

**Enantioselective Synthesis of 3-Substituted Indolines by Asymmetric Intramolecular  
Carbolithiation in the Presence of (-)-Sparteine**

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**Experimental Procedure**

**Typical procedure for the enantioselective carbolithiation. Synthesis of (3R)-1-Benzyl-3-methyl-2,3-dihydro-1H-indol<sup>1</sup> 3a**

A solution of *N*-Allyl-*N*-benzyl-2-bromoaniline (302 mg, 1 mmol) in dry toluene (1ml) was added dropwise at -90°C to a solution of *t*BuLi / hexane (1.3 ml, 2.2 mmol) in presence of (-)-sparteine (235  $\mu$ l, 1.5 mmol) in dry toluene (8 ml). After 18h at -90°C MeOH (1 ml) was added and the reaction mixture was poured into NH<sub>4</sub>Cl sat. The organic phase was dried over MgSO<sub>4</sub> and after evaporation of the solvent the residue was chromatographed on silical gel (eluent: petrolether / toluene : 4 / 1 containing a few drops of 32% NH<sub>3</sub>). Yield 85% (190 mg); ( $\alpha$ )<sub>D</sub><sup>20</sup> = -49.7° (c = 1, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat):  $\nu$  = 2958, 1605, 1448, 1451 cm<sup>-1</sup>; <sup>1</sup>H-MNR (250 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.30 (d, *J* = 6.8 Hz, 3H), 2.83 (t, *J* = 8.4 Hz, 1H), 3.30 (sext., *J* = 8.2 Hz, 1H), 3.51 (t, *J* = 8.5 Hz, 1H), 4.11 and 4.36 (AB-Signal, *J*<sub>AB</sub> = 14.8 Hz, 2H), 6.50 (dd, *J* = 1.0, 7.4 Hz, 1H), 6.70 (dt, *J* = 1.0, 7.3 Hz, 1H), 7.00-7.15 (m, 2H, C4-H), 7.20-7.40 (m, 5H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 18.6, 35.2, 53.4, 61.6, 107.0, 117.7, 123.1, 127.0, 127.4, 127.9, 128.4, 135.0, 138.5, 152.1; MS, *m* / *e* (rel. intensity) 223 (95) (M<sup>+</sup>), 208 (45) (M<sup>+</sup>-CH<sub>3</sub>), 91 (base) (C<sub>6</sub>H<sub>5</sub>N<sup>+</sup>). Anal. Calcd. for C<sub>16</sub>H<sub>17</sub>BrN: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.20; H, 7.70; N, 6.40.

**Synthesis of (3R)-1-Benzyl-6-benzyloxy-3-methyl-2,3-dihydro-1H-indol 3c**

Yield 86% (283 mg); ( $\alpha$ )<sub>D</sub><sup>20</sup> = -39.0° (c = 0.65, CH<sub>2</sub>Cl<sub>2</sub>); IR (CH<sub>2</sub>Cl<sub>2</sub>):  $\nu$  = 2926, 2870, 2826, 1620 (C=C), 1495 cm<sup>-1</sup>; <sup>1</sup>H-MNR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 1.26 (d, *J* = 6.6 Hz, 3H), 2.85 (t, *J* = 8.6 Hz, 1H), 3.24 (sext., *J* = 7.0 Hz, 1H), 3.51 (t, 8.6 Hz, 1H), 4.10 and 4.31 (AB-Signal, *J*<sub>AB</sub> = 14.8 Hz, 2H), 4.98 (s, 2H), 6.18 (d, *J* = 2.2 Hz, 1H), 6.29 (dd, *J* = 2.2, 8.2 Hz, 1H), 6.93 (dd, *J* =

<sup>1</sup> Sole, D; Cancho, Y; Llebaria, A; Moreto, J.M; Delgado, A. *J. Org. Chem.* 1996, 61, 5895-5904.

0.9, 8.2 Hz, 1H), 7.22-7.46 (m, 10H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 19.0, 34.5, 53.0, 61.9, 70.1, 95.4, 102.4, 123.3, 127.1, 127.5, 127.77, 127.83, 127.87, 128.4, 128.5, 137.4, 138.2, 153.3, 159.4; MS  $m/e$  (rel. intensity) 329 (5) ( $\text{M}^+$ ), 238 (41) ( $\text{M}^+ - \text{CH}_2\text{Ph}$ ), 91 (base) ( $\text{C}_6\text{H}_5\text{N}^+$ ). Anal. Calcd. for  $\text{C}_{23}\text{H}_{23}\text{NO}$ : C, 83.85; H, 7.04; N 4.25. Found: C, 83.65; H, 7.05; N, 4.36.

**Procedure for NMR-determination of enantiomeric purity of (3R)-1-Benzyl-6-benzyloxy-3-methyl-2,3-dihydro-1H-indol 3c**

Into a dried NMR tube were introduced the chiral indoline (5-10 mg), binaphthylphosphonic acid (1.0 equiv) and  $\text{CDCl}_3$  (700  $\mu\text{l}$ ). The tube was shaking until completed dissolution and the  $^1\text{H}$  spectrum was recorded; ee = 88%.

**Typical procedure for the deprotection of N-bezylindolines. Synthesis of (3R)-3-Methyl-2,3-dihydro-1-H-indol<sup>2</sup>**

To a flask were added **3a** (223 mg, 1.0 mmol), NaI (300 mg, 2.0 mmol), 1-chloroethyl chloroformate (0.2 ml, 1.8 mmol), and acetone (3 ml). The resulting mixture was stirred at room temperature for 3h, after which time the solvent was removed, dissolved in a minimum amount of ether and was eluted down a flash column using 9:1 petrolether/ether as eluent. The carbamat was collected and dissolved in methanol (3ml). The solution was heated to reflux for 90 min, cooled to room temperature and poured into a separatory funnel containing ether and  $\text{NaHCO}_3$  solution. The organic layer was collected, washed with water and brine, dried over  $\text{MgSO}_4$  and the solvent were removed by rotary evaporation. The product was isolated by flash chromatography to give 114 mg (86%) of a colorless oil. IR (neat):  $\nu$ : 3383 (NH), 2960, 2925, 2874, 1608, 1488, 1462, 1240  $\text{cm}^{-1}$ .  $^1\text{H}$ -MNR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.30 (d,  $J$ = 7.0, 1H), 3.09 (t,  $J$ = 8.6 Hz, Hz, 1H), 3.57 (br s, 1H), 3.67 (t,  $J$ = 8.6 Hz, 1H), 6.62 (d,  $J$ = 7.4 Hz, 1H), 6.73 (t,  $J$ = 7.4 Hz, 1H), 7.02 (t,  $J$ = 7.8 Hz, 1H), 7.08 (d,  $J$ = 7.4 Hz, 1H).  $^{13}\text{C}$ -NMR (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 18.5, 36.5, 55.3, 109.4, 118.6, 123.3, 127.2, 134.3, 151.1; MS  $m/e$  (rel. intensity) 133 (12), 118 (base) ( $\text{M}^+ - \text{CH}_3$ ), 91 (47) ( $\text{C}_6\text{H}_5\text{N}^+$ ). GC analysis was performed using CYCLOSIL-B chiral column. flow rate 30 mL/min, method 50°C fo 2 min, ramp @ 10°C/min to 220 for 15 min, Tr : 14.83 (3S) and 15.01 (3R) provided the ee = 87%.

<sup>2</sup> Buchwald, S.L.; Tidwell, J.H. *J. Am. Chem. Soc.* 1994, 116, 11797-11810.

