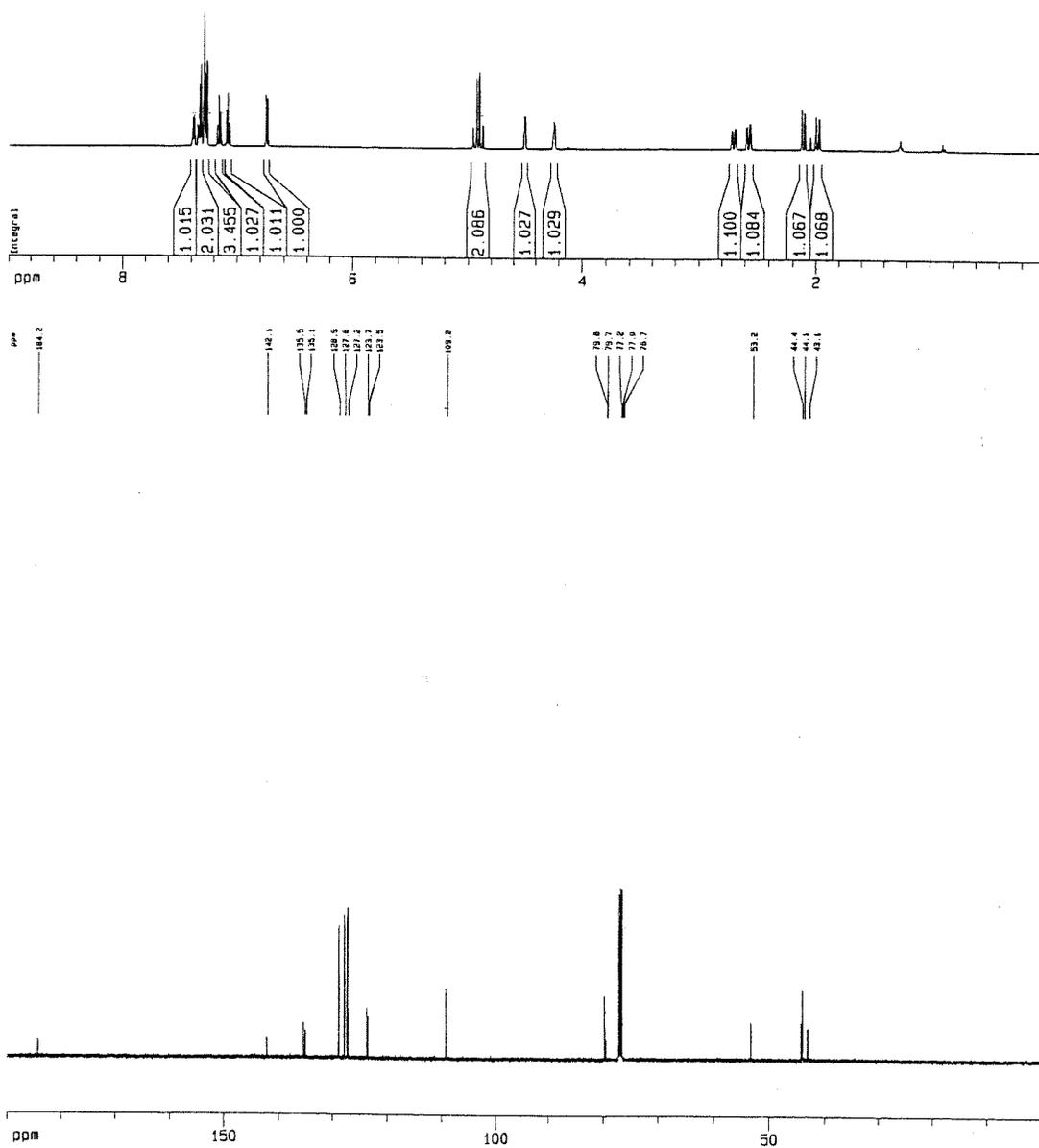


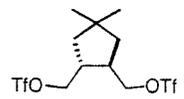
36c: C<sub>29</sub>H<sub>36</sub>N<sub>2</sub>O<sub>6</sub>  
 Exact Mass: 508.2573



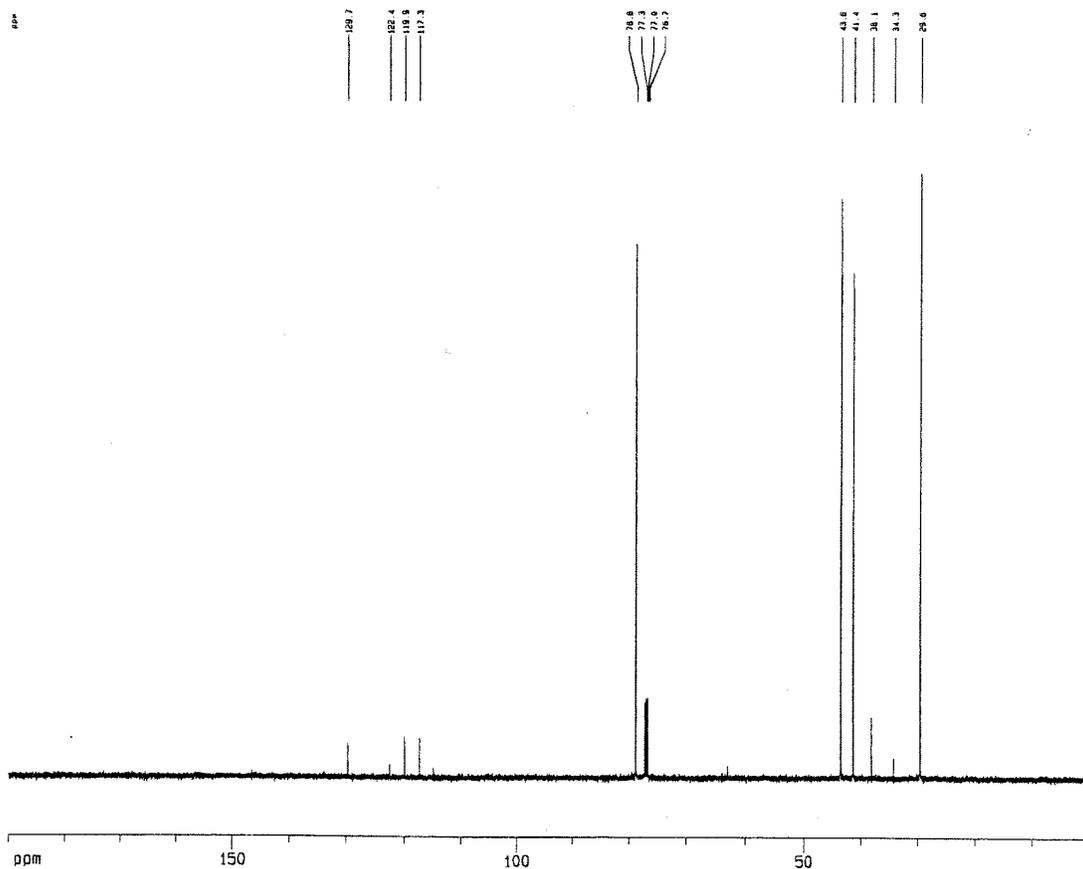
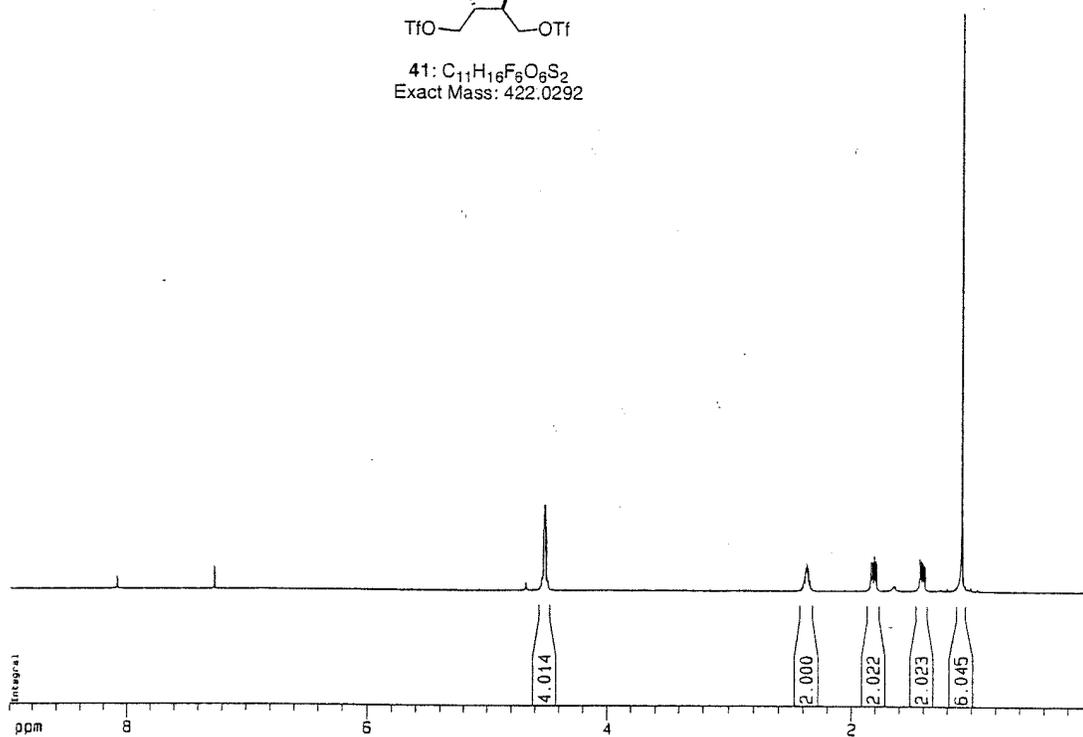


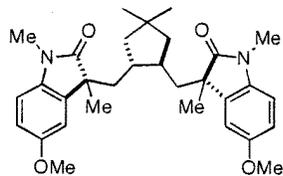
37: C<sub>19</sub>H<sub>19</sub>NO<sub>3</sub>  
 Exact Mass: 309.1365



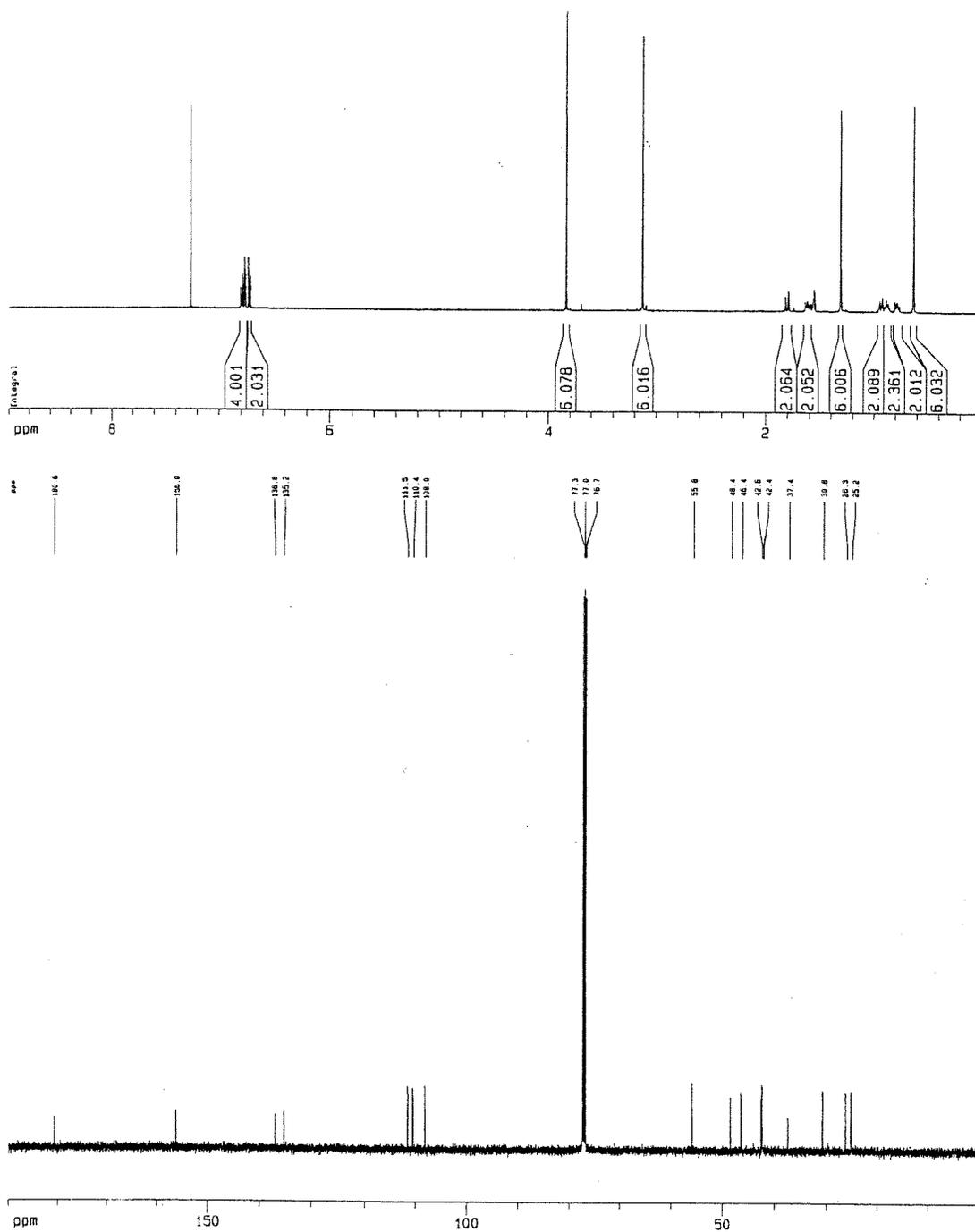


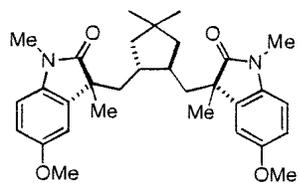
41: C<sub>11</sub>H<sub>16</sub>F<sub>6</sub>O<sub>6</sub>S<sub>2</sub>  
 Exact Mass: 422.0292



