A Convergent Stereoselective Synthesis of Quinolizidines and Indolizidines: Chemoselective Coupling of 2-Hydroxymethyl Substituted Allylic Silanes with Imines

Dexi Yang and Glenn C. Micalizio*

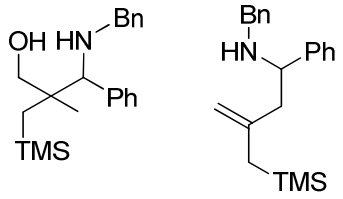
Department of Chemistry, The Scripps Research Institute, Scripps Florida, Jupiter, Florida 33458

Supporting Information

General Information: ^{1}H NMR data were recorded at 400 MHz on a Bruker AM-400 in CD_3Cl or CD_2Cl_2. ^{13}C NMR data were recorded at 100 MHz on a Bruker AM-400. Infrared spectra were recorded on a PerkinElmer SpectrumOne FT-IR instrument. Low resolution mass spectra were acquired on a Varian 500-MS mass spectrometer under soft ionization mode. HRMS data (ESI-TOF-MS) were obtained by the University of Florida Mass Spectrometry lab.

Diethyl ether, tetrahydrofuran, and dichloromethane were dried over activated alumina columns and sparged with argon prior to use. Ti(O*i*-Pr)$_4$ (Aldrich, 97%) was distilled prior to use (69-70 ^{o}C, < 1 Torr). Butyllithium and *c*-C_5H_9MgCl (Aldrich) were titrated by the method of Love et al.[1] Allylsilanes **6**, **8**, **10**, **12** were prepared according to Trost.[2] Imines **14**, **17**, **20**, **23**, **26**, **29** were prepared according to Jacobsen.[3] Imines **14**, **17**, **20** were purified by vacuum distillation (< 1 Torr). Imines **23**, **26**, **29** were used without any purification.

All reactions were conducted in flame-dried glass flasks under an argon atmosphere unless otherwise specified. Flash column chromatography was performed using Silicycle SiliaFlash P60 silica gel, 40-63 μm particle size.

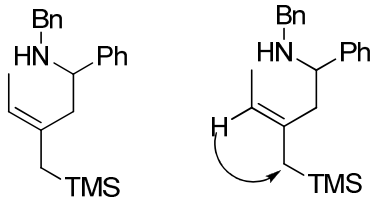


7 **7a**

3-(benzylamino)-2-methyl-3-phenyl-2-((trimethylsilyl)methyl)propan-1-ol (7) and *N*-benzyl-1-phenyl-3-((trimethylsilyl)methyl)but-3-en-1-amine (7a): To a solution of 262 mg (1.33 mmol) of imine **5** in 6 mL of dry diethyl ether was added 0.61 mL (2.0 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 2.0 mL (4.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of the lithium alkoxide of alcohol **6** in 2 mL of THF, prepared by deprotonation of 0.28 g (2.0 mmol) of alcohol **6** at -78 °C with 0.88 mL (2.2 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1) to give 320 mg (75%) of amines **7** (a mixture of inseparable diastereomers) and 80 mg (19%) of homoallylic amine **7a** as colorless oils.

Data for amines **7:** IR (neat) 3307, 2853, 1644, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 0.43 and 0.96 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H_2}$TMS), 3.42 and 3.54 (ABq, *J* = 12.8 Hz, 2H, C$\underline{H_2}$OH), 3.56 (s, 3H, 1H, $CH_2C\underline{H}NC\underline{H_2}Ph$), 7.30 (m, 10H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 17.6 (t), 23.1 (q), 40.2 (s), 50.6 (t), 72.7 (d), 72.8 (t), 126.4 (d), 127.1 (d), 127.5 (d), 127.6 (d), 138.2 (s), 138.3 (s); LRMS $C_{21}H_{31}NOSi$ + H^+ calcd. *m*/*z* 342.2, found *m*/*z* 342.6.

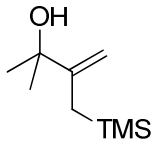
Data for amine **7a:** IR (neat) 2235, 2953, 1632, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.40 and 1.51 (ABq, J = 13.2 Hz, 2H, C$\underline{H}_2$TMS), 1.81 (br, 1H, NH), 2.26 (m, 2H, C$\underline{H}_2$CHN), 3.48 and 3.70 (ABq, J = 12.0 Hz, 2H, NC$\underline{H}_2$Ph), 3.77 (dd, J = 9.2, 4.8 Hz, 1H, $CH_2C\underline{H}N$), 4.62 (s,1H, =C$\underline{H}_2$), 4.68 (s, 1H, =C$\underline{H}_2$), 7.35 (m, 10H, benzene); LRMS $C_{21}H_{29}NSi$ + H^+ calcd. m/z 324.2, found m/z 324.5.



9 nOe

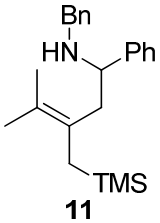
(*E*)-*N*-benzyl-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (9): To a solution of 260mg (1.33 mmol) of imine **5** in 6 mL of dry diethyl ether was added 0.61 mL (2.0 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^oC, and 2.0 mL (4.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 ^oC for 1.5 h. Next, a solution of lithium alkoxide of alcohol **8** in 2 mL of THF, prepared by deprotonation of 0.30 g (2.0 mmol) of alcohol **8** at -78 ^oC with 0.85 mL (2.13 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1) to give 320 mg (70%) of homoallylic amine **9** as a colorless oil. No evidence for the production of a minor isomer was found in the ^1H NMR of the crude material. Alkene geometry was determined by nOe. Data for amine **9**: IR (neat) 3584, 2953, 1652, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS),

1.35 and 1.43 (d, *J* = 13.6 Hz, 2H, C<u>H</u>$_2$TMS), 1.57 (d, *J* = 6.4 Hz, 3H, =C<u>H</u>CH$_3$), 1.82 (br, 1H, NH), 2.13 (dd, *J* = 13.6, 5.2 Hz, 1H, C<u>H</u>$_2$CHN), 2.56 (dd, *J* = 13.2, 9.2 Hz, 1H, C<u>H</u>$_2$CHN), 3.52 and 3.73 (ABq, *J* = 13.6 Hz, 2H, NC<u>H</u>$_2$Ph), 3.81 (dd, *J* = 9.2, 5.2 Hz, 1H, CH$_2$C<u>H</u>N), 5.19 (q, *J* = 6.4 Hz, 1H, =C<u>H</u>CH$_3$), 7.36 (m, 10H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.8 (q), 27.8 (t), 42.4 (t), 52.7 (t), 61.5 (d), 121.2 (d), 127.9 (d), 128.1 (d), 128.5 (d), 129.1 (d), 129.45 (d), 129.49 (d), 129.54(d), 135.4(s), 141.8 (s), 145.4 (s); LRMS $C_{22}H_{31}NSi$ + H^+ calcd. *m*/*z* 338.2, found *m*/*z* 338.5.



10

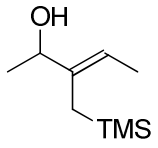
2-methyl-3-((trimethylsilyl)methyl)but-3-en-2-ol (10): IR (neat) 3401, 3093, 2976, 1628, 1461 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 9H, TMS), 1.33 (s, 7H, CH_3 + OH), 1.59 (s, 2H, C<u>H</u>$_2$TMS), 4.62 (s, 1H, =CH_2), 4.95 (s, 1H, =CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 21.7 (t), 29.9 (q), 74.3 (s), 106.9 (d), 154.4 (s); LRMS $C_9H_{20}OSi$ + Na^+ calcd. *m*/*z* 195.2, found *m*/*z* 195.5.



11

***N*-benzyl-4-methyl-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (11):** To a solution of 390 mg (2.0 mmol) of imine **5** in 8 mL of dry diethyl ether was added 0.91 mL (3.0 mmol) of Ti(O^{i}Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^{o}C, and 3.0 mL (6.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark

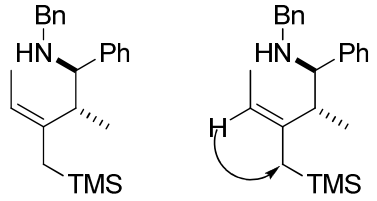
brown after stirring at -78 °C for 1.5 h. Next, a solution of lithium alkoxide of alcohol **10** in 2 mL of THF, prepared by deprotonation of 0.17 g (1.0 mmol) of alcohol **10** at -78 °C with 0.44 mL (1.1 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was warmed to room temperature over 2 h, then stirred for 12 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 20:1) to give 240 mg (70%) of homoallylic amine **11** as a colorless oil. Data for amine **11**: IR (neat) 3318, 2953, 1602, 1585, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.33 and 1.60 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H}_2$TMS), 1.62 (s, 3H, =C(C$\underline{H}_3$)$_2$), 1.65 (s, 3H, =C(C$\underline{H}_3$)$_2$), 1.78 (s, 1H, NH), 2.13 (dd, *J* = 13.6, 5.2 Hz, 1H, C$\underline{H}_2$CHN), 2.53 (dd, *J* = 13.2, 9.2 Hz, 1H, C$\underline{H}_2$CHN), 3.51 and 3.73 (ABq, *J* = 14.0 Hz, 2H, NC$\underline{H}_2$Ph), 3.80 (dd, *J* = 9.2, 5.2 Hz, 1H, CH$_2$C$\underline{H}$N), 7.26 (m, 4H), 7.32 (m, 4H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 21.1 (q), 22.1 (q), 23.3 (t), 44.2 (t), 52.0 (t), 61.4 (d), 125.0 (s), 127.1 (s), 127.3 (d), 127.8 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.8 (d), 129.2 (d), 141.5 (s), 145.4 (s); LRMS $C_{23}H_{33}NSi + H^+$ calcd. *m*/*z* 352.2, found *m*/*z* 352.6.



12

(*Z*)-3-((trimethylsilyl)methyl)pent-3-en-2-ol (12): IR (neat) 3368, 2956, 1660, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 9H, TMS), 1.25 (d, *J* = 6.4 Hz, 3H, CH3), 1.35 (br, 1H, OH), 1.43 and 1.66 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H}_2$TMS), 1.56 (d, *J* = 6.8 Hz, 3H, CH_3). 4.10 (q, *J* = 6.4 Hz, 1H, C$\underline{H}$OH), 5.43 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}$CH$_3$); ^{13}C NMR ($CDCl_3$,

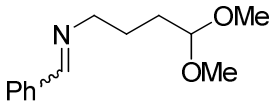
100 MHz) δ 0.0 (q), 14.2 (q), 18.6 (t), 22.7 (q), 42.0 (s), 72.6 (d), 115.4 (d), 142.8 (s); LRMS $C_9H_{20}OSi + Na^+$ calcd. *m*/*z* 195.2, found *m*/*z* 195.4.



13 nOe

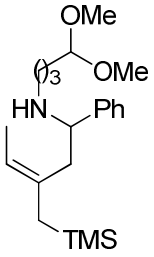
(*E*)-*N*-benzyl-2-methyl-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (13): To a solution of 131 mg (0.67 mmol) of imine **5** in 6 mL of dry diethyl ether in a 50 mL seal tube was added 0.30 mL (1.0 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 1.0 mL (2.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of lithium alkoxide of alcohol **12** in 1 mL of THF, prepared by deprotonation of 0.17 g (1.0 mmol) of alcohol **12** at -78 °C with 0.44 mL (1.1 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. After the mixture was slowly warmed up to room temperature, and stirred for 16 h, the reaction was heated to 80 °C and stirred for 24 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was separated and extracted with 2 portions of 10 mL of ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 20:1) to give 123 mg (51%) of homoallylic amine **13** as a colorless oil. No evidence of the presence of a minor isomer was found in the ^1H NMR of the crude material. Relative stereochemistry was assigned by analogy to previous examples, and alkene geometry was determined by nOe.[4] Data for amine **13**: IR (neat) 3323, 2958, 1602 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 0.58 (d, *J* = 7.2 Hz, 3H, $CHC\underline{H}_3$), 1.20 (t, *J* = 1.2 Hz, 2H, $C\underline{H}_2TMS$), 1.64 (br, 1H, NH), 1.69 (d, *J* = 6.8 Hz, 3H, CH3CH=), 2.82 (m, 1H, $CH_3C\underline{H}CHN$), 3.33 (d, *J* = 10.0 Hz, 1H, $C\underline{H}N$), 3.51 and

3.73 (d, *J* = 14.0 Hz, 2H, NC<u>H</u>$_2$Ph), 5.30 (q, *J* = 6.8 Hz, 1H, =C<u>H</u>CH$_3$), 7.20 (m, 6H), 7.32 (m, 2H), 7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 13.9 (q), 16.4 (q), 20.0 (t), 42.3 (d), 51.8 (t), 65.3 (d),121.6 (d), 127.1 (d), 127.5 (d), 128.59 (d), 128.62 (d), 128.63 d), 129.2 (d), 139.5 (s), 141.4 (s), 143.9 (s); LRMS $C_{23}H_{33}NSi$ + H^+ calcd. *m*/*z* 352.2, found *m*/*z* 352.6.



14

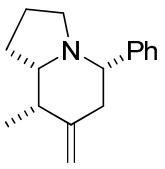
***N*-benzylidene-4,4-dimethoxybutan-1-amine (14):** IR (neat) 3278, 2950, 1651, 1580, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (m, 2H, CH_2), 1.79 (m, 2H, CH_2), 3.32 (s, 6H, CH(O<u>Me</u>)$_2$), 3.65 (td, *J* = 6.4, 1.2 Hz, 2H, NC<u>H</u>$_2$), 4.44 (t, *J* = 5.6 Hz, 1H, C<u>H</u>(OMe)$_2$), 7.42 (m, 3H, benzene), 7.74 (m, 2H, benzene), 8.29 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0 (t), 30.3 (t), 52.7 (q), 61.3 (t), 104.4 (d), 128.0 (d), 128.6 (d), 130.5 (d), 136.3 (s), 161.1 (d); LRMS $C_{13}H_{19}NO_2$ + H^+ calcd. *m*/*z* 222.1, found *m*/*z* 222.6.



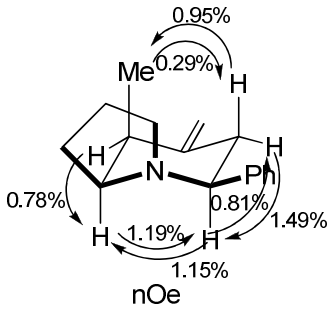
15

(*E*)-*N*-(4,4-dimethoxybutyl)-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (15): To a solution of 240 mg (1.33 mmol) of imine **14** in 10 mL of dry diethyl ether was added 0.61 mL (2.0 mmol) of Ti(O^{i}Pr)$_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^{o}C, and 2.0 mL (4.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 ^{o}C for 1.5 h. Next, a solution of lithium alkoxide of alcohol

8 in 2 mL of THF, prepared by deprotonation of 312 mg (2.0 mmol) of alcohol **8** at -78 ^{o}C with 0.88 mL (2.2 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with 2 portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1 to 2:1) to give 323 mg (66%) of homoallylic amine **15** as a colorless oil. No evidence of the presence of a minor isomer was found in the ^{1}H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **15**: IR (neat) 3320, 2951, 1602, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.45 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H}_2$TMS), 1.50 (d, *J* = 6.8 Hz, 3H, C$\underline{H}_3$CH=), 1.59 (m, 5H, NH and -(C$\underline{H}_2$)$_2$CH(OMe)$_2$), 2.16 (dd, *J* = 13.2, 5.2 Hz, 1H, C$\underline{H}_2$CHN), 2.52 (dd, *J* = 13.2, 8.8 Hz, 1H, C$\underline{H}_2$CHN), 3.30 (s, 6H, CH(O$\underline{Me}$)$_2$), 3.76 (d, *J* = 8.8, 5.2 Hz, 1H, C$\underline{H}$N), 4.33 (t, *J* = 5.6 Hz, 1H, C$\underline{H}$(OMe)$_2$), 5.16 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}$CH$_3$), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.8 (q), 26.1 (t), 27.9 (t), 31.3 (t), 42.2 (t), 48.7 (t), 53.8 (q), 53.9 (q), 62.8 (d), 105.6 (d), 121.1(d), 128.1 (d), 128.4 (d), 129.4 (d), 129.4 (s), 135.3 (s); HRMS $C_{21}H_{37}NO_2Si$ + H^+ calcd. *m*/*z* 364.2666, found *m*/*z* 364.2684.

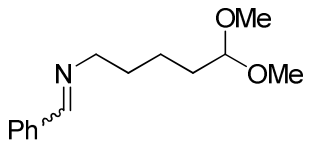


16



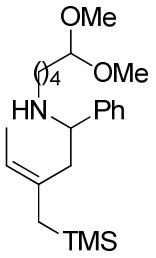
(5*S, 8*S**, 8a*S**)-8-methyl-7-methylene-5-phenyloctahydroindolizine (16):** To a solution of 50 mg (0.15 mmol) of imine **15** in 1 mL of THF was added 0.75 mL (0.75

mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 1 h, the reaction was quenched by addition of 0.1 g (0.75 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 10 mL of CH_2Cl_2. The organic extract was dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 40:1) to give 30 mg (88%) of indolizidine **16** as a yellow oil. No evidence for the presence of a minor isomer was observed in the ^{1}H NMR of the crude material. Stereochemistry was assigned by nOe. Data for indolizidine **16**: IR (neat) 3584, 2970, 151, 1601 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.09 (d, *J* = 7.2 Hz, 3H, CH_3), 1.52 (m, 4H, -$(CH_2)_2$-), 1.65 (q, *J* = 8.8 Hz, 1H, NC$\underline{H}_2$), 2.04 (dd, *J* = 13.6, 3.2 Hz, 1H, C$\underline{H}_2$CHN), 2.12 (td, *J* = 8.4, 2.8 Hz, 1H, C(9)H), 2.35 (dd, *J* = 10.2, 8.7 Hz, 1H, C$\underline{H}_2$CHN), 2.42 (qd, *J* = 7.2, 3.2 Hz, C(9)$\underline{H}$), 2.61 (m, 1H, NC$\underline{H}_2$), 2.80 (dd, *J* = 11.2, 3.2 Hz, 1H, C(5)H), 4.54 (s, 1H, =CH_2), 4.66 (s, 1H, =CH_2), 7.22 (m, 5H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 13.4 (q), 21.4 (t), 26.6 (t), 40.6 (d), 40.7 (t), 52.7 (t), 68.3 (d), 70.6 (d), 107.3 (t), 127.3 (d), 127.6 (d), 128.6 (d), 145.1 (s), 153.0 (s); HRMS $C_{16}H_{21}N$ + H^+ calcd. *m*/*z* 228.1747, found *m*/*z* 228.1753.



17

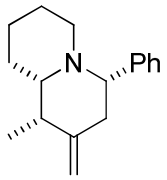
***N*-benzylidene-5,5-dimethoxypentan-1-amine (17):** IR (neat) 3278, 2945, 1651, 1580, 1452 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 3.33 (s, 6H, CH(O$\underline{Me}$)$_2$), 3.63 (td, *J* = 6.4, 1.2 Hz, 2H, NC$\underline{H}_2$), 4.39 (t, *J* = 5.6 Hz, 1H, C$\underline{H}$(OMe)$_2$), 7.42 (m, 3H, benzene), 7.74 (m, 2H, benzene), 8.29 (s, 1H, N=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4 (t), 30.7 (t), 32.3 (t), 52.7 (q), 61.6 (t), 104.5 (d), 128.0 (d), 128.6 (d), 130.5 (d), 136.3 (s), 160.9 (d); LRMS $C_{14}H_{21}NO_2$ + H^+ calcd. *m*/*z* 236.2, found *m*/*z* 236.5.



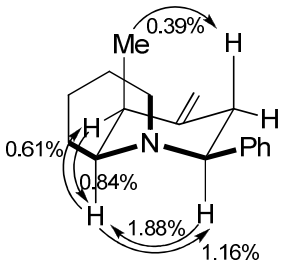
18

(*E*)-*N*-(5,5-dimethoxypentyl)-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (18): To a solution of 160 mg (0.67 mmol) of imine **17** in 6 mL of dry diethyl ether was added 0.30 mL (1.0 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^oC, and 1.0 mL (2.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 ^oC for 1.5 h. Next, a solution of lithium alkoxide of alcohol **8** in 2 mL of THF, prepared by deprotonation of 156 mg (1.0 mmol) of alcohol **8** at -78 ^oC with 0.44 mL (2.2 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with two portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1 to 2:1) to give 170 mg (66%) of homoallylic amine **18** as a colorless oil. No evidence for the presence of a minor isomer was found in ^1H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **18**: IR (neat) 3321, 2919, 1652, 1602, 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.33 (m, 2H, C$\underline{H}_2$), 1.45 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H}_2$TMS), 1.48 (m, 3H, NH and C$\underline{H}_2$), 1.50 (d, *J* = 6.8 Hz, 3H, C$\underline{H}_3$CH=), 1.58 (m, 2H, C$\underline{H}_2$), 2.11 (dd, *J* = 13.2, 5.6 Hz, 1H, C$\underline{H}_2$CHN), 2.43 (t, *J* = 7.2 Hz, 2H, NC$\underline{H}$2), 2.48 (dd, *J* = 13.2, 8.8 Hz, 1H, C$\underline{H}_2$CHN), 3.30 (s, 6H, CH(O$\underline{Me}$)$_2$), 3.76 (dd, *J* = 8.8, 5.6 Hz, 1H,

C<u>H</u>N), 4.34 (t, *J* = 6.0 Hz, 1H, C<u>H</u>$(OMe)_2$), 5.16 (q, *J* = 6.8 Hz, 1H, =C<u>H</u>CH_3), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.7 (q), 23.5 (t), 27.9 (t), 31.1 (t), 33.5 (t), 42.4 (t), 49.0 (t), 53.7 (q), 53.8 (q), 62.9 (d), 105.6 (d), 120.9 (d), 127.9 (d), 128.3 (d), 129.3 (d), 135.5 (s), 146.1 (s); HRMS $C_{22}H_{39}NO_2Si$ + H^+ calcd. *m*/*z* 378.2823, found *m*/*z* 378.2839.