**(3S)-1-Benzyl-3-bromomethyl-2,3-dihydro-1H-indol 8a**

A solution of *N*-Allyl-*N*-benzyl-2-bromoaniline (302 mg, 1 mmol) in dry toluene (1ml) was added dropwise at -90°C to a solution of *t*BuLi / hexane (1.3 ml, 2.2 mmol) in presence of (-)-sparteine (235  $\mu$ l, 1.5 mmol) in dry toluene (8 ml). After 18h at -90°C dibromoethan (172 $\mu$ l, 2 mmol) in 1ml toluene was added and the reaction mixture was poured into NH<sub>4</sub>Cl sat. The organic phase was dried over MgSO<sub>4</sub> and after evaporation of the solvent the residue was chromatographed on silical gel (eluent: cyclohexane / toluene : 4 / 1 containing a few drops of 32% NH<sub>3</sub>). Yield 70% (210 mg) ; ( $\alpha$ )<sub>D</sub><sup>20</sup> = -50.8° (c = 1, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H-MNR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 3.28 (dd, *J*= 5.3, 9.8 Hz, 1H), 3.43 (t, *J*= 11.0 Hz, 1H), 3.53 (t, *J*= 8.95 Hz, 1H), 3.60-3.70 (m, 2H, C3-H), 4.27 (s, 1H), 6.51 (d, *J*= 8.2 Hz, 1H), 6.69 (t, *J*= 7.4 Hz, 1H), 7.09-7.13 (m, 2H), 7.27-7.35 (m, 5H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 35.6, 43.5, 52.8, 58.5, 107.4, 117.6, 124.3, 127.2, 127.7, 128.5, 128.8, 129.8, 137.9, 152.3; MS *m/e* (rel. intensity) 301 / 303 (35) (M<sup>+</sup>), 222 (40) (M<sup>+</sup>-CH<sub>2</sub>Br), 91 (base) (C<sub>6</sub>H<sub>5</sub>N<sup>+</sup>); Anal. Calcd. for C<sub>16</sub>H<sub>16</sub>BrN: C, 63.59; H, 5.34; N 4.63. Found: C, 63.80; H, 5.10; N, 4.23.

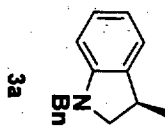
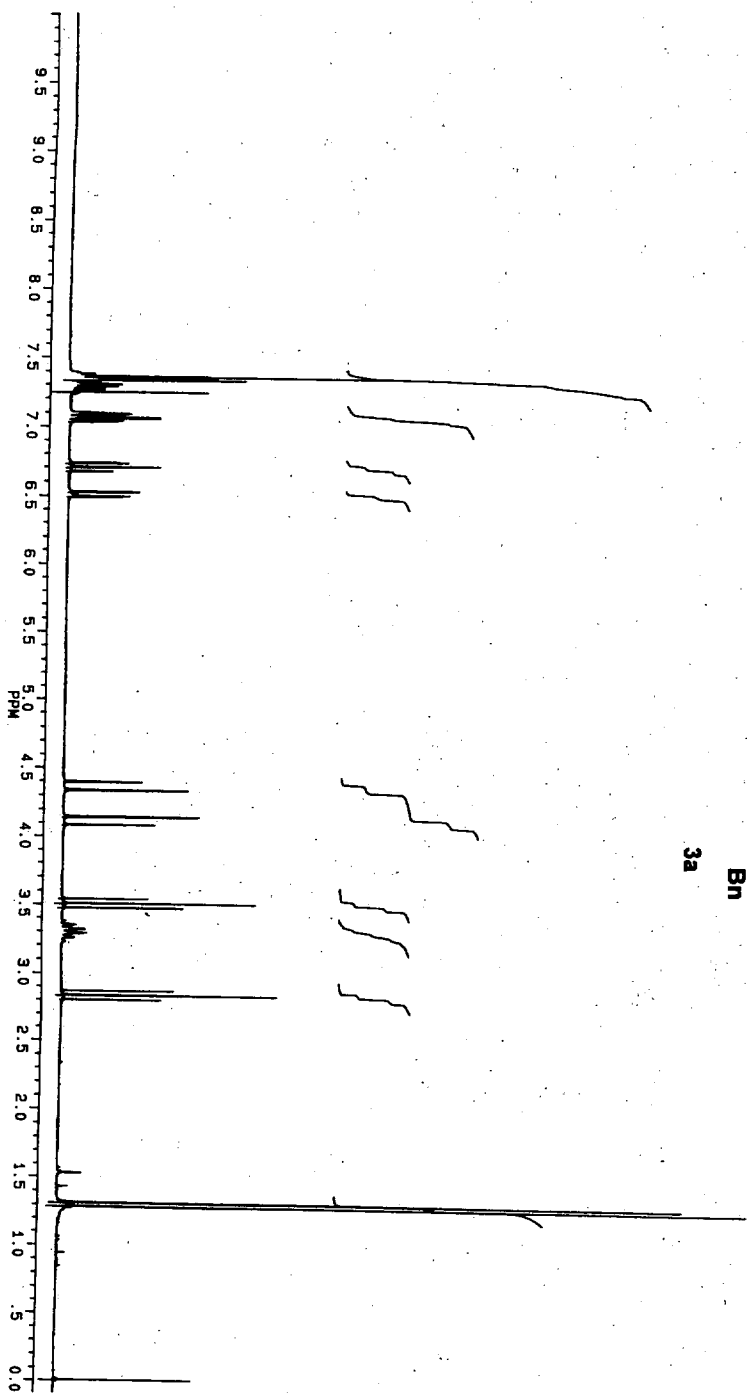
**1,3-Dibenzyl-2,3-dihydro-1H-indol<sup>3</sup> 7**

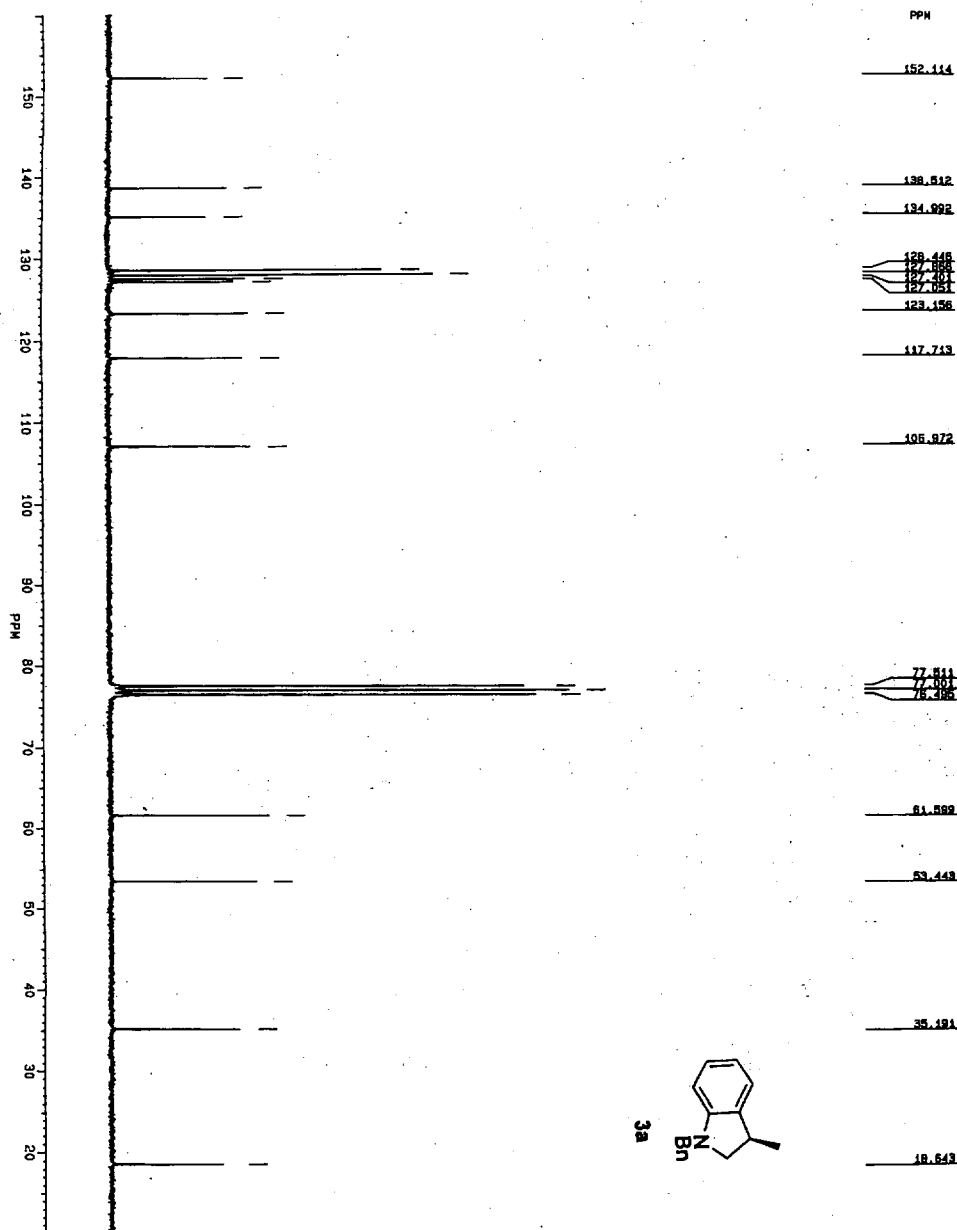
A solution of **6E** or **6Z** (287 mg, 1 mmol) in dry toluene (1ml) was added dropwise at -78°C to a solution of *t*BuLi / hexane (1.3 ml, 2.2 mmol) in presence of (-)-sparteine (235  $\mu$ l, 1.5 mmol) in dry toluene (8 ml). After 18h at -50°C MeOH (1 ml) was added and the reaction mixture was poured into NH<sub>4</sub>Cl sat. The organic phase was dried over MgSO<sub>4</sub> and after evaporation of the solvent the residue was chromatographed on silical gel (eluent: petrolether / toluene : 10 / 1 containing a few drops of 32% NH<sub>3</sub>). Yield 90% (270 mg) ; ( $\alpha$ )<sub>D</sub><sup>20</sup> = -34.6° (c = 1, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat):  $\nu$  = 3064, 3025, 2920, 2851, 1603, 1495, 1452 cm<sup>-1</sup>; <sup>1</sup>H-MNR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.78 (dd, *J*= 9.1, 13.7 Hz, 1H), 3.04 (dd, *J*= 6.5, 8.7 Hz, 1H), 3.09 (dd, *J*= 5.7, 13.7 Hz, 1H), 3.31 (t, *J*= 8.8, 1H), 3.52 (qn, *J*= 8.3 Hz, 1H), 4.17 and 4.24 (AB- Signal, *J*<sub>AB</sub>= 15.3 Hz, 2H), 6.48 (d, *J*= 8.1 Hz, 1H), 6.65 (t, *J*= 7.3 Hz, 1H), 6.95 (d, *J*= 7.2 Hz, 1H), 7.06 (t, *J*= 7.6 Hz, 1H), 7.12-7.34 (m, 10H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 40.4, 42.1, 53.1, 59.0, 107.0, 117.5, 123.9, 126.1, 127.0, 127.6, 127.7, 128.3, 128.4, 129.0, 132.9, 138.4, 140.0, 152.2; MS *m/e* (rel. intensity) 299 (19) [M<sup>+</sup>], 208 (62), [M<sup>+</sup>-CH<sub>2</sub>Ph<sup>+</sup>], 91 (100) [C<sub>6</sub>H<sub>5</sub>N<sup>+</sup>]; Anal. Calcd. for C<sub>22</sub>H<sub>21</sub>N: C, 88.25; H, 7.07; N, 4.68. Found: C, 87.90; H, 7.28; N, 4.47.

