# Use of the Intramolecular Heck Reaction for Forming Highly Congested Quaternary Carbon Centers. Stereocontrolled Total Synthesis of (±)-Gelsemine

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## Supporting Information

*(79 pages)*

**Experimental details and characterization data for new compounds[1]**



### A. The Final Route to Gelsemine

**(1*R**,2*R**,6*S**,7*R**,8*S**)-7-Bromo-4-methoxy-3-trifluoromethanesulfonyloxy-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (64)**. Potassium hexamethyldisilazide (9.9 mL, 0.5 M in toluene, 5.0 mmol) was added to a –78 °C solution of ketone **5**[4] (1.41 g, 4.50 mmol) in THF (22.5 mL). After 30 min, chlorotriethylsilane (1.5 mL, 9.0 mmol) was added and the solution was allowed to warm to rt. After 30 min, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (3×). The combined extracts were dried ($Na_2SO_4$), filtered, and concentrated to give 1.96 g (~100%) of enoxysilane **62** as a pale yellow oil, which was used immediately. Diagnostic data: $^{1}$H NMR (500 MHz,

$CDCl_3$)[5] δ *5.94* (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.93 (dd, *J* = 17.6, 11.0 Hz), *5.21* (d, *J* = 11.0 Hz, 1 H), 5.20 (d, *J* = 11.0 Hz), *5.15* (d, *J* = 17.6 Hz, 1 H), 5.12 (d, *J* = 17.7 Hz), 4.68–4.66 (m, 1 H), 4.66–4.65 (m, 1 H), *4.53* (dd, *J* = 2.9, 1.7 Hz, 1 H), 4.18–4.17 (m, 1 H), *4.15–4.14* (m, 1 H), 3.74 (s), *3.73* (s, 3 H), 3.54 (d, *J* = 10.0 Hz), *3.50* (d, *J* = 10.1 Hz, 1 H), 3.29 (ap t, *J* = 10.2 Hz, 1 H), 2.33–2.29 (m, 1 H), 2.16 (br s, 1 H), 2.03–1.99 (m, 1 H), *0.97* (t, *J* = 7.9 Hz, 9 H), 0.96 (t, *J* = 7.9 Hz), *0.66* (q, *J* = 7.9 Hz, 6 H), 0.65 (q, *J* = 7.9 Hz).

A solution of iodosobenzene (1.16 g, 5.26 mmol) and methanol (22.5 mL) was cooled to –78 °C, then $BF_3{\cdot}OEt_2$ (1.2 mL, 9.9 mmol) was added. A solution of crude enoxysilane **62** prepared above and $CH_2Cl_2$/MeOH (8.2 mL/5.9 mL) was slowly added to the cold solution of freshly prepared oxidant. The reaction was allowed to warm to 0 °C over 1 h, aged for 2.5 h at 0 °C, and then concentrated at 0 °C to remove methanol. The resulting crude residue was quenched with $H_2O$ and diluted with $CH_2Cl_2$. The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3×). The combined extracts were dried ($Na_2SO_4$), filtered and concentrated to give a mixture of ethers as an oily solid. The crude α-methoxy ketone **63** showed the following diagnostic resonances in the $^1$H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, $NCO_2CH_3$), 3.44 (s, $OCH_3$). The crude material was used without further purification.

2-[*N*,*N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (2.65g, 6.75 mmol) was added to the crude α-methoxyketone **63** prepared above. The mixture was azeotroped with benzene (3 × 25 mL) by concentration on the rotary evaporator and then dissolved in THF (45 mL). The resulting solution was cooled to –78 °C and potassium hexamethyldisilazide (10.8 mL, 0.5M in toluene, 5.4 mmol) was slowly added. The solution was allowed to stand at –78 °C for 30 min at which time it was diluted with $Et_2O$ (25 mL), then quenched with saturated aqueous $NaHCO_3$. After allowing this mixture to warm to rt, the layers were separated and the aqueous phase was extracted with $Et_2O$ (3×). The combined ethereal layers were dried ($Na_2SO_4$), filtered and concentrated. The resulting crude residue was purified by chromatography (20% EtOAc/hexanes → 25% EtOAc/hexanes gradient) to afford 1.29 g (61% for 3 steps) of triflate **64** as a colorless foam: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 5.90 (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.33 (d, *J*