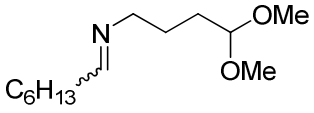


19



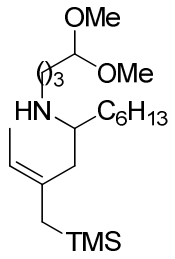
nOe

(1*S,4*S**,9a*S**)-1-methyl-2-methylene-4-phenyloctahydro-1H-quinolizine (19):** To a solution of 100 mg (0.26 mmol) of imine **18** in 2 mL of THF was added 1.3 mL (1.3 mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 12 h, the reaction was quenched by addition of 0.15 g (1.1 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 2 x 5 mL of diethyl ehter. The organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (hexanes-ethyl acetate, 20:1) to give 55 mg (88%) of quinolizidine **19** as a yellow oil. No evidence for the presence of a minor isomer was found in the ^{1}H NMR of the crude material. Stereochemistry was assigned by nOe. Data for quinolizidine **19**: IR (neat) 3643, 2936, 1656 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (d, *J* = 7.2 Hz, 3H, CH_3), 1.38 (m, 2H, -CH_2-), 1.42 (m, 2H, -CH_2-), 1.51 (m, 2H, -CH_2-), 1.64 and 2.58 (m, 2H, NC<u>H</u>$_2$), 1.98 (td, *J* = 11.6, 3.2 Hz, 1H, C(9)H), 2.04 (m, 1H,1H, C<u>H</u>$_2$CHN), 2.18 (qd, *J* = 6.8, 2.8 Hz, C(1)<u>H</u>), 2.39 (dd, *J* = 13.6, 12.0 Hz, 1H, C(3)H), 2.78 (dd, *J* = 12.0, 4.0 Hz, 1H, C(4)H), 4.48 (s, 1H, =CH_2), 4.60 (s, 1H, =CH_2), 7.28 (m, 5H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 14.6 (q), 25.3 (t), 26.6 (t), 31.1 (t), 41.0 (t), 43.7 (d), 54.6 (t), 66.8 (d), 72.6 (d), 105.5 (t), 127.1 (d), 127.7 (d), 128.7 (d), 146.0 (s), 152.8 (s); HRMS $C_{17}H_{23}N$ + H^+ calcd. *m*/*z* 242.1903, found *m*/*z* 242.1914.



20

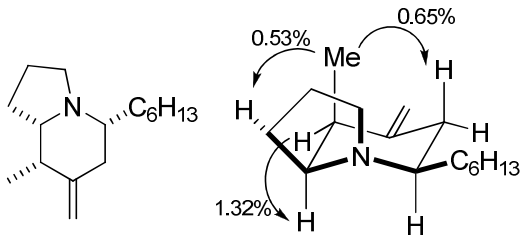
***N*-heptylidene-4,4-dimethoxybutan-1-amine (20):** IR (neat) 3323, 2927,1669, 1463 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (t, *J* = 6.8 Hz, 3H, CH_3), 1.22 (m, 6H, 3 x CH_2), 1.46 (m, 2H, CH_2), 1.57 (m, 4H, 2 x CH_2), 2.16 (m, 2H, $C\underline{H}_2CH(OMe)_2$), 3.25 (s, 6H, $CH(O\underline{Me})_2$), 3.28 (t, *J* = 6.4 Hz, 2H, $NC\underline{H}_2$), 4.31 (t, *J* = 5.6 Hz, 1H, $C\underline{H}(OMe)_2$), 7.57 (t, *J* = 4.8 Hz, 1H, N=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (q), 22.6 (t), 25.8 (t), 26.0 (t), 28.9 (t), 30.2 (t), 31.6 (t), 35.8 (t), 52.5 (q), 52.6 (q), 61.0 (t), 104.4 (d), 165.4 (d); LRMS $C_{13}H_{27}NO_2 + H^+$ calcd. *m*/*z* 230.2, found *m*/*z* 230.5.



21

(*E*)-*N*-(4,4-dimethoxybutyl)-3-((trimethylsilyl)methyl)undec-2-en-5-amine (21): To a solution of 569 mg (2.0 mmol) of $Ti(O^iPr)_4$ in 10 mL of diethyl ether was added 1.6 mL (4.0 mmol) of 2.5 M *n*-BuLi in hexanes over 2 min at -78 °C under argon. After 10 min, a solution of 459 mg (2.0 mmol) of imine **20** in 2 mL of dry diethyl ether was added via a syringe. The mixture was stirred at -78 °C for 0.5 h, then was raised to rt over 30 min. The solution turned from pale yellow to red. The red homogeneous solution was cooled back to -78 °C, and a solution of lithium alkoxide of alcohol **8** in 4 mL of THF, prepared by deprotonation of 156 mg (1.0 mmol) of alcohol **8** at -78 °C with 0.44 mL (1.1 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added immediately to the red solution via cannula. The mixture was slowly warmed to room temperature, and stirred

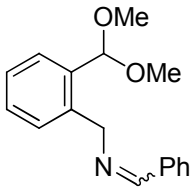
for 16 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with two portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 5:1 to 1:1) to give 261 mg (70%) of homoallylic amine **21** as a yellow oil. No evidence for the presence of a minor isomer was found in the ^1H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **21**: IR (neat) 3311, 2928, 1652, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 0.89 (t, *J* = 6.8 Hz, 3H, C$\underline{H}_3(CH_2)_5$-), 1.31 (m, 10H, C$\underline{H}_2$TMS and $CH_3(C\underline{H}_2)_5$-), 1.51 (m, 5H, NH + C$\underline{H}_2$), 1.61 (d, *J* = 6.8 Hz, 3H, C$\underline{H}_3$CH=), 1.97 (dd, *J* = 13.2, 5.6 Hz, 1H, C$\underline{H}_2$CHN), 2.17 (dd, *J* = 13.2, 8.4 Hz, 1H, C$\underline{H}_2$CHN), 2.53 (dd, *J* = 8.4, 5.6 Hz, 1H, C$\underline{H}$N), 2.64 (m, 2H, CH_2), 3.32 (s, 6H, OC$\underline{H}_3$), 4.37 (t, *J* = 5.6 Hz, 1H, C$\underline{H}(OMe)_2$), 5.16 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.9 (q), 15.3 (q), 23.8 (t), 26.7 (t), 27.1 (t), 28.1 (t), 30.8 (t), 31.5 (t), 33.1 (t), 35.6 (t), 38.0 (t), 48.5 (t), 53.8 (q), 53.9 (q), 57.5 (d), 105.6 (d), 120.3 (d), 136.3 (s); HRMS $C_{21}H_{44}NO_2Si + H^+$ calcd. *m*/*z* 372.3292, found *m*/*z* 372.3307.



22 nOe

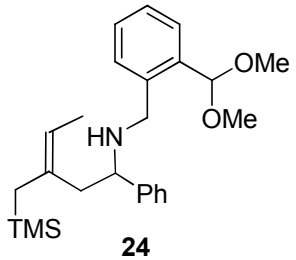
(5*R,8*S**,8a*S**)-5-hexyl-8-methyl-7-methyleneoctahydroindolizine (22):** To a solution of 75 mg (0.20 mmol) of imine **21** in 5 mL of THF was added 1.0 mL (1.0 mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 16 h, the reaction was quenched by addition of 0.15 g (1.1 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 2 x 5 mL of diethyl ehter. The organic extracts were dried ($MgSO_4$),

and concentrated *in vacuo* to afford pale yellow oil. The residue was purified by chromatography over 20 g of silica gel (hexanes-ethyl acetate, 20:1) to give 45 mg (95%) of indolizidine **22** as a yellow oil. No evidence for the presence of a minor isomer was found in ^{1}H NMR of the crude. Stereochemistry was assigned by nOe. Data for indolizidine **22**: IR (neat) 3584, 2931, 1651 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (d, *J* = 6.0 Hz, 3H, CH_3), 0.95 (d, *J* = 7.2 Hz, 3H, C(8)HCH_3), 1.18 (m, 10H, -$(CH_2)_5$-), 1.54 (m, 3H), 1.62 (m, 1H, C(6)H$_2$), 1.73 (m, 1H), 1.78 (dd, *J* = 8.4 Hz, 8.0 Hz, 1H, C(6)H$_2$), 1.97 (m, 1H, C(9)H), 2.00 (m, 2H, NCH_2), 2.32 (qd, *J* = 6.4, 3.2 Hz, C(8)HCH_3), 3.14 (dd, *J* = 8.0, 6.0 Hz, C(5)H), 4.51 (s, 1H, CH$_2$), 4.58 (s, 1H, CH$_2$); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 13.3 (q), 14.1 (q), 21.0 (t), 22.6 (t), 25.3 (t), 26.1 (t), 29.7 (t), 31.8 (t), 34.7 (t), 35.7 (t), 40.1 (d), 51.8 (t), 65.0 (d), 68.3 (d), 106.9 (t), 152.8 (s); HRMS $C_{16}H_{29}N + H^+$ calcd. *m*/*z* 236.2373, found *m*/*z* 236.2380.



23

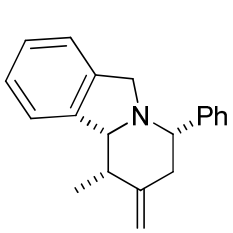
***N*-benzylidene-1-(2-(dimethoxymethyl)phenyl)methanamine (23):** IR (neat) 3272, 2829, 1651, 1580, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (s, 6H, CH(OMe)$_2$), 4.95 (d, *J* = 1.2 Hz, 2H, NCH$_2$), 5.65 (s, 1H, CH(OMe)$_2$), 7.28 (m, 2H, benzene), 7.41 (m, 4H, benzene), 7.61 (m, 1H, benzene), 7.78 (m, 2H, benzene), 7.79 (m, 1H, N=CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.3 (q), 61.5 (t), 101.7 (d), 126.7 (d), 126.8 (d), 128.2 (d), 128.6 (d), 128.7 (d), 128.9 (d), 130.7 (d), 135.4 (s), 136.3 (s), 137.5 (s), 162.0 (d); LRMS $C_{17}H_{19}NO_2 + H^+$ calcd. *m*/*z* 270.1, found *m*/*z* 270.5.



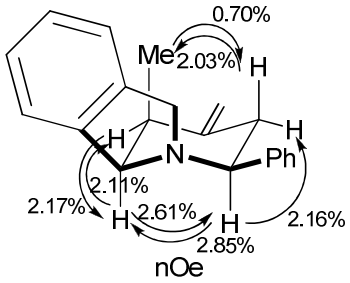
24

(*E*)-*N*-(2-(dimethoxymethyl)benzyl)-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (24): To a solution of 458 mg (1.7 mmol) of imine **23** in 8 mL of dry diethyl ether was added 0.77 mL (2.55 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^oC, and 2.55 mL (5.1 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 ^oC for 1.5 h. Next, a solution of lithium alkoxide of alcohol **8** in 4 mL of THF, prepared by deprotonation of 399 mg (2.55 mmol) of alcohol **8** at -78 ^oC with 1.1 mL (2.8 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with two portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (hexanes-ethyl acetate, 10:1) to give 420 mg (61%) of homoallylic amine **24** as colorless oil. No evidence for the presence of a minor isomer was observed in the ^1H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **24:** IR (neat) 3323, 2593, 1651m 1455 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.37 and 1.43 (ABq, *J* = 14.0 Hz, 2H, C$\underline{H}_2$TMS), 1.53 (d, *J* = 6.8 Hz, 3H, CH_3), 1.82 (br, 1H, NH), 2.15 (dd, *J* = 13.2, 4.2 Hz, 1H, C$\underline{H}_2$CHN), 2.52 (dd, *J* = 13.2, 8.8 Hz, 1H, C$\underline{H}_2$CHN), 3.30 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.33 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.62 and 3.71 (ABq, *J* = 13.2 Hz, 2H, NC$\underline{H}_2$), 3.76 (dd, *J* = 8.8, 5.2 Hz, 1H, C$\underline{H}$N), 5.16 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}$CH$_3$), 5.46 (s, 1H, C$\underline{H}$(OMe)$_2$), 7.29 (m, 4H, benzene), 7.36 (m, 2H), 7.45 (m, 2H), 7.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.7 (q), 27.9 (t), 42.6 (t), 49.7 (t), 54.5 (q), 54.7 (q), 62.1

(d), 102.9 (d), 121.0 (d), 127.8 (d), 128.1 (d), 128.6 (d), 129.5 (d), 129.6 (d), 130.8 (d), 135.4 (s), 137.2 (s), 139.7 (s), 145.9 (s); HRMS $C_{25}H_{37}NO_2Si$ + H^+ calcd. *m*/*z* 412.2666, found *m*/*z* 412.2681.

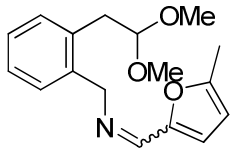


25



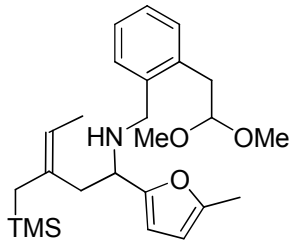
nOe

(1*S,4*S**,10b*R**)-1-methyl-2-methylene-4-phenyl-1,2,3,4,6,10b-hexahydropyrido-[2,1-a]isoindole (25):** To a solution of 85 mg (0.21 mmol) of imine **24** in 5 mL of THF was added 0.5 mL (0.5 mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 16 h, the mixture turned green, and was quenched by addition of 0.15 g (1.1 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 2 x 5 mL of diethyl ehter. The organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford a dark green oil. The residue was purified by chromatography over 20 g of silica gel (hexanes-ethyl acetate, 40:1) to give 52 mg (90%) of indolizidine **25** as a yellow oil. No evidence for the presence of a minor isomer was found in the ^{1}H NMR of the crude material (spectrum provided). Stereochemistry was assigned by nOe. Data for indolizidine **25**: IR (neat) 3390, 2902, 2759, 1645, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (d, *J* = 6.0 Hz, 3H, CH_3), 2.22 (dd, *J* = 14.0 Hz, 3.2 Hz, 1H, C(3)$\underline{H}_2$), 2.53 (dd, *J* = 14.0, 11.2 Hz, 1H, C(3)$\underline{H}_2$), 2.99 (qd, *J* = 6.0, 3.2 Hz, 1H, C(1)H), 3.09 and 3.74 (ABq, *J* = 12.4 Hz, NC$\underline{H}_2$), 3.40 (dd, *J* = 11.2, 3.2 Hz, 1H, C(4)$\underline{H}$), 3.59 (m, 1H, C(9)H), 4.69 (s, 1H, =C$\underline{H}_2$), 4.84 (s, 1H, =C$\underline{H}_2$), 7.05 (m, 3H, benzene), 7.10 (m, 1H, benzene), 7.19 (m, 1H, benzene), 7.28 (m, 2H, benzene), 7.35 (m, 2H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6 (q), 39.3 (d), 40.9 (t), 55.7 (t), 68.5 (d), 71.5 (d), 108.7 (t), 121.2 (d), 122.5 (d), 126.5 (d), 126.6 (d), 127.2 (d), 127.4 (d), 128.5 (d), 140.8 (s), 141.8 (s), 143.6 (s), 150.9 (s); HRMS $C_{20}H_{21}N$ + H^+ calcd. *m*/*z* 276.1747, found *m*/*z* 276.1766.



26

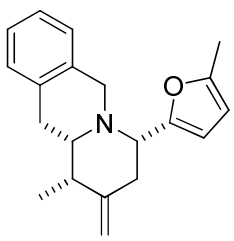
1-(2-(2,2-dimethoxyethyl)phenyl)-*N*-((5-methylfuran-2-yl)methylene)methanamine (26): IR (neat) 3584, 2933, 1737, 1645, 1453 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.28 (s, 3H, CH_3), 2.90 (d, *J* = 5.6 Hz, 2H, CH_2), 3.25 (s, 6H, $CH(O\underline{Me})_2$), 4.48 (t, *J* = 5.6 Hz, 1H, $C\underline{H}(OMe)_2$), 4.78 (s, 2H, CH_2), 6.00 (s, 1H, furan), 6.54 (m, 1H, furan), 7.16 (m, 4H, benzene), 7.91 (s, 1H, $C\underline{H}$=NR) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 36.6 (t), 53.9 (q), 62.1 (q), 105.7 (d), 108.0 (d), 116.1 (d), 126.8 (d), 127.2 (d), 129.4 (d), 130.6 (d), 135.4 (s), 137.5 (s), 150.1 (d), 150.4 (s), 155.5 (s); LRMS $C_{17}H_{21}NO_3$ + H^+ calcd. *m*/*z* 288.2, found *m*/*z* 288.5.



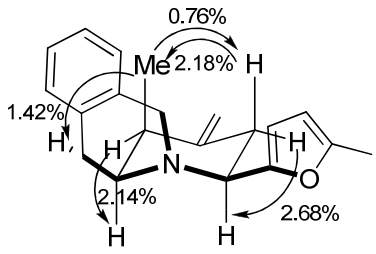
27

(*E*)-*N*-(2-(dimethoxymethyl)benzyl)-1-phenyl-3-((trimethylsilyl)methyl)pent-3-en-1-amine (27): To a solution of 575 mg (2.0 mmol) of imine **26** in 8 mL of dry diethyl ether was added 0.91 ml (3.0 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 ^oC, and 3.0 mL (6.0 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 ^oC for 1.5 h. Next, a solution of lithium alkoxide of alcohol **8** in 4 mL of THF, prepared by deprotonation of 156 mg (1.0 mmol) of alcohol **8** at -78 ^oC with 0.44 mL (1.1 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential

addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with two portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 10:1 to 5:1) to give 235 mg (55%) of homoallylic amine **27** as a yellow oil. No evidence for the presence of a minor isomer was found in the ^1H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **27:** IR (neat) 3319, 2952, 1605, 1566, 1454 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.31 and 1.39 (ABq, *J* = 13.6 Hz, 2H, C$\underline{H}_2$TMS), 1.54 (d, *J* = 6.8 Hz, 3H, C$\underline{H}_3$CH=), 1.74 (br, 1H, NH), 2.32 (s, 3H, CH_3), 2.40 (dd, *J* = 13.2, 7.2 Hz, 1H, C$\underline{H}_2$CHN), 2.54 (dd, *J* = 13.2, 7.2 Hz, 1H, C$\underline{H}_2$CHN), 2.95 (d, *J* = 5.6 Hz, 2H, C$\underline{H}_2$CH(OMe)$_2$), 3.33 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.34 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.66 and 3.78 (ABq, *J* = 13.2 Hz, 2H, NHC$\underline{H}_2$Ph), 3.80 (t, *J* = 7.2 Hz, 1H, C$\underline{H}$N), 4.56 (t, *J* = 5.6 Hz, 1H, C$\underline{H}$(OMe)$_2$), 5.12 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}$CH$_3$), 5.91 (m, 1H, furan), 6.08 (m, 1H, furan), 7.22 (m, 4H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.0 (q), 14.7 (q), 14.9 (q), 27.8 (t), 37.4 (t), 38.7 (t), 50.5 (t), 54.9 (q), 55.9 (q), 106.9 (d), 107.0 (d), 108.7 (d), 120.8 (d), 127.7 (d), 128.2 (d), 130.6 (d), 131.8 (d), 135.2 (s), 136.9 (s), 139.9 (s), 152.2 (s), 155.7 (s); HRMS $C_{25}H_{39}NO_3Si$ + H^+ calcd. *m*/*z* 430.2772, found *m*/*z* 430.2782.