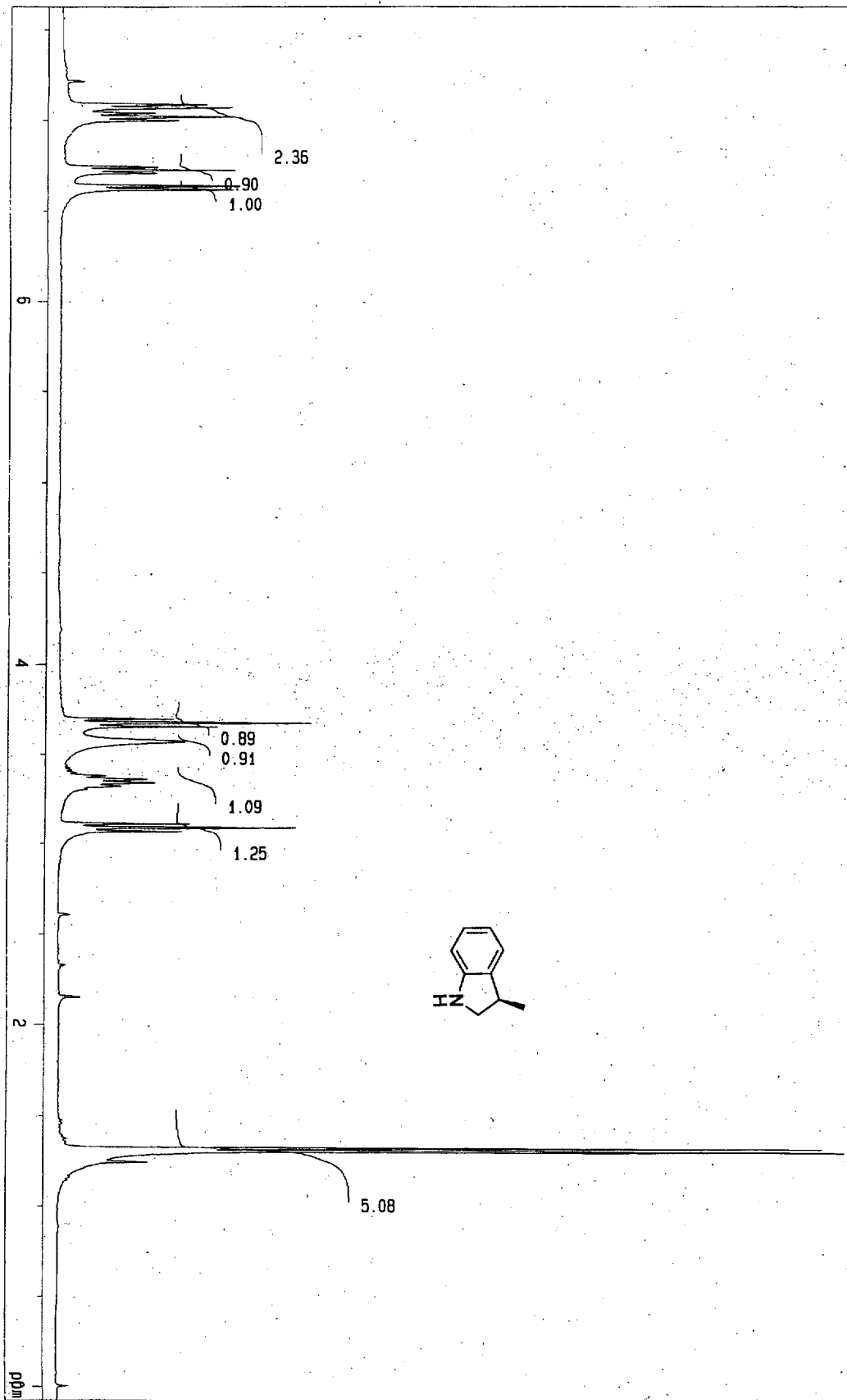
<sup>3</sup> J. Inanaga, J.; Ujikawa, O; Yamaguchi, M. *Tetrahedron Lett.* 1991, 32, 1737-1740.

