

*Supporting Information for:*

**Catalytic enantioselective synthesis of A-86929, a dopamine D1 Agonist**

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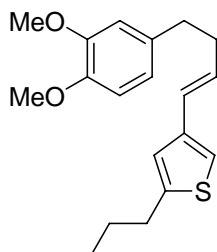
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## Instrumentation and Chemicals

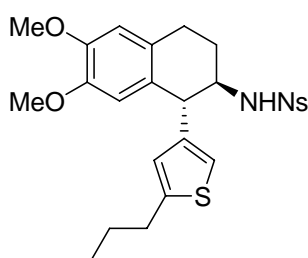
All reactions were conducted using oven-dried glassware under an atmosphere of Argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using silica gel (230-400 mesh). TLC was performed on aluminium-backed plates coated with Silica gel 60 with F<sub>254</sub> indicator. The <sup>1</sup>H NMR spectra were recorded with a 200 and a 400 MHz and <sup>13</sup>C NMR spectrum were recorded with a 50 and a 100 MHz using CDCl<sub>3</sub> and CD<sub>3</sub>OD. <sup>1</sup>H NMR chemical shifts are expressed in parts per million (δ) relative to CDCl<sub>3</sub> (δ = 7.26) and CD<sub>3</sub>OD (δ = 3.31); <sup>13</sup>C NMR chemical shifts are expressed in parts per million (δ) relative to the CDCl<sub>3</sub> resonance (δ = 77.0) and CD<sub>3</sub>OD resonance (δ = 49.0). Mass spectra were obtained under positive electron spray ionization (*m/z* values are given) on API-2000. HPLC analyses were done by Chiralpak AD-H and OD-H column (0.46 cm X 15 cm). Specific optical rotation values were measured on a Jasco-P1200 polarimeter. Elemental analyses were carried out on a ParkinElmer 2400-II, Department of Chemistry, Indian Institute of Technology, Kharagpur, India. Melting points were measured in Toshniwal (India) melting points apparatus.

## Experimental Procedure and Characterization Data



### 4-[4-(3,4-Dimethoxy-phenyl)-but-1-enyl]-2-propyl-thiophene (4)

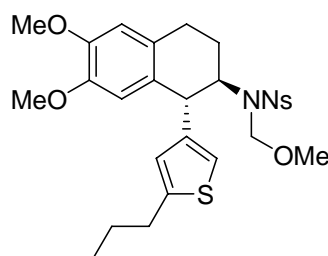
To a stirred solution of alkyne **5** (2.0 g, 10.52 mmol) in 25 mL THF was added catecholborane (3.3 g, 26.31 mmol) slowly over a period of 5 min at ice cold condition. Then the reaction mixture was refluxed for 3 h. Reaction mixture again cooled to ice cold condition, 4-Bromo-2-propylthiophene **7** (2.1 g, 10.52 mmol) added slowly over 1 min then  $(\text{Ph}_3\text{P})_4\text{Pd}$  (0.607 g, 0.50 mmol) added in the reaction mixture and allowed the mixture to stir at rt for 25 min. The reaction mixture was recooled to 0 °C and 10.52 mL 20% aqueous  $\text{Na}_2\text{CO}_3$  solution was added slowly over the reflux condenser. Then the reaction mixture was allowed to reflux for 12 h. On completion of the reaction, it was cooled to rt, diluted with 50 mL of EtOAc and the organic portion was washed with brine and dried with  $\text{Na}_2\text{SO}_4$ . Concentration and column purification (EtOAc/petroleum-ether 7/93) gave the titled alkene **4** (2.05 g, 62% yield) as light yellow liquid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.97 (t,  $J$  = 7.6 Hz, 3H), 1.71-1.65 (dd,  $J$  = 7.2, 14.8 Hz, 2H), 2.48-2.44 (m, 2H), 2.75-2.68 (m, 4H), 3.86 (s, 6H), 6.07-6.00 (m, 1H), 6.34 (d,  $J$  = 16.0 Hz, 1H), 6.75-6.73 (m, 2H), 6.82-6.79 (m, 2H), 6.85 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.6, 24.7, 32.1, 34.9, 35.4, 55.7, 55.8, 111.0, 111.7, 118.5, 120.1, 121.7, 125.0, 129.2, 134.3, 139.8, 146.0, 147.0, 148.6. ESI-MS  $m/z$ : 317  $[\text{M}+\text{H}]^+$



### (1S, 2R)-N-[6,7-Dimethoxy-1-(5-propyl-thiophen-3-yl)1,2,3,4-tetrahydronaphthalen-2-yl]-4-nitrobenzenesulfonamide (2)

A 10 mL two-necked round bottom flask was charged with (*R*)-bis-oxazoline ligand **8** (0.010g, 0.037 mmol, 0.12 equiv),  $\text{Cu}(\text{OTf})_2$  (0.009 g, 0.032mmol, 0.10 equiv) and 0.2 g of powdered molecular sieves (4Å). Anhydrous DCM (1.2 mL) was injected and the resulting mixture was stirred for 30 min at rt. Then the reaction mixture was placed at -25° C and to this solution,

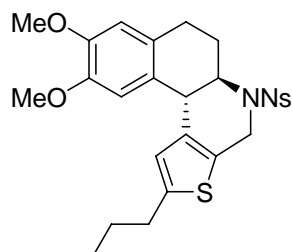
alkene **4** (0.389 g, 1.23 mmol, 5.0 equiv) in 1.2 mL DCM, PhINNs (0.1 g, 0.247 mmol, 1.0 equiv) were added and the reaction mixture was allowed to stir at  $-25\text{ }^{\circ}\text{C}$  under an argon atmosphere for 10 h. Then reaction was quenched by diluting with ethyl acetate (10 mL) and filtering through a short plug of silica gel. The silica gel was washed with additional 10 mL of ethyl acetate. The filtrate was concentrated by rotary evaporation under reduced pressure. The crude mass was subjected to purification by flash column chromatography using EtOAc/petroleum-ether as an eluent, which provided aminotetralin **2** (0.105 g, 82% yield) as yellow solid. mp  $106\text{--}108\text{ }^{\circ}\text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J = 7.6$  Hz, 3H), 1.55–1.50 (m, 2H), 1.75–1.70 (m, 1H), 2.27–2.23 (m, 1H), 2.59–2.47 (m, 2H), 2.88–2.73 (m, 2H), 3.56–3.59 (m, 1H), 3.61 (s, 3H), 3.79 (d,  $J = 6.8$  Hz, 1H), 3.83 (s, 3H), 4.86 (d,  $J = 6.8$  Hz, 1H), 6.13 (s, 1H), 6.19 (s, 1H), 6.56 (s, 2H), 7.84 (d,  $J = 8.8$  Hz, 2H), 8.25 (d,  $J = 8.8$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.7, 24.8, 26.1, 27.9, 32.1, 47.2, 55.91, 55.94, 55.98, 110.9, 112.6, 121.2, 123.8, 124.3 (2C), 127.21, 127.28, 128.2 (2C), 142.9, 146.3, 147.2, 147.5, 148.1, 149.8. ESI-MS  $m/z$ : 517  $[\text{M}+\text{H}]^+$ .  $[\alpha]_{\text{D}}^{23} -39$  (c 1.00, DCM) for 95% ee (HPLC, Daicel Chiralpak AD-H, hexane/*i*-propanol = 90/10, 1.0 ml/min, 220 nm, major 16.1 min and minor 29.6 min). Anal. Calcd for  $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_6\text{S}_2$ : C, 58.12; H, 5.46; N, 5.42. Found: C, 57.93; H, 5.62; N, 5.30.