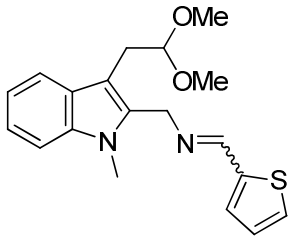
28



nOe

(1*S,4*S**,11a*S**)-1-methyl-2-methylene-4-(5-methylfuran-2-yl)-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline (28):** To a solution of 50 mg (0.12 mmol) of imine **27** in 5 mL of THF was added 1.0 mL (1.0 mmol) of 1N HCl aqueous solution at rt under argon. The reaction was warmed to 50 ^oC with stirring for 16 h, and then was

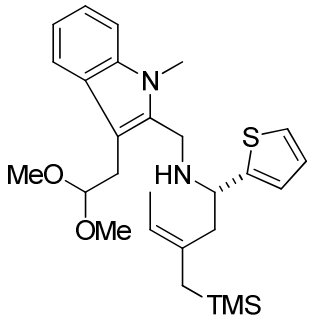
quenched by addition of 0.15 g (1.1 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 2 x 10 mL of diethyl ehter. The organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 20 g of silica gel (hexanes-ethyl acetate, 40:1) to give 28 mg (81%) of quinolizidine **28** as a yellow oil. No evidence for the presence of a minor isomer was found in the ^{1}H NMR of the crude material. Stereochemistry was assigned by nOe. Data for quinolizidine **28**: IR (neat) 3385, 2960, 1644, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 6.8 Hz, 3H, CH_3), 2.23 (dd, *J* = 13.6 Hz, 3.2 Hz, 1H, C(3)$\underline{H}_2$), 2.30 (s, 3H, CH_3), 2.50 (qd, *J* = 6.8, 3.6 Hz, 1H, C(1)H), 2.61 (m, 1H, C(10)H), 2.65 (dd, *J* = 6.4, 4.4 Hz, 1H, C(9)$\underline{H}_2$), 2.92 (dd, *J* = 13.6, 12.4 Hz, 1H, C(3)$\underline{H}_2$), 3.12 (m, 1H, C(9)$\underline{H}_2$), 3.14 (dd, *J* = 12.4, 3.2 Hz, 1H, C(4)$\underline{H}$), 3.21 and 3.85 (ABq, *J* = 15.6 Hz, 2H, NC$\underline{H}_2$), 4.66 (s, 1H, =C$\underline{H}_2$), 4.77 (s, 1H, =C$\underline{H}_2$), 5.92 (s, 1H, furan), 6.13 (s, 1H, furan), 6.90 (m, 1H, benzene), 7.08 (m, 3H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (q), 14.5 (q), 33.0 (t), 36.7 (t), 41.7 (d), 56.6 (t), 62.0 (d), 65.4 (d), 105.8 (d), 106.5 (t), 107.9 (d), 125.5 (d), 126.1 (d), 127.8 (d), 133.8 (s), 133.9 (s), 150.7 (s), 151.6 (s), 153.7 (s); LRMS $C_{21}H_{29}NSi$ + H^+ calcd. *m*/*z* 294.2, found *m*/*z* 294.5.



29

1-(3-(2,2-dimethoxyethyl)-1-methyl-1H-indol-2-yl)-*N*-(thiophen-2-ylmethylene)methanamine (29): IR (in $CHCl_3$) 3054, 2929, 1673, 1633, 1471 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.10 (d, *J* = 5.6 Hz, 2H, CH_2), 3.34 (s, 6H, CH(O$\underline{Me}$)$_2$), 3.77 (s, 3H, NMe), 4.55 (t, *J* = 5.6 Hz, 1H, C$\underline{H}$(OMe)$_2$), 5.03 (s, 2H, =NCH_2), 7.05 (m,1H) , 7.17 (m, 1H), 7.24 (m, 2H), 7.35 (m, 1H), 7.40 (m, 1H), 7.66 (m, 1H), 8.24 (s, 1H, C$\underline{H}$=NR); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.3 (t), 30.1 (q), 52.0 (t), 54.1 (q), 105.5 (d), 109.08 (d), 109.11 (s), 118.9 (d),

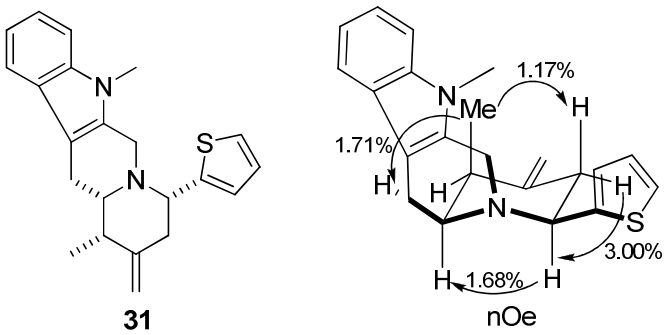
119.0 (d), 121.6 (d), 127.4 (d), 127.6 (s), 129.0 (d), 130.6 (d), 134.2 (s), 137.0 (s), 142.8 (s), 155.5 (d); LRMS $C_{19}H_{22}N_2O_2S$ + H^+ calcd. *m*/*z* 343.1, found *m*/*z* 343.3.



30

(*E*)-*N*-((3-(2,2-dimethoxyethyl)-1-methyl-1H-indol-2-yl)methyl)-1-(thiophen-2-yl)-3-((trimethylsilyl)methyl)pent-3-en-1-amine (30): To a solution of 295 mg (0.86 mmol) of imine **29** in 10 mL of dry diethyl ether was added 0.39 mL (1.29 mmol) of $Ti(O^iPr)_4$ via a syringe at rt under argon. After stirring for 10 min, the solution was cooled to -78 °C, and 1.29 mL (2.58 mmol) of 2.0 M *c*-C_5H_9MgCl in diethyl ether was added via a syringe over 2 min. The solution turned from yellow to dark brown after stirring at -78 °C for 1.5 h. Next, a solution of lithium alkoxide of alcohol **8** in 2 mL of THF, prepared by deprotonation of 201 mg (1.29 mmol) of alcohol **8** at -78 °C with 0.55 mL (1.37 mmol) of 2.5 M *n*-BuLi in hexanes followed by 10 min stirring, was added to the brown solution via cannula. The mixture was slowly warmed to room temperature, and stirred for 16 h. The reaction was quenched by sequential addition of 10 mL of ethyl ether and 5 mL of saturated aqueous $NaHCO_3$, followed by vigorous stirring for 1 h. The aqueous phase was extracted with two portions of 10 mL of diethyl ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow oil. The residue was purified by chromatography over 50 g of silica gel (hexanes-ethyl acetate, 20:1) to give 290 mg (70%) of homoallylic amine **30** as a yellow oil. No evidence for the presence of a minor isomer was observed in the ^1H NMR of the crude material. Stereochemistry was assigned by analogy to previous examples.[4] Data for amine **30:** IR (neat) 3584, 2952, 1614, 1471 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 9H, TMS), 1.35 and 1.43 (ABq, *J* = 14.8 Hz, 2H, C<u>H</u>$_2$TMS), 1.50 (d, *J* = 6.8 Hz, 3H, C<u>H</u>$_3$CH=), 1.74

(br, 1H, NH), 2.30 (dd, *J* = 13.2, 6.4 Hz, 1H, C$\underline{H}_2$CHN), 2.57 (dd, *J* = 13.2, 8.0 Hz, 1H, C$\underline{H}_2$CHN), 3.03 (dd, *J* = 6.0, 2.4 Hz, 2H, C$\underline{H}_2$CH(OMe)$_2$), 3.34 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.35 (s, 3H, CH(O$\underline{Me}$)$_2$), 3.77 (s, 3H, NCH$_3$), 3.81 (s, 2H, NHC$\underline{H}_2$Ph),4.20 (dd, *J* = 7.2, 7.2 Hz, 1H, C$\underline{H}$N), 4.52 (t, *J* = 5.2 Hz, 1H, C$\underline{H}$(OMe)$_2$), 5.16 (q, *J* = 6.8 Hz, 1H, =C$\underline{H}$CH$_3$), 6.99 (m, 2H), 7.09 (m, 1H), 7.22 (m, 1H), 7.30 (m,1H), 7.61 (m, 1H); LRMS $C_{27}H_{40}N_2O_2SSi$ + H^+ calcd. *m*/*z* 485.3, found *m*/*z* 485.4.

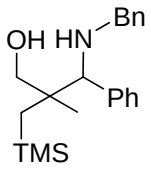


31 nOe

(8*S,11*S**,11a*S**)-5,11-dimethyl-10-methylene-8-(thiophen-2-yl)-5,6,8,9,10,11,11a, 12-octahydroindolo[3,2-b]quinolizine (31):** To a solution of 56 mg (0.12 mmol) of imine **30** in 5 mL of THF was added 0.5 mL (0.5 mmol) of 1N HCl aqueous solution at rt under argon. After stirring for 16 h,the reaction was quenched by addition of 0.15 g (1.1 mmol) of pulverized K_2CO_3. The neutralized mixture was extracted with 2 x 10 mL of diethyl ehter. The organic extracts were dried ($MgSO_4$), and concentrated *in vacuo* to afford a pale yellow gel. The residue was purified by chromatography over 30 g of silica gel (hexanes-ethyl acetate, 40:1) to give 26 mg (75%) of quinolizidine **31** as a white solid. No evidence for the presence of a minor isomer was found in the ^{1}H NMR of the crude material. Stereochemistry was assigned by nOe. IR (in $CHCl_3$) 3585, 2919, 1660, 1471 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, *J* = 6.8 Hz, 3H, CH_3), 2.29 (dd, *J* = 13.6 Hz, 2.8 Hz, 1H, C(3)$\underline{H}_2$), 2.55 (qd, *J* = 6.4, 2.8 Hz, 1H, C(1)H), 2.70 (dd, *J* = 14.8, 3.6 Hz, 1H,m C(9)$\underline{H}_2$), 2.75 (m, 1H, C(10)H), 2.80 (dd, *J* = 13.6, 12.0 Hz, 1H, C(3)$\underline{H}_2$), 3.04 (dd, *J* = 12.4, 10.4 Hz, C(9)$\underline{H}_2$), 3.12 and 3.99 (ABq, *J* = 14.8 Hz, 1H, NC(6)H_2), 3.61 (dd, *J* = 11.6, 3.6 Hz, 1H, C(4)H), 4.60 (s, 1H, =C$\underline{H}_2$), 4.73 (s, 1H, =C$\underline{H}_2$), 6.89 (m, 1H, thiophene), 6.91 (m, 2H, thiophene), 6.98 (m, 1H, benzene), 7.14 (m, 1H, benzene),

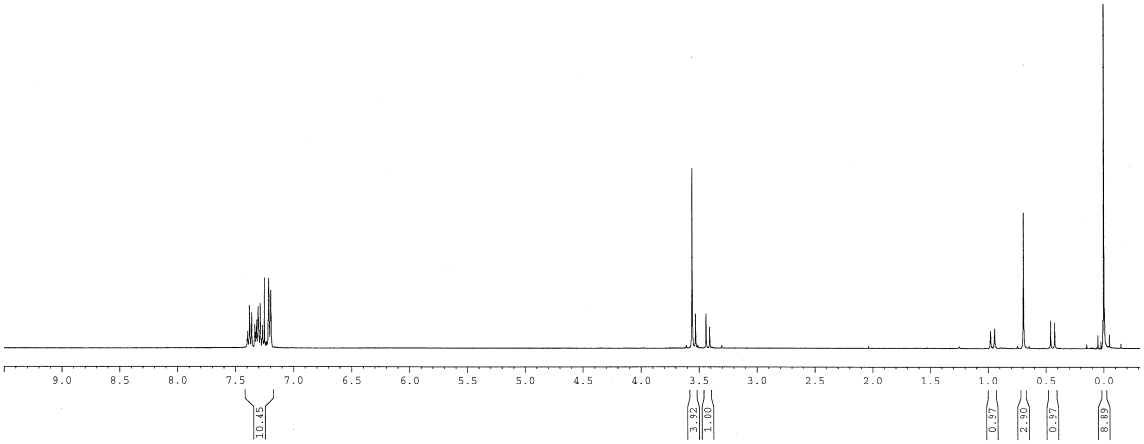
7.18 (m, 1H, benzene), 7.38 (d, J = 7.2 Hz, 1H, benzene); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (q), 26.0 (t), 29.1 (q), 41.3 (t), 42.2 (d), 50.4 (t), 62.5 (d), 68.1 (d), 106.2 (t), 108.6 (d), 117.8 (d), 118.8 (d), 120.7 (d), 124.2 (d), 124.7 (d), 126.2 (d), 126.4 (s), 132.4 (s), 137.2 (s), 148.6 (s), 150.7 (s), (one quaternary ^{13}C peak missing due to overlap); LRMS $C_{22}H_{24}NOS + H^+$ calcd. m/z 412.2, found m/z 412.5.

1 Love, B. E.; Jones, E. G., *J. Org. Chem.* **1999**, *64*, 3755-3756.
2 Trost, B. M.; Chan, D. M. T.; Nanninga, T. N., *Org. Syn.* **1984**, *62*, 58.
3 Joly, G. D.; Jacobsen, E. N., *J. Am. Chem. Soc.* **2004**, *126*, 4102.
4 Takahashi, M.; McLaughlin, M.; Micalizio, G. C., *Angew. Chem. Int. Ed.* **2009**, *48*, 3648-3652

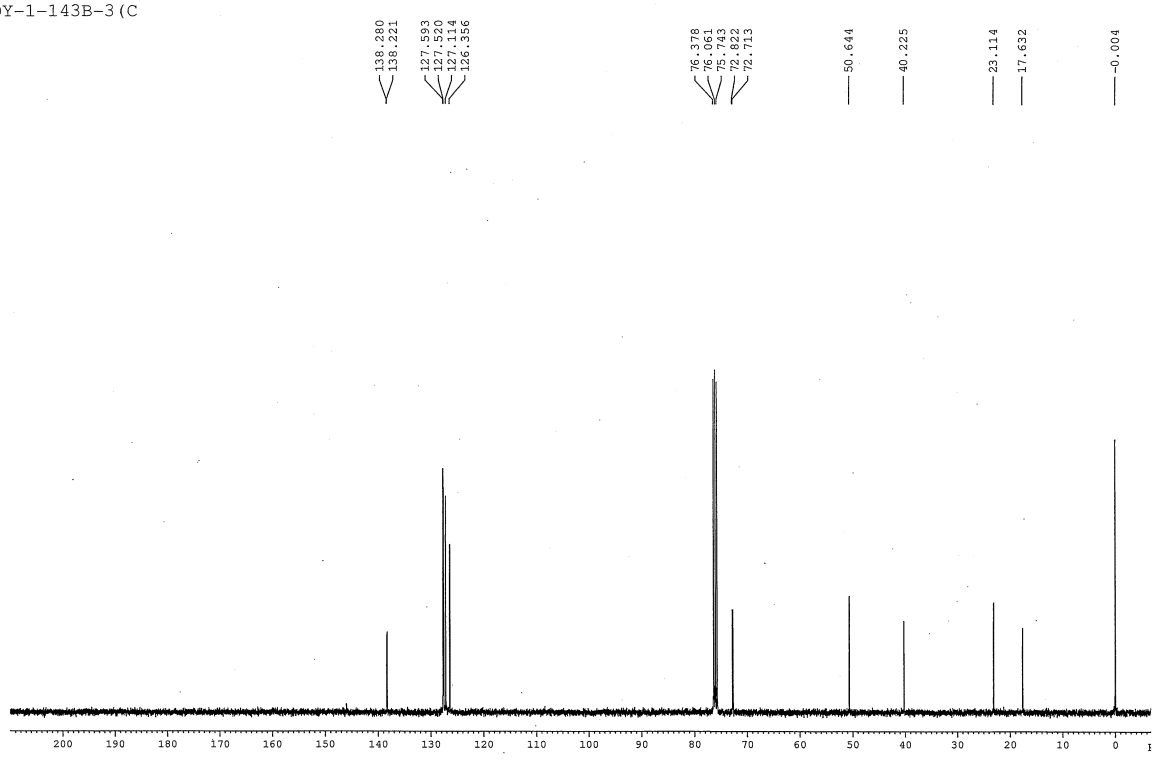


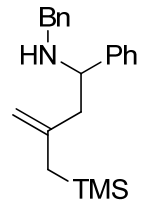
7

DY-1-143B

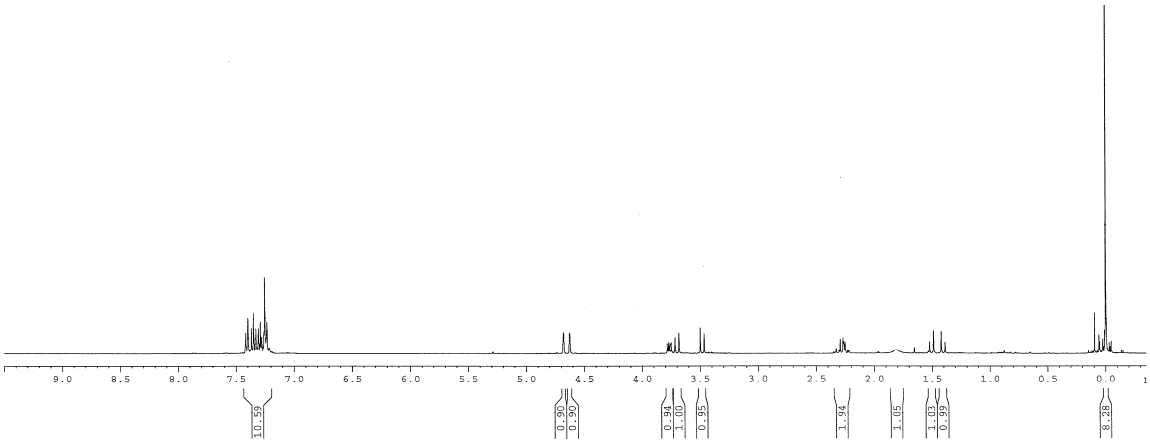


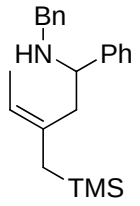
DY-1-143B-3(C




Bn
HN
Ph
TMS

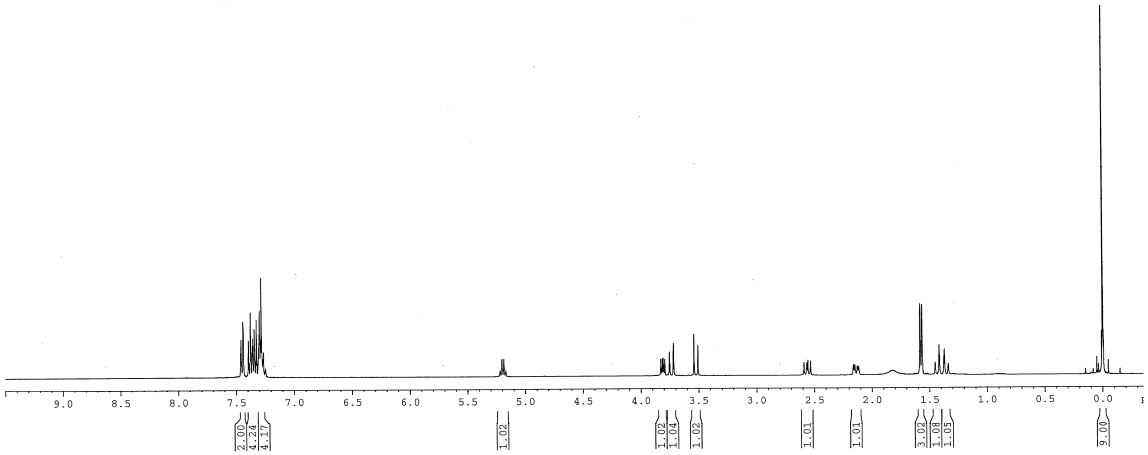
7a
DY-1-143A

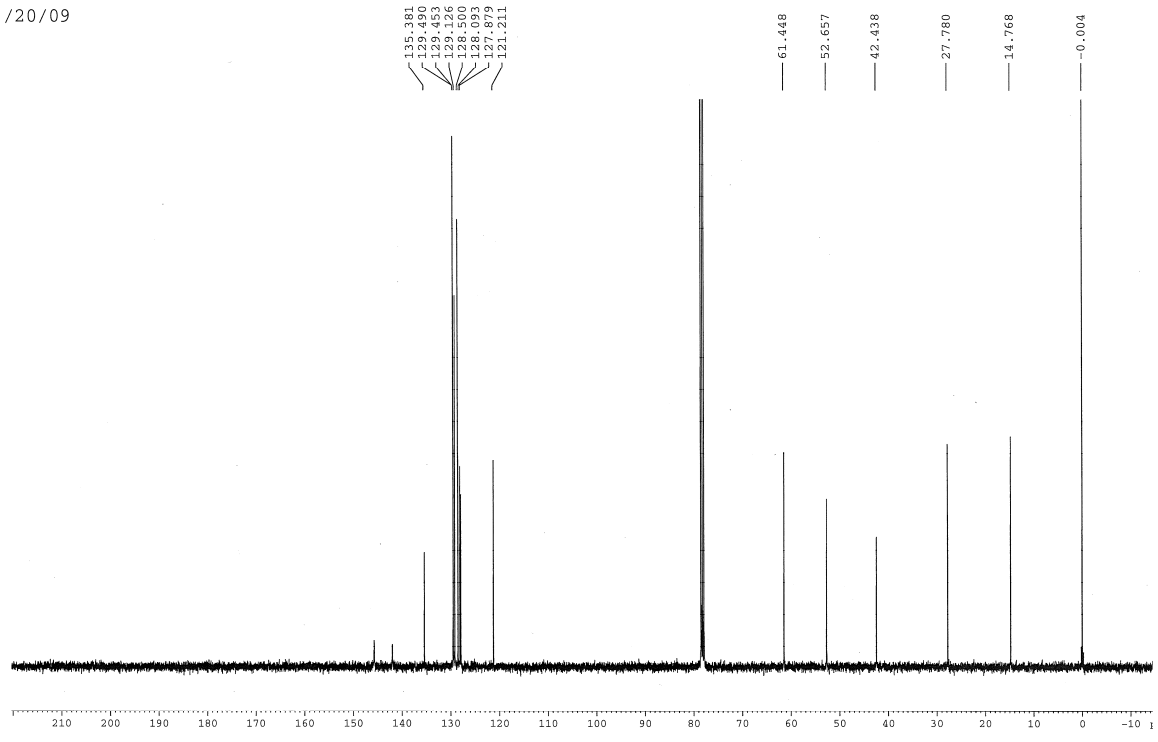

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10.59
0.90
0.99
0.94
1.00
0.95
1.94
1.05
1.03
0.99
8.28