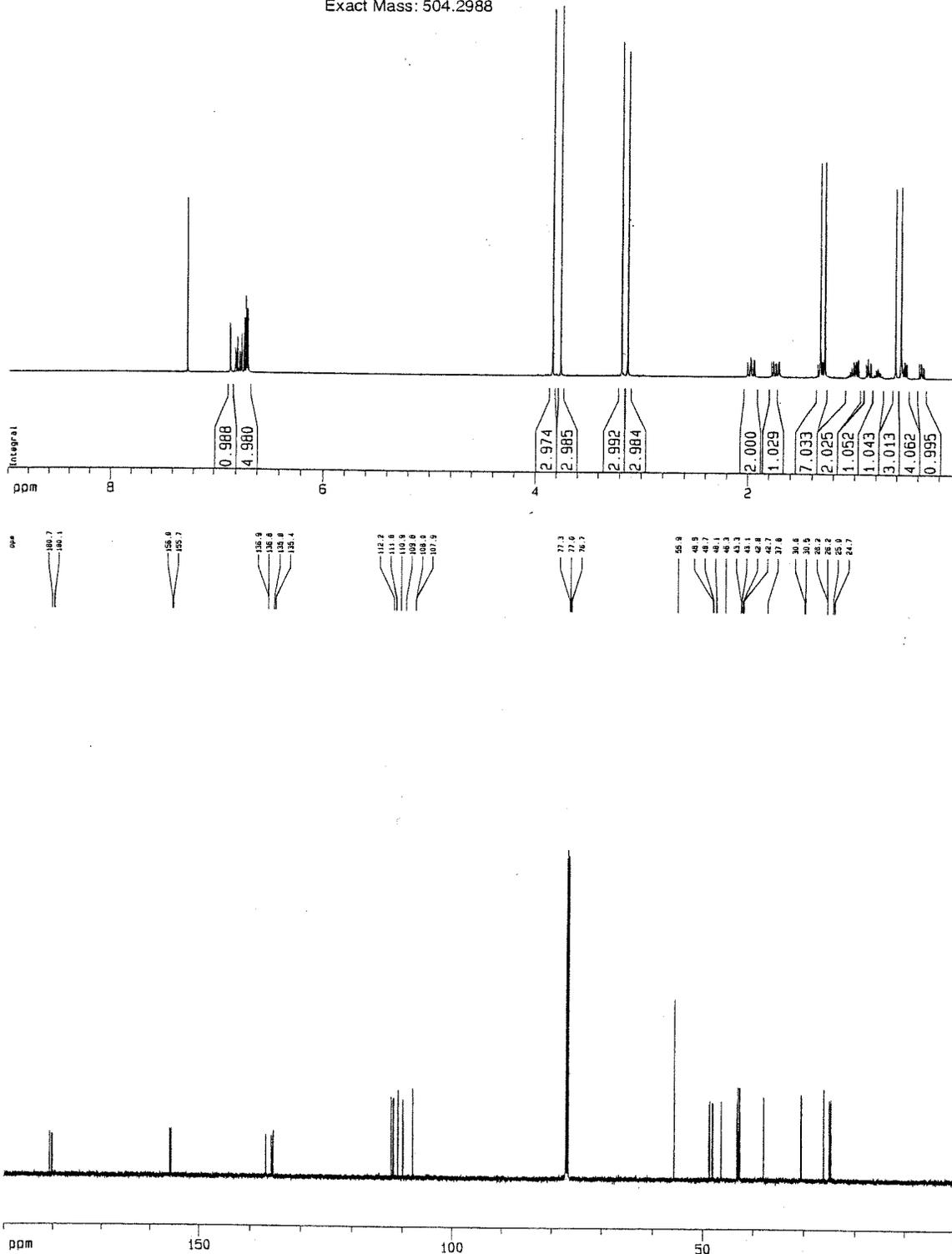


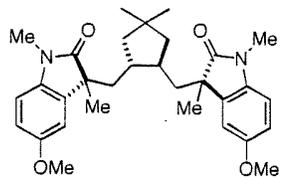
42: C<sub>31</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 504.2988



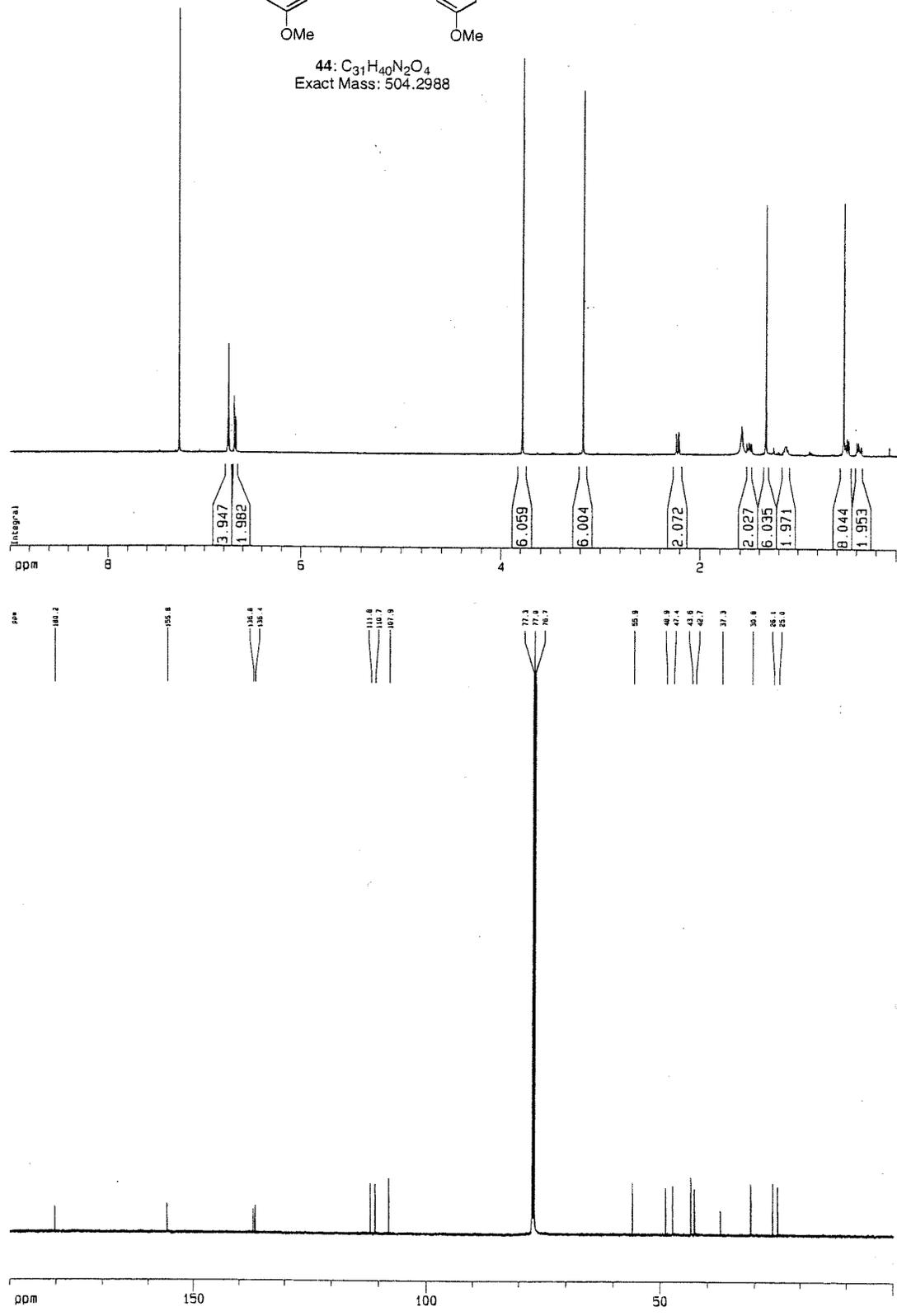


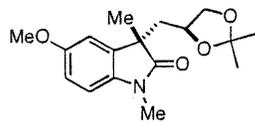
43: C<sub>31</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 504.2988



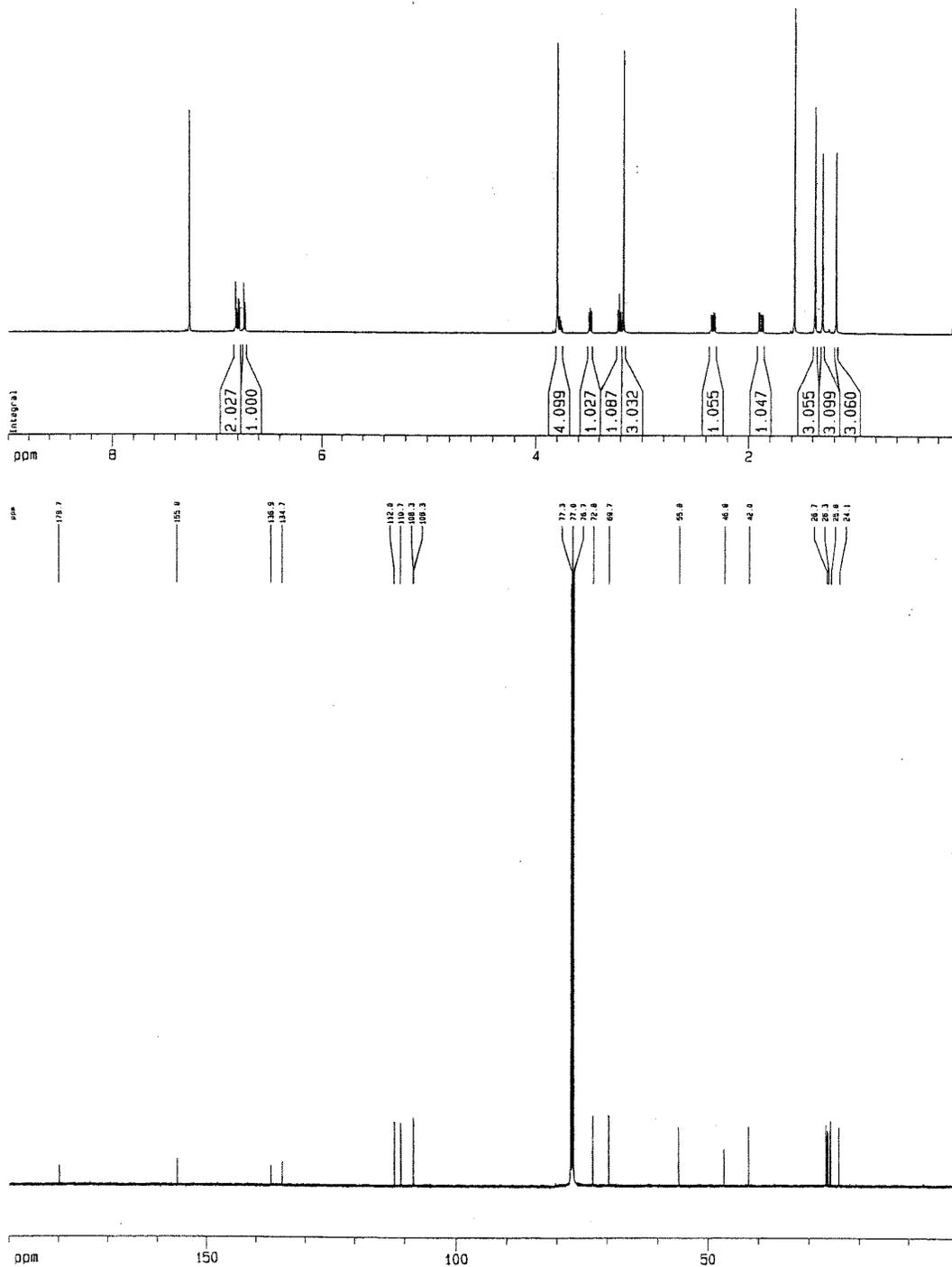


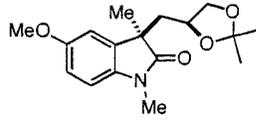
44: C<sub>31</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 504.2988