**(1S, 2R)-N-[6,7-Dimethoxy-1-(5-propyl-thiophen-3-yl)1,2,3,4-tetrahydronaphthalen-2-yl]-N-methoxymethyl-4-nitrobenzenesulfonamide (**9**)**

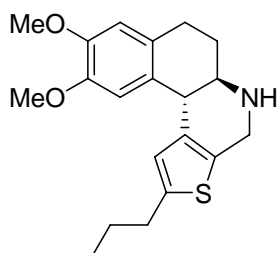
To a suspension of NaH (0.018 g, 0.37 mmol) in 2 mL THF was added **2** (0.1 g, 0.19 mmol) taken in 2 mL THF at  $0\text{ }^{\circ}\text{C}$  slowly over a period of 5 min. The mixture was stirred for 30 min at rt. Reaction mixture again cooled to  $0\text{ }^{\circ}\text{C}$  and MOMCl (0.03 g, 0.37 mmol) was added slowly over 1 min. Reaction mixture was allowed to stir at rt for 30 min. On completion of the reaction, it was quenched with 2 mL of saturated  $\text{NH}_4\text{Cl}$  solution. The reaction mixture extracted with 25 mL EtOAc. Concentration and column chromatography (15% EtOAc in petroleum ether) gave titled compound **9** as gummy liquid (0.104 g, 96% yield).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.90 (t,  $J = 6.4$  Hz, 3H), 1.55–1.50 (m, 2H), 2.20–2.10 (m, 2H), 2.52–2.44 (m, 2H), 2.80–2.84 (m, 1H), 2.95–3.05 (m, 1H), 3.35 (s, 3H), 3.57 (s, 3H), 3.84 (s, 3H), 4.08–4.02 (dt,  $J = 3.2, 11.2, 14.0, 21.6$  Hz, 1H), 4.29 (d,  $J = 10.4$  Hz, 1H), 4.70 (d,  $J = 11.2$  Hz, 1H), 5.06 (d,  $J = 11.2$  Hz, 1H), 6.09 (d,  $J = 1.6$  Hz, 1H), 6.15 (s, 1H), 6.55 (s, 1H), 6.72 (d,  $J = 1.6$  Hz, 1H), 7.76 (d,  $J = 8.8$  Hz, 2H), 8.17 (d,  $J = 8.8$  Hz, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.3, 24.6, 29.1, 30.0, 31.8, 44.1, 55.59, 55.61, 55.7, 61.7, 76.9, 110.5, 112.2, 120.9, 123.6 (2C), 124.1, 127.1, 128.2 (2C), 129.5, 143.0, 146.0, 146.6, 147.2, 147.4, 149.4. ESI-MS  $m/z$ : 561  $[\text{M}+\text{H}]^+$ .  $[\alpha]_{\text{D}}^{23} -38$  (c 1.00, DCM)

for 95% ee (HPLC, Daicel Chiralpak AD-H, hexane/*i*-propanol = 97/3, 1.0 ml/min, 250 nm, major 46.9 min and minor 52.1 min). Anal. Calcd for C<sub>27</sub>H<sub>32</sub>N<sub>2</sub>O<sub>7</sub>S<sub>2</sub>: C, 57.84; H, 5.75; N, 5.00. Found: C, 57.99; H, 5.67; N, 4.85.



**(5aR,11bS)-9,10-Dimethoxy-5-(4-nitro-benzenesulfonyl)-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopenta[*c*]phenanthrene (10)**

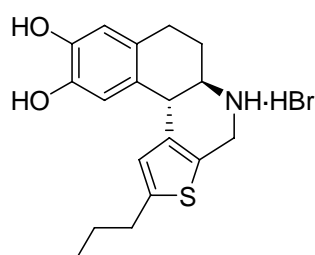
To a solution of **9** (0.1 g, 0.17 mmol) taken in DCM (8 mL) was added TMSOTf (0.034 mL, 0.17 mmol) over 1 min at -60 °C, and the mixture was stirred for 12 min. The mixture was quenched with Et<sub>3</sub>N (0.24 mL, 1.7 mmol) at -60 °C. Then reaction mixture was diluted with 25 mL of AcOEt. The organic layer washed with saturated NaHCO<sub>3</sub> (5 mL) and the dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and column chromatography (15% EtOAc in petroleum ether) gave titled compound **10** as yellowish white solid (0.084 g, 89% yield). mp 162-164 °C. [ $\alpha$ ]<sub>D</sub><sup>23</sup> -2 (c 1.00, DCM). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.84 (t, *J* = 6.0 Hz, 3H), 1.55-1.42 (m, 2H), 2.23-2.18 (m, 1H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.78-2.74 (m, 1H), 2.93-2.87 (m, 1H), 3.01-2.97 (m, 1H), 3.28-3.21 (m, 1H), 3.79 (s, 3H), 3.83 (d, *J* = 11.2 Hz, 1H), 3.86 (s, 3H), 4.69 (s, 2H), 6.55 (s, 1H), 6.65 (s, 1H), 6.91 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  13.4, 25.1, 29.2, 29.9, 31.9, 42.7, 45.8, 55.0, 56.0, 61.7, 111.0, 111.8, 122.3, 123.8 (2C), 126.9, 128.4, 128.7 (2C), 130.0, 138.0, 144.4, 145.0, 147.1, 147.9, 149.7. ESI-MS *m/z*: 528 [M]<sup>+</sup>. Anal. Calcd for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub>: C, 59.07; H, 5.34; N, 5.30. Found: C, 58.97; H, 5.26; N, 5.40.



**(5aR,11bS)-9,10-Dimethoxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopenta[*c*]phenanthrene (11)**

To a solution of **10** (0.075 g, 0.142 mmol) in 3 mL CH<sub>3</sub>CN:DMSO (49:1) was added *p*-methoxythiophenol (0.059 g, 0.426 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.058 g, 0.426 mmol) and the reaction mixture was allowed to stir for 3 h at rt. On completion of the reaction, it was concentrated in high vacuum at rt and the crude reaction mixture was subjected to column purification by using

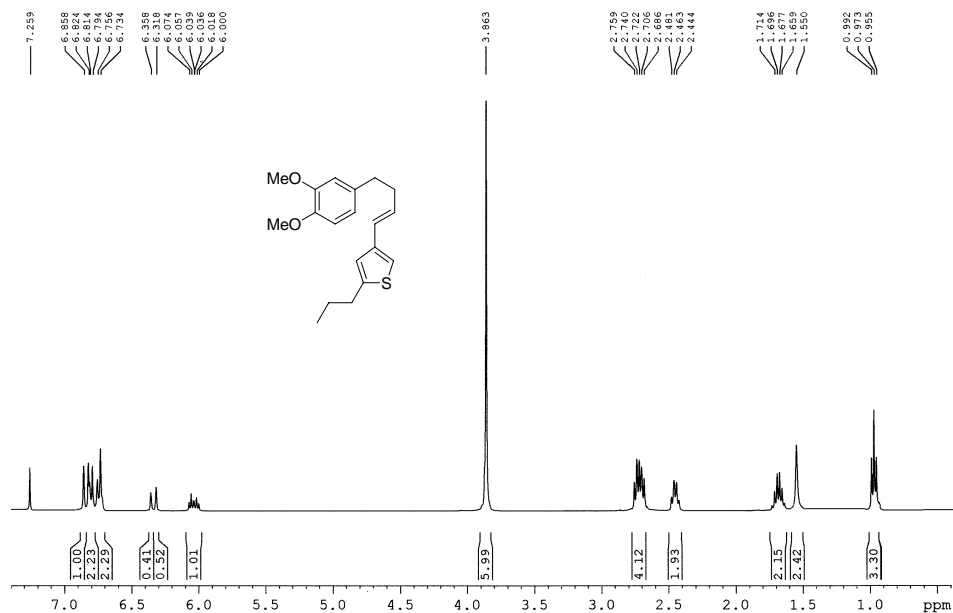
2% MeOH in DCM to give titled compound **11** as light yellow solid (0.046 g, 94% yield). mp 83-85 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.87 (t, *J* = 7.2 Hz, 3H), 1.75-1.64 (m, 3H), 2.12 (bs, 1H), 2.26-2.17 (m, 1H), 2.72-2.65 (m, 1H), 2.85-2.78 (m, 3H), 2.99-2.90 (m, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 4.04 (s, 2H), 6.71 (s, 1H), 6.88 (s, 1H), 6.98 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 13.7, 25.1, 27.1, 28.3, 32.3, 43.6, 45.5, 56.1 (2C), 58.4, 109.1, 111.9, 124.9, 130.3, 132.0, 133.8, 134.5, 142.7, 146.9, 147.2. ESI-MS *m/z*: 343 [M]<sup>+</sup>. [α]<sub>D</sub><sup>23</sup> −310 (c 0.43, MeOH) for 95% ee (HPLC, Daicel Chiralpak OD-H, hexane/*i*-propanol = 90.9/9.1, 1.0 ml/min, 250 nm, major 7.1 min and minor 9.1 min). Anal. Calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>2</sub>S: C, 69.93; H, 7.34; N, 4.08. Found: C, 69.99; H, 7.76; N, 3.85.