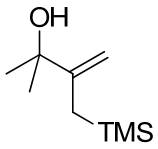

Bn
HN
Ph
TMS

9

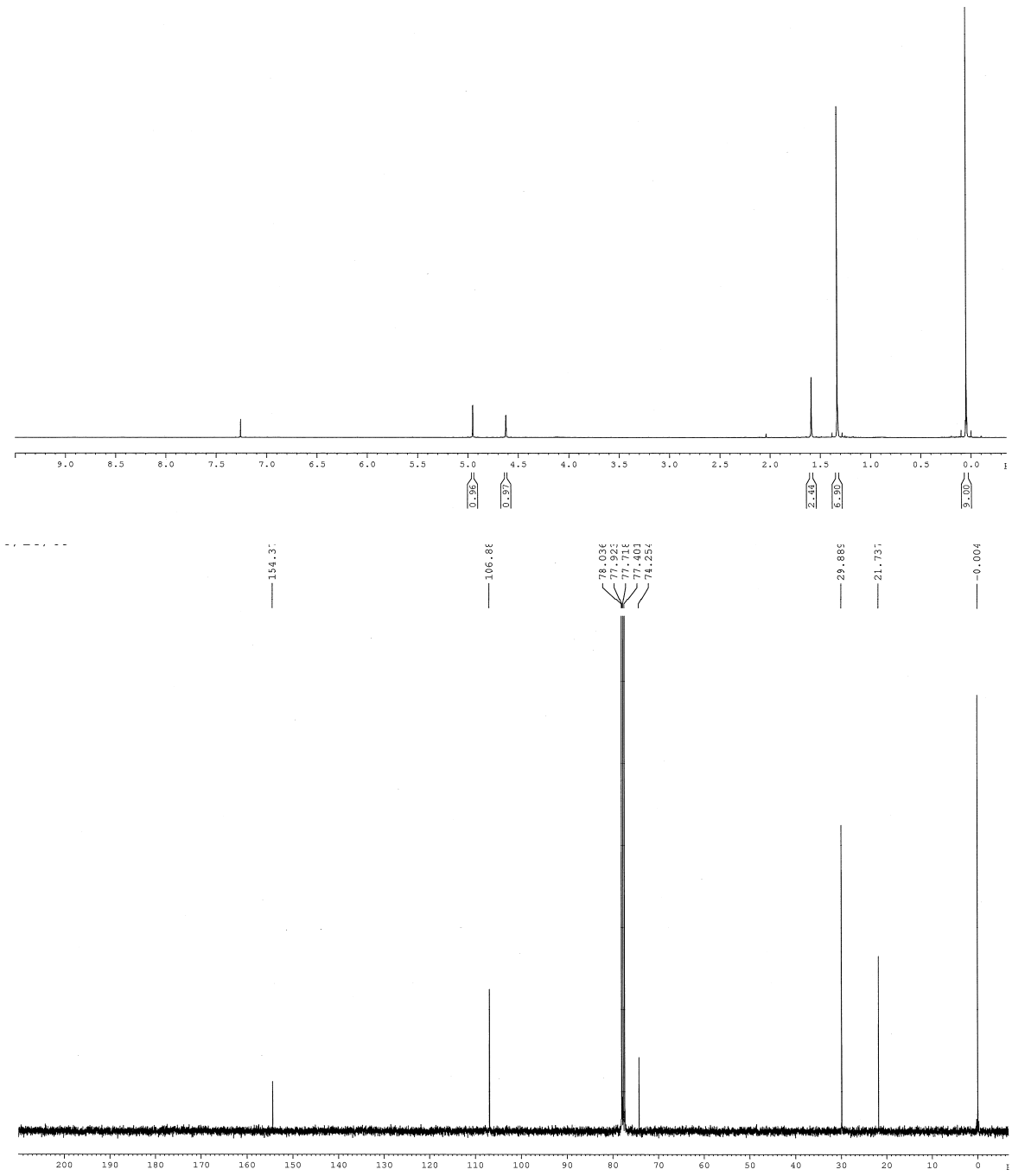
DY-1-35

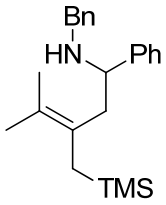

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.00
4.24
4.11
1.02
1.02
1.04
1.02
1.01
1.01
3.02
1.08
1.05
9.00


/20/09
135.381
129.490
129.453
129.126
128.500
128.093
127.879
121.211
61.448
52.657
42.438
27.780
14.768
-0.004
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10


OH
TMS

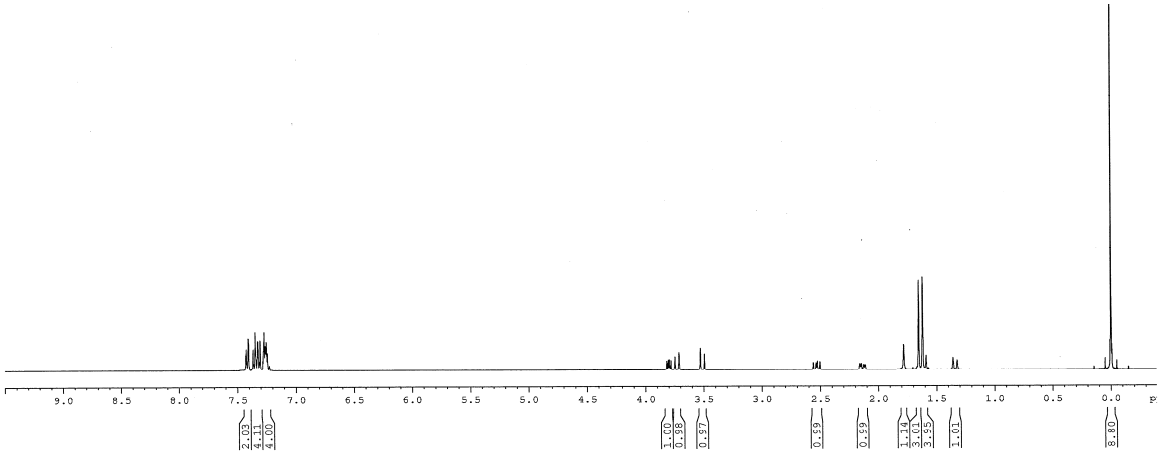
10
DY-1-222B

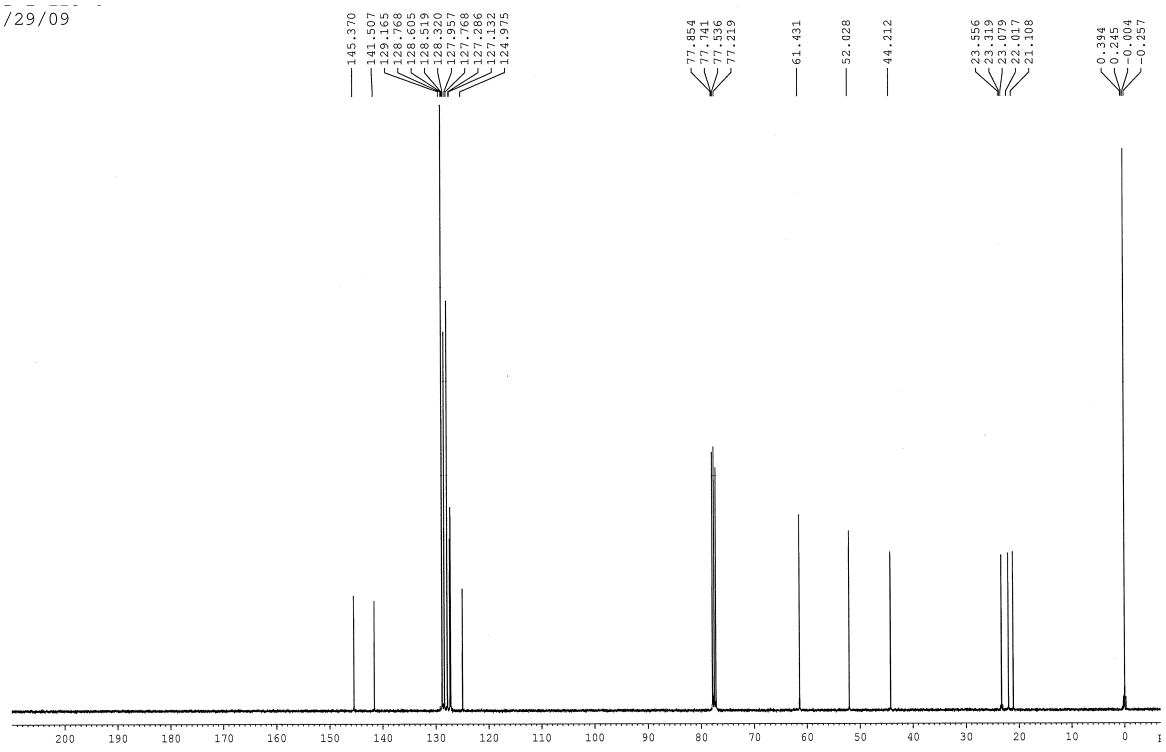

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
0.96
0.97
2.44
6.90
9.00
154.3
106.8
78.03
77.92
77.71
77.40
74.25
29.88
21.73
-0.00
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

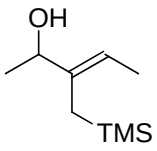

Bn
HN
Ph
TMS

11

DY-1-223

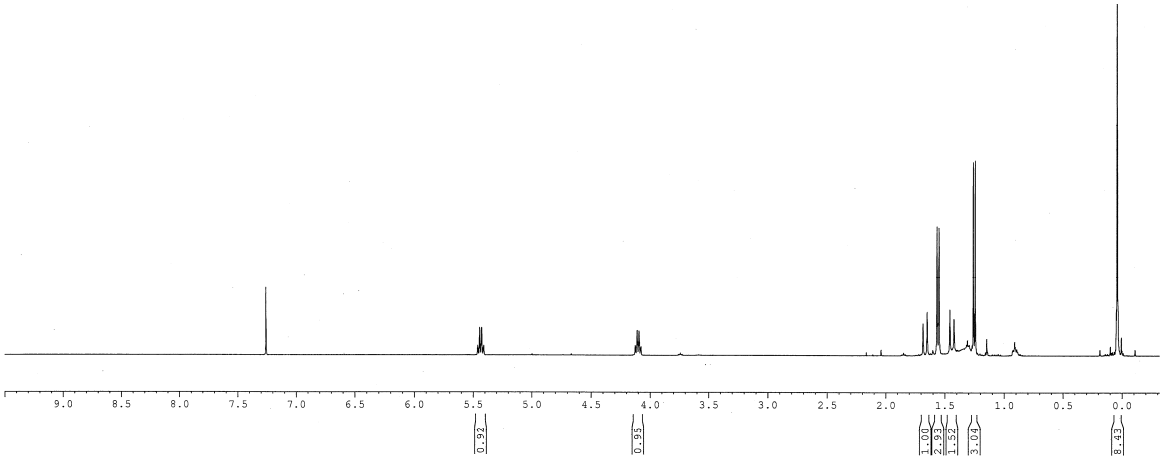

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2.03
4.18
4.00
1.00
0.98
0.97
0.59
0.69
1.14
3.01
3.55
1.01
8.40


/29/09
145.370
141.507
129.165
128.768
128.605
128.519
128.320
127.957
127.768
127.286
127.132
124.975
77.854
77.741
77.536
77.219
61.431
52.028
44.212
23.556
23.319
23.079
22.017
21.108
0.394
0.245
-0.004
-0.257
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