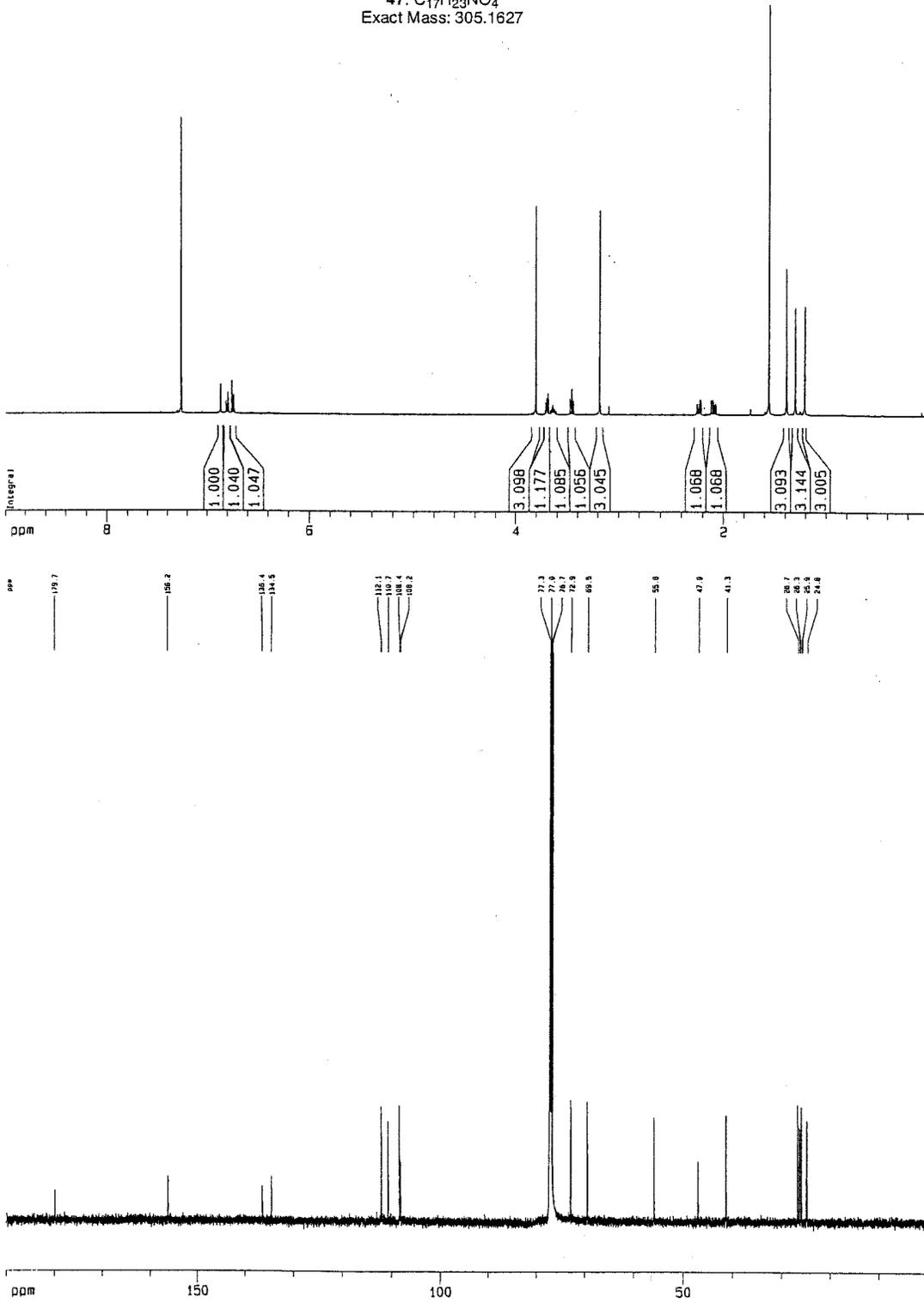


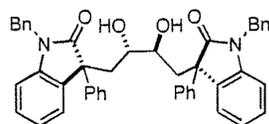
46: C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>  
 Exact Mass: 305.1627



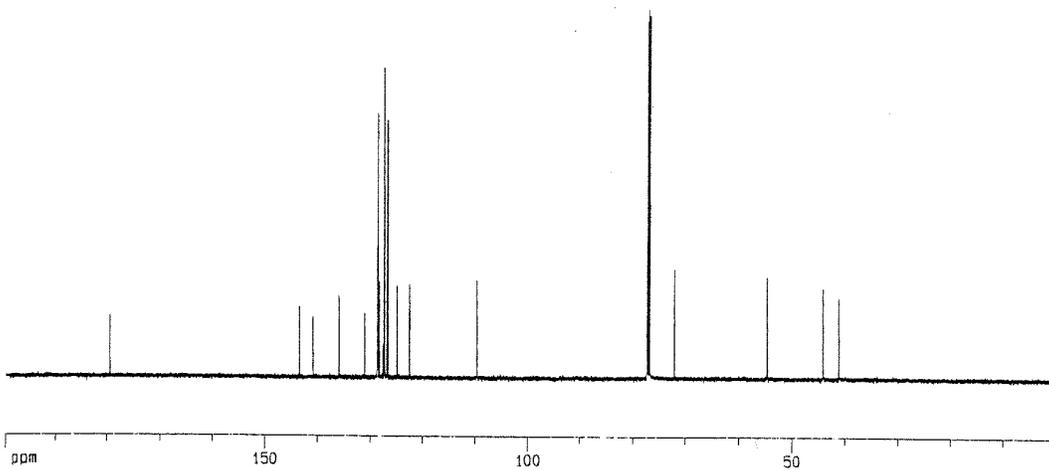
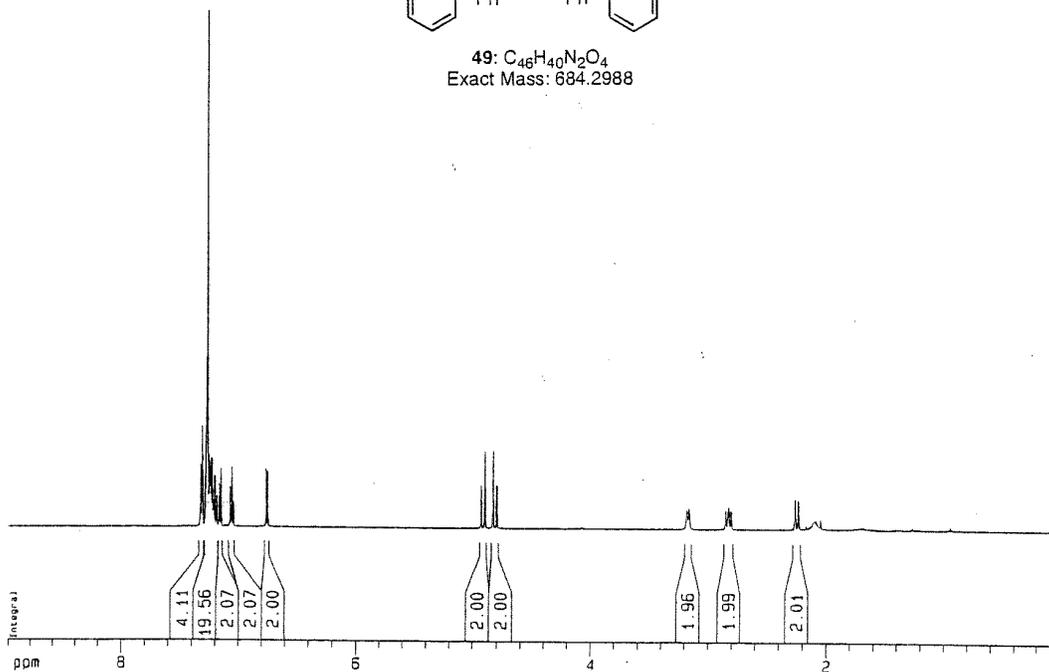


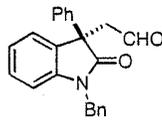
47: C<sub>17</sub>H<sub>23</sub>NO<sub>4</sub>  
Exact Mass: 305.1627



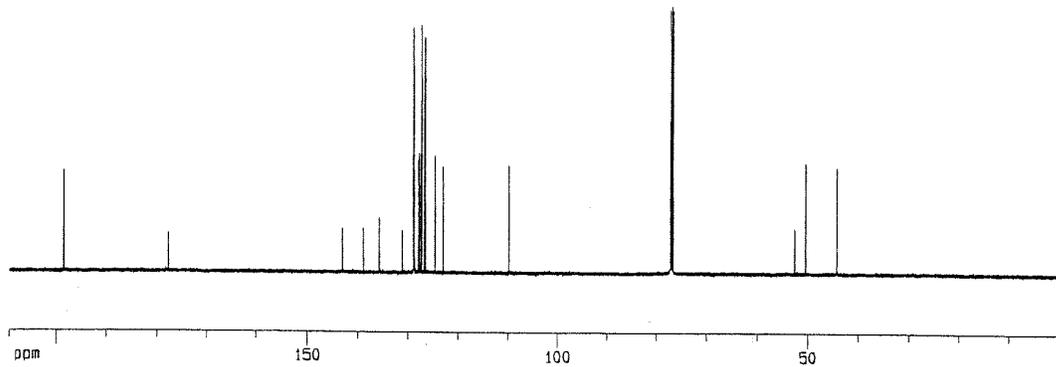
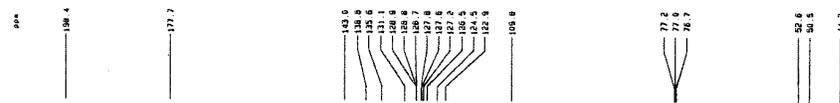
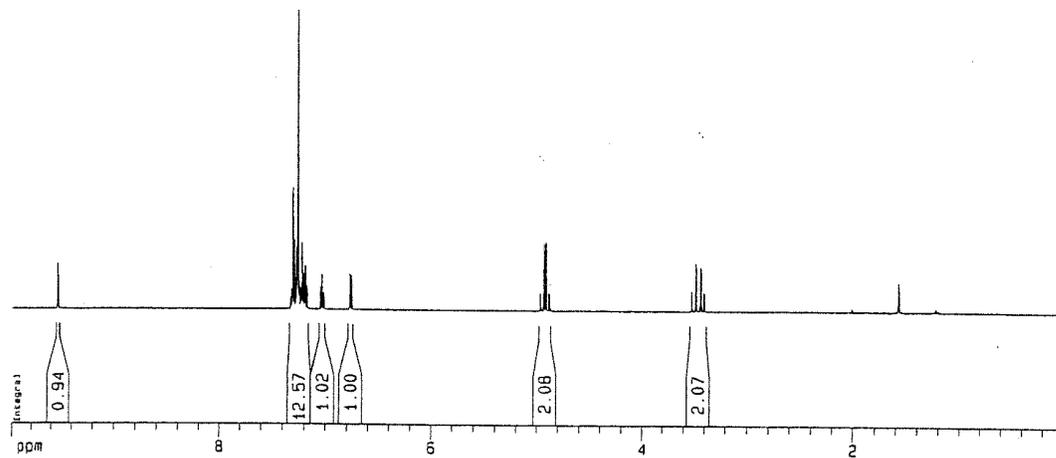


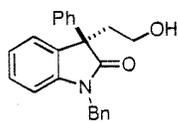
49: C<sub>46</sub>H<sub>40</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 684.2988



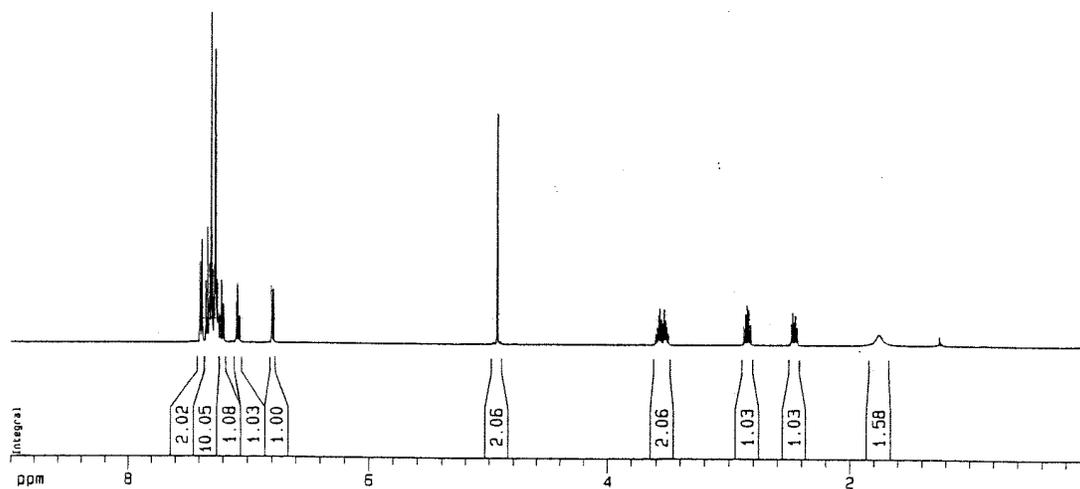


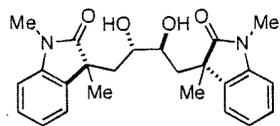
50: C<sub>23</sub>H<sub>19</sub>NO<sub>2</sub>  
Exact Mass: 341.1416