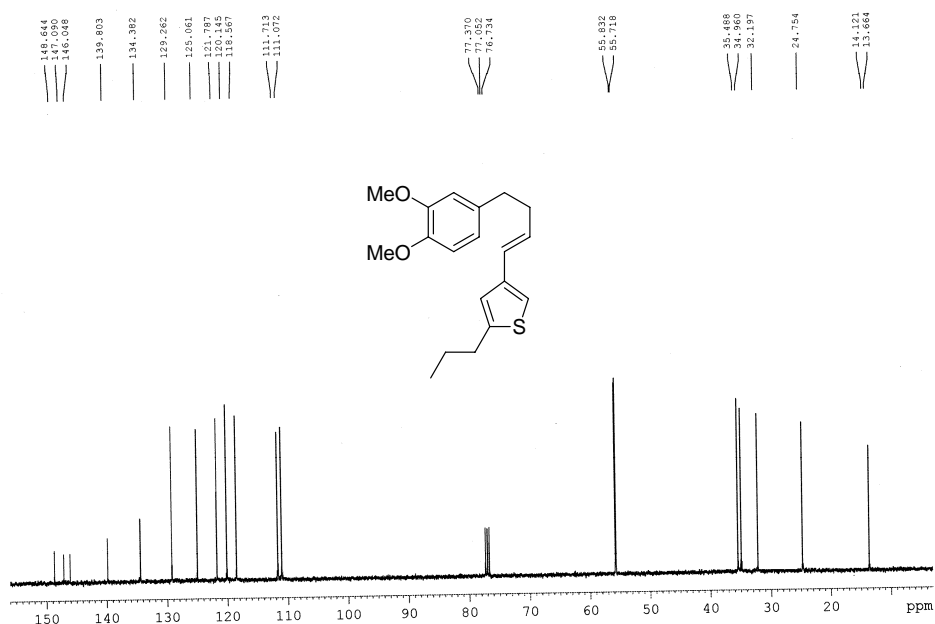
**(5aR,11bS)-4,5,5a,6,7,11b-Hexahydro-2-propyl-3-thia-5-azacyclopenta[*c*]-phenanthrene-9,10-diol hydrobromide (1a·HBr)**

To a solution of **11** (0.025 g, 0.07 mmol) in DCM (3.0 mL) was added BBr<sub>3</sub> (0.33 mL, 1M in DCM, 0.35 mmol) over 5 min at −78 °C, and the mixture was stirred for 30 min. Then reaction mixture was warmed to 0 °C and stirred for 30 min. The mixture was recooled to −78 °C and carefully quenched with 0.5 mL of MeOH. Now the reaction mixture was placed at rt and stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure, and the product was triturated with DCM/MeOH/Et<sub>2</sub>O to get **1a·HBr** (0.024 g, 86% yield) as pale yellow solid of mp >154 °C dec. ESI-MS *m/z*: 316 [M+H]<sup>+</sup>. [α]<sub>D</sub><sup>23</sup> −161 (c 0.75, MeOH). <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD): δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.77-1.71 (m, 2H), 1.94-1.85 (m, 1H), 2.40-2.31 (m, 1H), 2.87-2.79 (m, 3H), 2.96-2.91 (m, 1H), 3.12-3.21 (m, 1H), 4.01 (d, *J* = 10.8 Hz, 1H), 4.45 (s, 2H), 6.66 (s, 1H), 6.88 (s, 1H), 7.00 (s, 1H). <sup>13</sup>C NMR (100 MHz, CD<sub>3</sub>OD): δ 12.5, 24.6, 24.8, 25.1, 31.6, 39.3, 42.9, 57.3, 112.0, 115.1, 124.4, 125.3, 127.3, 127.7, 133.2, 143.2, 143.9, 145.7.

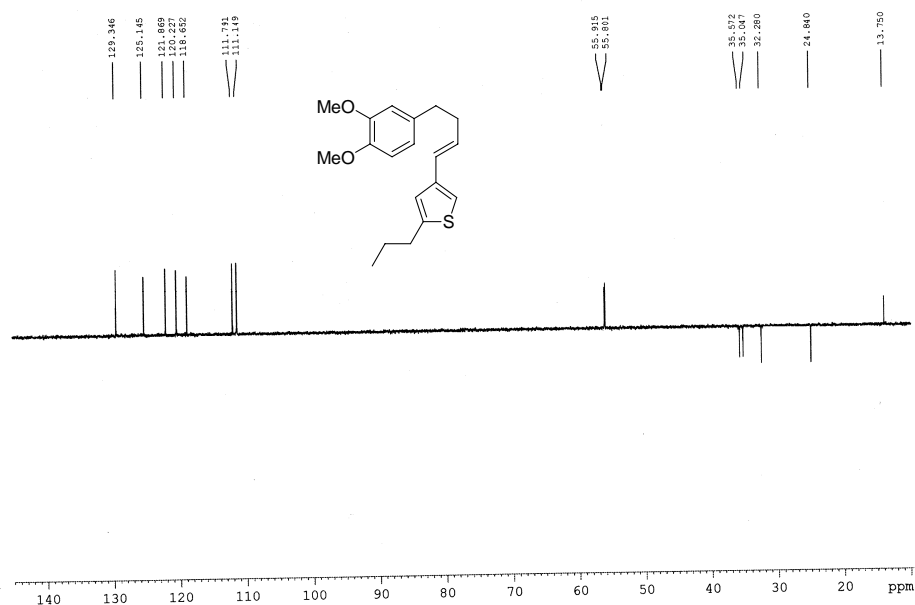
## NMR Spectra



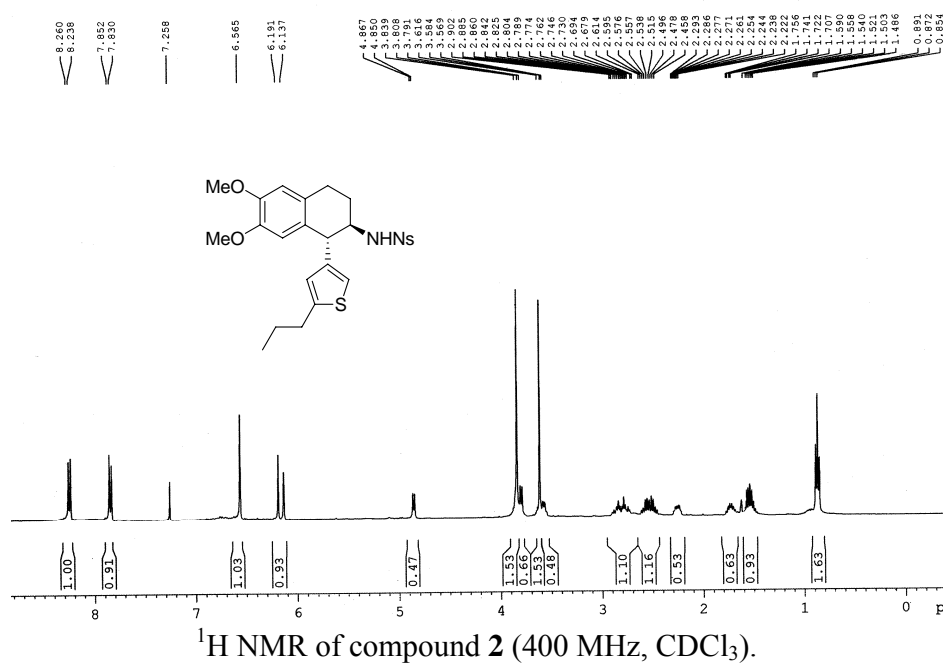
<sup>1</sup>H NMR of compound **4** (400 MHz, CDCl<sub>3</sub>).