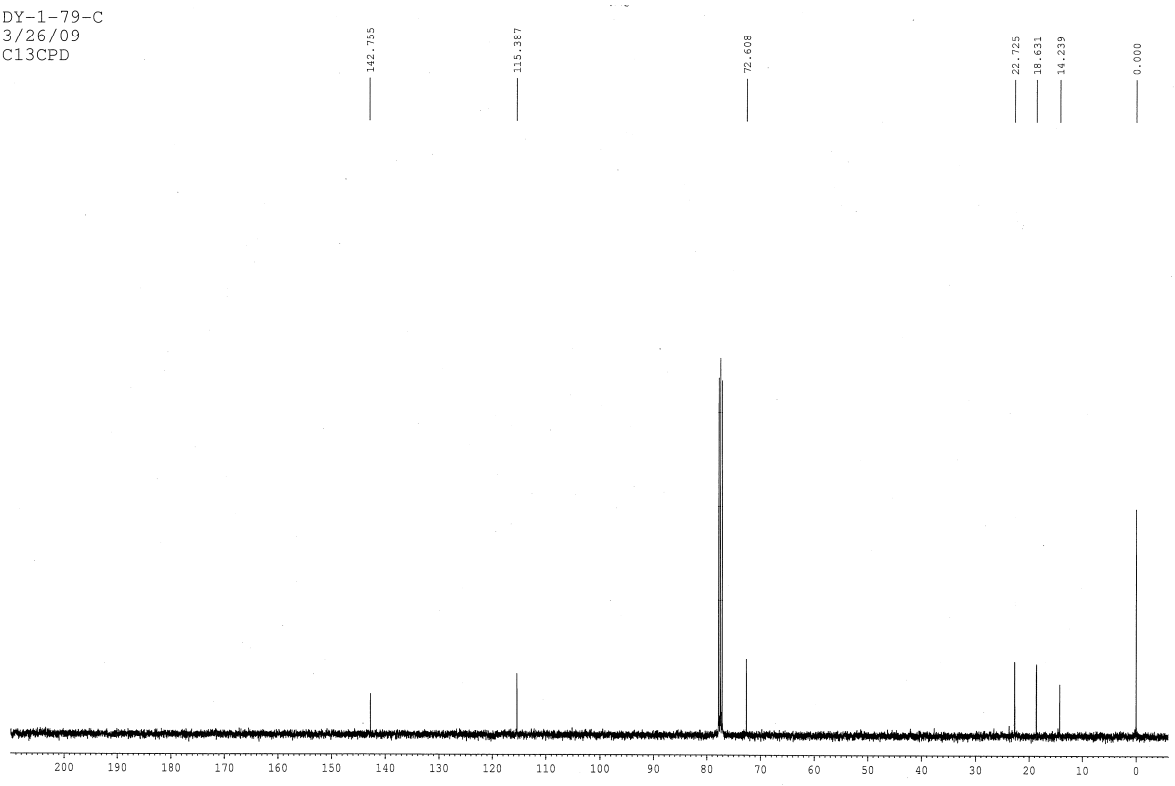


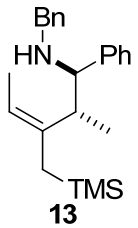
12

DY-1-79



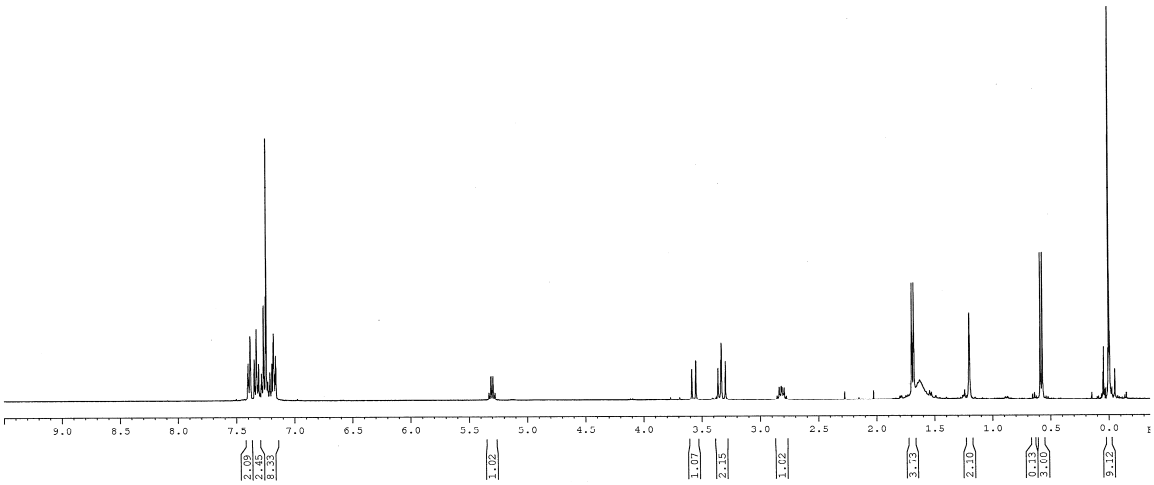
DY-1-79-C
3/26/09
C13CPD



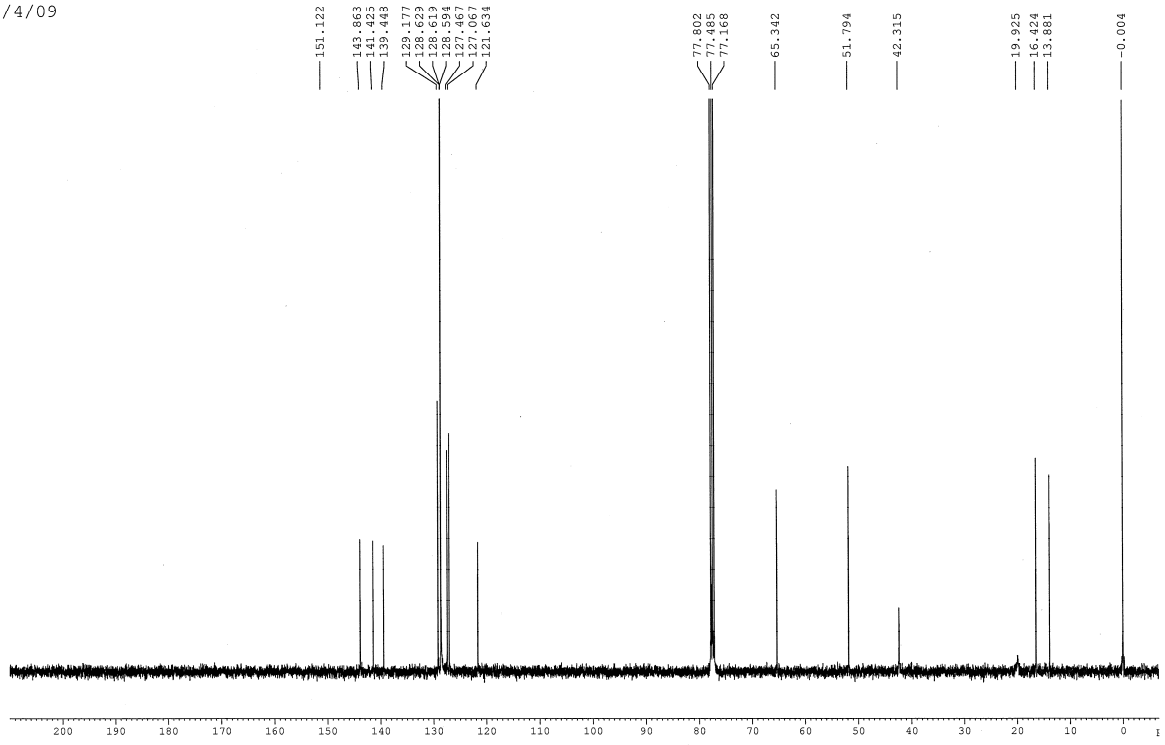


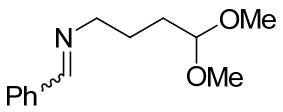
13

DY-1-227

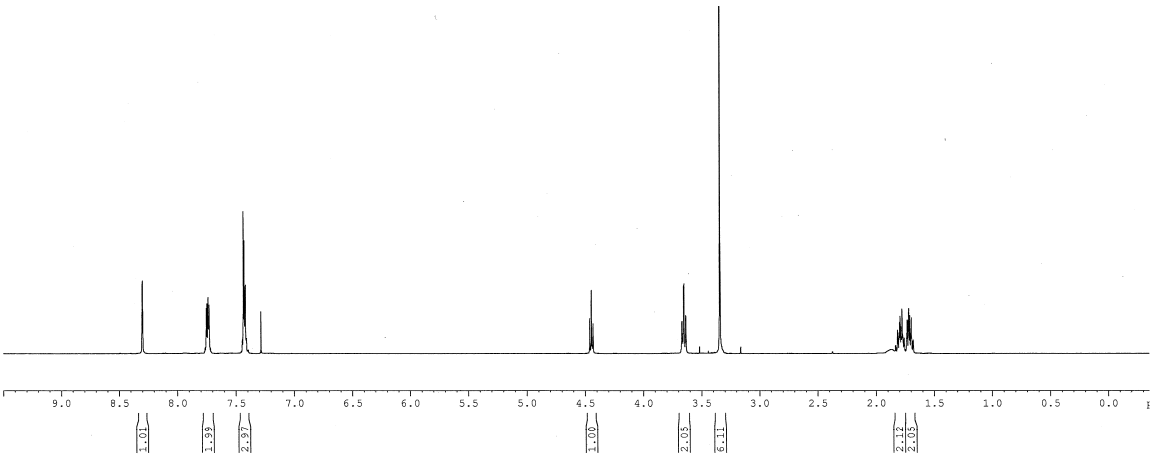


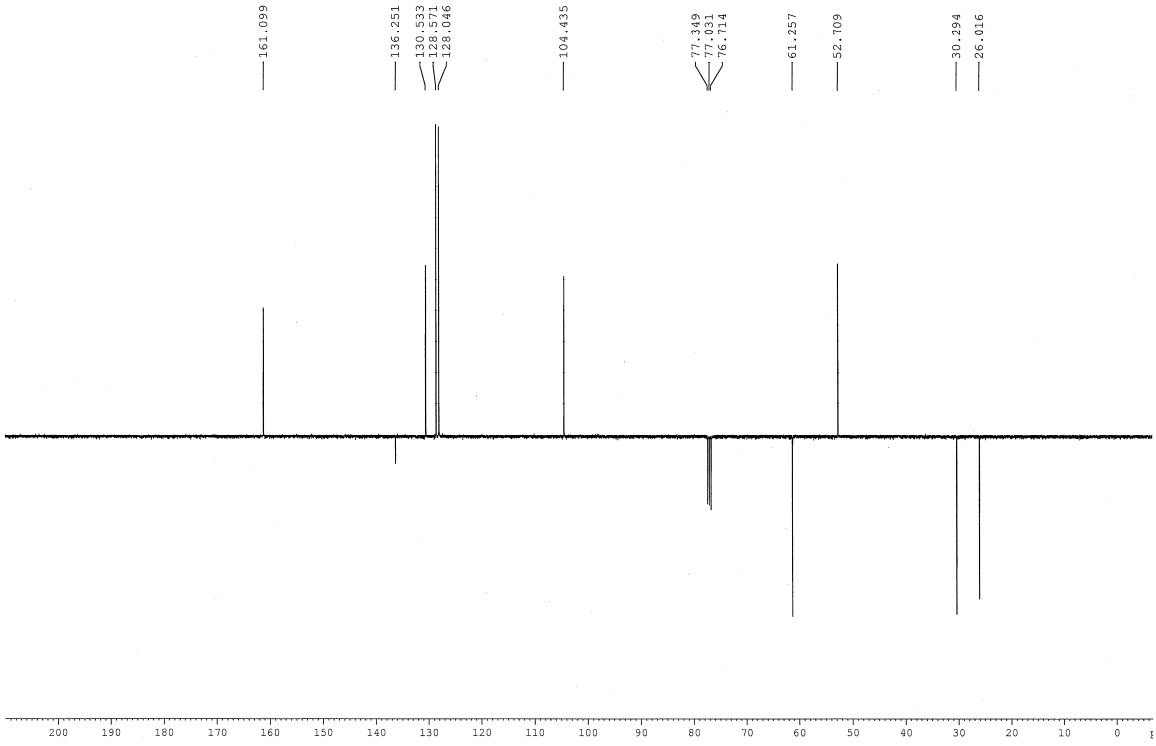
DY-1-227-C
7/4/09

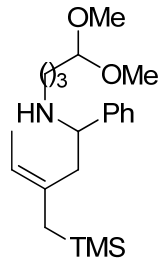



N
OMe
OMe
Ph

14

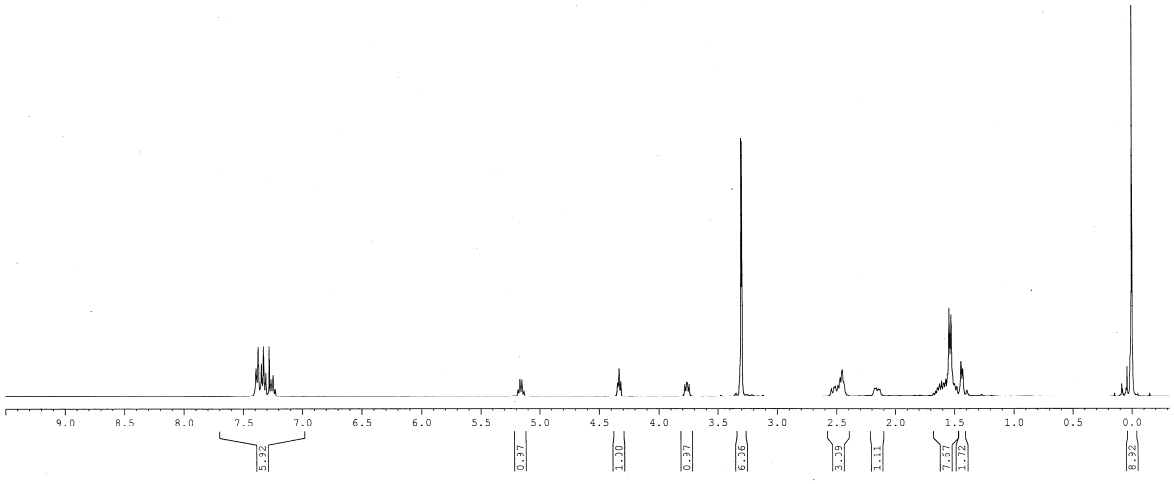

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.01
1.99
2.97
1.00
2.05
6.11
2.12
2.05


161.099
136.251
130.533
128.571
128.046
104.435
77.349
77.031
76.714
61.257
52.709
30.294
26.016
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

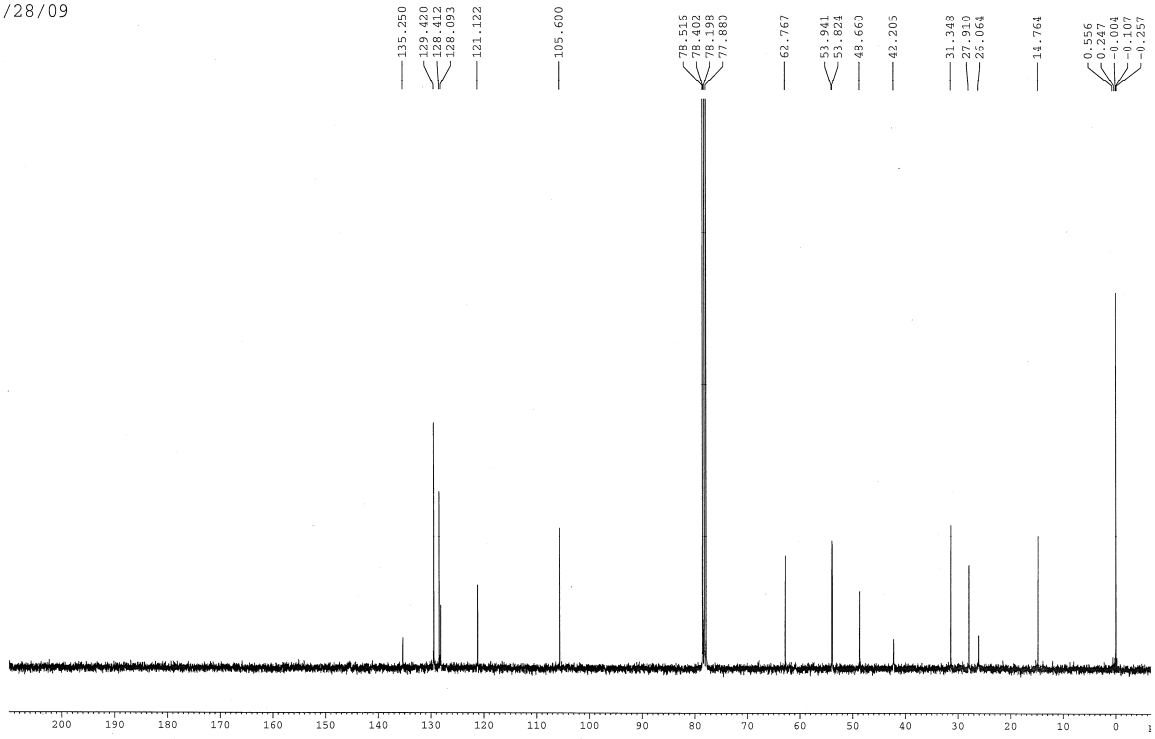


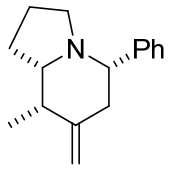
15

DY-1-120

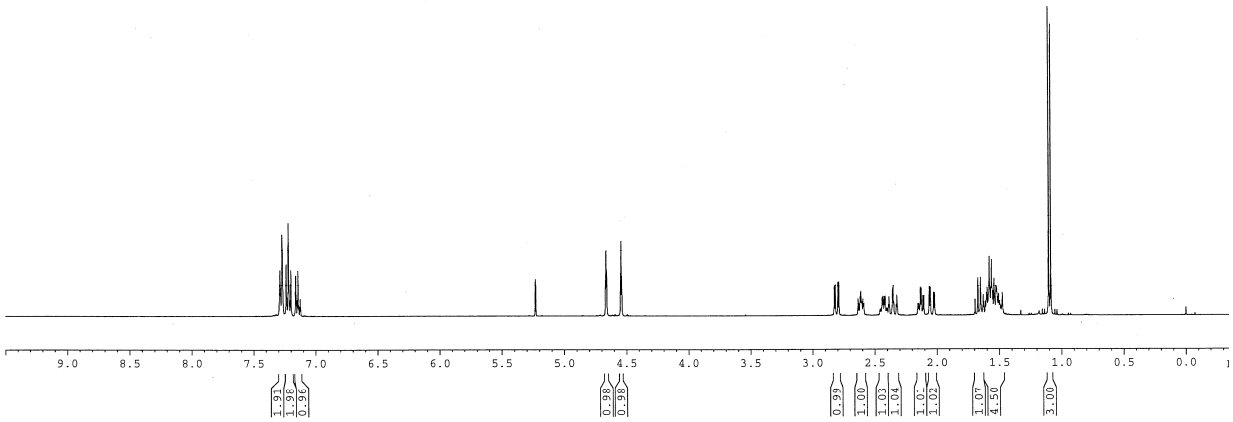


DY-1-120-C
4/28/09

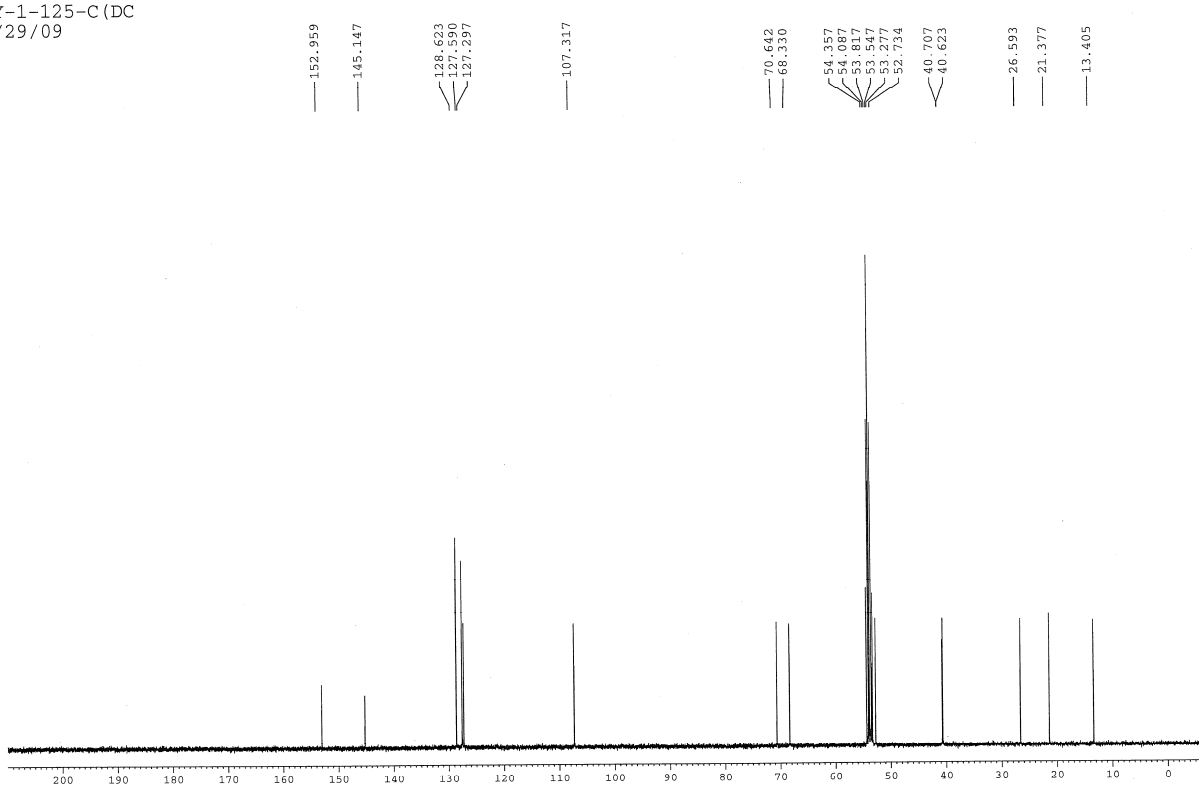


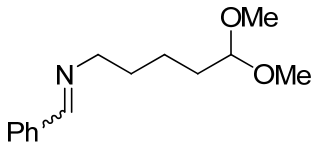


16
DY-1-125

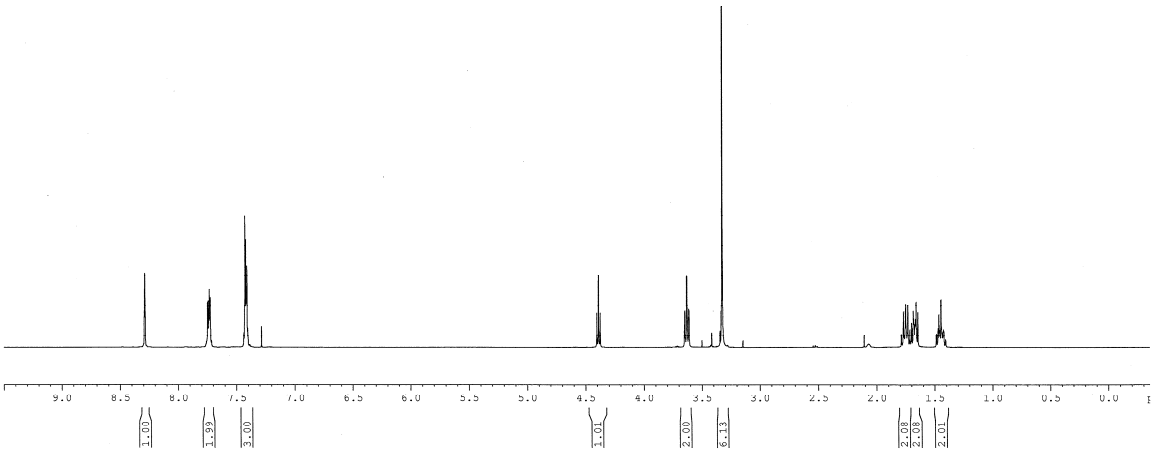


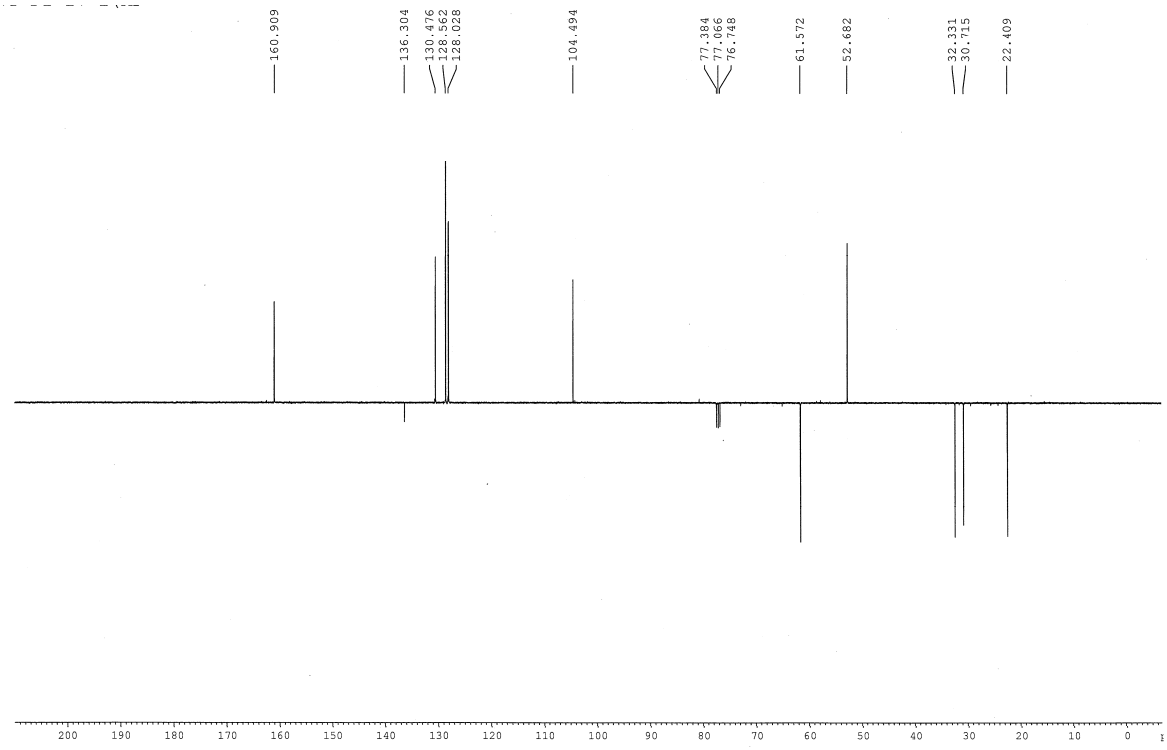
DY-1-125-C(DC
4/29/09

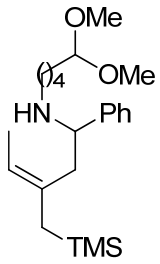



OMe
N
OMe
Ph

17

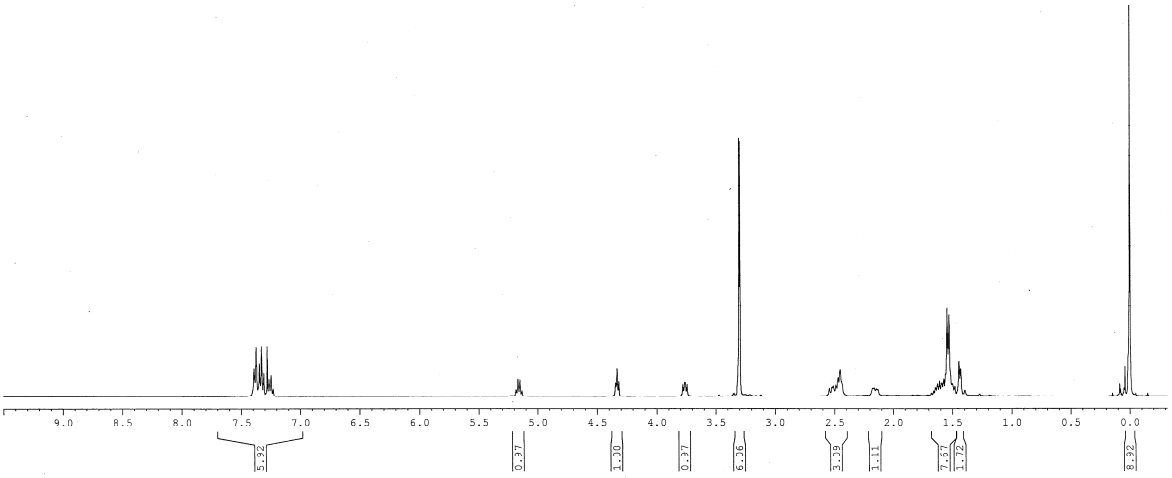

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.00
1.99
3.00
1.01
2.00
6.13
2.08
2.08
2.01


160.909
136.304
130.476
128.562
128.028
104.494
77.384
77.066
76.748
61.572
52.682
32.331
30.715
22.409
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