= 11.0 Hz, 1 H), *5.23* (d, *J* = 17.7 Hz, 1 H), 5.22 (d, *J* = 17.7 Hz), 4.79 (m), *4.66–4.64* (m, 1 H), 4.17 (d, *J* = 1.3 Hz), *4.13* (d, *J* = 1.3 Hz, 1 H), 3.73 (s), *3.72* (s, 3 H), 3.65 (s, 3 H), *3.54* (d, *J* = 10.3 Hz, 1 H), 3.51 (d, *J* = 10.3 Hz), *3.30* (d, *J* = 10.3 Hz, 1 H), 3.29 (d, *J* = 10.3 Hz), 2.65–2.59 (m, 2 H), 2.38–2.35 (m, 1 H), 2.34 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 154.9, 154.5, 145.9, 145.8, 132.7, 132.6, 124.2, 124.1, 119.7, 118.8, 118.7, 117.2, 66.6, 66.3, 55.7, 54.0, 53.9, 52.7, 52.5, 52.2, 52.16, 52.1, 51.3, 50.3, 50.2, 49.8, 30.0; IR (film): 2954, 1711, 1456, 1416, 1210, 1139 cm$^{-1}$; MS (CI) *m/z* 475.9994 (MH, 475.9990 calcd for $C_{15}H_{17}BrF_3NO_6S$). Anal. Calcd for $C_{15}H_{17}BrF_3NO_6S$: C, 37.83; H, 3.60; N, 4.01. Found C, 38.07; H, 3.65; N, 2.91.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-4-methoxy-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-3,9-dicarboxylic acid dimethyl ester (66)**. A solution of triflate **64** (552 mg, 1.16 mmol), tributylamine (0.77 mL, 3.2 mmol), DMF (5.8 mL) and methanol (11.6 mL) in a high pressure reaction vessel was degassed with argon, then bis(diphenylphosphinoferrocene)palladium(II) chloride (104 mg, 0.127 mmol) was added. The resulting orange solution was degassed with argon and then with carbon monoxide, and then pressurized to 50 psi with carbon monoxide. The reaction vessel was placed in an 80 °C bath for 18 h, and then was allowed to cool to rt. The reaction mixture was concentrated to remove the organic solvents, and the residue was partitioned between $H_2O$ and EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (3×). The combined organic extracts were washed with 1 M HCl (2×), $H_2O$ (2×) and brine, then dried ($Na_2SO_4$), filtered and concentrated. The resulting crude solid was purified by chromatography (5:4:1 EtOAc/hexanes/$CHCl_3$ → 3:2:1 EtOAc/hexanes/$CHCl_3$) to afford 421 mg (94%) of the ester **66** as a white solid: mp = 193–195 °C; $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *5.82* (dd, *J* = 17.5, 11.1 Hz, 1 H), 5.81 (dd, *J* = 17.5, 11.1 Hz), *5.24* (dd, *J* = 11.1, 1.0 Hz, 1 H), 5.23 (dd, *J* = 11.1, 1.0 Hz), *5.14* (dd, *J* = 17.5, 1.0 Hz, 1 H), 5.13 (dd, *J* = 17.5, 1.0 Hz), 4.59 (dd, *J* = 3.6, 2.0 Hz), *4.45* (dd, *J* = 3.2, 2.0 Hz, 1 H), 4.09 (dd, *J* = 3.6, 1.6 Hz), *4.05* (dd, *J* = 3.2, 1.2 Hz, 1 H), *3.73* (s, 3 H) 3.71 (s, 3 H), *3.69* (br s, 3 H), 3.68 (br s), *3.50* (d, *J* = 10.3 Hz, 1 H), 3.47 (d, *J* = 10.1 Hz), *3.28* (d, *J* = 10.2 Hz, 1 H), 3.26 (d, *J* = 10.1 Hz), *3.11* (t, *J* = 2.4 Hz, 1 H), 3.07 (t, *J* = 2.4 Hz), *2.63* (dd, *J* = 18.0, 3.8 Hz, 1 H), 2.62 (dd, *J* = 18.0, 3.8 Hz), *2.44* (dd, *J* =