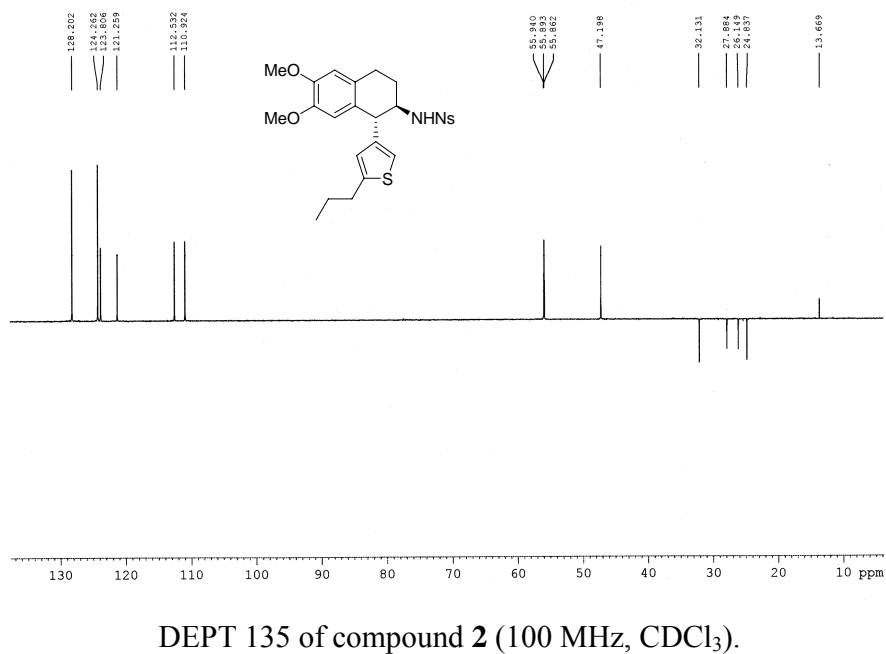
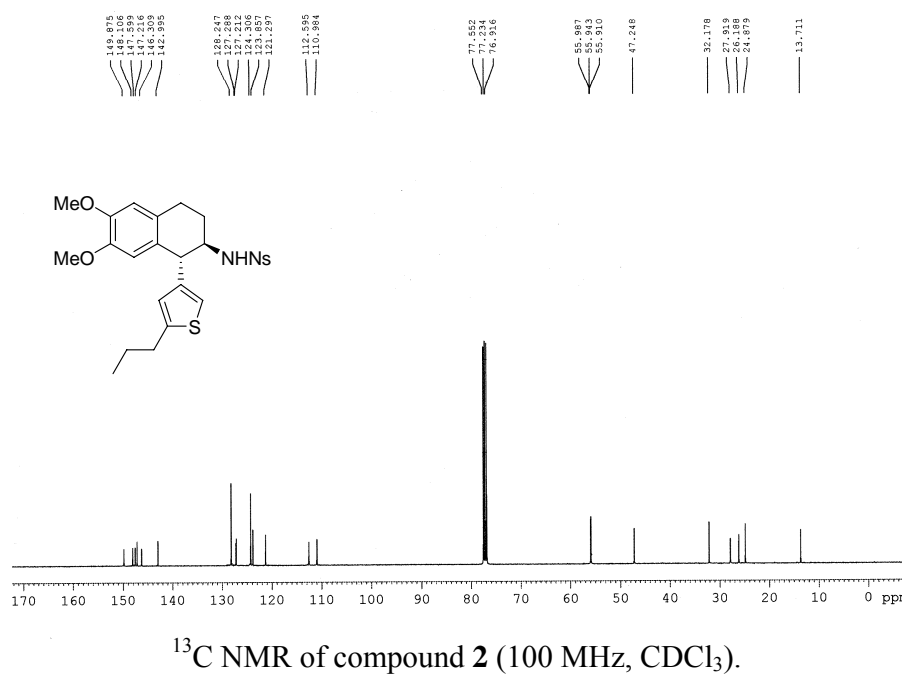
<sup>13</sup>C NMR of compound **4** (100 MHz, CDCl<sub>3</sub>).

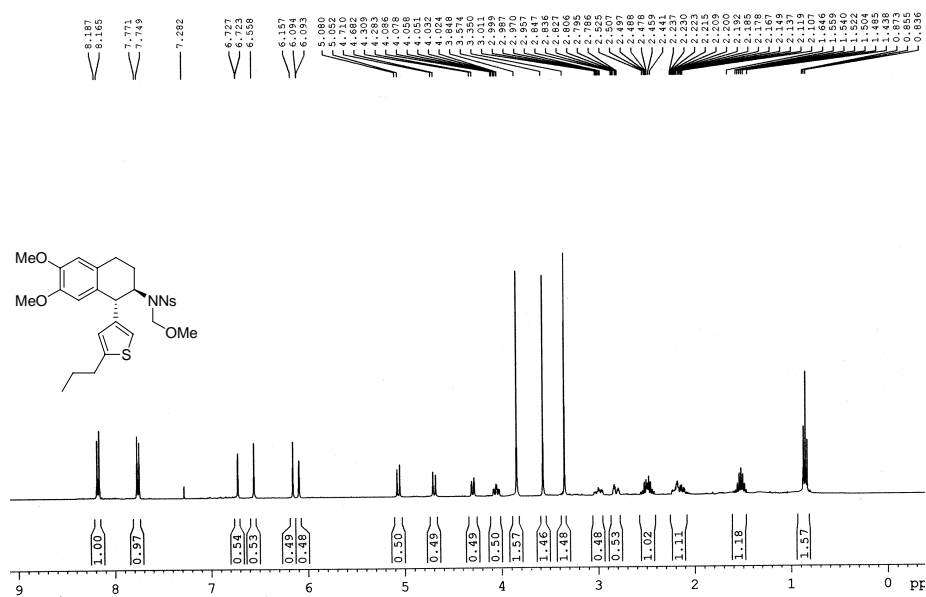


DEPT 135 of compound 4 (100 MHz, CDCl<sub>3</sub>).