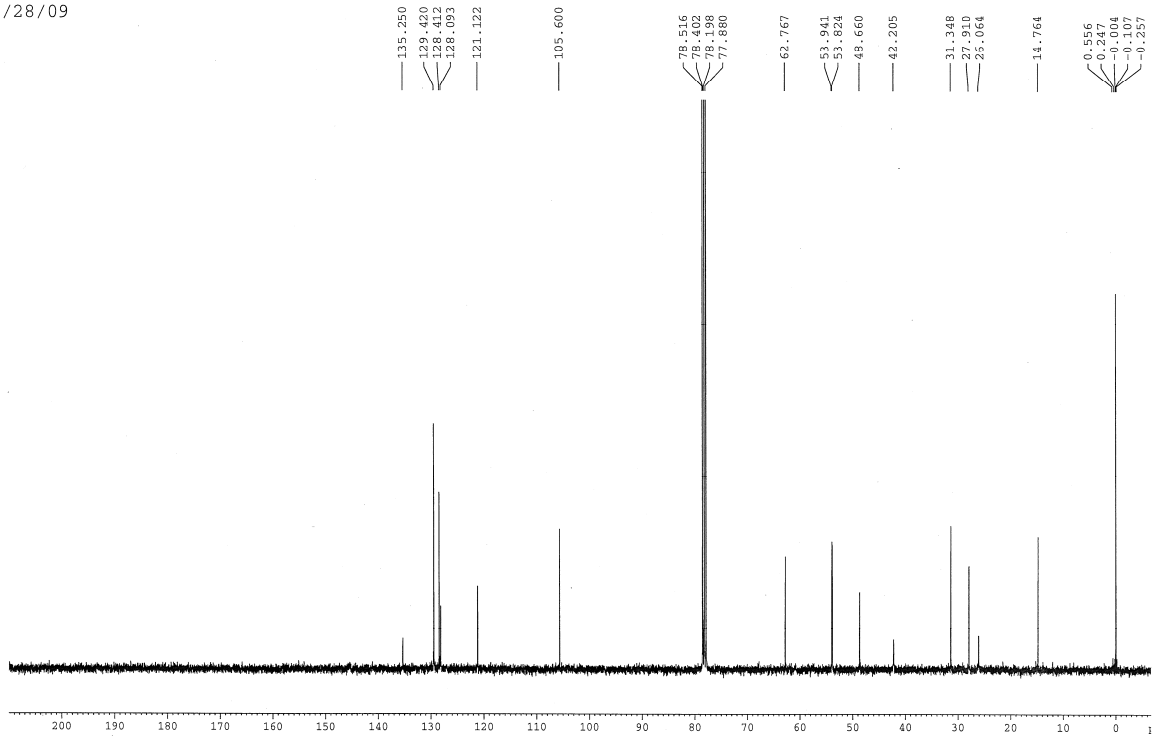


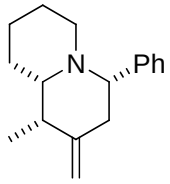
18

DY-1-120



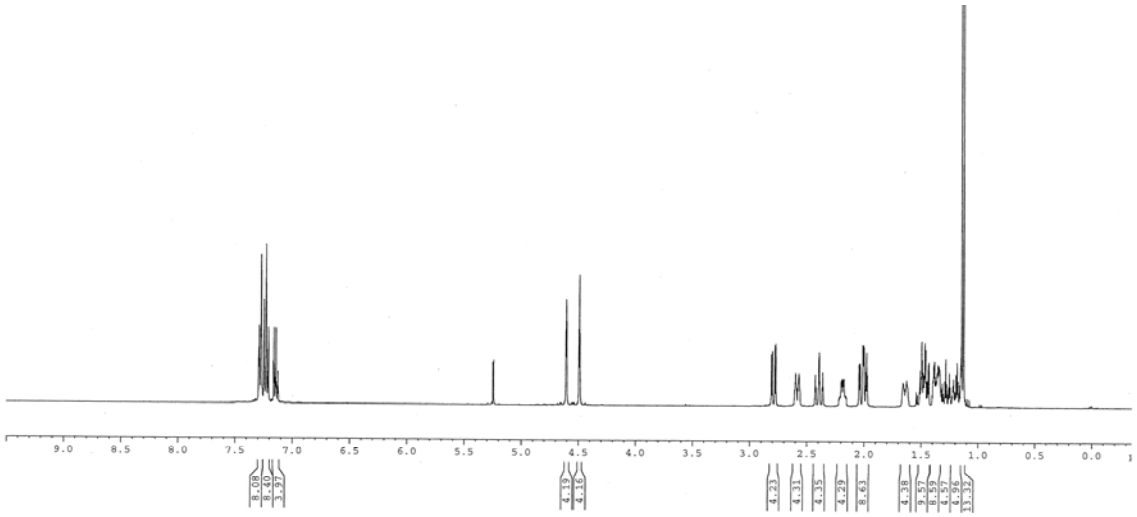
DY-1-120-C
4/28/09

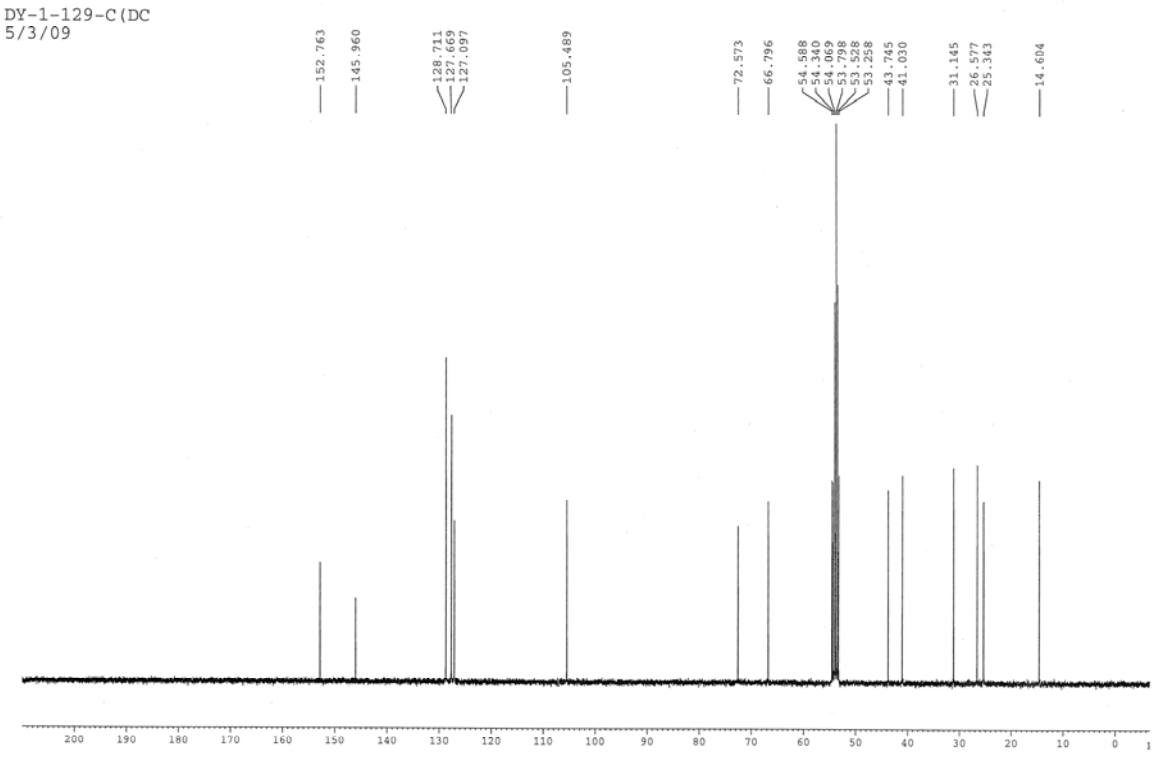


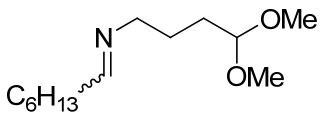

N
Ph

19

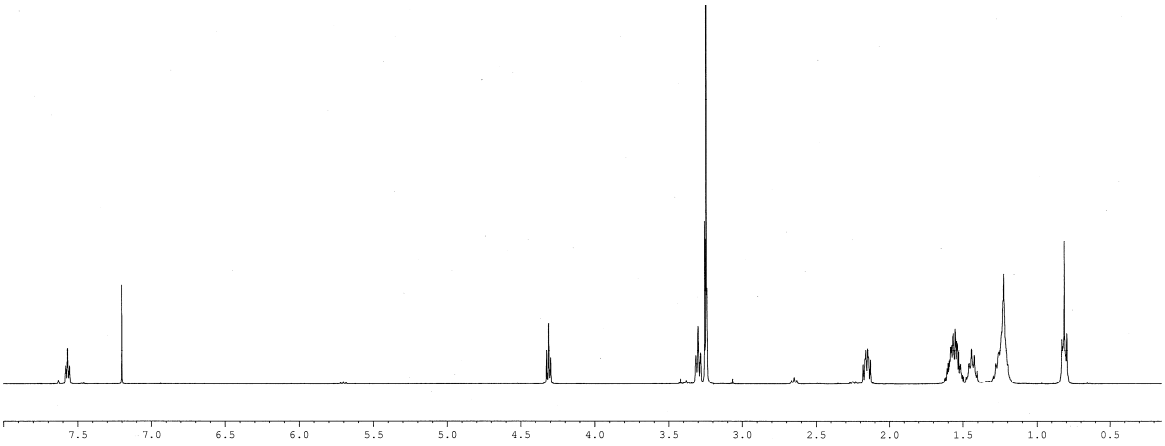
DY-1-129

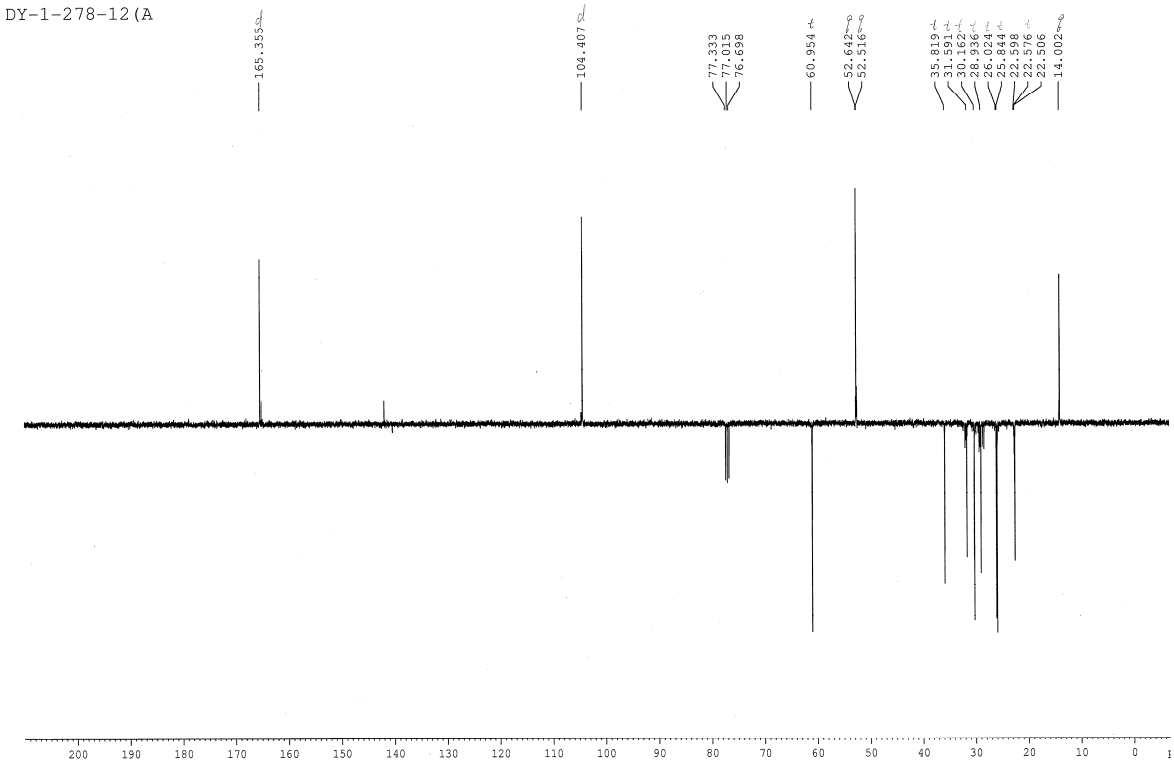

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
8.08
8.40
3.97
4.18
4.15
4.23
4.31
4.35
4.29
8.63
4.38
9.57
4.59
4.96
13.32

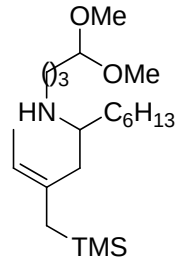

DY-1-129-C(DC
5/3/09
152.763
145.960
128.711
127.669
127.097
105.489
72.573
66.796
54.588
54.340
54.069
53.798
53.528
53.258
43.745
41.030
31.145
26.577
25.343
14.604
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


N
OMe
OMe
C6H13

20
DY-1-278

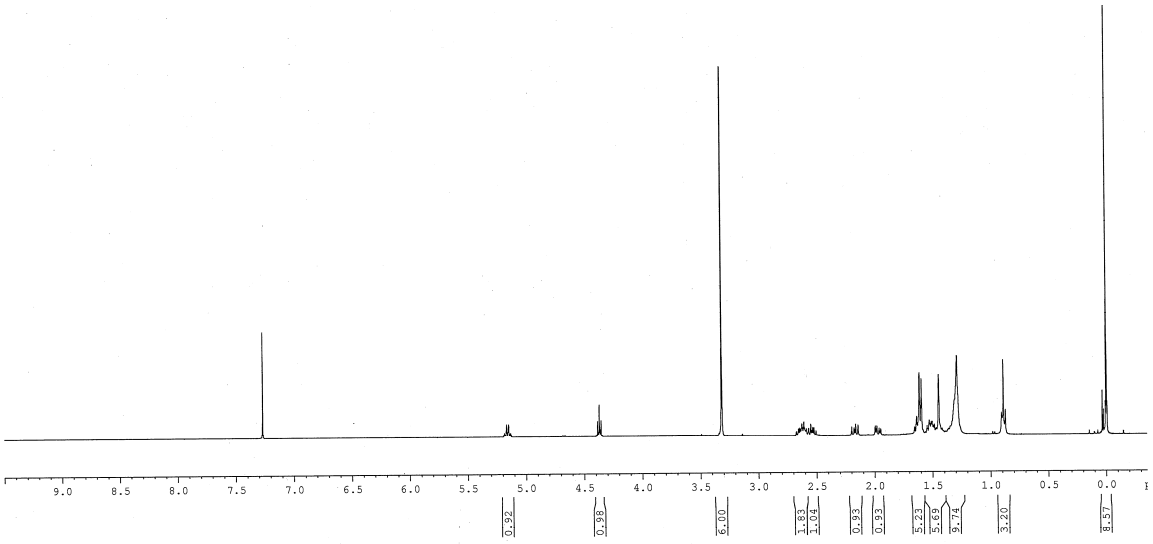

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

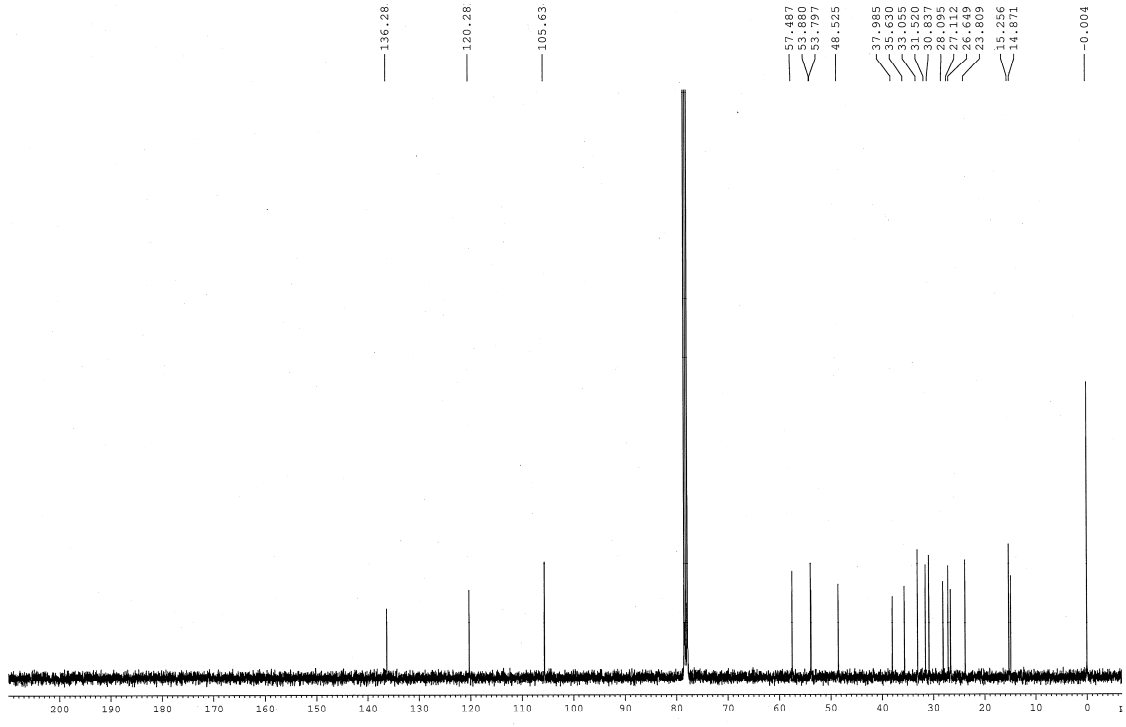

DY-1-278-12(A
165.355
104.407
77.333
77.015
76.698
60.954
52.642
52.516
35.819
31.591
30.162
28.936
26.024
25.844
22.598
22.376
22.306
14.002
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

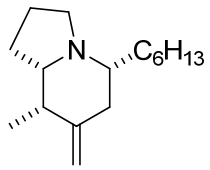

OMe
3
OMe
HN
C_6H_{13}
TMS

21

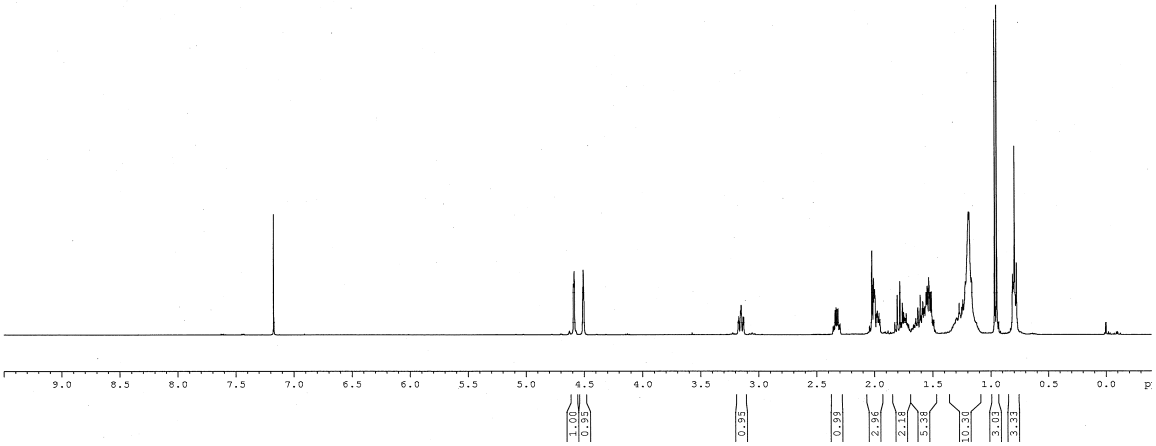
DY-1-279

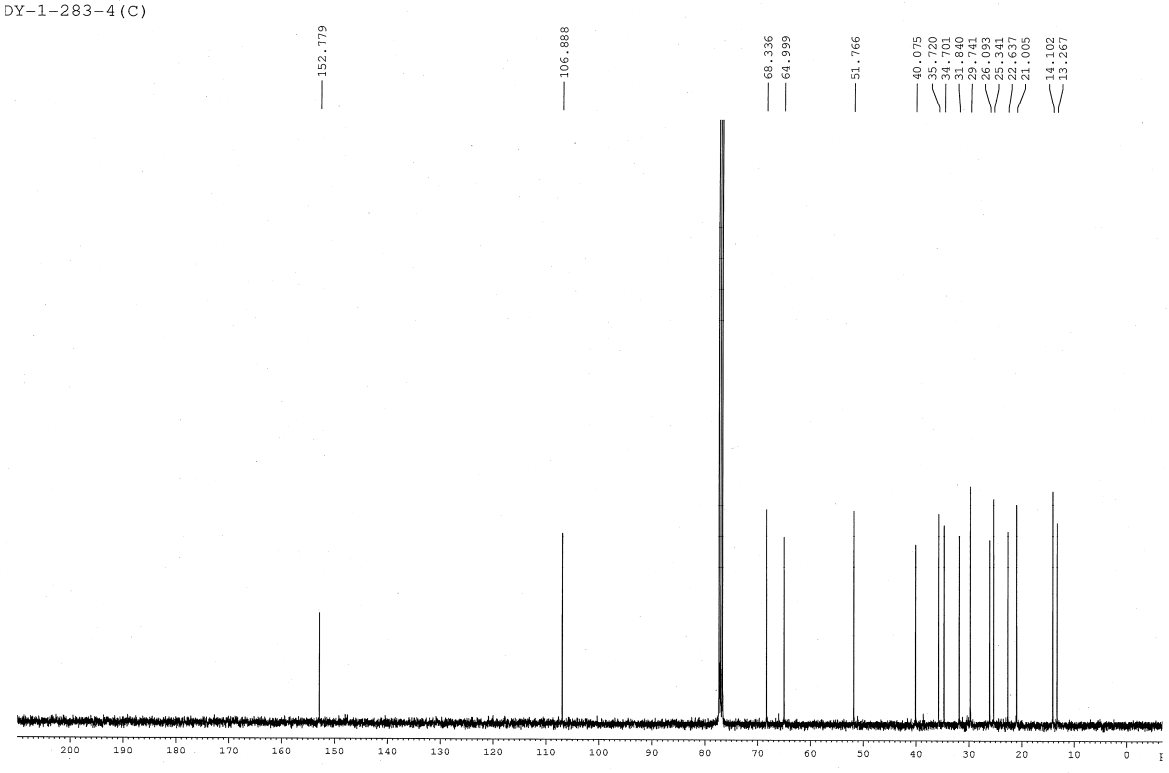

9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.92
0.98
6.00
1.83
1.04
0.93
0.93
5.23
5.69
9.74
3.20
8.57