18.0, 2.8 Hz, 1 H), 2.41 (dd, *J* = 18.0, 2.8 Hz), 2.29 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 166.1, 165.8, 163.1, 163.0, 154.9, 154.6, 133.5, 133.4, 118.2, 118.1, 101.9, 101.8, 67.0. 66.8, 55.6, 54.8, 54.7, 52.7, 52.6, 52.4, 52.3, 51.4, 51.3, 49.74, 49.69, 49.1, 48.1, 47.6, 32.8; IR ($CHCl_3$) 3031, 1699, 1614, 1521, 1422, 1046 cm$^{-1}$; MS (CI) *m/z* 386.0585 (MH, 386.0603 calcd for $C_{16}H_{20}BrNO_5$), 356, 354, 306. Anal. Calcd for $C_{16}H_{20}BrNO_5$: C, 49.76; H, 5.22; N, 3.63. Found: C, 49.47; H, 5.28; N, 3.48.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-(2-iodophenylcarbamoyl)-4-methoxy-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (67)**. A 0.5 M solution of dimethylaluminum-2-iodoanilide was prepared by adding trimethylaluminum (5.88 mL, 2.0 M in toluene, 11.8 mmol) to a –10 °C solution of 2-iodoaniline (2.68 g, 12.2 mmol) and $CH_2Cl_2$ (17.6 mL). The solution was allowed to warm to rt and aged for 1 h. An aliquot of the 0.5 M aluminum amide solution (7.1 mL, 3.6 mmol) was added to a solution of ester **66** (457 mg, 1.18 mmol) and $CH_2Cl_2$ (11.8 mL) at 0 °C. After 1 h, an additional portion of the 0.5 M aluminum amide solution (7.1 mL, 3.6 mmol) was added to the reaction mixture. The reaction mixture was allowed to warm to rt over a period of 1.5 h, at which time it was diluted with $CH_2Cl_2$ (10 mL) and slowly quenched with a saturated aqueous solution of Rochelle's salt. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3×). The combined organic phases were washed with 1 M HCl, $H_2O$ and brine, then dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by chromatography (40% EtOAc/petroleum ether) to provide 548 mg (81%) of amide **67** as a brown foam: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *9.77* (br s, 1 H), 9.75 (br s), *8.40* (dd, *J* = 8.3, 1.4 Hz, 1 H), 8.39 (dd, *J* = 8.3, 1.4 Hz), *7.78* (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.77 (dd, *J* = 7.8, 1.2 Hz), 7.32 (dt, *J* = 7.8, 1.3 Hz, 1 H), 6.80 (dt, *J* = 7.6, 1.4 Hz, 1 H), *5.87* (dd, *J* = 17.6, 10.8 Hz, 1 H), 5.84 (dd, *J* = 17.6, 10.8 Hz), *5.26* (d, *J* = 10.8 Hz, 1 H), 5.24 (d, *J* = 10.8 Hz), *5.17* (d, *J* = 17.6 Hz, 1 H), 5.15 (d, *J* = 17.6 Hz), 4.65–4.64 (m), *4.54* (dd, *J* = 3.3, 2.0 Hz, 1 H), 4.12–4.11 (m), *4.09* (dd, *J* = 3.3, 1.2 Hz, 1 H), *3.93* (s, 3 H), 3.91 (s), 3.71 (s), *3.69* (s, 3 H), *3.56* (d, *J* = 10.1 Hz, 1 H), 3.52 (d, *J* = 10.1 Hz), 3.48–3.47 (m), *3.45* (t, *J* = 2.3 Hz, 1 H), *3.31* (d, *J* = 10.1 Hz, 1 H), 3.29 (d, *J* = 10.1 Hz), *2.76* (dd, *J* = 17.8, 3.7 Hz, 1 H), 2.74 (dd, *J* = 17.8, 3.7 Hz), 2.51 (dd, *J* =