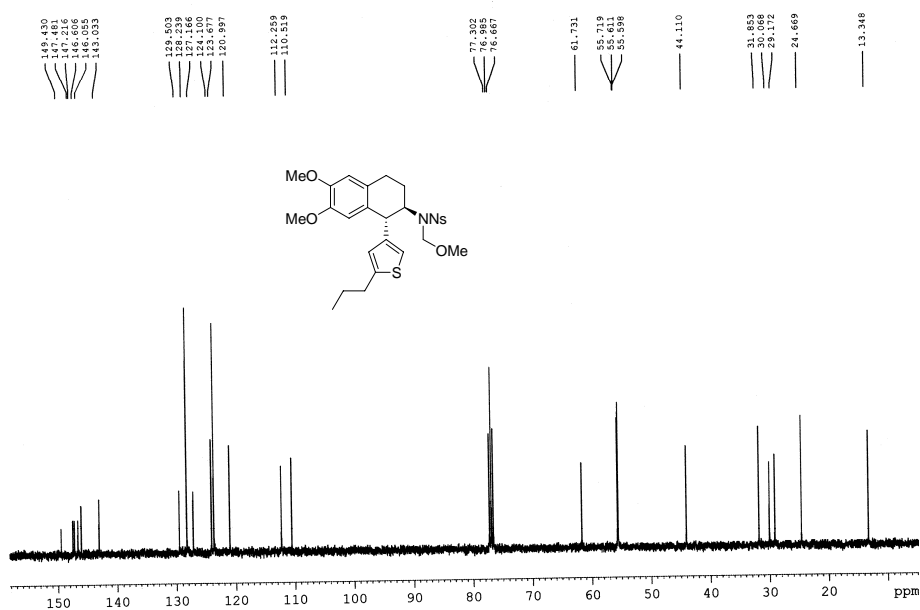




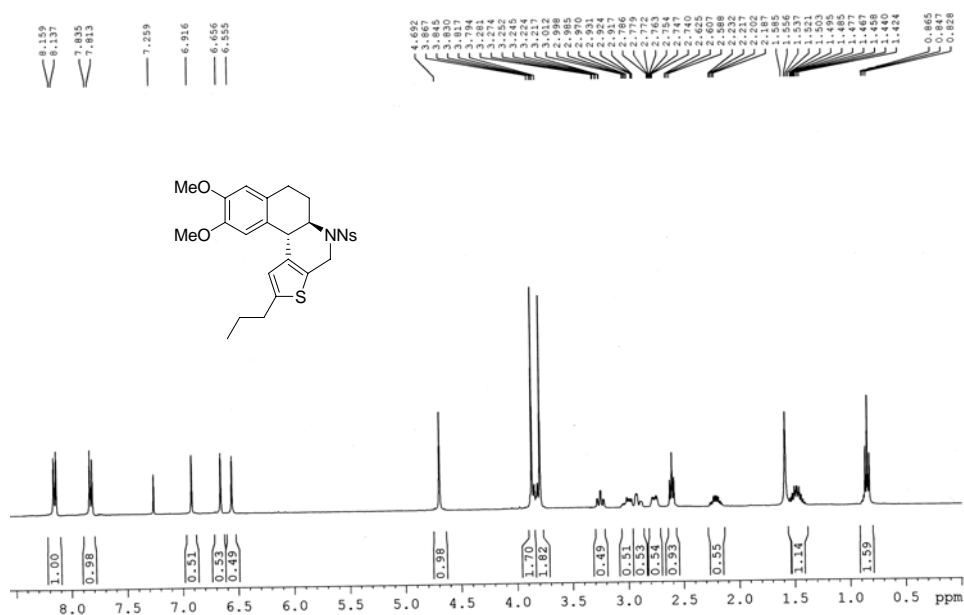
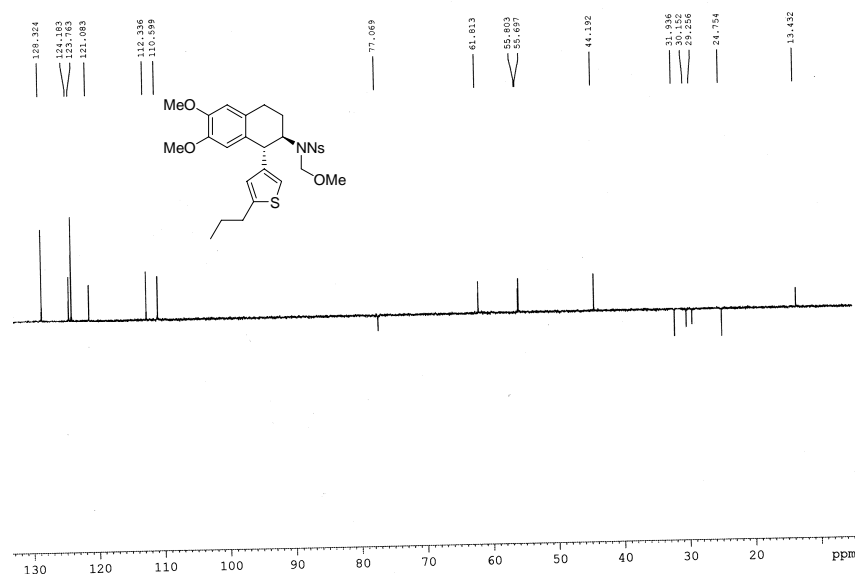


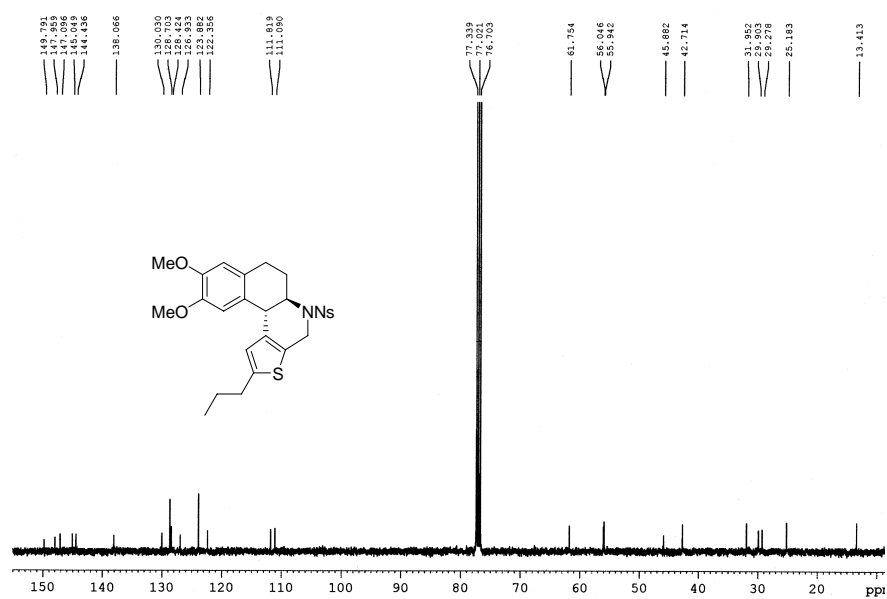


<sup>1</sup>H NMR of compound **9** (400 MHz, CDCl<sub>3</sub>).

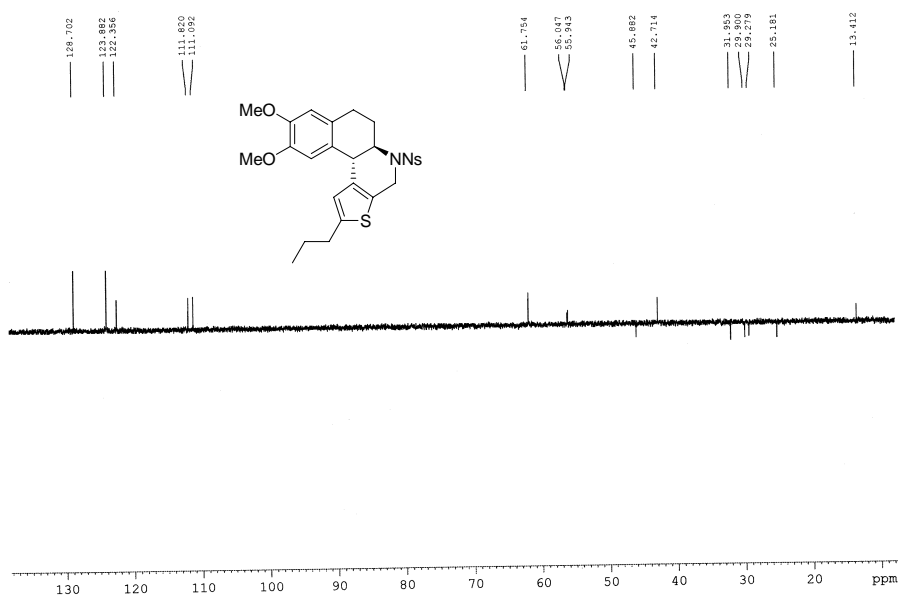


<sup>13</sup>C NMR of compound **9** (100 MHz, CDCl<sub>3</sub>).