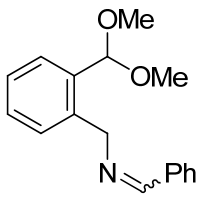

136.28
120.28
105.63
57.487
53.880
53.797
48.525
37.985
35.630
33.055
31.520
30.837
28.095
27.112
26.649
23.809
15.256
14.871
-0.004
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


N
C_6H_{13}

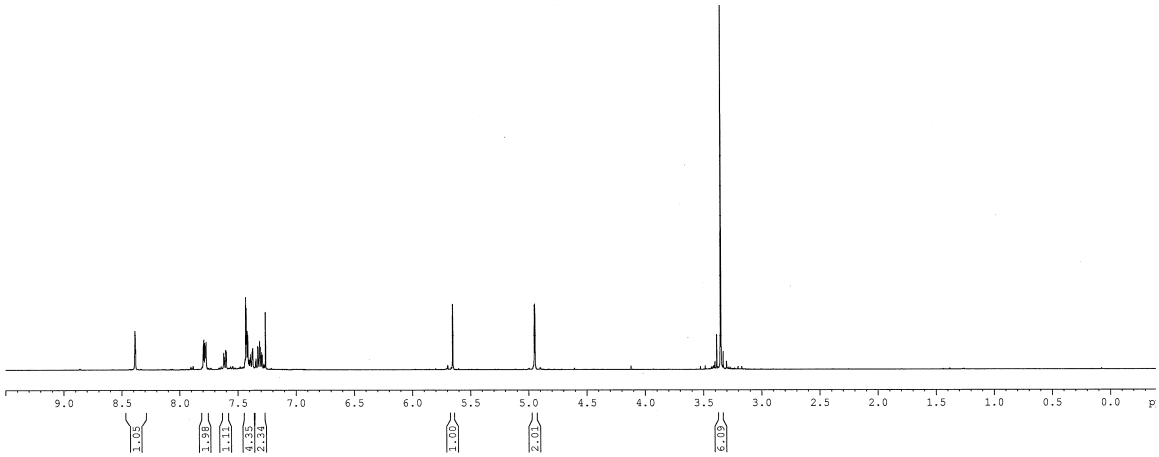
22
DY-1-283


9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1.00
0.96
0.95
0.99
2.96
2.18
5.38
10.30
3.03
3.33

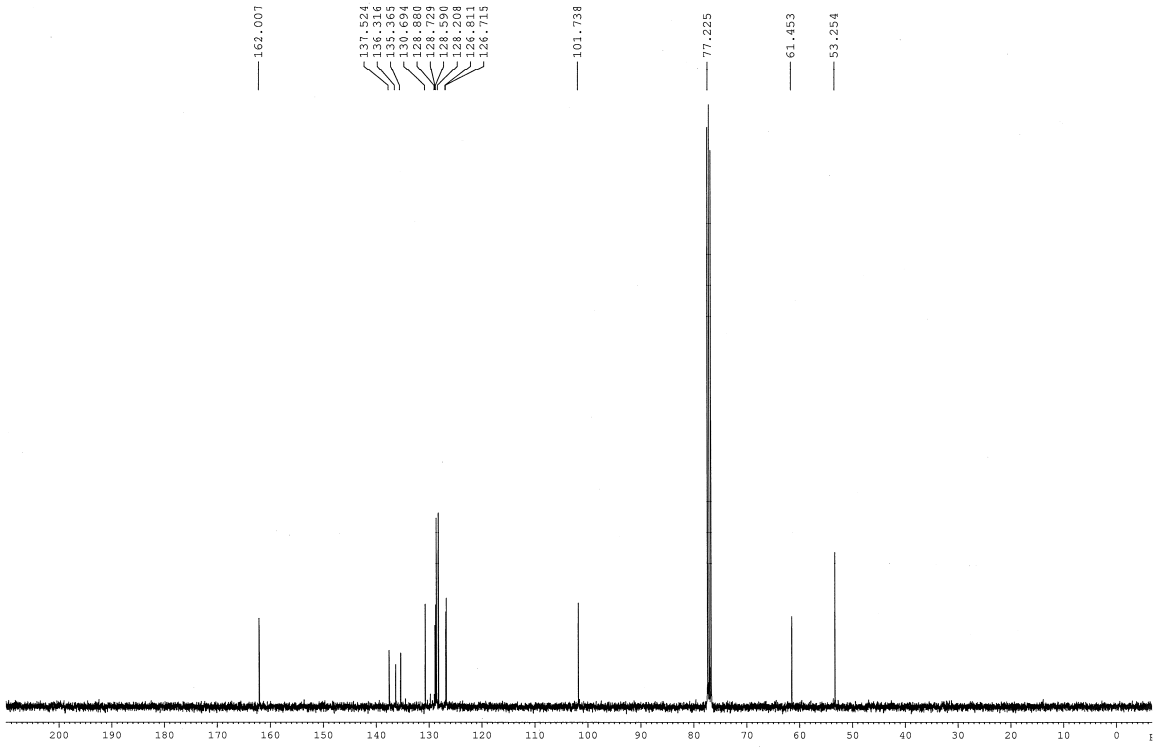

DY-1-283-4(C)
152.779
106.888
68.336
64.999
51.766
40.075
35.720
34.701
31.840
29.741
26.093
25.341
22.637
21.005
14.102
13.267
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

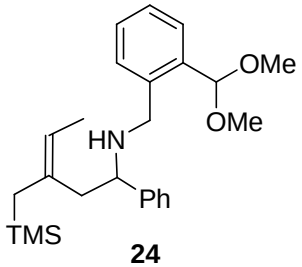


23
DY-1-256



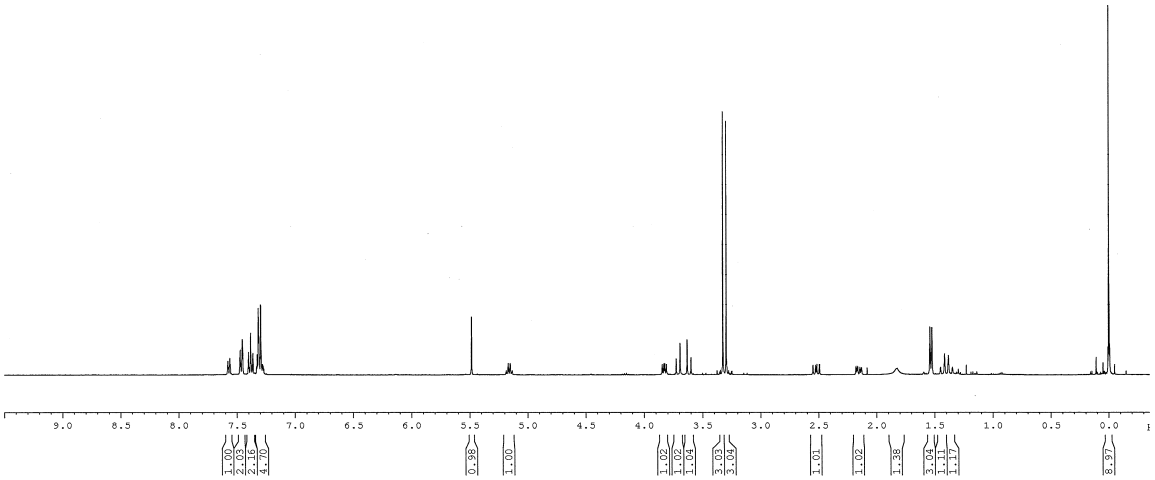
DY-1-256-3(C)



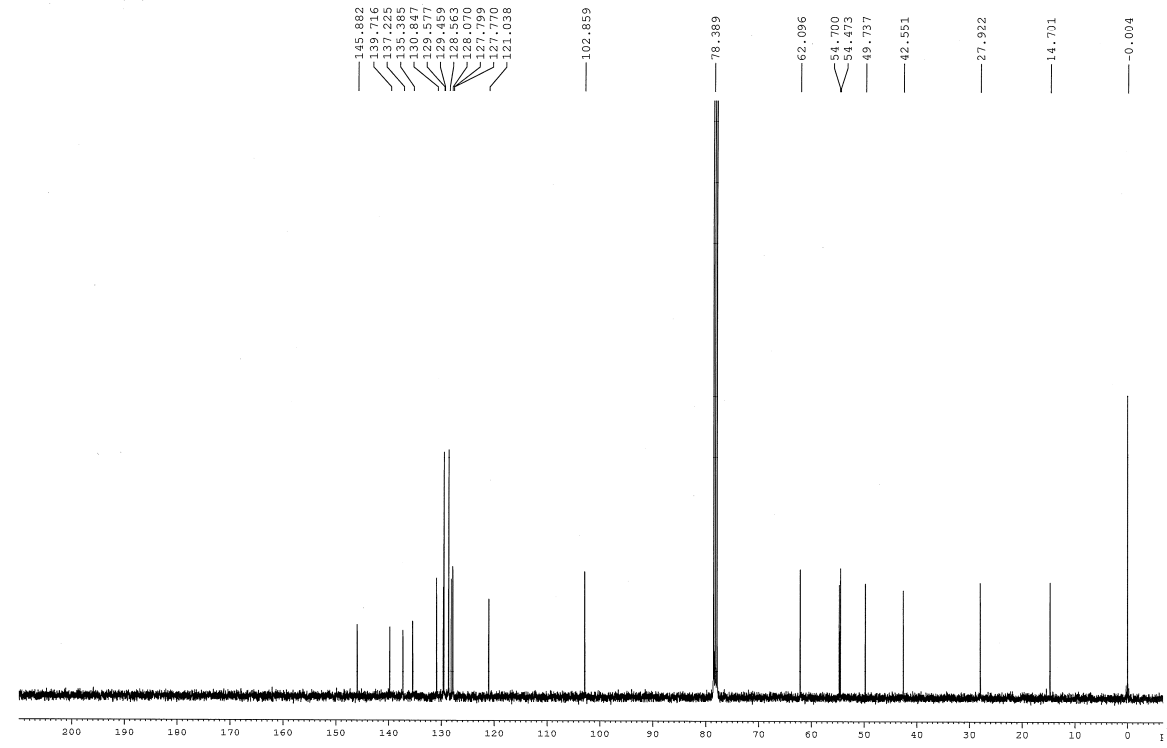


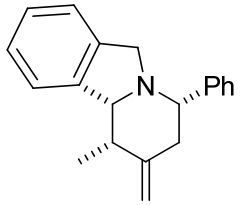
24

DY-1-261

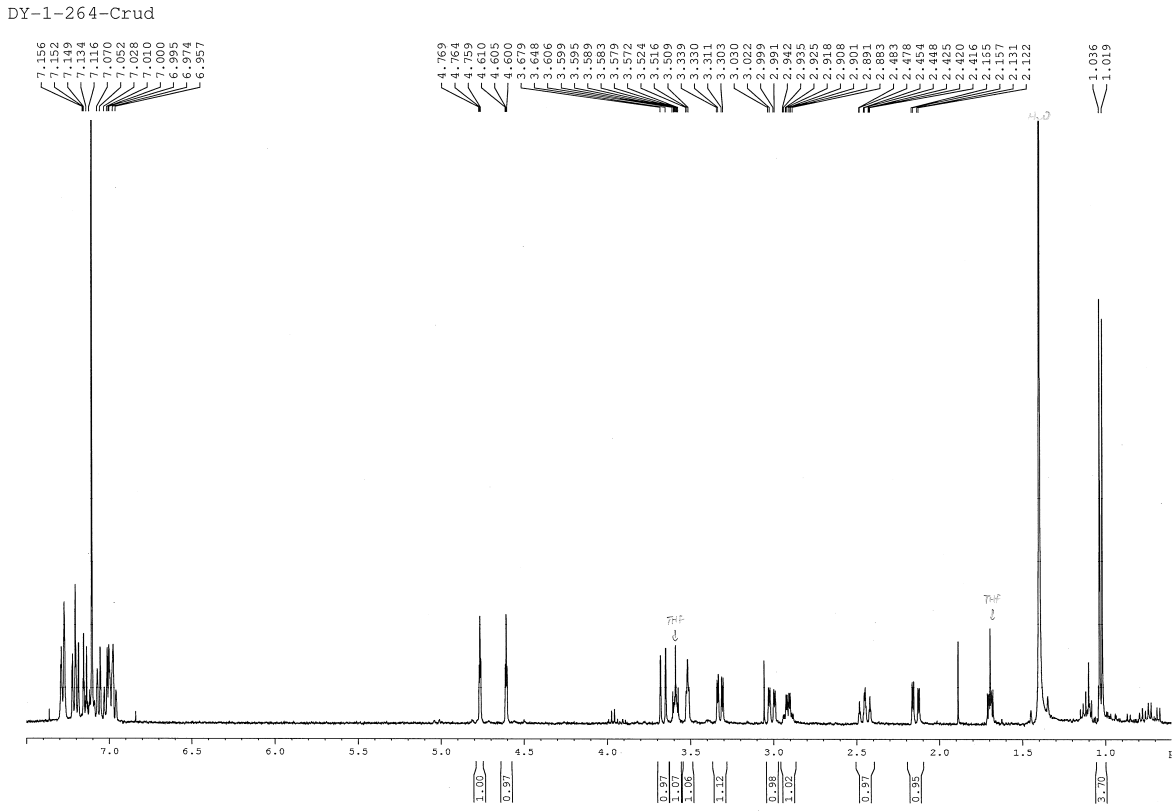


DY-1-261-4(C)

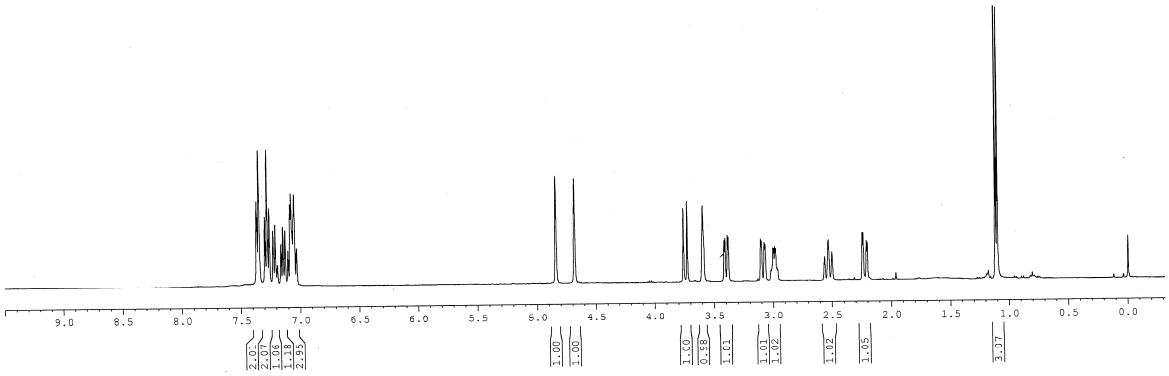




25
DY-1-264

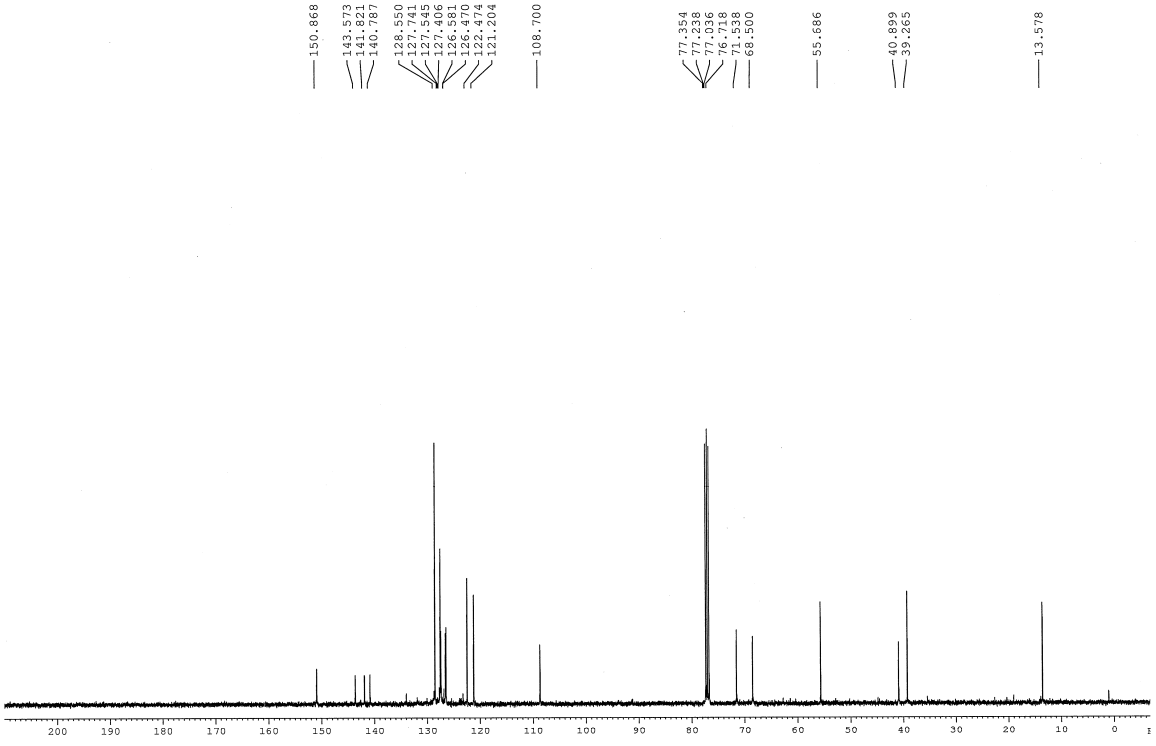


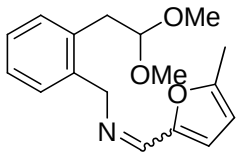
^{1}H NMR of **25** before purification



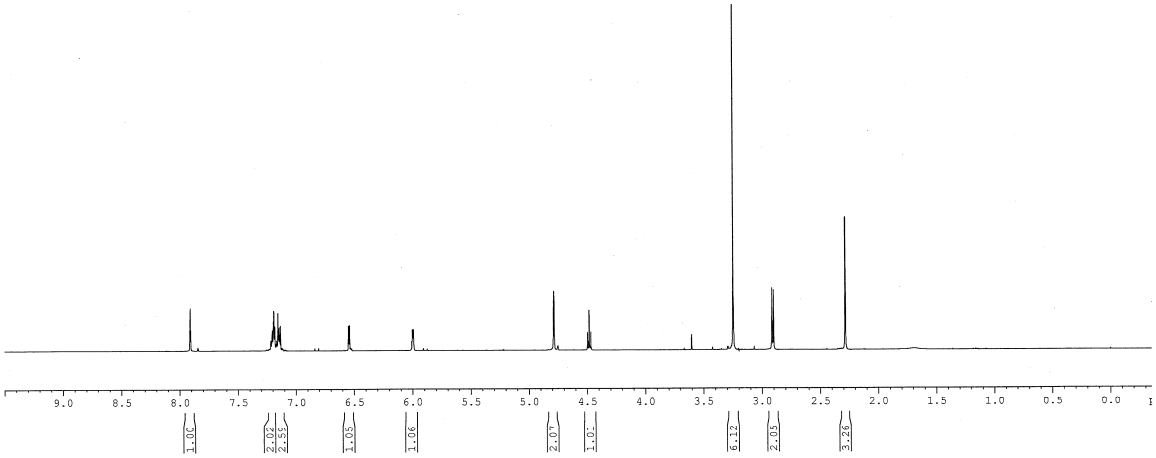
1H NMR of **25** after purification

DY-1-264-14(C

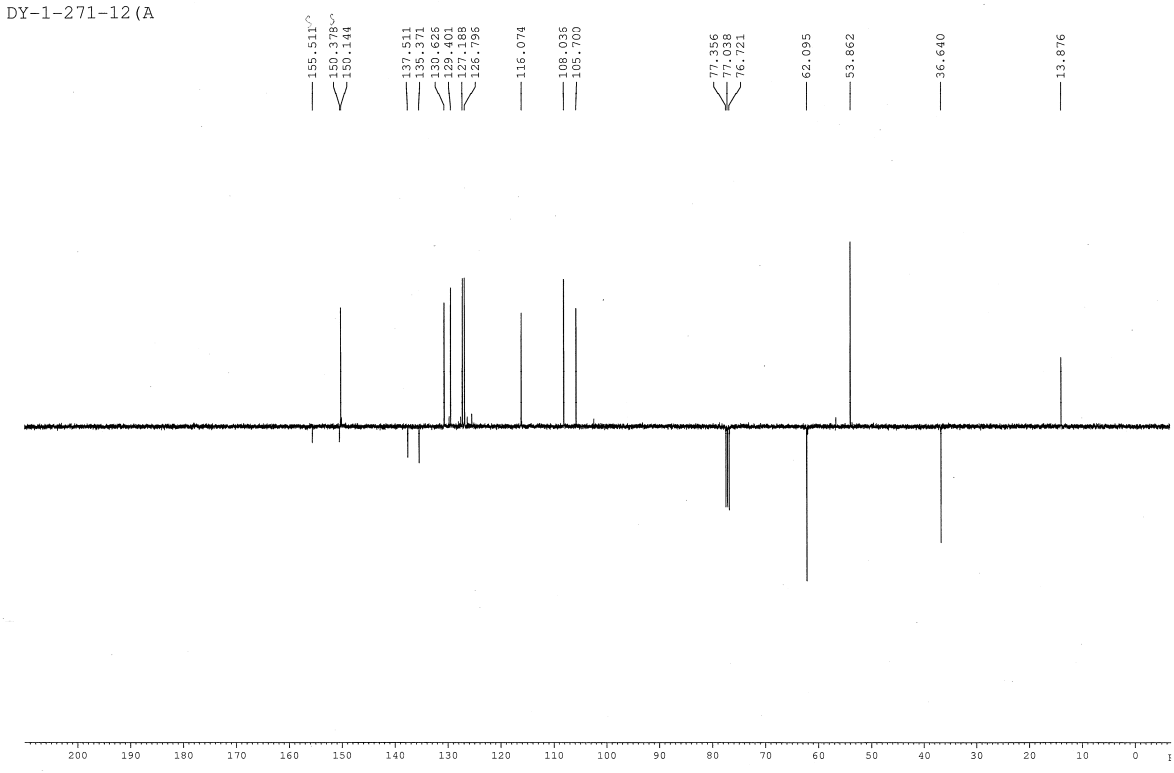

150.868
143.573
141.821
140.787
128.550
127.741
127.545
127.406
126.581
126.470
122.474
121.204
108.700
77.354
77.238
77.036
76.718
71.538
68.500
55.686
40.899
39.265
13.578
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