17.8, 2.4 Hz, 1 H), 2.37 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 163.7, 163.4, 158.7, 158.3, 155.0, 154.4, 139.8, 139.7, 139.0, 138.9, 133.6, 133.5, 129.02, 128.98, 125.3, 125.2, 122.2, 122.1, 118.3, 118.2, 88.9, 88.8, 67.1, 66.8, 56.0, 54.9, 54.1, 52.9, 52.7, 52.5, 52.3, 49.9, 49.3, 48.6, 48.3, 47.1, 46.6, 32.6, 30.6; IR (film) 3312 (br), 2950, 1701, 1654, 1522, 1458, 1432, 1400, 1293, 1207, 1158 cm$^{-1}$; MS (CI) *m/z* 572.9883 (MH, 572.9888 calcd for $C_{21}H_{22}BrIN_2O_4$), 493, 419, 391. Anal. Calcd for $C_{21}H_{22}BrIN_2O_4$: C, 44.00; H, 3.87; N, 4.89. Found: C, 43.87; H, 3.90; N, 4.84.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-[(2-iodophenyl)methoxymethylcarbamoyl]-4-methoxy-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (68)**. Sodium hydride (142 mg, 60% dispersion in oil, 3.54 mmol) was added to a solution of amide **67** (507 mg, 0.884 mmol) and THF (8.85 mL). After 10 min, chloromethyl methyl ether (134 μL, 1.77 mmol) was added, the resulting solution was aged for 12 h and then quenched with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with EtOAc (3×), and the combined organic extracts were washed with $H_2O$, brine and then dried ($Na_2SO_4$), filtered and concentrated. The resulting residue was purified by chromatography (40% EtOAc/petroleum ether) to provide 469 mg (86%) of tertiary amide **68** as a brown oil: $^1$H NMR (500 MHz, $CDCl_3$, extremely complex due to two sets of conformational isomer, integrations omitted on purpose) δ 8.00 (d, *J* = 7.2 Hz), 7.94 (d, *J* = 7.7 Hz), 7.91–7.88 (m), 7.84 (d, *J* = 7.7 Hz), 7.39–7.30 (m), 7.13–7.09 (m), 7.07–7.03 (m), 5.79–5.63 (m), 5.31 (d, *J* = 17.5 Hz), 5.29 (d, *J* = 17.6 Hz), 5.23 (d, *J* = 11.0 Hz), 4.94–4.85 (m), 4.76 (br s), 4.72 (br s), 4.64–4.62 (m), 4.51 (d, *J* = 10.4 Hz), 4.48 (d, *J* = 10.4 Hz), 4.46 (d, *J* = 10.0 Hz), 4.41 (d, *J* = 10.4 Hz), 4.28 (br s), 4.25 (br s), 4.24–4.20 (m), 4.09 (br s), 4.06 (d, *J* = 2.4 Hz), 4.03 (br s), 3.70 (s), 3.68 (s), 3.66–3.63 (m), 3.54–3.44 (m), 3.42–3.38 (m), 3.32–3.28 (m), 3.16–3.13 (m), 3.10 (br s), 2.84 (s), 2.64–2.62 (m), 2.60–2.58 (m), 2.41 (d, *J* = 3.6 Hz), 2.38 (d, *J* = 3.6 Hz), 2.35–2.32 (m), 2.22 (d, *J* = 4.0 Hz), 2.19 (d, *J* = 4.4 Hz), 2.13 (s), 2.10–2.08 (m), 1.97 (dd, *J* = 17.3, 2.6 Hz), 1.95 (dd, *J* = 17.3, 2.6 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$, extremely complex due to two sets of conformational isomers) δ 170.0, 169.9, 169.7, 155.0, 154.9, 154.5, 154.3, 150.7, 150.6, 150.1, 150.0, 143.0, 139.8, 139.7, 139.6,

139.5, 133.44, 133.38, 133.3, 131.2, 131.0, 130.8, 130.4, 130.2, 129.9, 129.8, 129.4, 129.0, 128.5, 128.4, 128.2, 128.1, 118.6, 118.2, 117.5, 117.4, 108.7, 108.4, 108.0, 101.1, 100.7, 100.0, 99.8, 82.5, 77.9, 77.7, 67.93, 67.89, 67.5, 67.3, 56.9, 56.8, 56.7, 55.4, 55.1, 55.0, 54.9, 54.60, 54.56, 54.51, 52.5, 52.4, 52.35, 52.29, 52.1, 51.7, 51.5, 50.7, 50.6, 50.5, 50.1, 49.7, 49.4, 49.0, 48.8, 48.4, 47.7, 31.01, 30.95, 30.6, 30.3; IR (film) 2942, 1702, 1654, 1456, 1399, 1295 $cm^{-1}$; MS (CI) *m/z* 617.0145 (MH, 617.0148 calcd for $C_{23}H_{26}BrIN_2O_5$), 587, 585, 537. Anal. Calcd for $C_{23}H_{26}BrIN_2O_5$: C, 44.75; H, 4.25; N, 4.54. Found: C, 44.99; H, 4.24; N, 4.48.