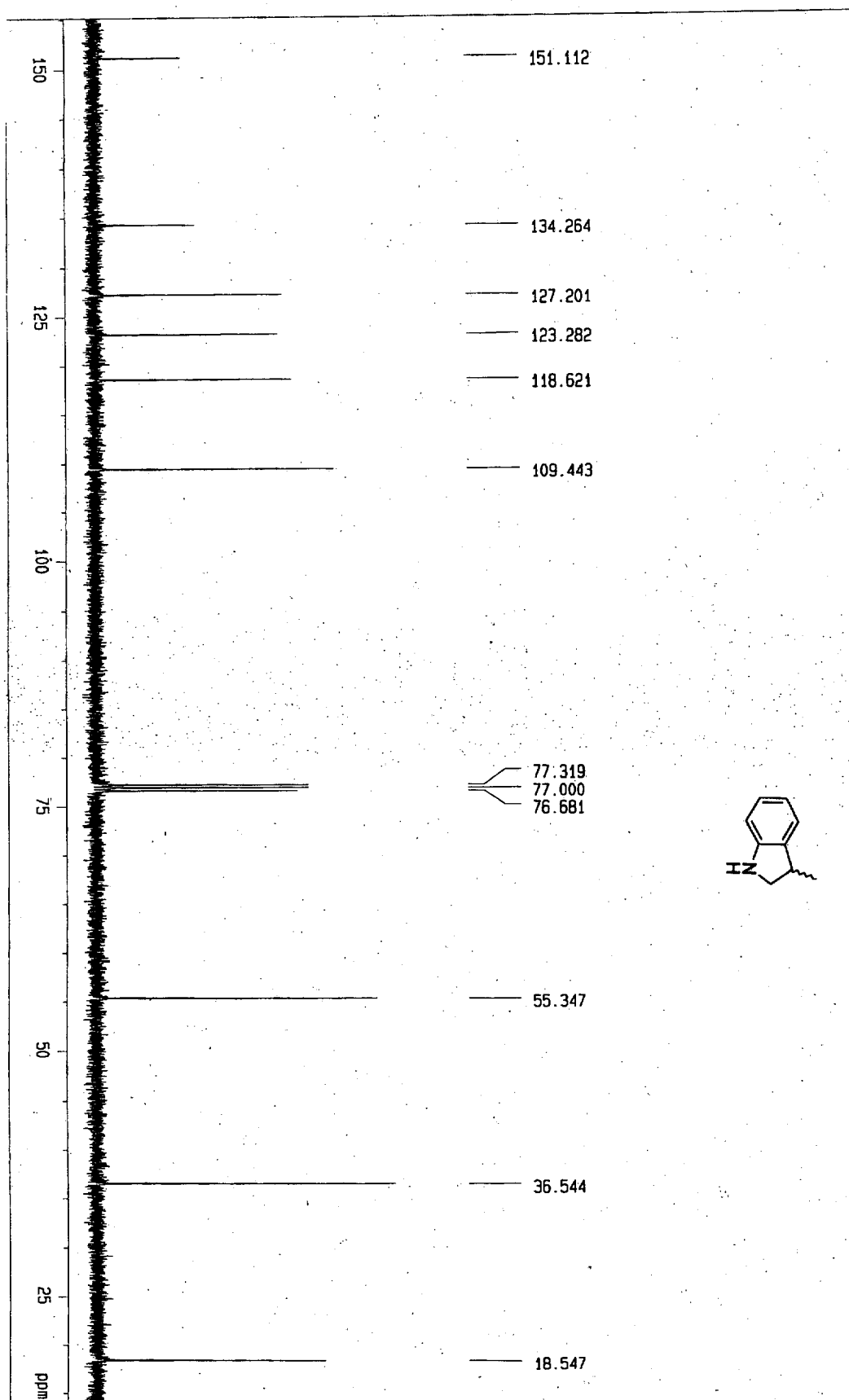
**1-Benzyl-3-vinyl-2,3-dihydro-1H-indol 9**

A solution of **8E** or **8Z** (346 mg, 1 mmol) in dry toluene (1ml) was added dropwise at  $-78^{\circ}\text{C}$  to a solution of *t*BuLi / hexane (1.3 ml, 2.2 mmol) in presence of (-)-sparteine (235  $\mu\text{l}$ , 1.5 mmol) in dry toluene (8 ml). After 18h at  $-90^{\circ}\text{C}$  MeOH (1 ml) was added and the reaction mixture was poured into  $\text{NH}_4\text{Cl}$  sat. The organic phase was dried over  $\text{MgSO}_4$  and after evaporation of the solvent the residue was chromatographed on silical gel (eluent: petrolether / toluene : 4 / 1 containing a few drops of 32%  $\text{NH}_3$ ). Yield 95% (223 mg) ; ee = 0%; IR ( $\text{CH}_2\text{Cl}_2$ ):  $\nu = 3064, 3033, 2989, 2926, 2820, 1589, 1493, 1474 \text{ cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 3.02$  (t,  $J = 9.0$  Hz, 1H), 3.53 (t,  $J = 8.6$  Hz, 1H), 3.87 (q,  $J = 8.6$  Hz, 1H), 4.11 and 4.39 (AB- Signal,  $J_{AB} = 14.4$  Hz, 2H), 5.09-5.20 (m, 2H), 5.84-5.93 (m, 1H), 6.53 (d,  $J = 7.8$  Hz, 1H), 6.71 (t,  $J = 7.4$  Hz, 1H), 7.03 (d,  $J = 7.4$  Hz, 1H), 7.09 (t,  $J = 7.4$  Hz, 1H), 7.11-7.37 (m, 5H);  $^{13}\text{C-NMR}$  (62.5 MHz,  $\text{CDCl}_3$ ):  $\delta = 45.5, 53.3, 59.4, 107.2, 115.8, 117.9, 124.4, 127.0, 127.8, 128.4, 129.1, 131.8, 138.1, 138.5$  and  $152.0$ ; MS  $m/e$  (rel. intensity) 235 (base) [ $\text{M}^+$ ], 144 (43) [ $\text{M}^+ - \text{C}_6\text{H}_5\text{N}$ ], 91 (65) [ $\text{C}_6\text{H}_5\text{N}^+$ ]; Anal. Calcd. for  $\text{C}_{17}\text{H}_{17}\text{N}$ : C, 86.77; H, 7.28; N, 5.95. Found: C, 87.10; H, 7.40; N, 6.10.

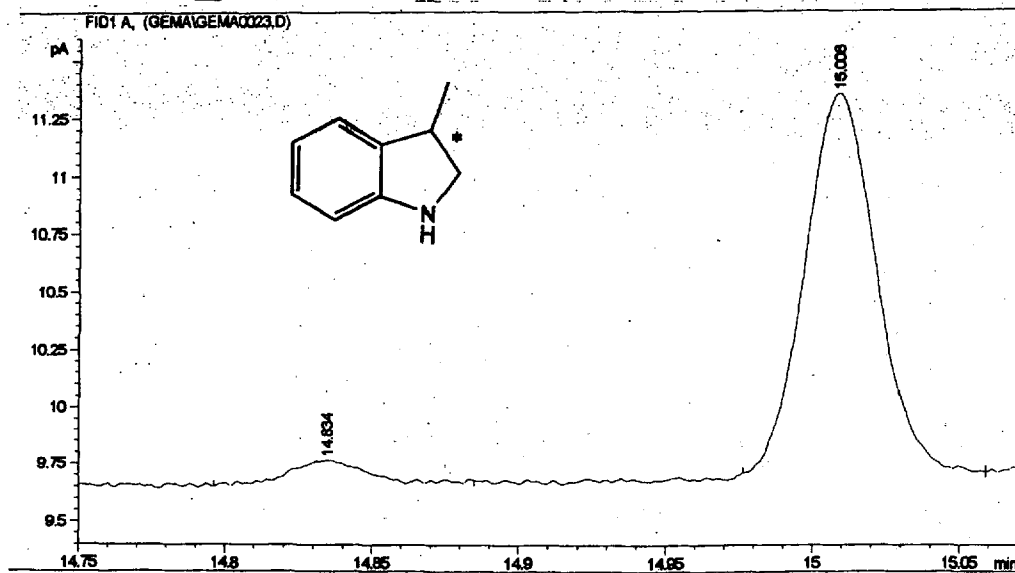
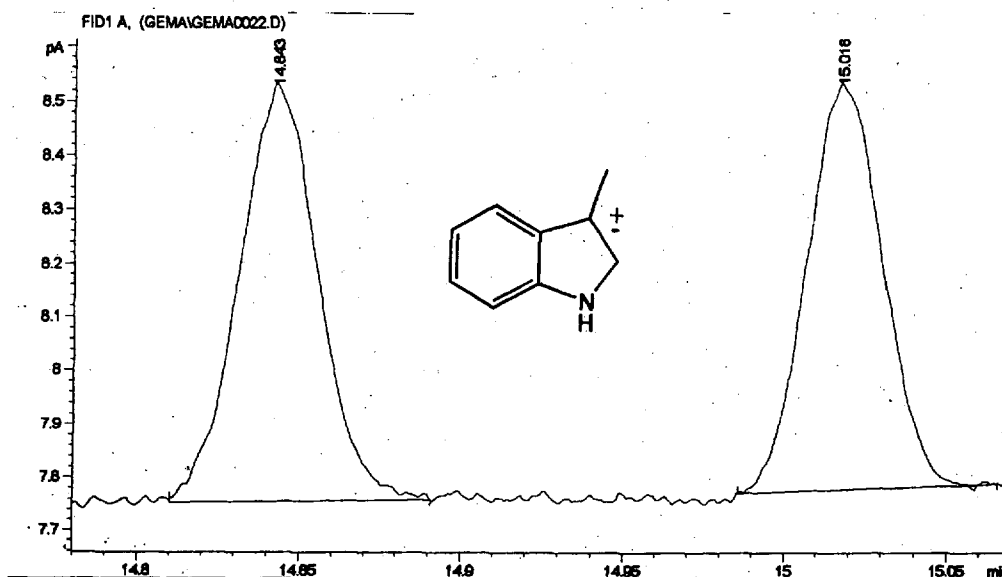