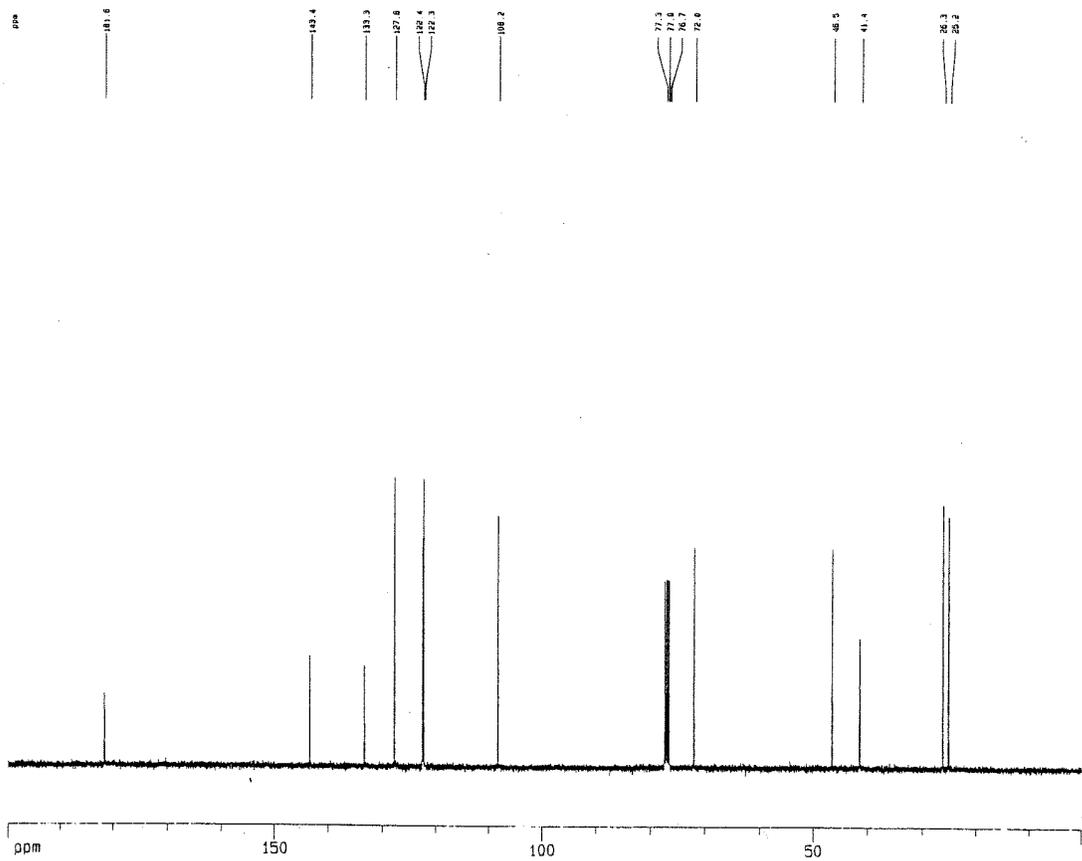
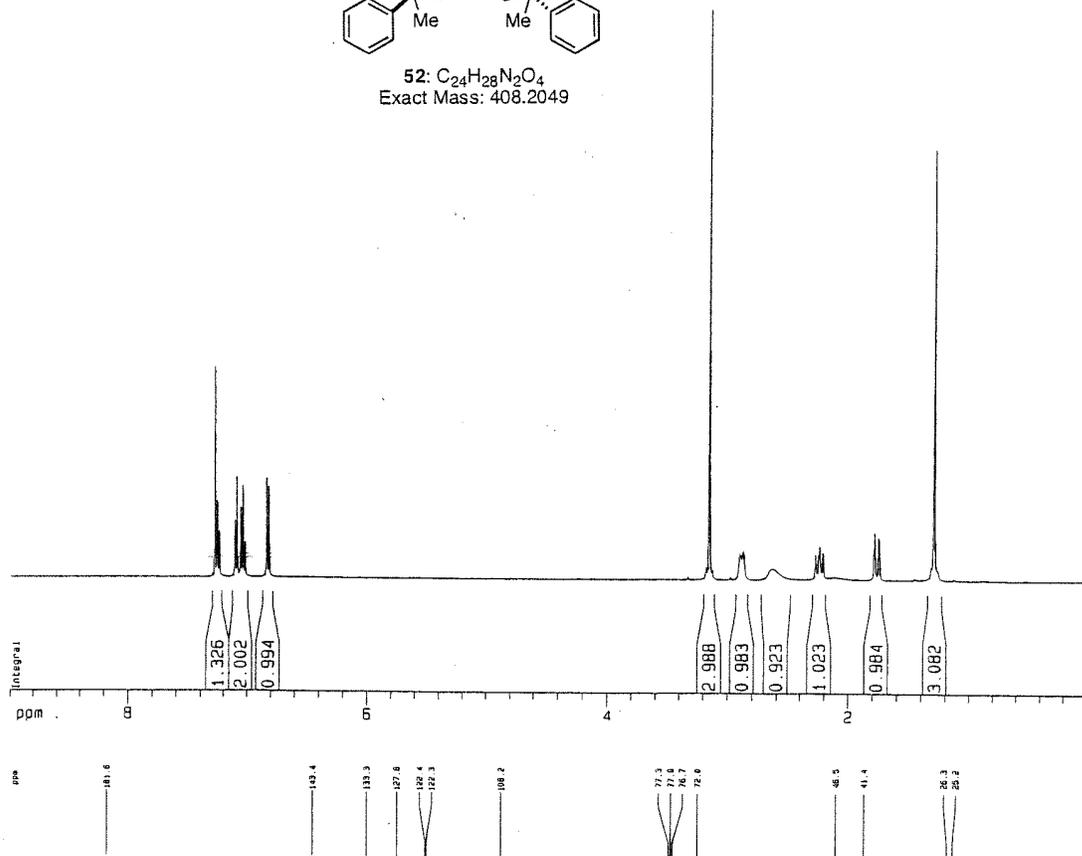


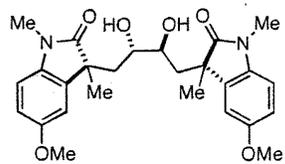
51: C<sub>23</sub>H<sub>21</sub>NO<sub>2</sub>  
Exact Mass: 343.1572



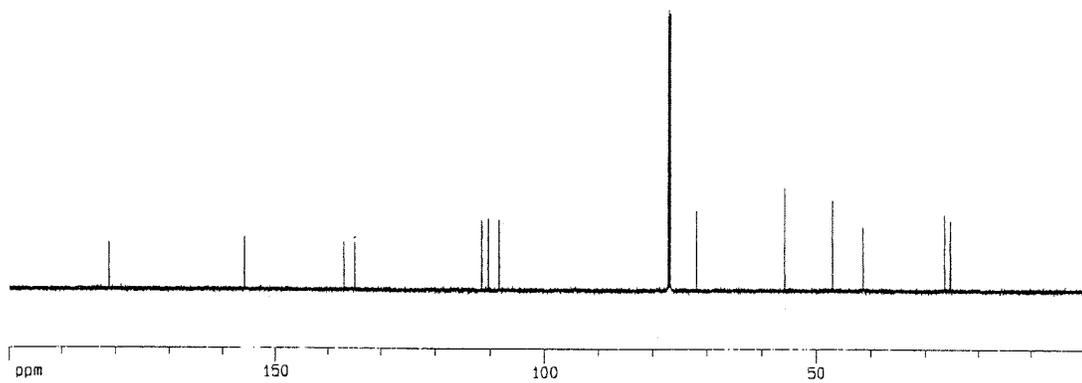
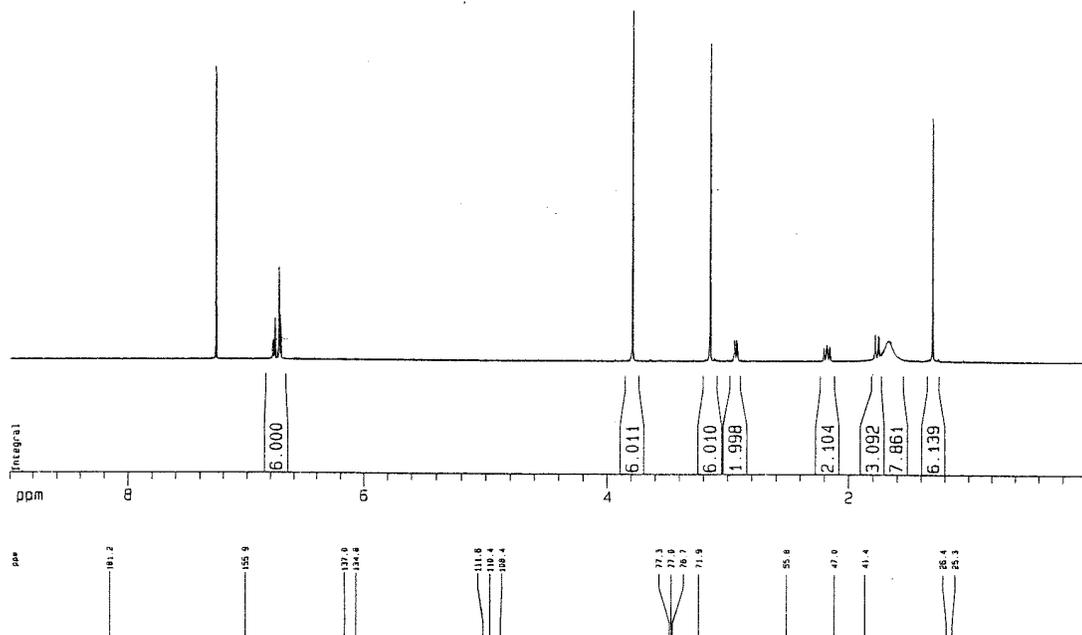


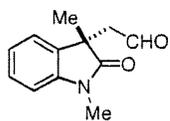
52: C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 408.2049



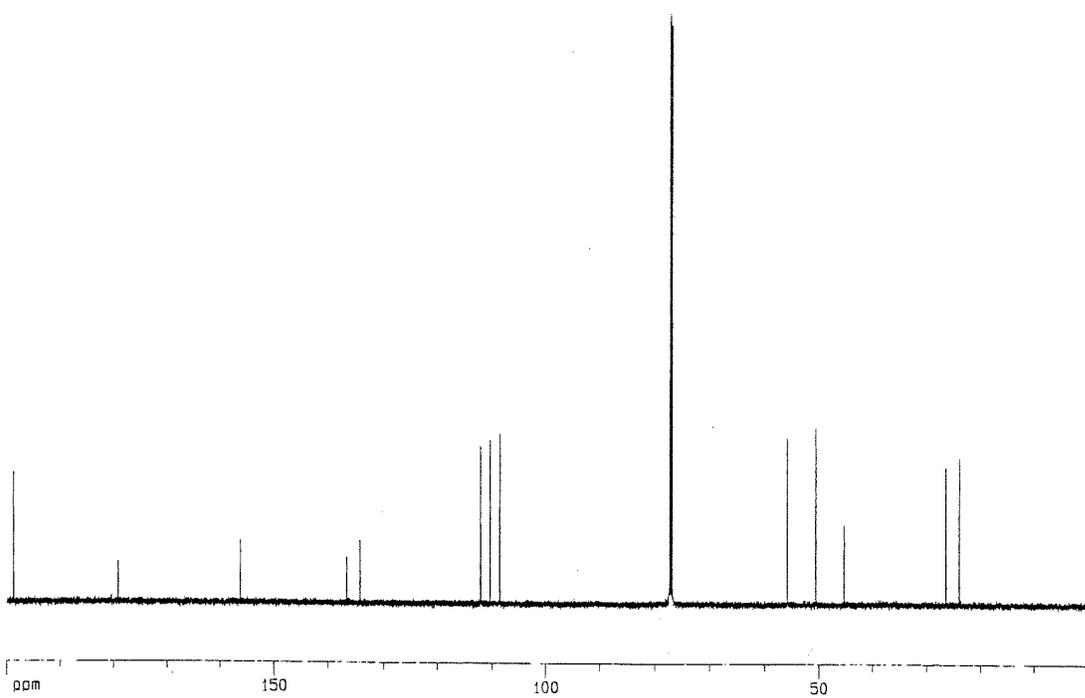
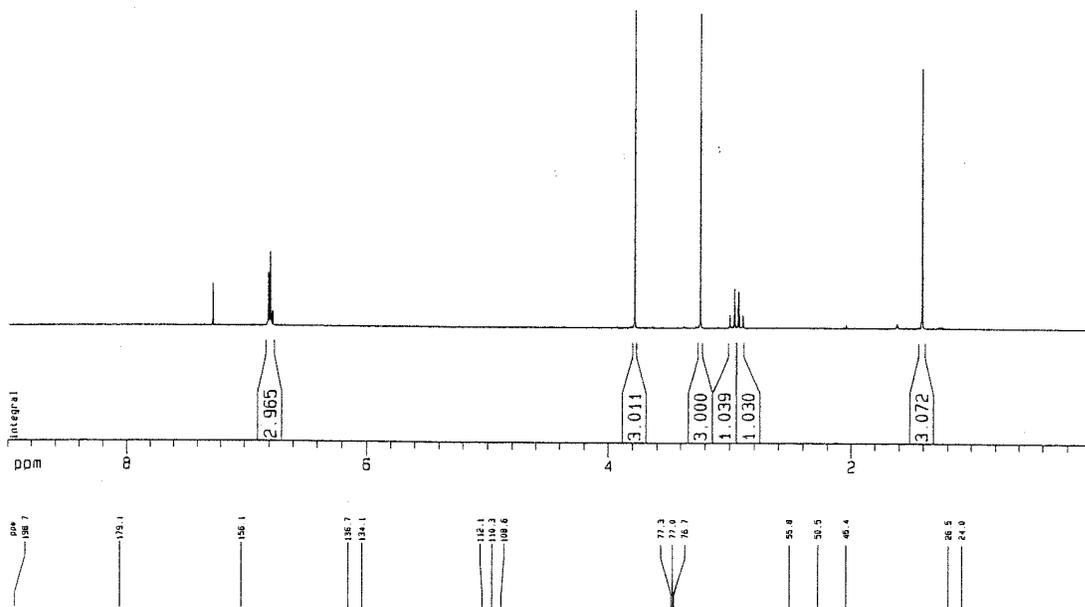