**(1*R**,2*S**,3*R**,6*S**,7*R**,8*S**)-7-Bromo-4-methoxy-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (69) and (1*R**,2*S**,3*S**,6*S**,7*R**,8*S**)-7-Bromo-4-methoxy-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (70)**. In a sealable reaction vessel, a solution of aryl iodide **68** (459 mg, 0.743 mmol), triethylamine (1.0 mL, 7.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (269 mg, 0.26 mmol), $Ag_3PO_4$ (622mg, 1.49 mmol) and THF (26.5 mL) was degassed (freeze-pump-thaw method) and then sealed under argon. The reaction was placed in a 66 °C bath for 13 h, then cooled and filtered through Celite, rinsing with EtOAc. The filtrate was concentrated and the residue was purified by chromatography (30% EtOAc/petroleum ether → 50% EtOAc/petroleum ether gradient) to afford 254 mg (70%) of **69** and 21 mg (5.8%) of **70** each as a brown foam. Data for **69**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *7.39* (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 7.5 Hz), 7.30–7.24 (m, 1 H), 7.06–7.01 (m, 2 H), *6.21* (dd, *J* = 17.8, 11.2 Hz, 1 H), 6.18 (dd, *J* = 17.8, 11.4 Hz), *5.52* (d, *J* = 8.3 Hz, 1 H), 5.51 (d, *J* = 8.2 Hz), *5.47* (d, *J* = 11.0 Hz, 1 H), 5.40 (d, *J* = 11.0 Hz), *5.28* (d, *J* = 17.7 Hz, 1 H), 5.26 (d, *J* = 17.7 Hz), *5.15* ($AB_q$, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 22.1 Hz, 2 H), 5.13 ($AB_q$, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 28.6 Hz), 5.02 (d, *J* = 3.7 Hz), *4.98* (d, *J* = 3.6 Hz, 1 H), 4.74 (dd, *J* = 3.7, 1.5 Hz), *4.62* (dd, *J* = 3.7, 1.6 Hz, 1 H), 3.69 (s), *3.68* (s, 3 H), *3.64* (d, *J* = 10.8 Hz, 1 H), 3.59 (d, *J* = 10.7 Hz), 3.41 (s, 3 H), *3.31* (s, 3 H), 3.30 (s), 3.31–3.26 (m, 1 H), 2.81 (d, *J* = 8.2 Hz), *2.80* (d, *J* = 8.2 Hz, 1 H), *2.40* (dd, *J* = 2.7, 1.6 Hz, 1 H), 2.36 (dd, *J* = 2.7, 1.6 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 176.5, 176.3, 154.9, 154.4, 154.0, 141.4, 141.3, 136.2, 131.3, 128.5, 125.3, 125.2, 123.2, 123.0, 119.1, 119.0, 109.8, 103.64,

103.61, 71.4, 64.3, 64.0, 57.8, 57.6, 56.2, 56.1, 56.0, 55.52, 55.48, 55.4, 55.2, 54.9, 52.4, 52.35, 52.27, 49.2, 49.1; IR (film) 2937, 1716, 1658, 1611, 1456, 1400, 1344 $cm^{-1}$; MS (CI) *m/z* 488.0964 (M, 488.0947 calcd for $C_{23}H_{25}BrN_2O_5$), 457, 409. Anal. Calcd for $C_{23}H_{25}BrN_2O_5$: C, 56.45; H, 5.15; N, 5.72. Found: C, 56.74; H, 5.32; N, 5.64.

Data for **70**: $^1H$ NMR (500 MHz, $CDCl_3$)[5] δ 7.37–7.29 (m, 1 H), 7.16–7.10 (m, 2 H), *7.06* (d, *J* = 7.8 Hz, 1 H), 7.03 (d, *J* = 7.8 Hz), 6.76 (dd, *J* = 17.8, 11.1 Hz, 1 H), *5.49* (d, *J* = 8.3 Hz, 1 H), 5.48 (d, *J* = 8.3 Hz), *5.25* (d, *J* = 11.1 Hz, 1 H), 5.24 (d, *J* = 11.1 Hz), 5.15–5.01 (m, 3 H), 4.65 (d, *J* = 3.4 Hz), *4.63* (d, *J* = 3.3 Hz, 1 H), 4.50 (dd, *J* = 3.4, 1.4 Hz), *4.34* (dd, *J* = 3.4, 1.4 Hz, 1 H), *3.74* (d, *J* = 10.7 Hz, 1 H), 3.69 (d, *J* = 10.5 Hz), *3.68* (s, 3 H), 3.65 (s), *3.42* (s, 3 H), 3.41 (s), *3.37* (d, *J* = 10.5 Hz, 1 H), 3.35 (d, *J* = 10.4 Hz), *3.29* (s, 3 H), 3.28 (s), 2.74 (d, *J* = 8.3 Hz), *2.73* (d, *J* = 8.3 Hz, 1 H), 2.41–2.40 (m), *2.39–2.38* (m, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$)[5] δ 176.9, 176.8, 154.7, 154.6, 154.5, 142.8, 142.6, 137.2, 137.0, 129.3, 128.3, 128.2, 123.7, 123.6, 123.5, 123.4, 115.5, 115.3, 110.3, 110.2, 103.9, 103.8, 71.4, 64.3, 63.9, 57.9, 57.7, 56.2, 56.1, 55.6, 55.4, 55.3, 55.1, 55.0, 54.9, 54.7, 52.7, 52.4, 51.9, 51.8, 50.54, 50.49; IR (film) 2926, 1724, 1706, 1654, 1610, 1456, 1400, 1343, 1230, 1136 $cm^{-1}$; MS (CI) *m/z* 488.0945 (M, 488.0947 calcd for $C_{23}H_{25}BrN_2O_5$), 475, 473, 409, 395, 378.