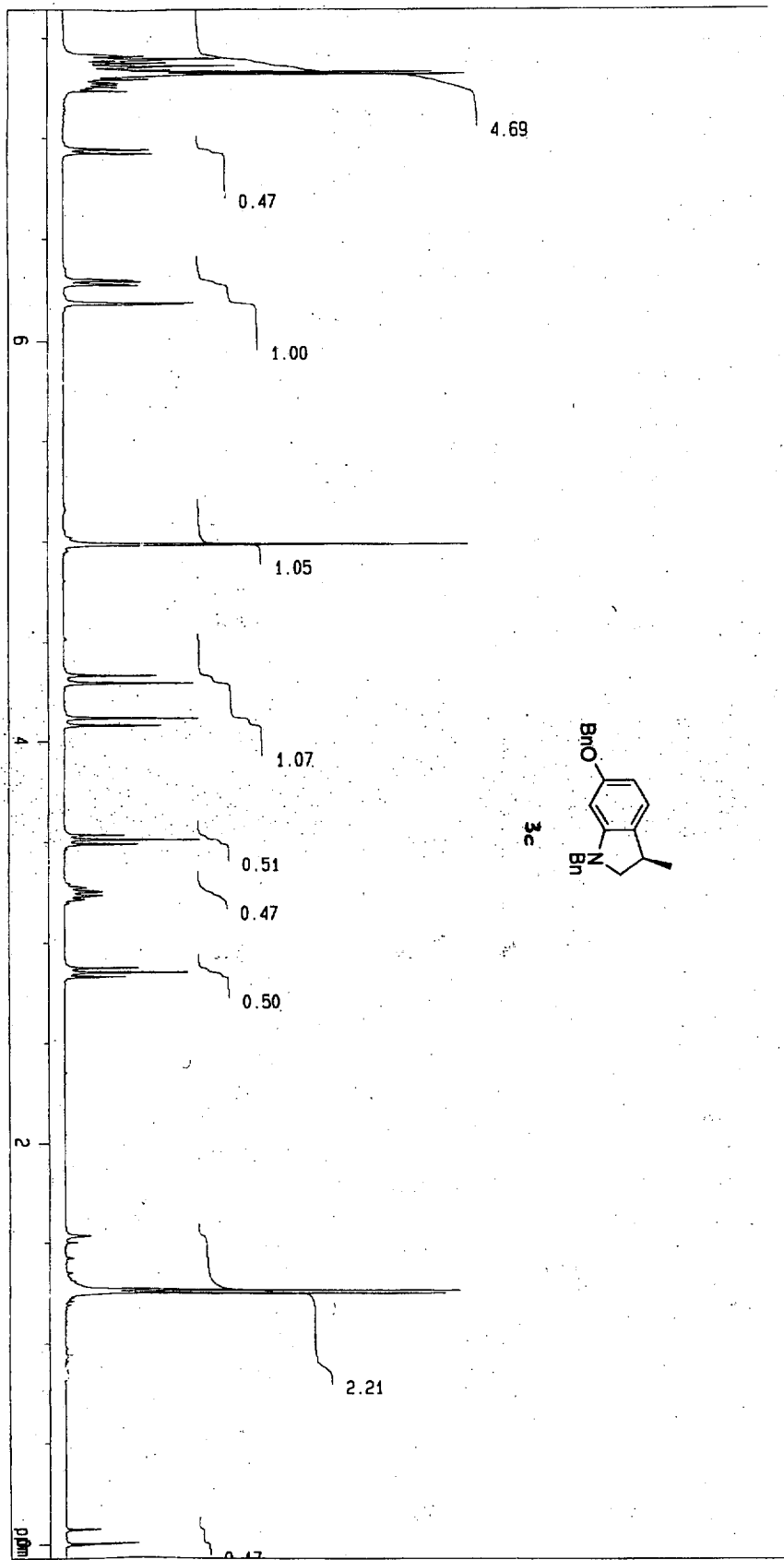


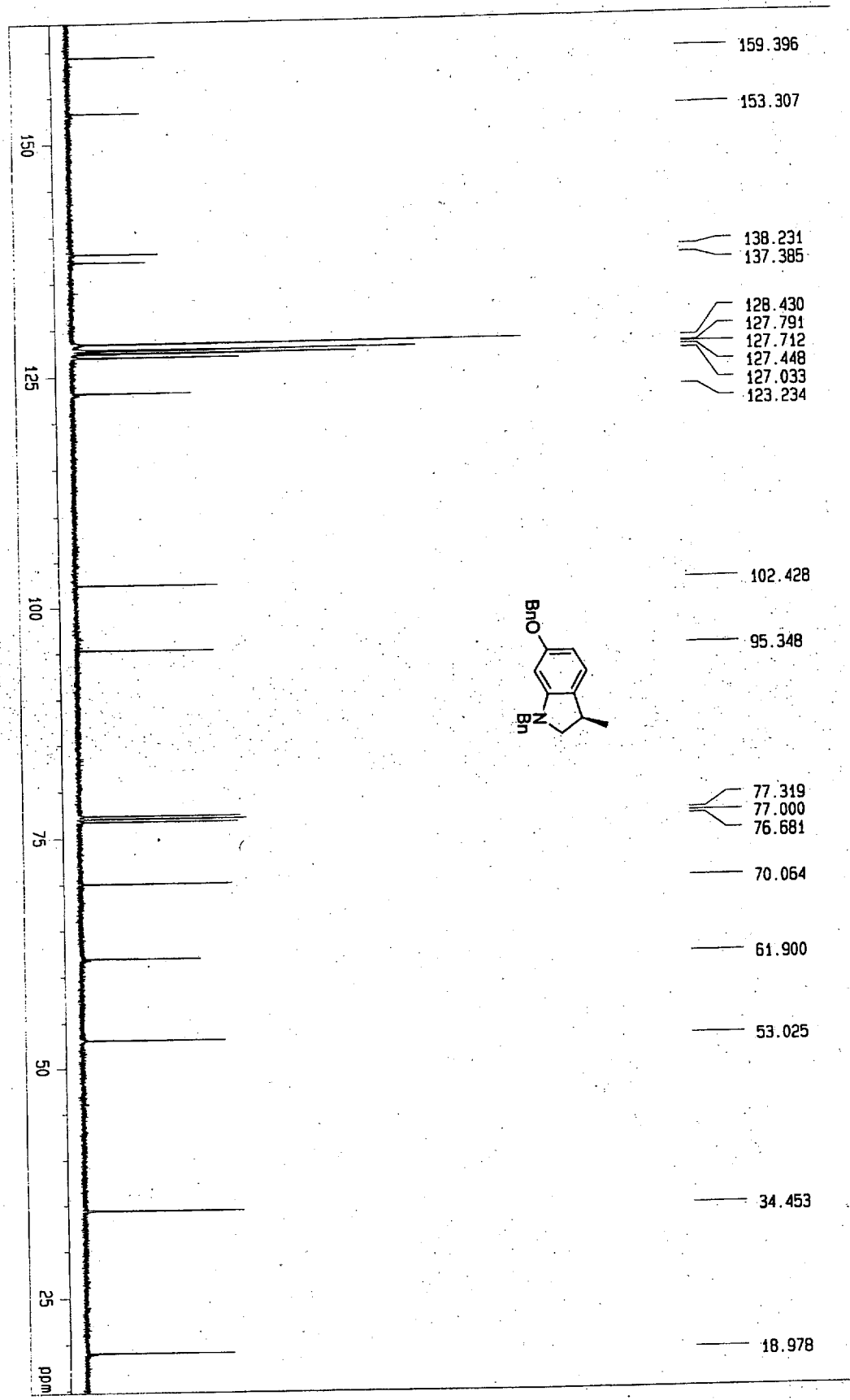


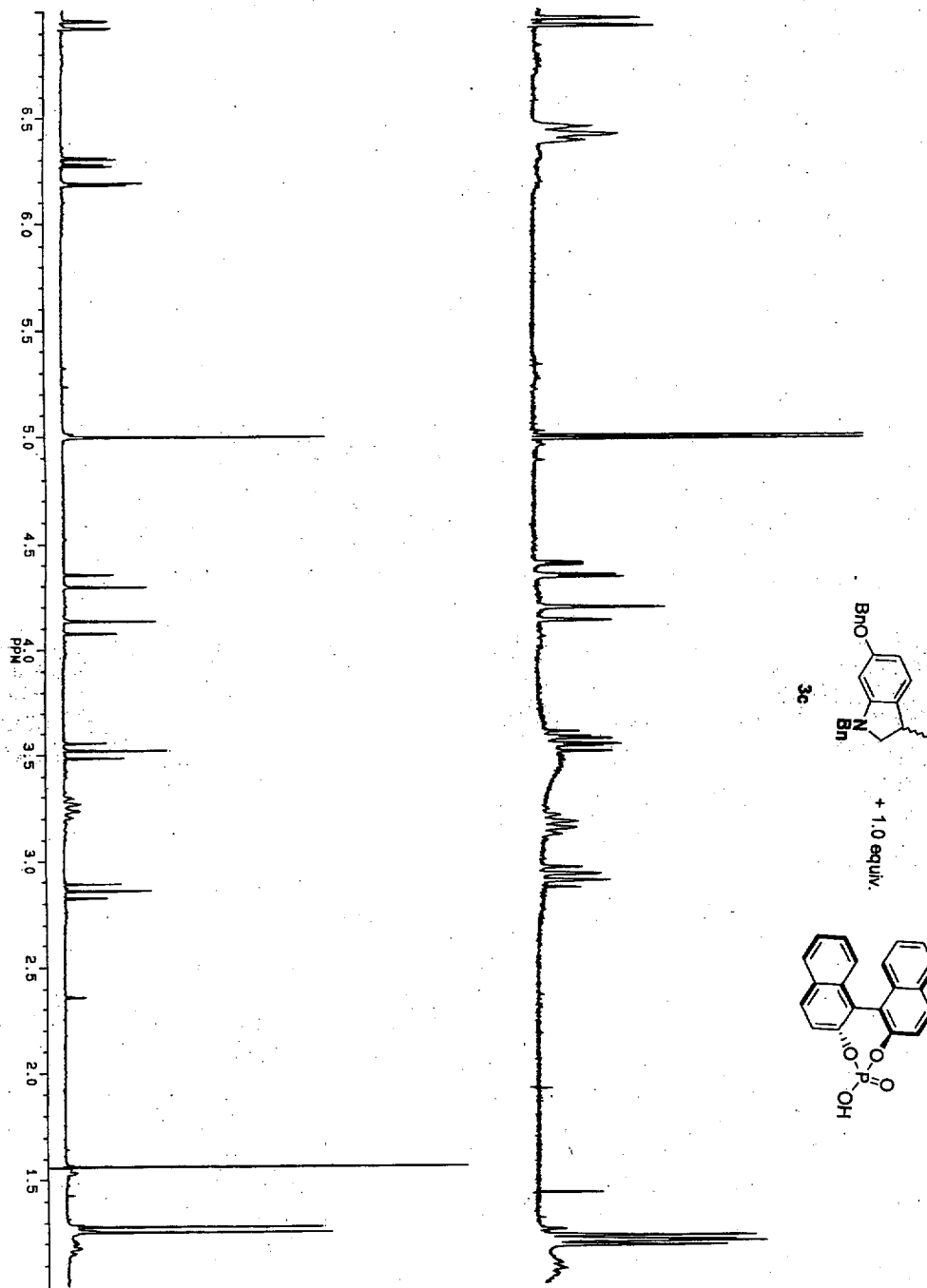


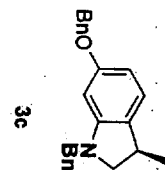
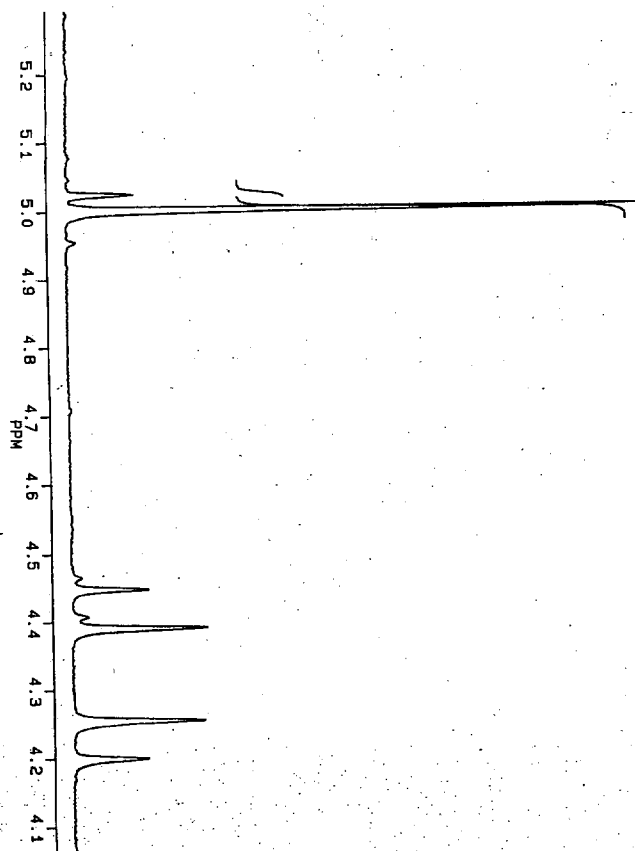
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3	4.280	1	VB	2688.32861	405.02103	57.53229
4	6.034	1	BB	409.82895	212.17941	8.77065
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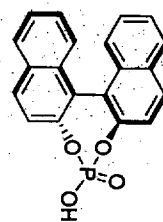