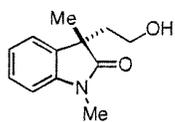
53: C<sub>26</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>  
Exact Mass: 468.2260



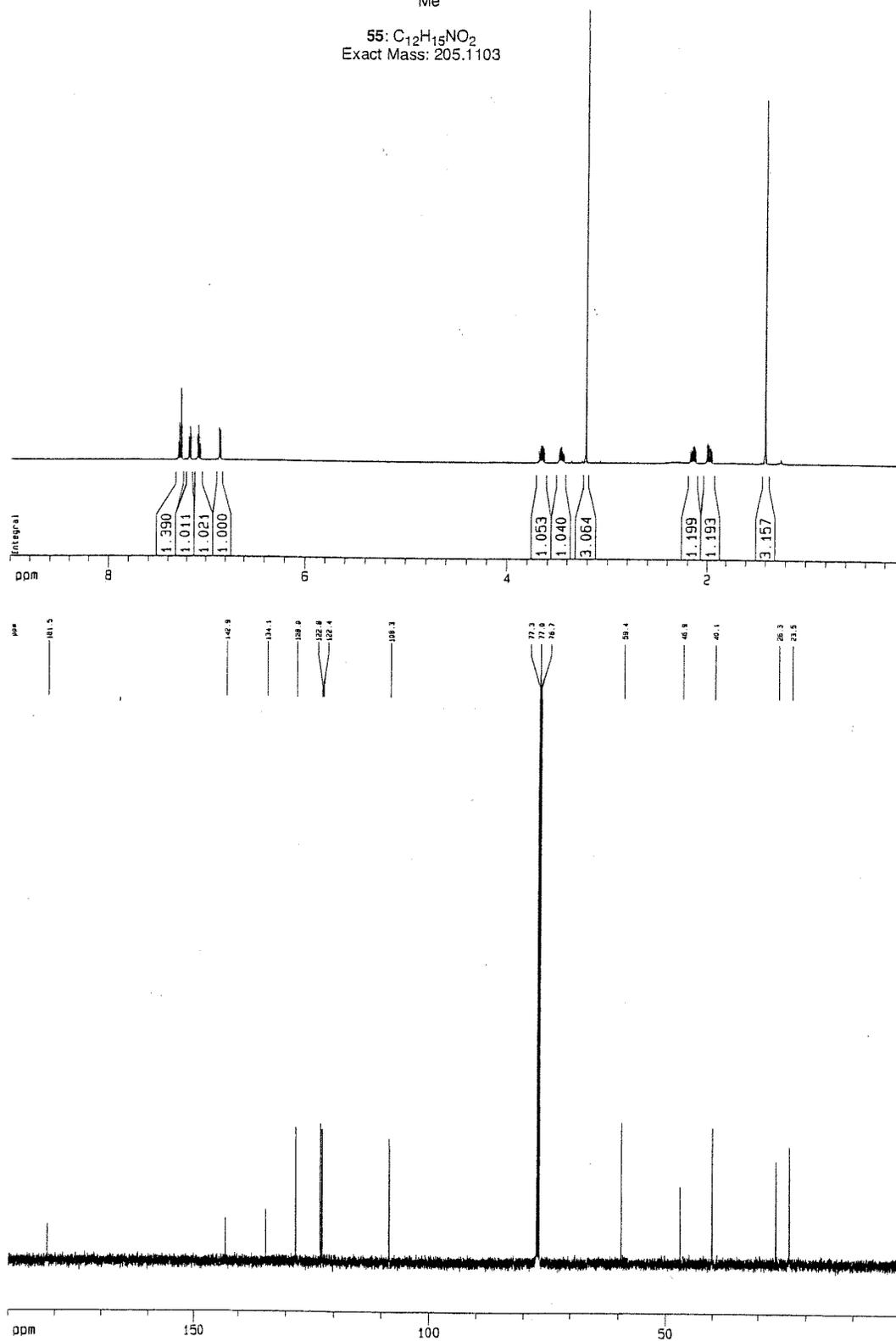


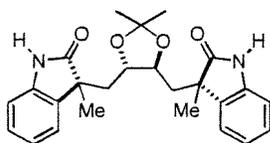
54: C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>  
Exact Mass: 203.0946



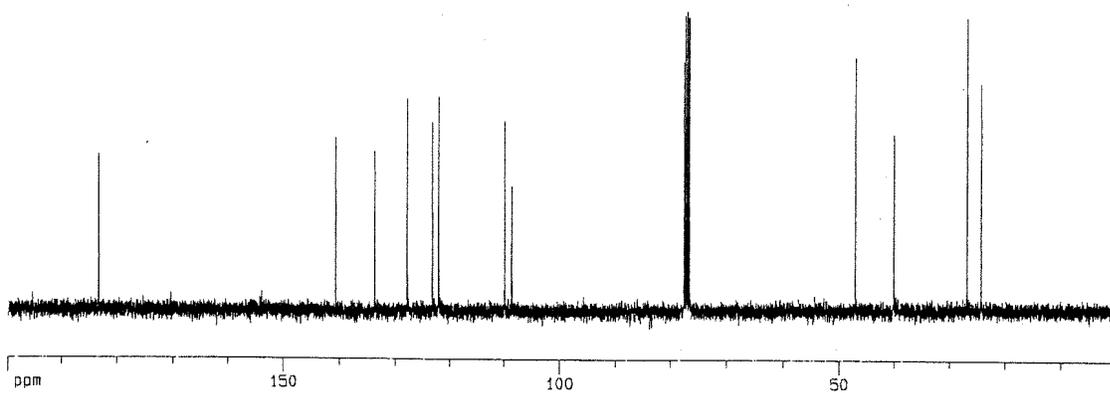
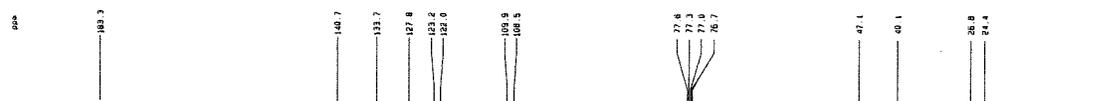
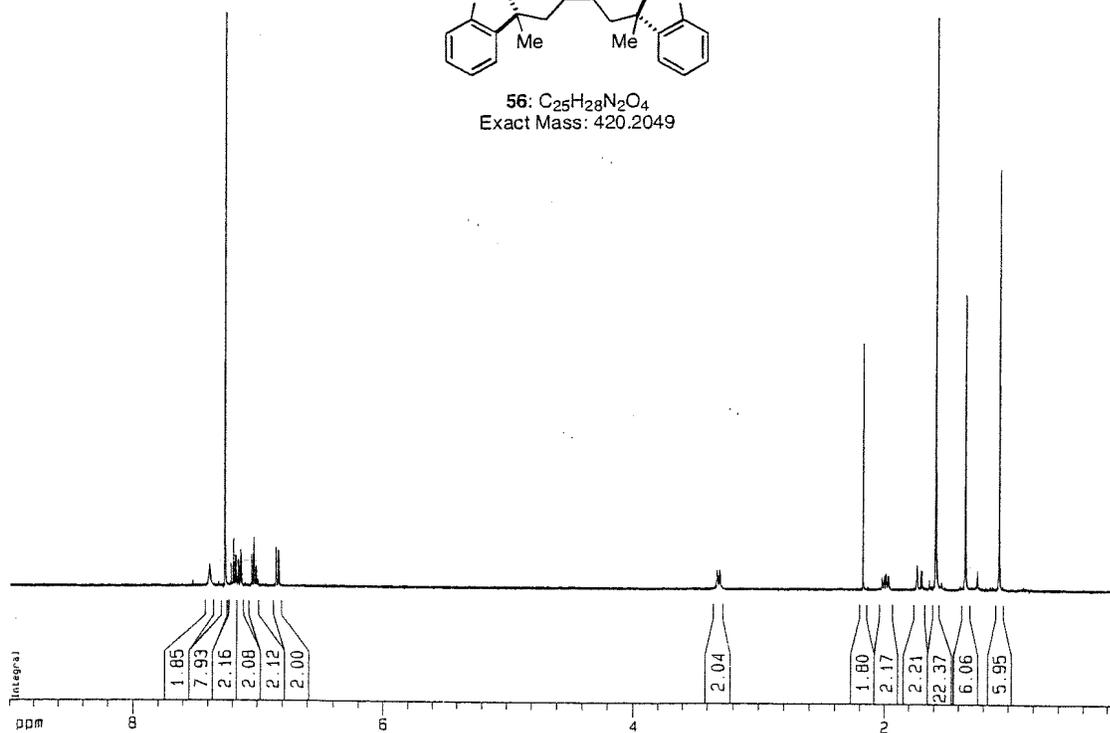


55: C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>  
Exact Mass: 205.1103

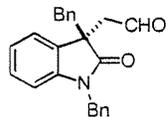




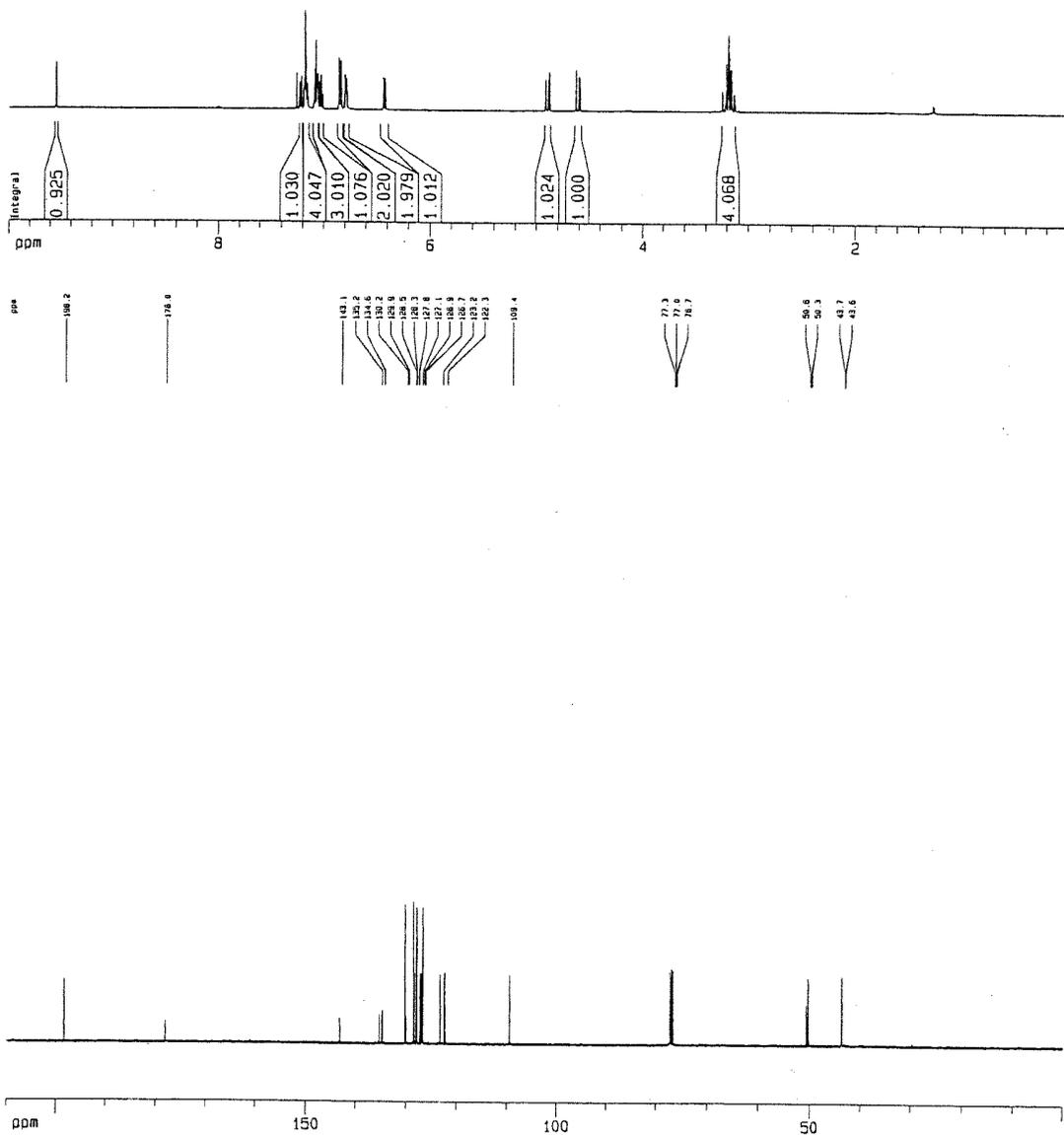
56: C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 420.2049