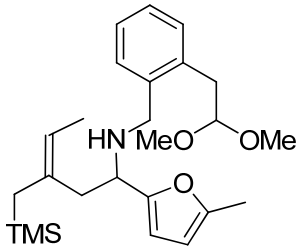


26
DY-1-271



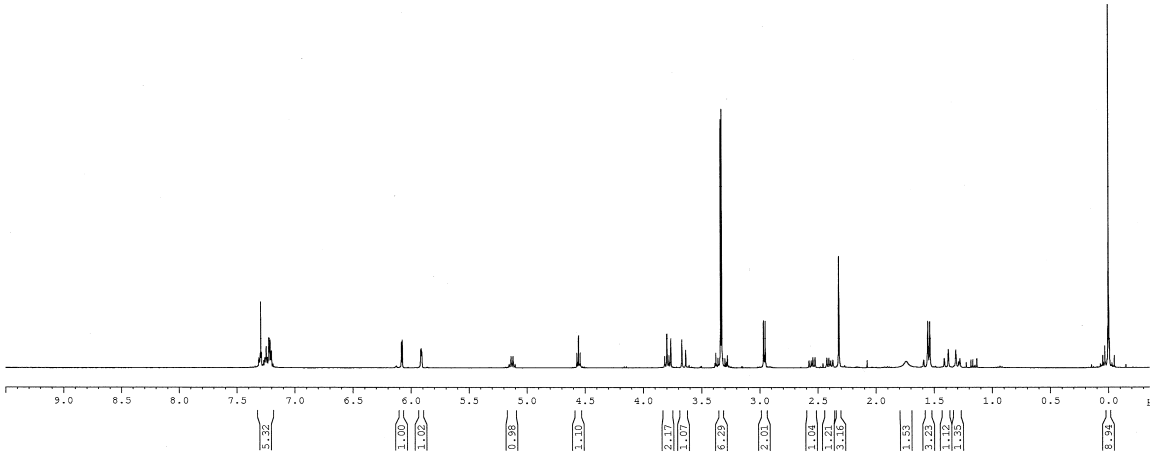
DY-1-271-12(A



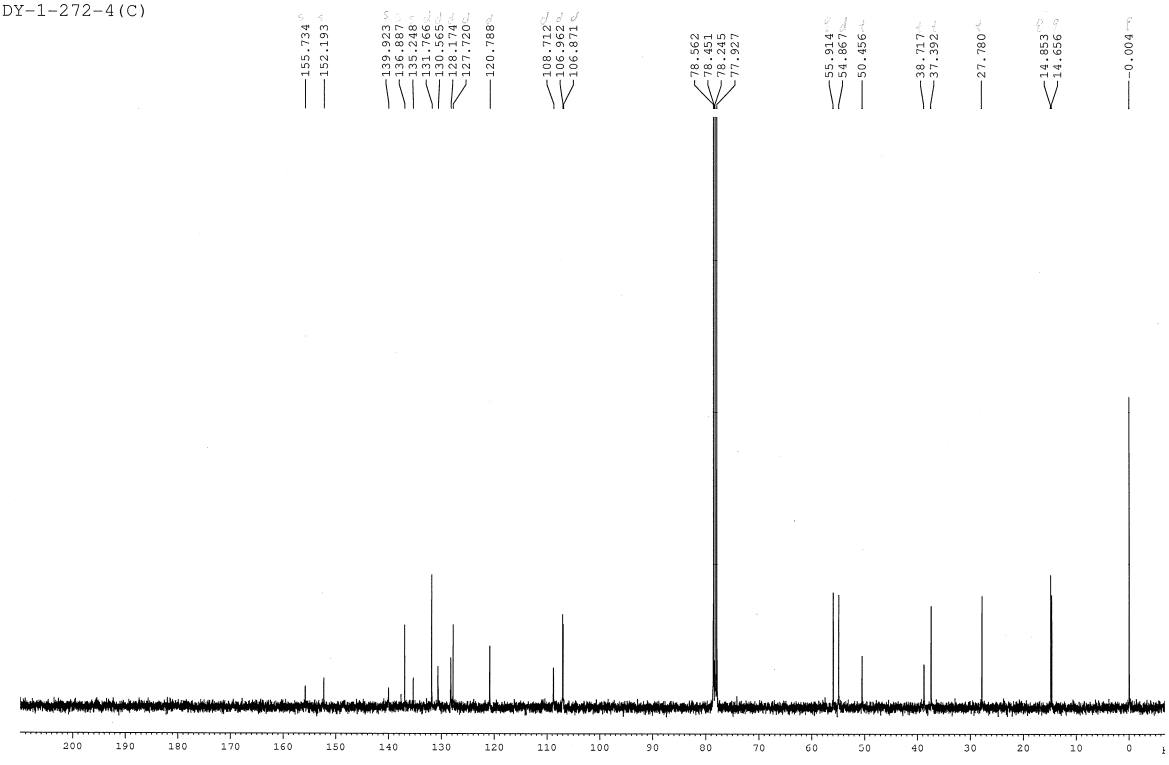


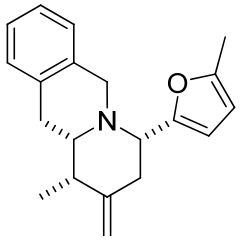
27

DY-1-272

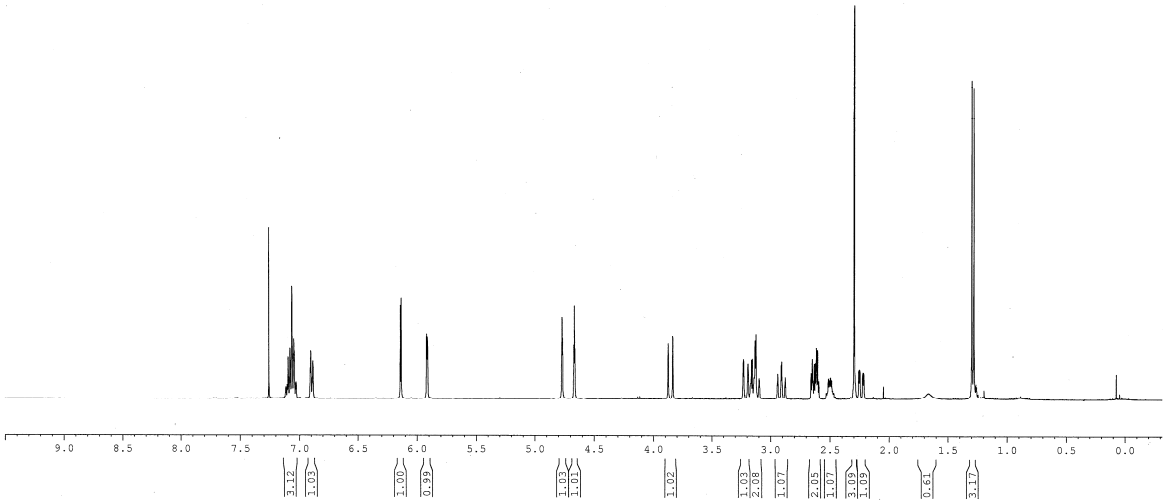


DY-1-272-4(C)

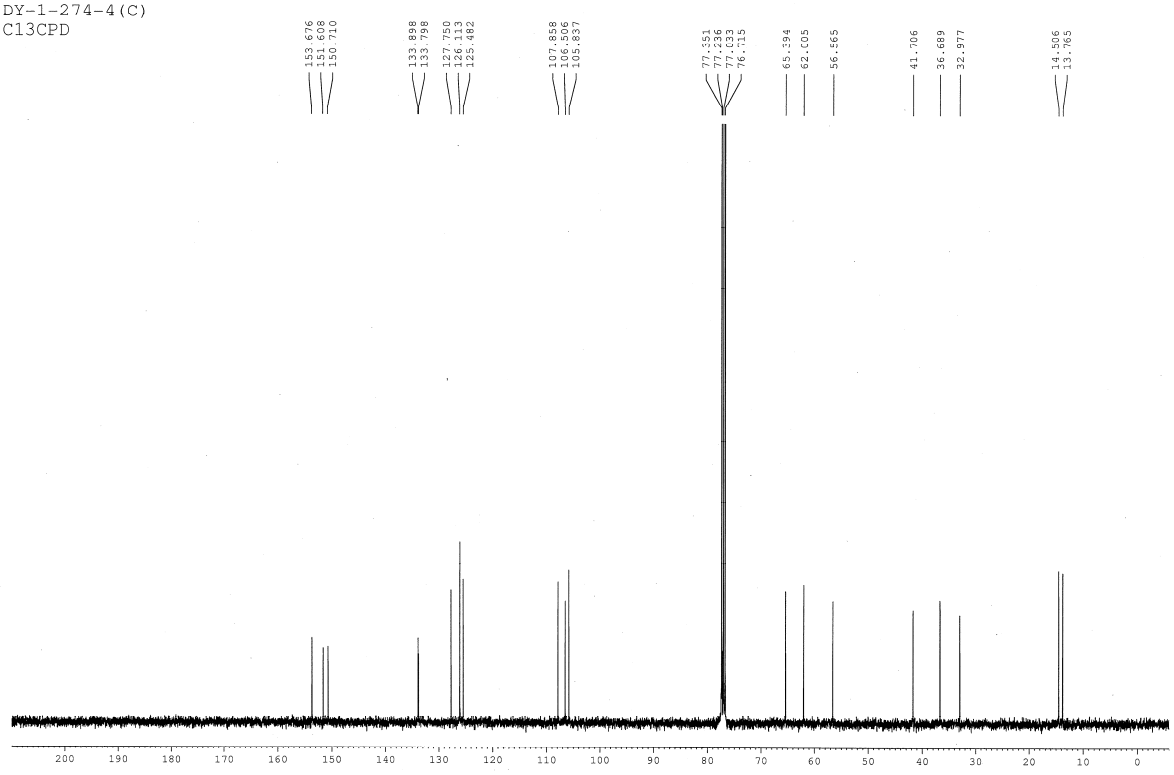


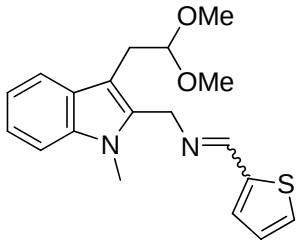


28
DY-1-274

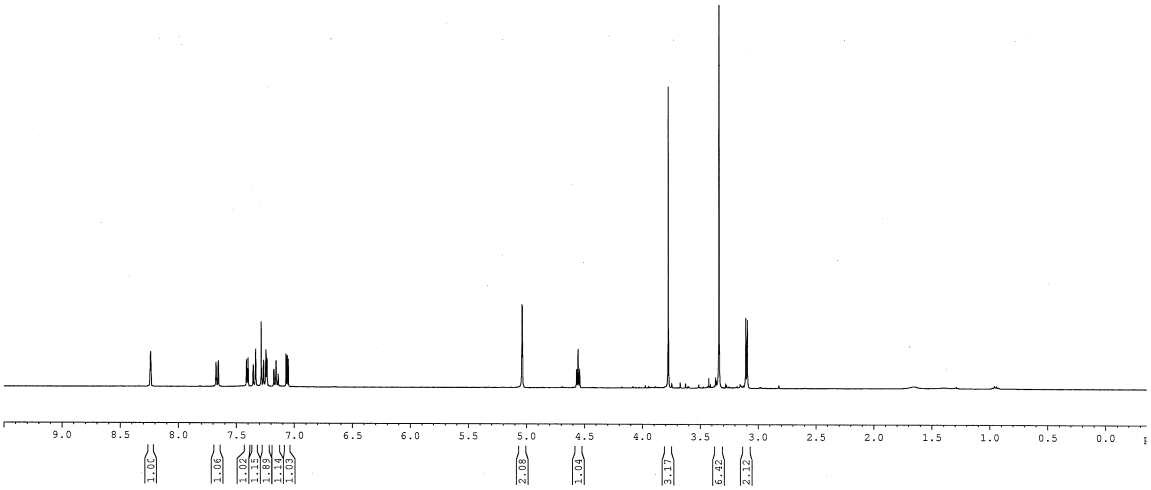


DY-1-274-4(C)
C13CPD

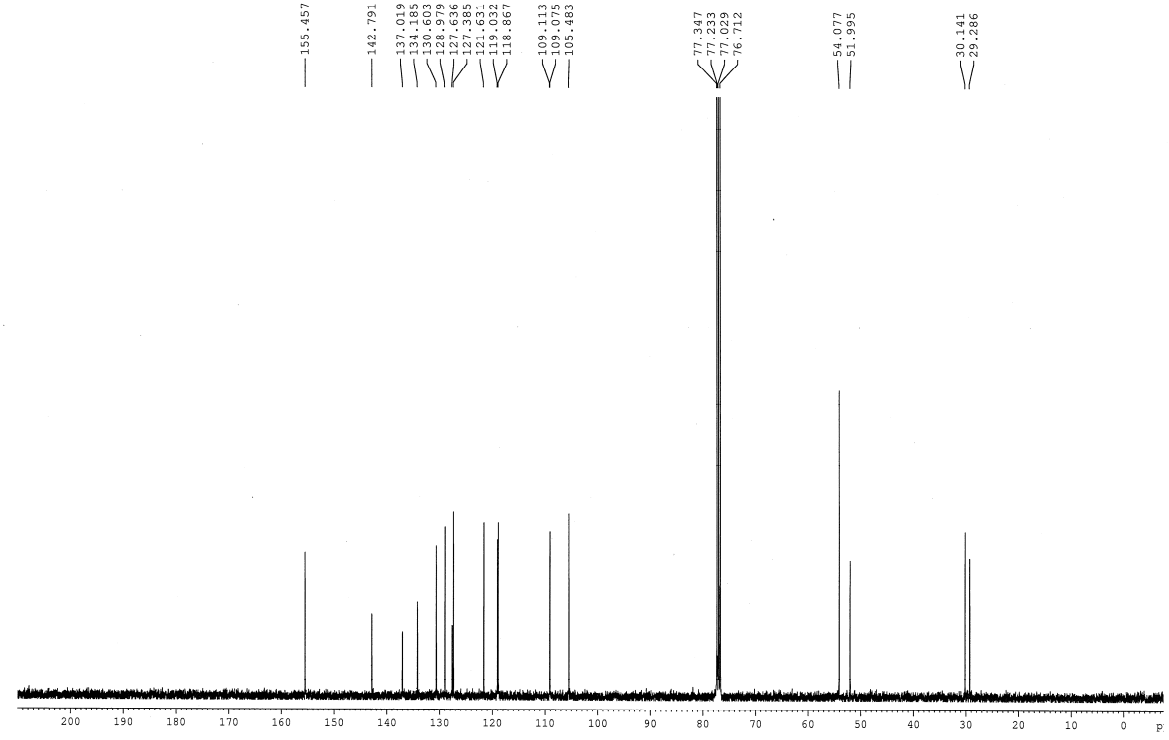


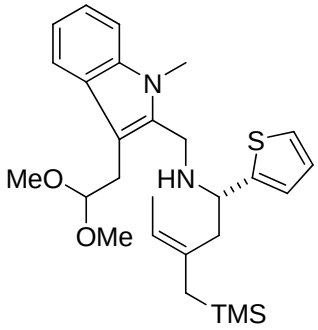


29
DY-1-309



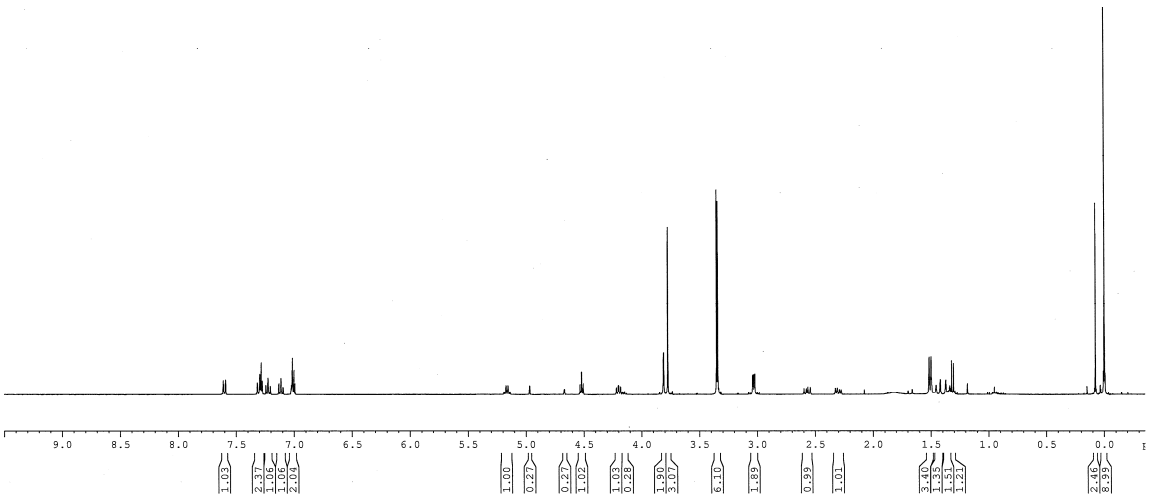
DY-1-309Final

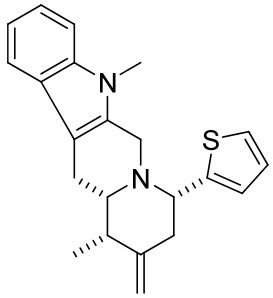



N
S
MeO
HN
OMe
TMS

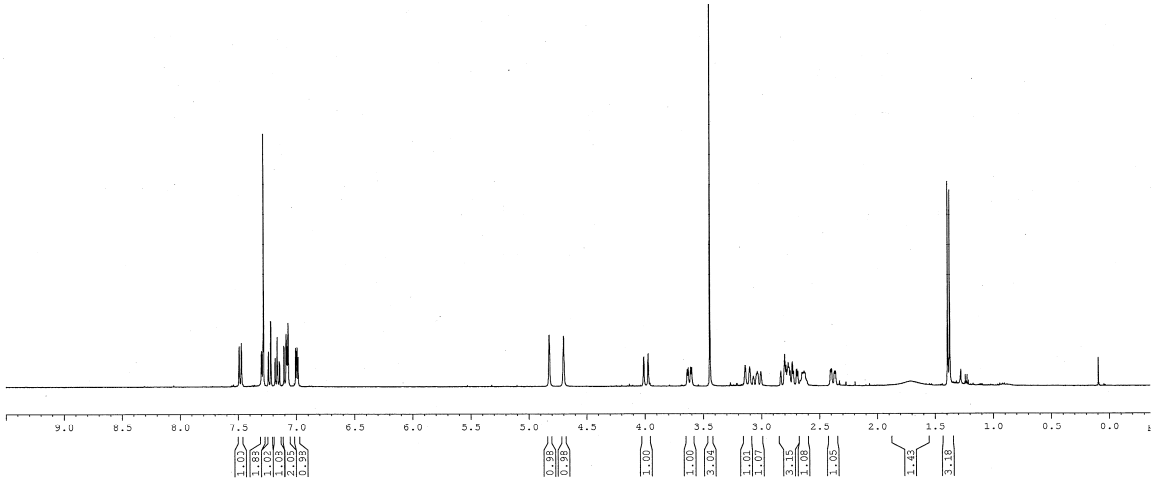
30

DY-1-310


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.03
2.37
1.06
1.06
2.04
1.00
0.27
0.27
1.02
1.03
0.28
1.90
3.07
6.10
1.89
0.99
1.01
3.40
1.35
1.51
1.29
2.46
8.99



31
DY-2-1



DY-2-1-13(C)