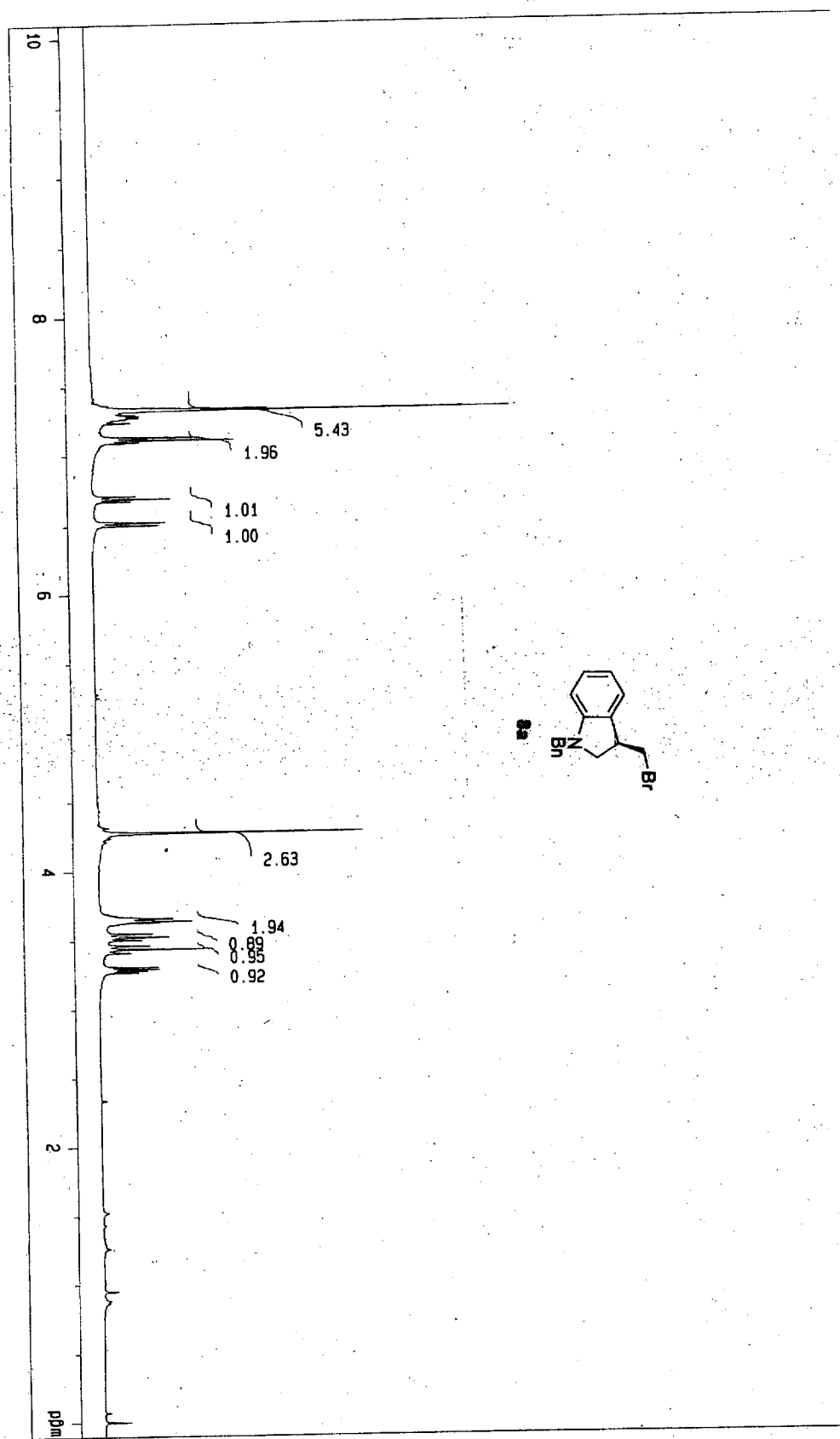


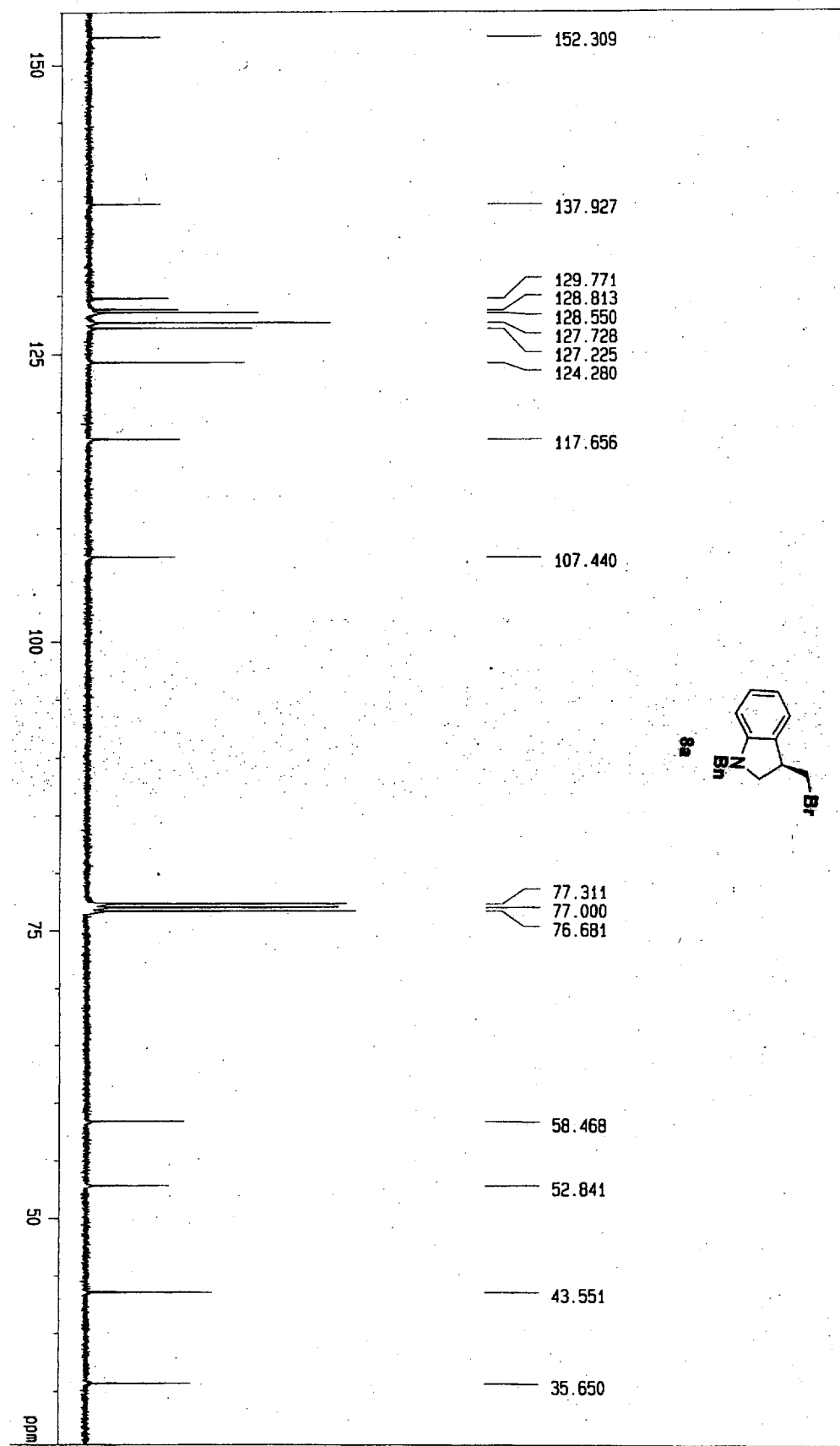


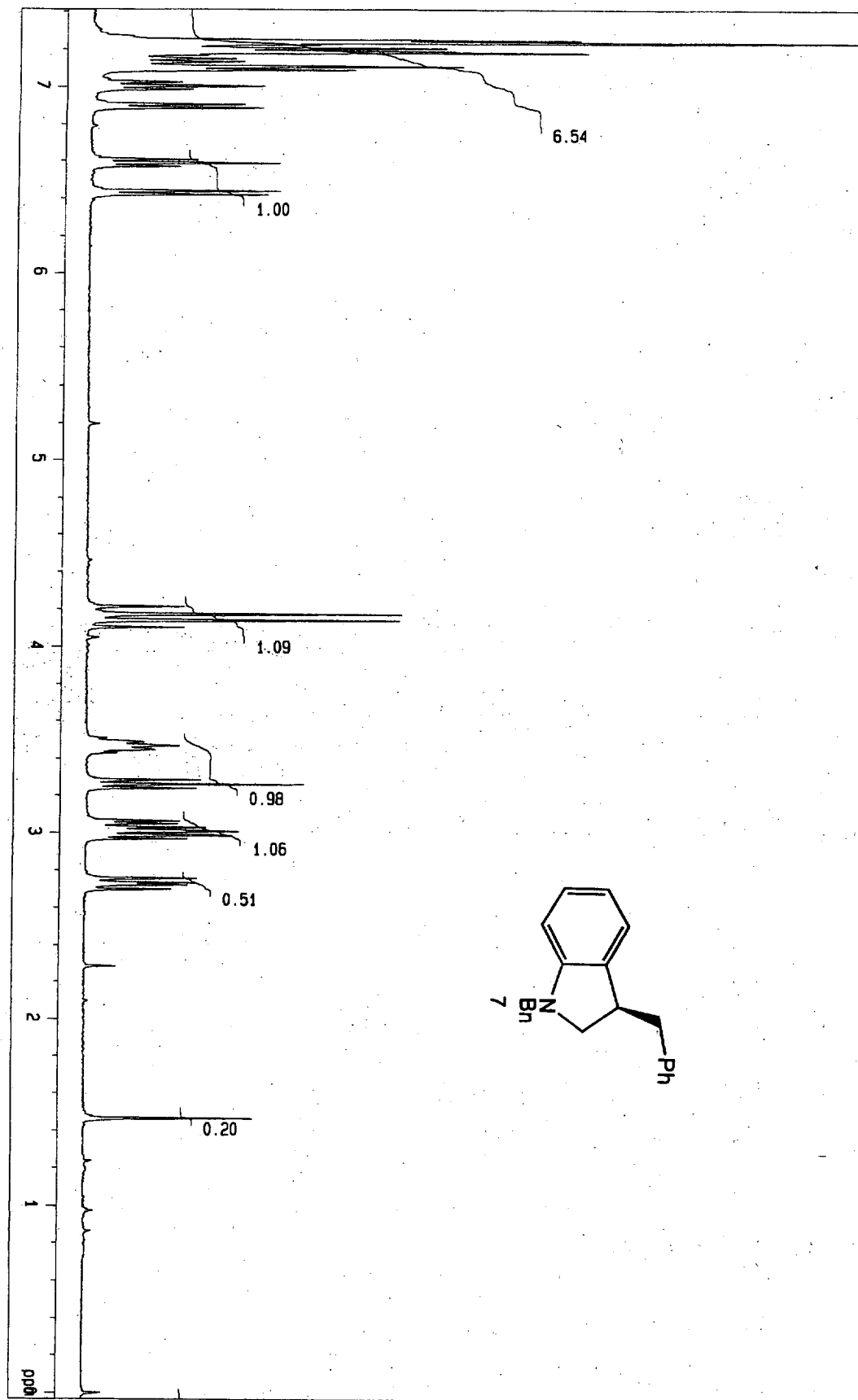


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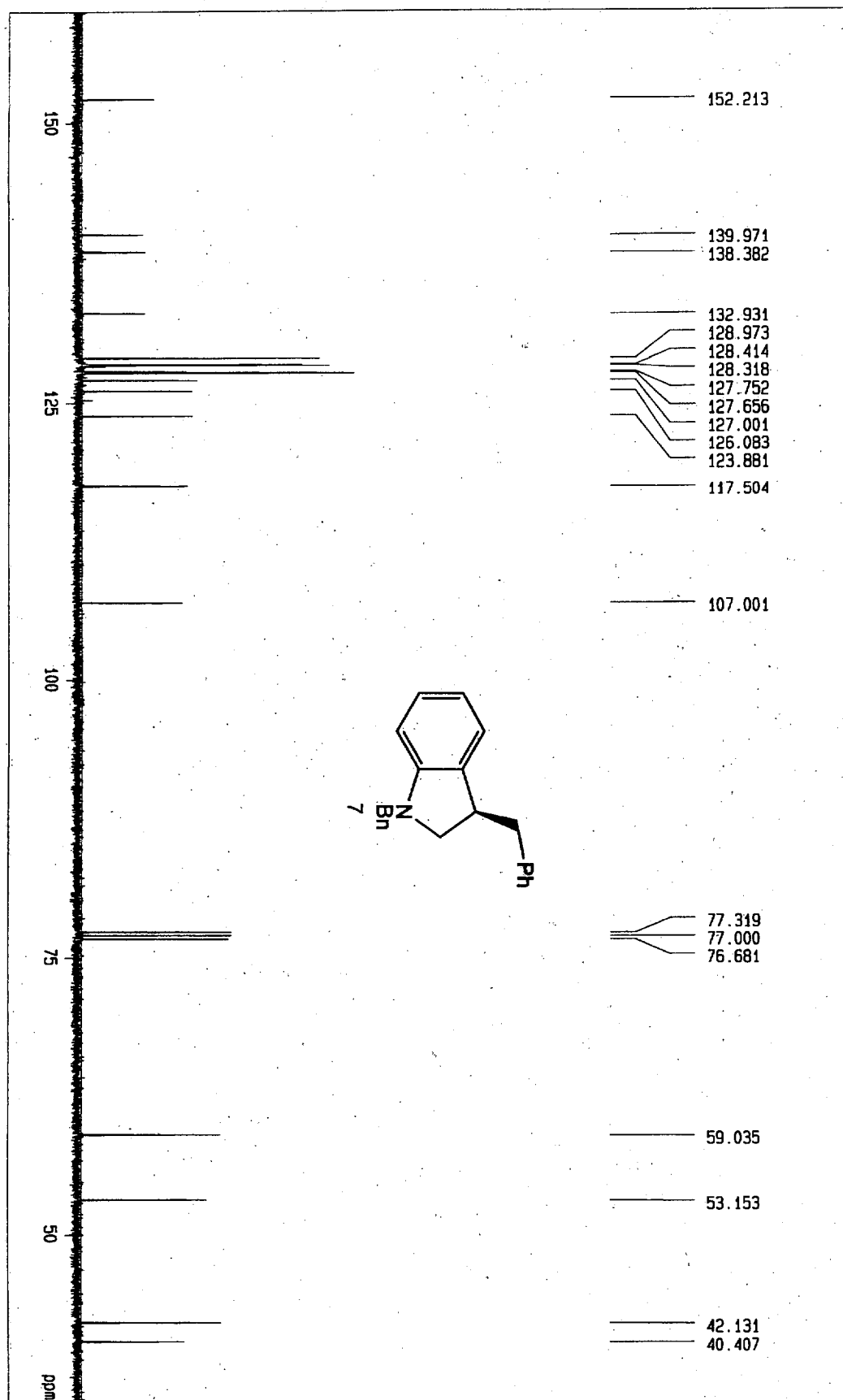


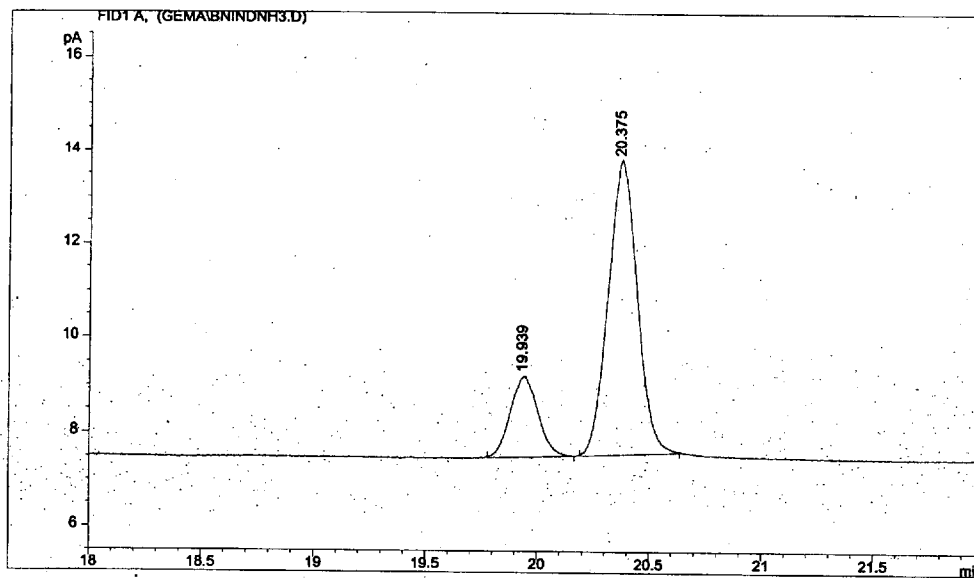
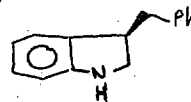












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 Area Percent Report  
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Sorted By : Retention Time  
 Multiplier : 1.0000  
 Dilution : 1.0000  
 Sample Amount : 1.00000 [ng/ul] (not used in calc.)

Signal 1: FID1.A,

Peak #	RetTime [min]	Sig	Type	Area [pA*s]	Height [pA]	Area %
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2	19.939	1	BP	14.53669	1.70853	17.53118
3	20.375	1	BB	56.21522	6.25381	67.79529

Totals : 82.91906 9.68341