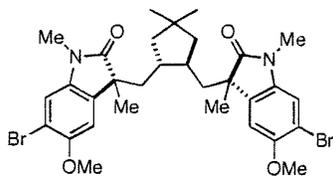




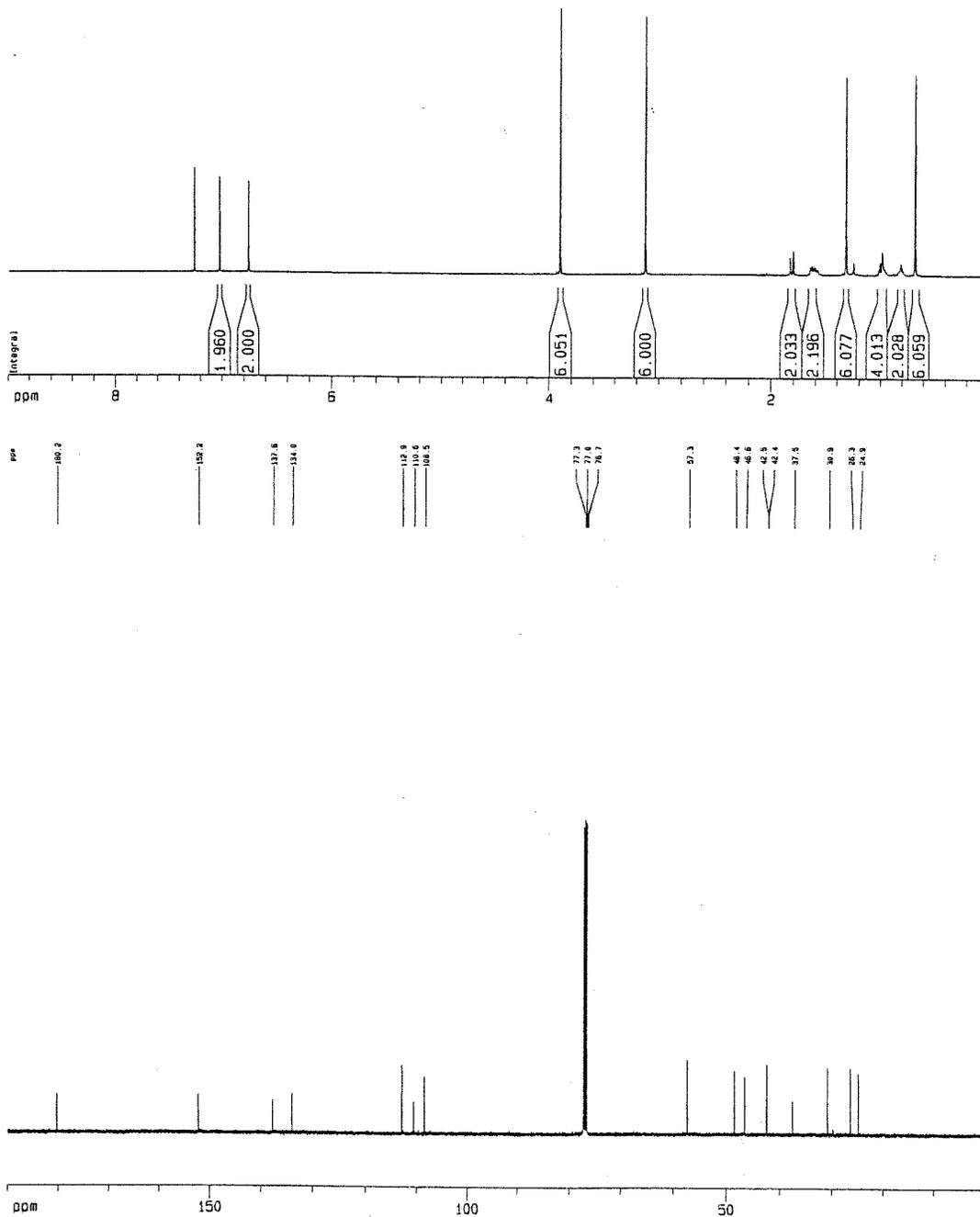


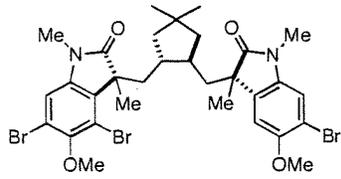
59: C<sub>24</sub>H<sub>21</sub>NO<sub>2</sub>  
 Exact Mass: 355.1572



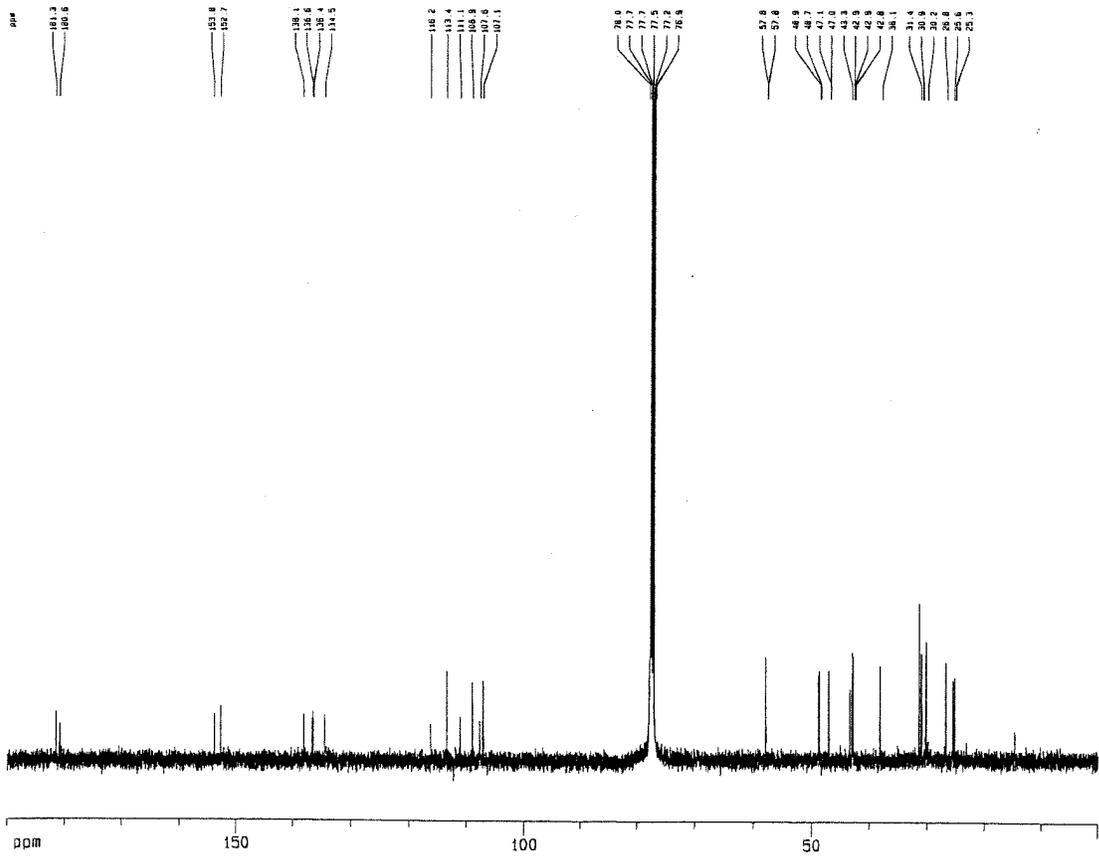
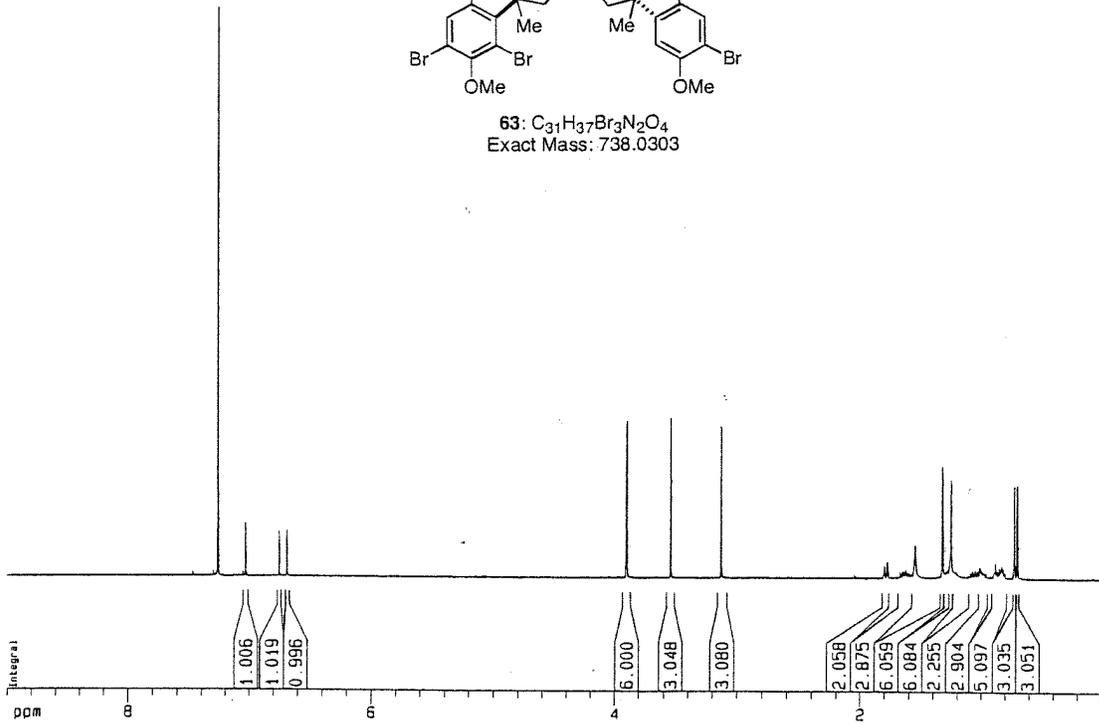


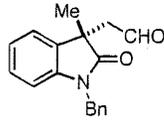
62: C<sub>31</sub>H<sub>38</sub>Br<sub>2</sub>N<sub>2</sub>O<sub>4</sub>  
Exact Mass: 660.1198



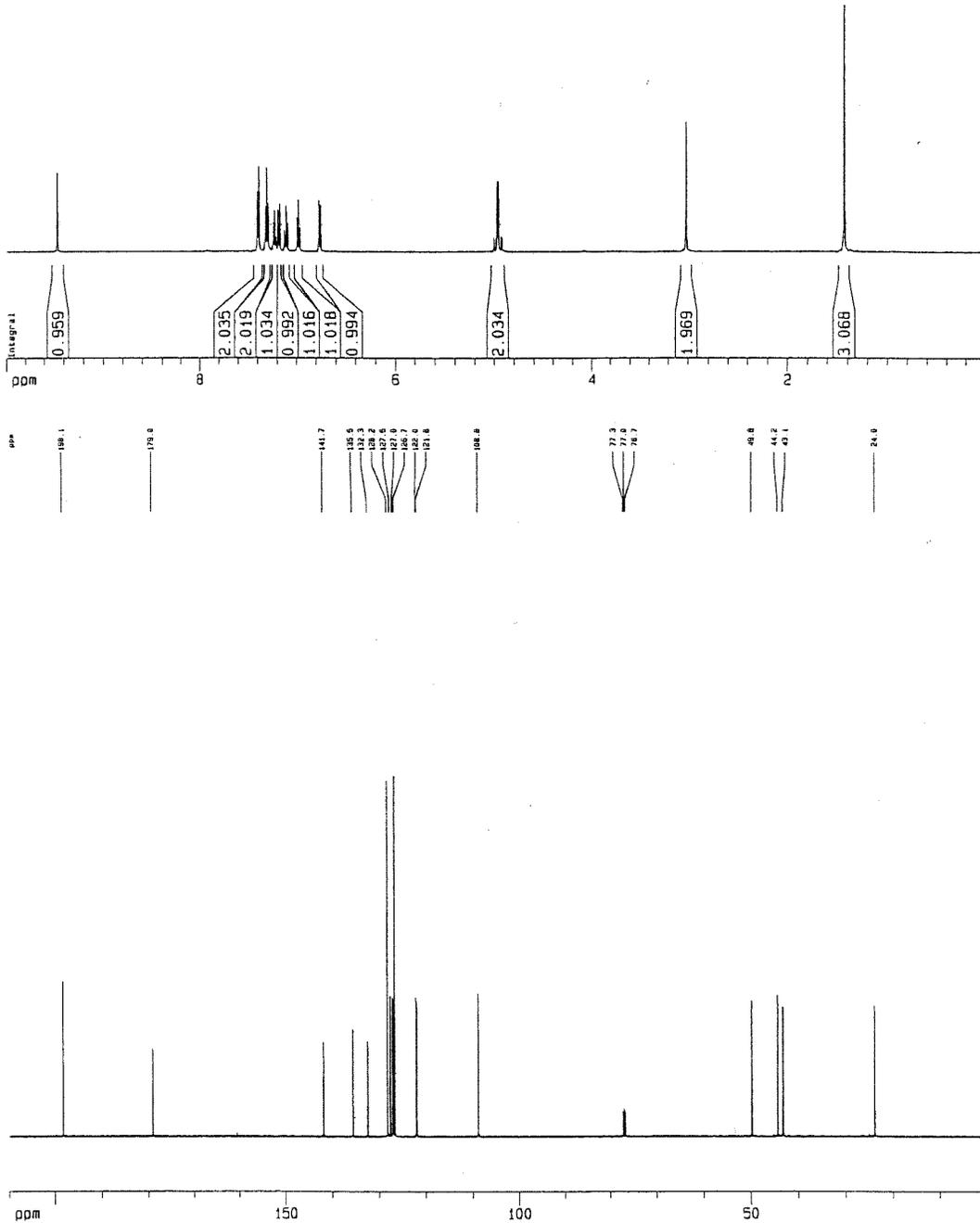


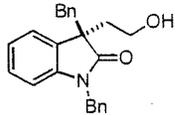
63: C<sub>31</sub>H<sub>37</sub>Br<sub>3</sub>N<sub>2</sub>O<sub>4</sub>  
 Exact Mass: 738.0303