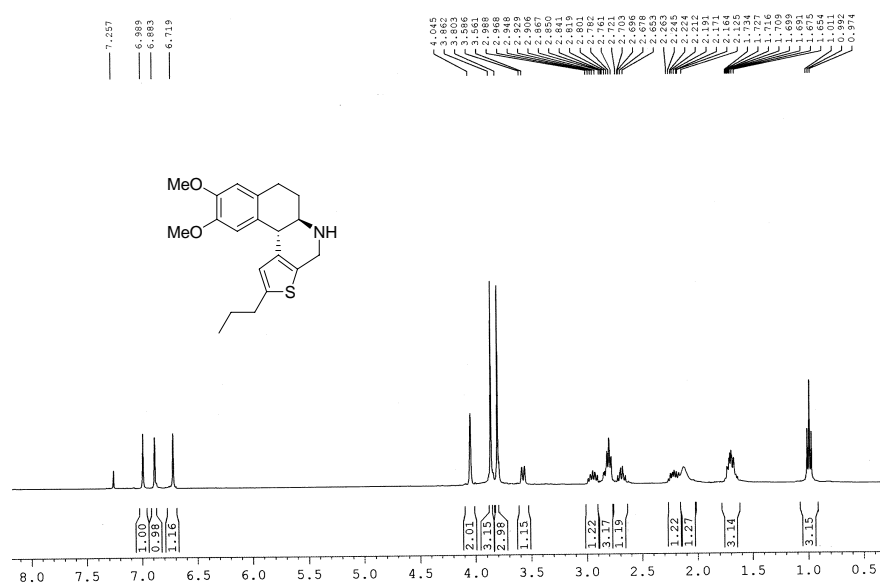




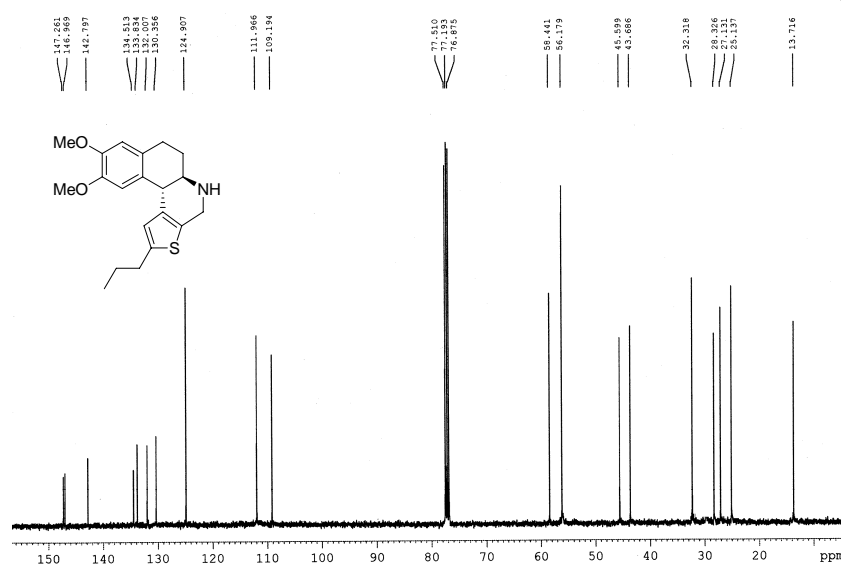
<sup>13</sup>C NMR of compound **10** (100 MHz, CDCl<sub>3</sub>).



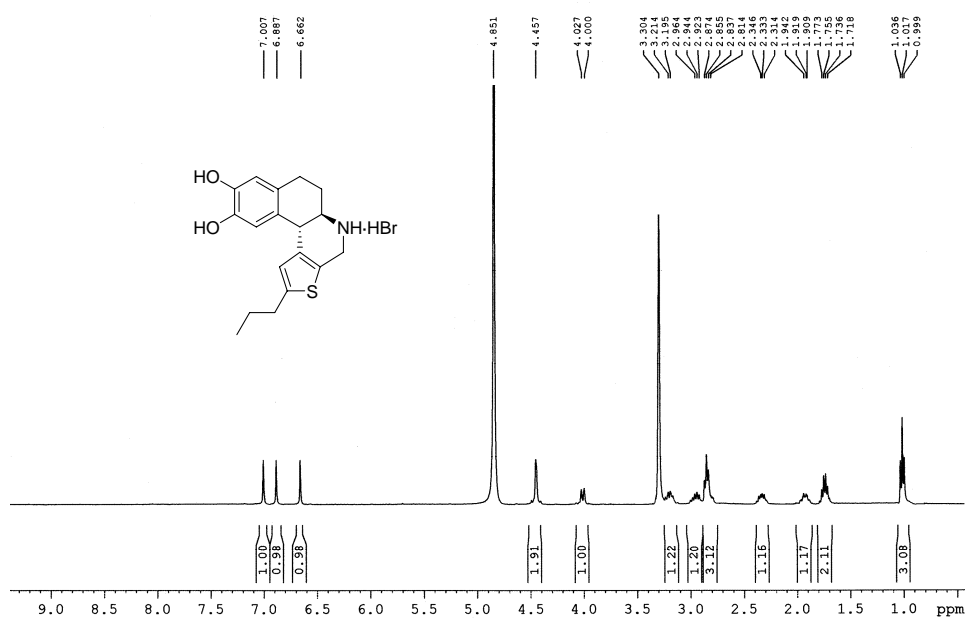
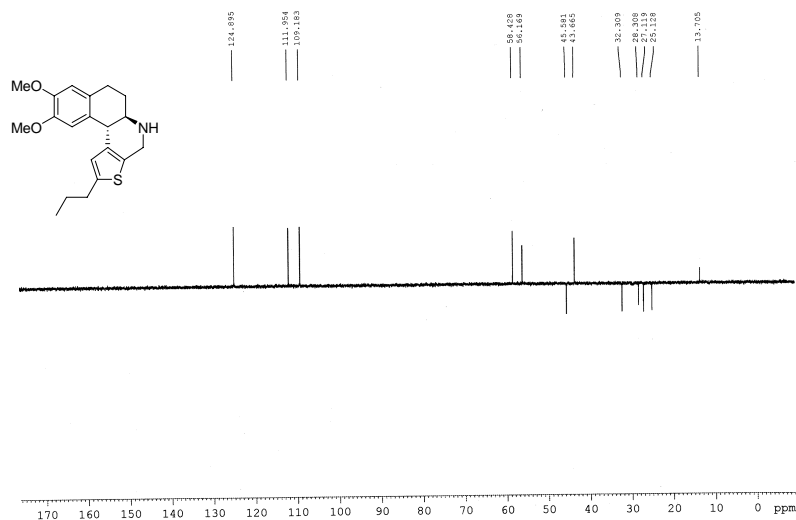
DEPT 135 of compound **10** (100 MHz, CDCl<sub>3</sub>).