**(1*R**,2*S**,3*R**,6*S**,7*R**,8*S**)-7-Bromo-4-oxo-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (72)**. Concentrated HCl (3.17 mL) was added to a solution of enol ether **69** (220 mg, 0.45 mmol) and MeOH (6.42 mL) at rt. The mixture was allowed to stir for 24 h and an additional portion of conc HCl (3.2 mL) and methanol (6.4 mL) was added. The mixture was allowed to stir for an additional 24 h and was then diluted with $CH_2Cl_2$ (25 mL) and slowly quenched with a saturated aqueous $NaHCO_3$ solution until bubbling ceased and the solution pH = 7. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic phases were washed with a saturated aqueous $K_2CO_3$ solution and then dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (35% EtOAc/petroleum ether → 40% EtOAc/petroleum ether gradient) to afford 209 mg (98%) of ketone **72** as a white solid. X-ray quality crystals were

prepared by recrystallizing a small portion of **72** from a 1:1 EtOAc/petroleum ether solution affording clear prisms: mp = 178–179 °C; $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.35–7.26 (m, 2 H), 7.04–7.01 (m, 2 H), *6.22* (dd, *J* = 17.8, 11.0 Hz, 1 H), 6.20 (dd, *J* = 17.8, 10.9 Hz), *5.59* (d, *J* = 11.0 Hz, 1 H), 5.58 (d, *J* = 10.9 Hz), *5.37* (d, *J* = 17.8 Hz, 1 H), 5.35 (d, *J* = 17.8 Hz), *5.10* ($AB_q$, $J_{AB}$ = 10.8 Hz, $\Delta\nu_{AB}$ = 29.5 Hz, 2 H), 5.12–5.04 (m), 4.99 (br s), *4.90* (br d, *J* = 2.1 Hz, 1 H), 4.87 (br s), *4.79* (br s, 1 H), 3.67 (br s, 3 H), *3.63* (d, *J* = 10.8 Hz, 1 H), 3.60 (d, *J* = 11.0 Hz), *3.32* (s, 3 H), 3.30 (s), *3.27* (d, *J* = 10.8 Hz, 1 H), 3.25 (d, *J* = 11.0 Hz), *3.13* (dd, *J* = 18.7, 3.2 Hz, 1 H), 3.10 (dd, *J* = 18.6, 3.4 Hz), 2.793 (d, *J* = 18.6 Hz), *2.788* (d, *J* = 18.7 Hz, 1 H), 2.75 (br s, 1 H), *2.54* (br s, 1 H), 2.51 (br s); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 204.0, 203.9, 174.5, 174.3, 154.8, 154.3, 141.9, 134.81, 134.78, 130.5, 130.3, 129.3, 124.8, 124.7, 123.4, 123.3, 119.52, 119.46, 110.4, 71.5, 63.8, 63.7, 63.3, 63.1, 56.3, 55.4, 55.3, 53.9, 53.8, 53.1, 52.6, 52.4, 48.7, 43.5; IR (film) 2953, 1728, 1703, 1609, 1487, 1467, 1456, 1400, 1345, 1124, 1092 cm$^{-1}$; MS (CI) *m/z* 474.0803 (M, 474.0790 calcd for $C_{22}H_{23}BrN_2O_5$) 445, 443, 395, 363. Anal. Calcd for $C_{22}H_{23}BrN_2O_5$: C, 55.59; H, 4.88; N, 5.89. Found: C, 55.28; H, 4.99; N, 5.76.