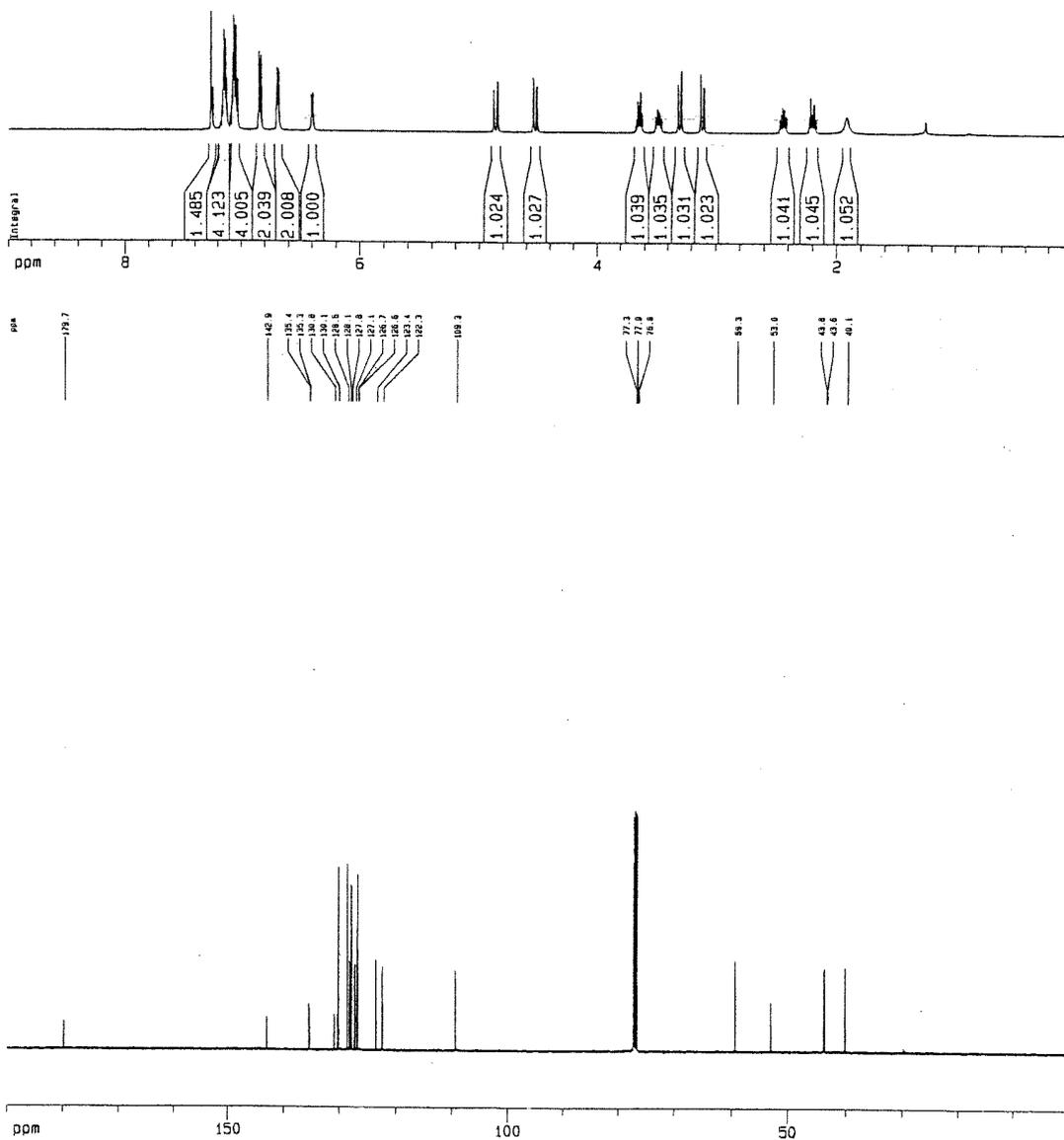


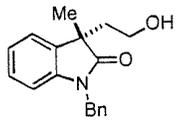
65: C<sub>18</sub>H<sub>17</sub>NO<sub>2</sub>  
Exact Mass: 279.1259



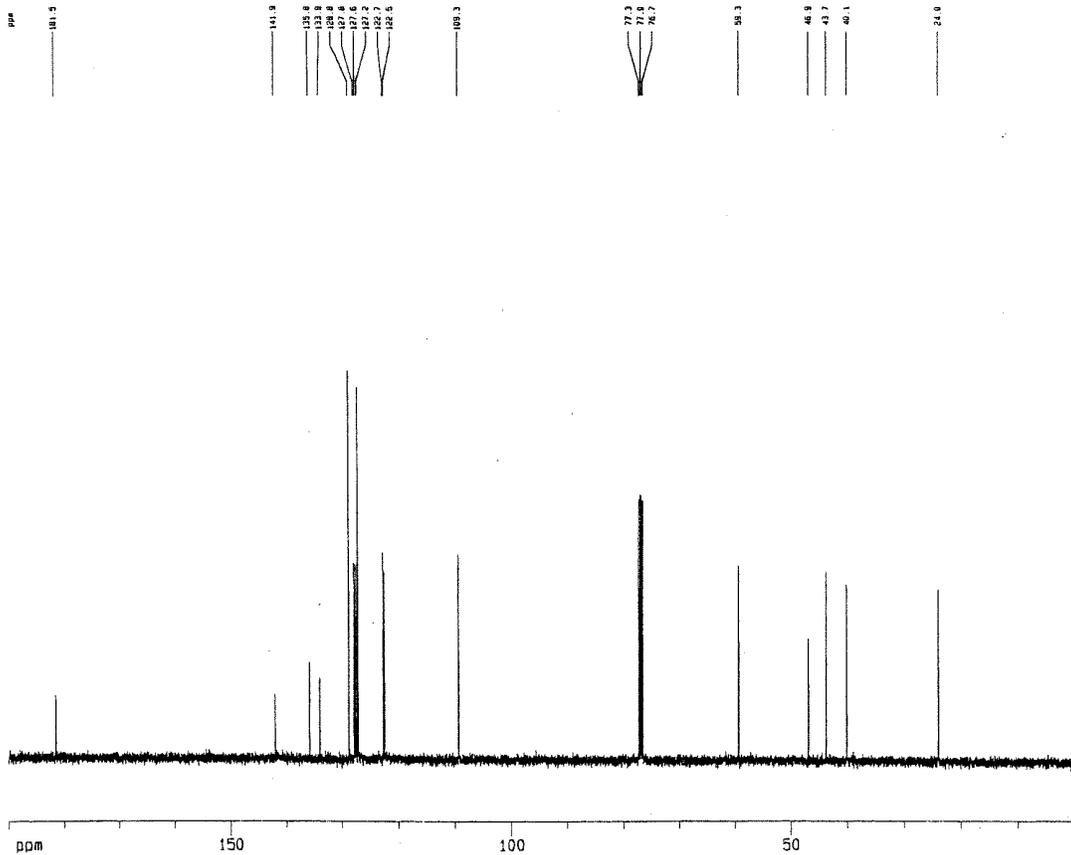
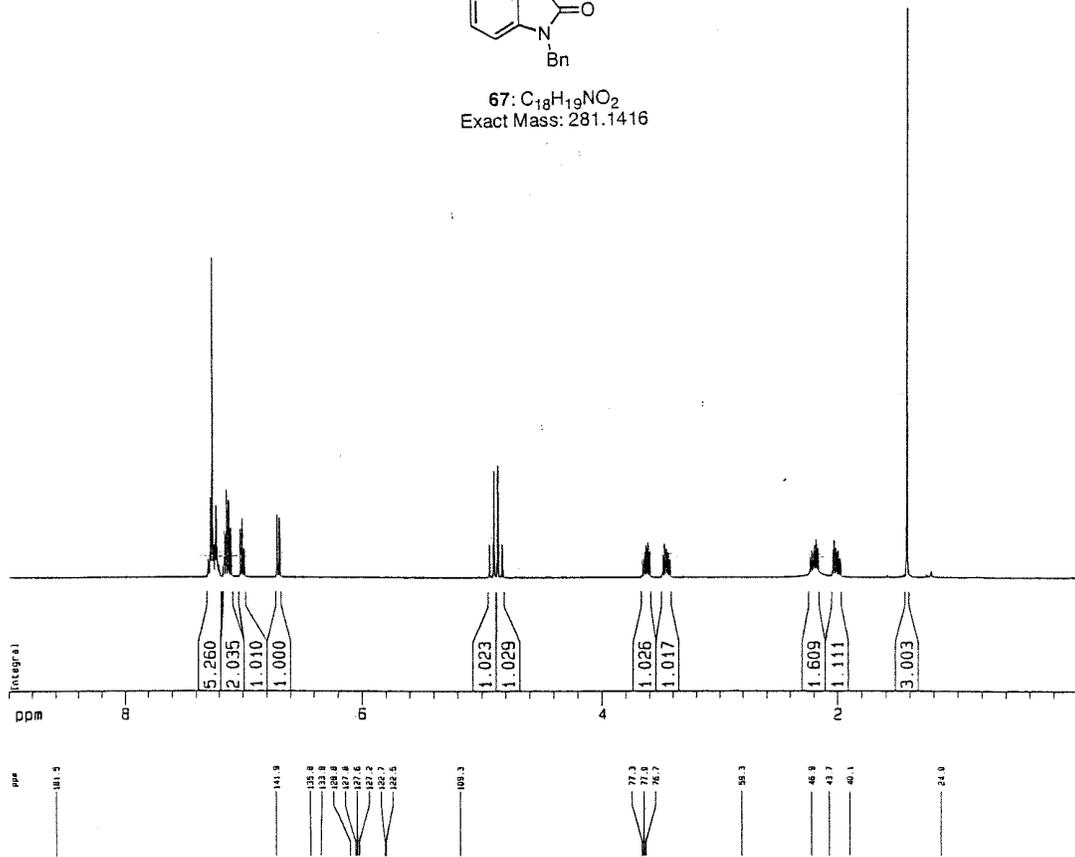


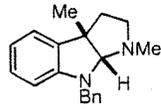
66: C<sub>24</sub>H<sub>23</sub>NO<sub>2</sub>  
Exact Mass: 357.1729