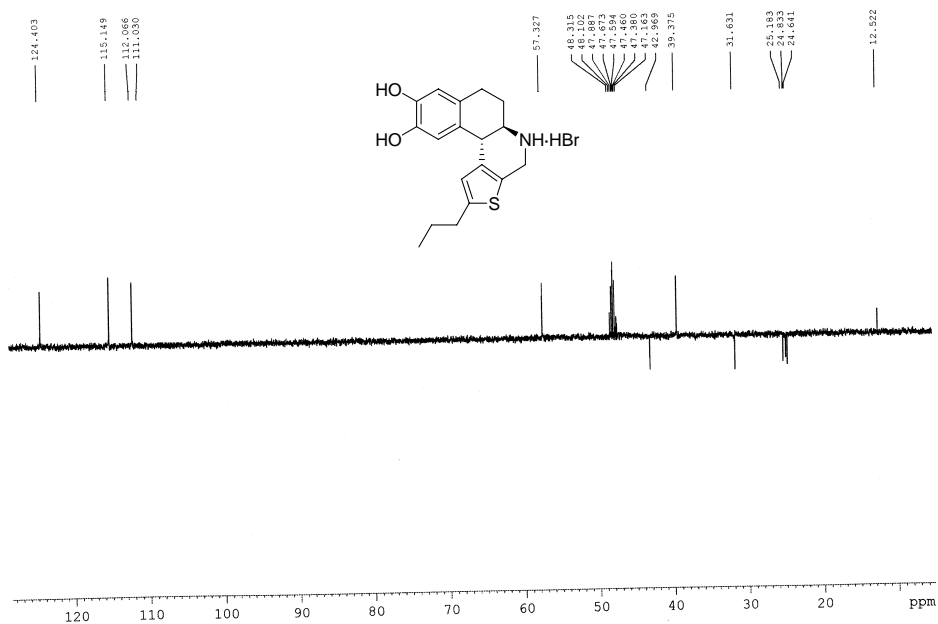
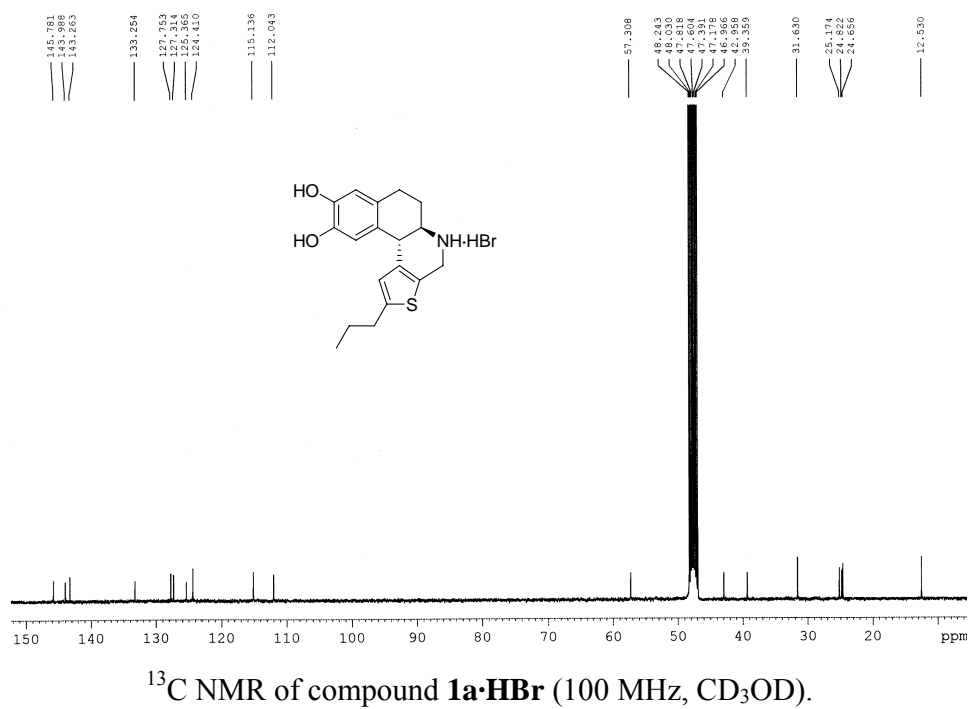


<sup>1</sup>H NMR of compound **11** (400 MHz, CDCl<sub>3</sub>).



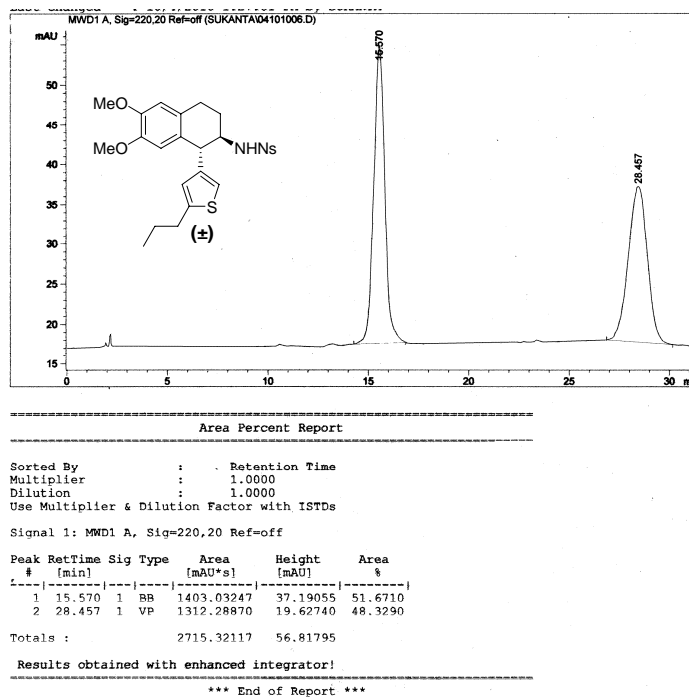
<sup>13</sup>C NMR of compound **11** (100 MHz, CDCl<sub>3</sub>).





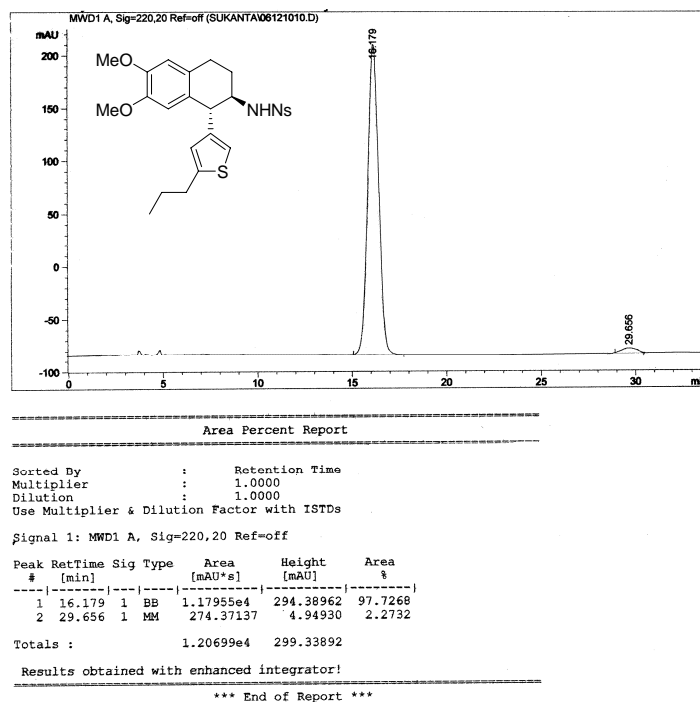
DEPT 135 of compound **1a·HBr** (100 MHz, CD<sub>3</sub>OD).

## HPLC Chromatogram

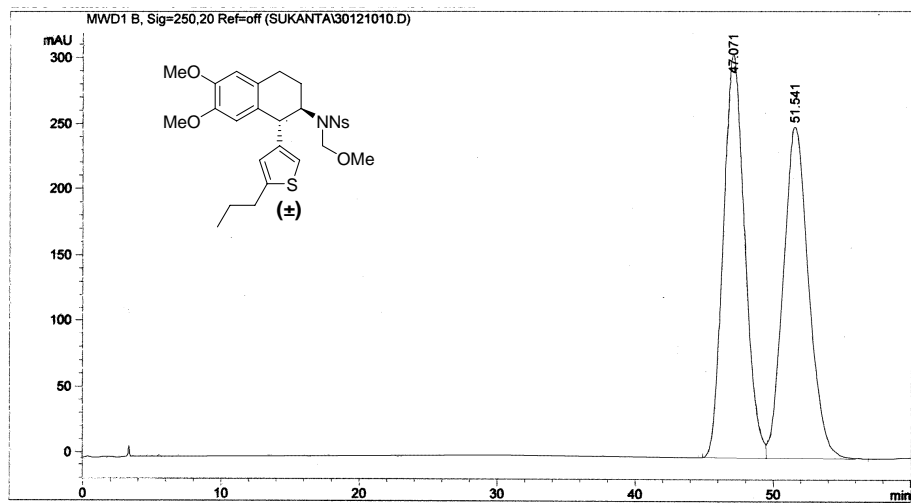


HPLC chromatogram of compound (±) 2.



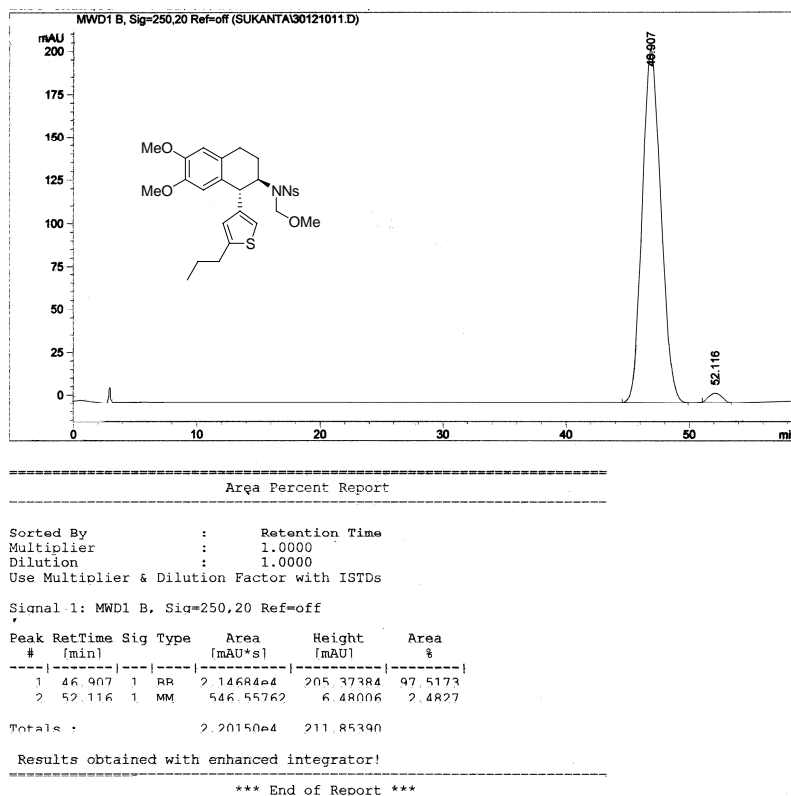


HPLC chromatogram of compound 2.

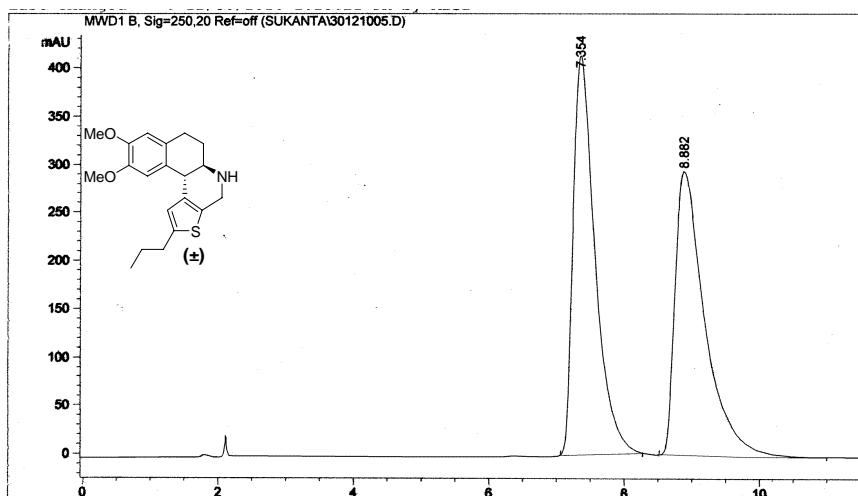


Area Percent Report						
Sorted By : Retention Time						
Multiplier : 1.0000						
Dilution : 1.0000						
Use Multiplier & Dilution Factor with ISTDs						
Signal 1: MWD1 B, Sig=250,20 Ref=off						
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	47.071	1	VV	3.30388e4	306.42233	50.5944
2	51.541	1	VB	3.22625e4	251.89355	49.4056
Totals :				6.53013e4	558.31589	
Results obtained with enhanced integrator!						
*** End of Report ***						

HPLC chromatogram of compound (±) 9.



HPLC chromatogram of compound **9**.



# Area Percent Report

Sorted By : Retention Time  
Multiplier : 1.0000  
Dilution : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: MWD1 B, Sig=250,20 Ref=off

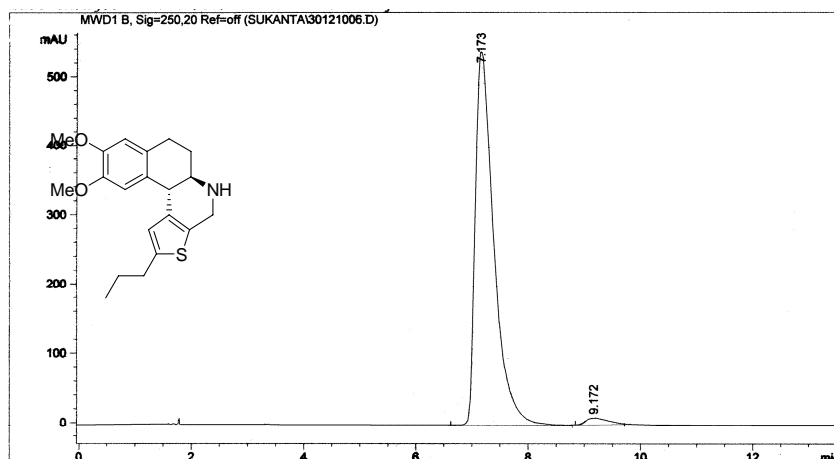
Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.354	1	MM	9237.25684	412.95224	50.4131
2	8.882	1	VB	9085.87988	295.35870	49.5869

Totals : 1.83231e4 708.31094

Results obtained with enhanced integrator!

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

HPLC chromatogram of compound (±) 11.



# Area Percent Report

Sorted By : Retention Time  
Multiplier : 1.0000  
Dilution : 1.0000  
Use Multiplier & Dilution Factor with ISTDs

Signal 1: MWD1 B, Sig=250,20 Ref=off

Peak #	RetTime [min]	Sig	Type	Area [mAU*s]	Height [mAU]	Area %
1	7.173	1	VB	1.21224e4	539.48578	97.7649
2	9.172	1	MM	277.13959	10.44672	2.2351

Totals : 1.23995e4 549.93250

Results obtained with enhanced integrator!

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

HPLC chromatogram of compound 11.