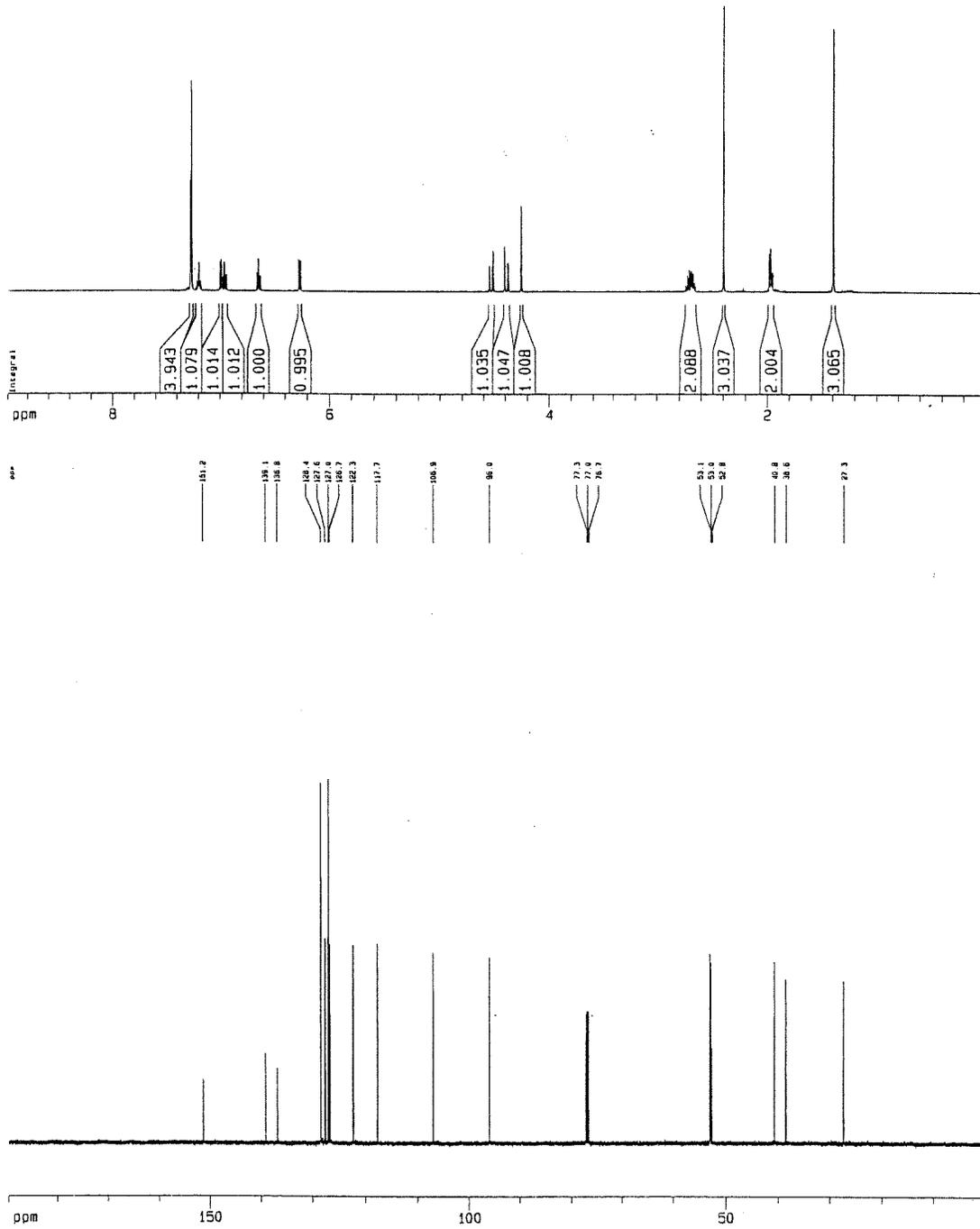


67: C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>  
Exact Mass: 281.1416





69: C<sub>19</sub>H<sub>22</sub>N<sub>2</sub>  
Exact Mass: 278.1783

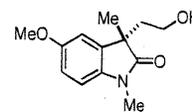


Injection Date : 10/27/03 10:50:34 AM  
 Sample Name : ah-II-79-oc  
 Acq. Operator : audris

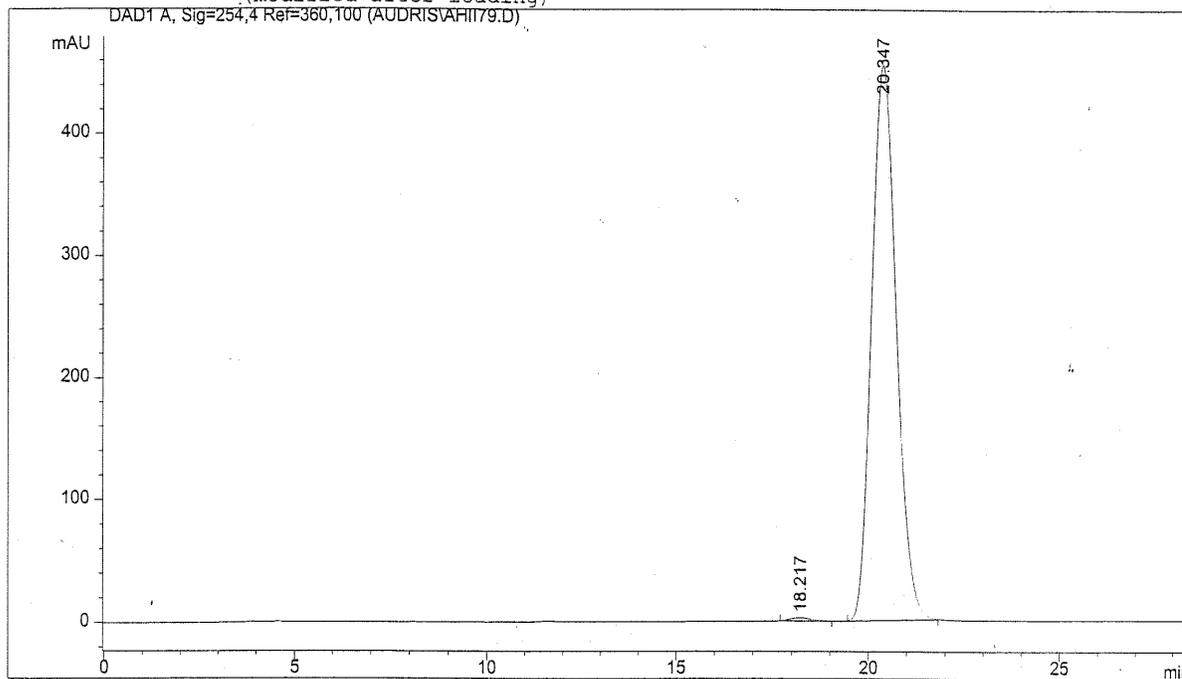
Location : Vial 81

Inj Volume : 5 µl

Method : C:\HPCHEM\1\METHODS\AHCHIRAL.M  
 Last changed : 10/27/03 9:18:00 AM by audris  
 (modified after loading)



48: C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub>  
 Exact Mass: 235.1208



=====  
 Area Percent Report  
 =====

Sorted By : Signal  
 Multiplier : 1.0000  
 Dilution : 1.0000  
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

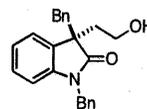
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.217	BB	0.4406	97.17242	2.67008	0.4740
2	20.347	BB	0.6997	2.04054e4	454.61688	99.5260

Totals : 2.05026e4 457.28696

Results obtained with enhanced integrator!

=====  
 \*\*\* End of Report \*\*\*

2% IPA in hexanes 0.8 mL/min  
chiralcel OJ

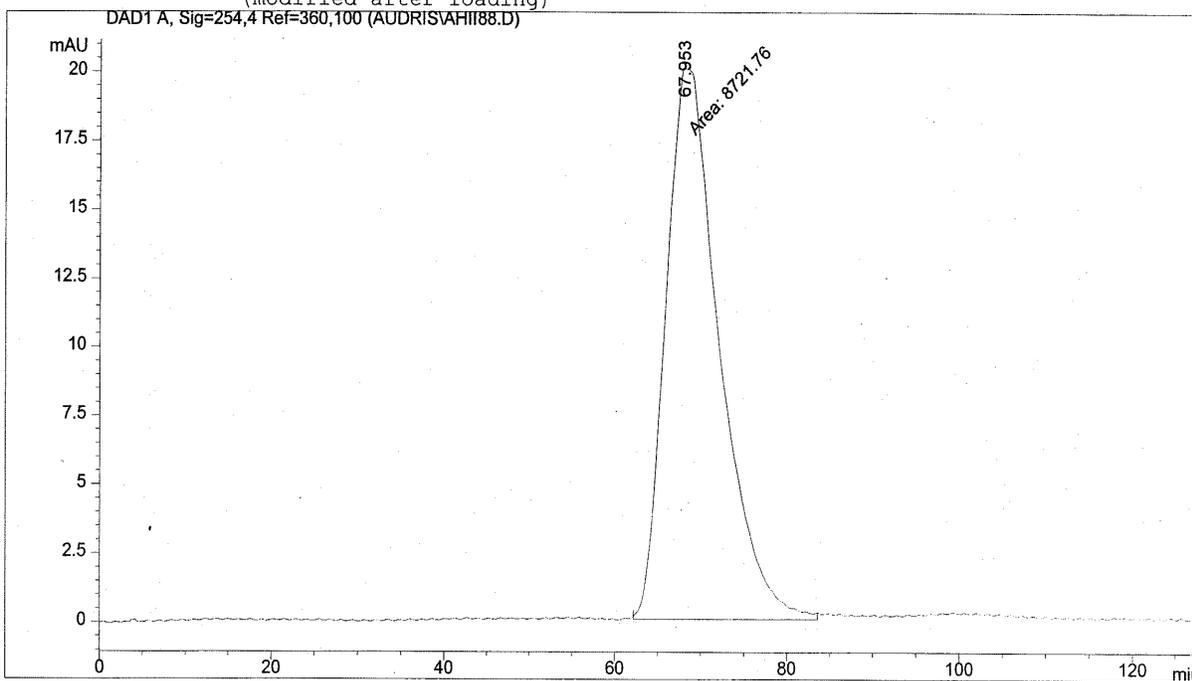


66: C<sub>24</sub>H<sub>23</sub>NO<sub>2</sub>  
Exact Mass: 357.1729

=====  
Injection Date : 1/7/04 1:15:54 PM  
Sample Name : ah-II-88-oc Location : Vial 81  
Acq. Operator : audris

Inj Volume : 5 µl

Method : C:\HPCHEM\1\METHODS\AHCHIRAL.M  
Last changed : 1/7/04 9:57:51 AM by audris  
(modified after loading)



=====  
Area Percent Report  
=====

Sorted By : Signal  
Multiplier : 1.0000  
Dilution : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	67.953	MM	7.2537	8721.76465	20.03967	100.0000

Totals : . 8721.76465 20.03967

Results obtained with enhanced integrator!

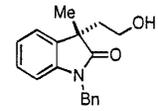
=====  
\*\*\* End of Report \*\*\*

2% IPA in hexanes 0.4 mL/min

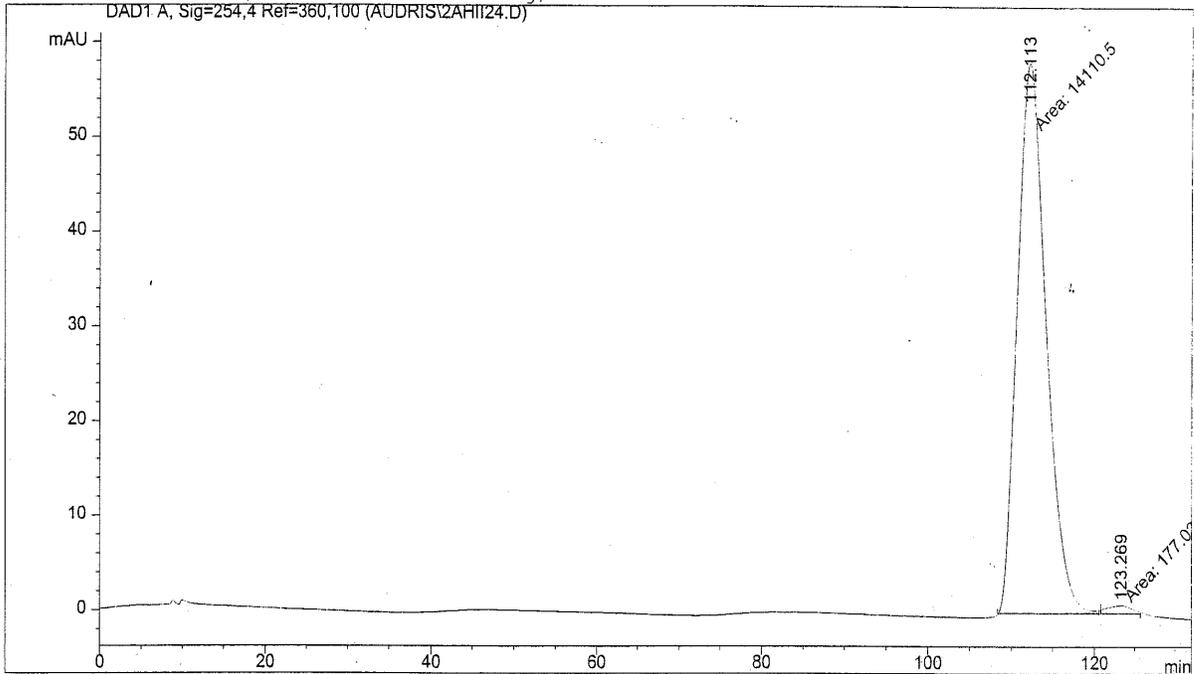
```

=====
Injection Date   : 12/11/03 12:39:38 PM
Sample Name     : ah-II-24
Acq. Operator   : audris
Location        : Vial 81
Inj Volume      : 0.5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\AHCHIRAL.M
Last changed    : 12/11/03 12:37:52 PM by audris
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\AHCHIRAL.M
Last changed    : 12/11/03 2:52:57 PM by audris
                  (modified after loading)
=====

```



67: C<sub>18</sub>H<sub>19</sub>NO<sub>2</sub>  
Exact Mass: 281.1416



=====  
Area Percent Report  
=====

```

Sorted By      : Signal
Multiplier     : 1.0000
Dilution       : 1.0000
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	112.113	MM	4.0394	1.41105e4	58.22099	98.7610
2	123.269	MM	3.4463	177.02098	8.56090e-1	1.2390

Totals : 1.42875e4 59.07708

Results obtained with enhanced integrator!

=====  
\*\*\* End of Report \*\*\*