**(1*R**,2*S**,3*R**,4*R**,6*S**,7*R**,8*S**)-7-Bromo-4-hydroxy-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (73) and (1*R**,2*S**,3*R**,4*S**,6*S**,7*R**,8*S**)-7-Bromo-4-hydroxy-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (74)**. Triisobutylaluminum (3.83 mL, 1 M in toluene, 3.83 mmol) was added to a solution of ketone **72** (182 mg, 0.383 mmol) and toluene (3.83 mL) at –50 °C. The reaction mixture was allowed to warm to rt over a period of 4 h at which time it was diluted with $CH_2Cl_2$ (10 mL) and slowly quenched with 1 M HCl (10 mL). The resulting heterogeneous solution was allowed to stir at rt for 1 h. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3×). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. The product ratio was determined to be 1:6.5 (**73**:**74**) by integration of the C19 proton in the crude $^1$H NMR. The crude residue was purified by chromatography (40% EtOAc/petroleum ether) to give 23 mg (12%) of alcohol **73** and 130 mg (71%) of alcohol **74** each as a colorless foam.

Data for **73**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.33–7.27 (m, 2 H), 7.18–7.13 (m, 1 H), 7.03 (d, *J* = 7.7 Hz, 1 H), *6.32* (dd, *J* = 17.7, 11.0 Hz, 1 H), 6.31 (dd, *J* = 17.7, 11.0 Hz), 5.68 (d, *J* = 3.7 Hz), *5.65* (d, *J* = 3.6 Hz, 1 H), 5.49–5.43 (m, 2 H), 5.19–5.08 (m, 2 H), *4.49* (t, *J* = 9.1 Hz, 1 H), 4.48 (t, *J* = 9.0 Hz), 4.44 (dd, *J* = 3.7, 1.4 Hz), *4.32* (dd, *J* = 3.7, 1.5 Hz, 1 H), 3.67 (s), *3.66* (s, 3 H), *3.44* (d, *J* = 10.9 Hz, 1 H), 3.39 (d, *J* = 10.8 Hz), *3.35* (s, 3 H), 3.33 (s), *3.22* (d, *J* = 10.8 Hz, 1 H), 3.20 (d, *J* = 10.5 Hz), 2.78–2.72 (m, 1 H), *2.67* (br s, 1 H), 2.65 (br s), *2.40* (br s, 1 H), 2.36 (br s), 1.95 (ddd, *J* = 14.5, 9.1, 5.6 Hz, 1 H), 1.62 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 176.3, 176.2, 154.6, 154.3, 141.24, 141.18, 136.0, 134.8, 134.7, 128.7, 123.9, 123.7, 123.1, 122.9, 117.7, 117.5, 109.7, 109.6, 71.4, 68.7, 68.4, 63.9, 63.6, 58.4, 58.1, 56.4, 55.89, 55.85, 55.2, 55.1, 53.9, 53.75, 53.71, 53.3, 52.5, 52.4, 48.0, 47.9, 36.7; IR (film) 3426 (br), 2951, 1706, 1612, 1467 cm$^{-1}$; MS (CI) *m/z* 477 (MH), 447, 445, 396, 365.

Data for **74**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *7.58* (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 7.7 Hz), 7.34–7.30 (m, 1 H), 7.11–7.04 (m, 2 H), 5.98 (dd, *J* = 17.9, 11.0 Hz), *5.97* (dd, *J* = 18.0, 11.0 Hz, 1 H), *5.44* (d, *J* = 11.0 Hz, 1 H), 5.43 (d, *J* = 11.0 Hz), *5.25* (d, *J* = 18.0 Hz, 1 H), 5.23 (d, *J* = 17.9 Hz), *5.12* ($AB_q$, $J_{AB}$ = 10.9 Hz, $\Delta\nu_{AB}$ = 21.4 Hz, 2 H), 5.09 ($AB_q$, $J_{AB}$ = 10.9 Hz, $\Delta\nu_{AB}$ = 15.3 Hz), 4.91–4.84 (m, 1 H), 4.81 (br s, 1 H), 4.47–4.44 (m, 1 H), *3.66* (s, 3 H), 3.64 (s), 3.31–3.27 (m, 4 H), 3.10 (d, *J* = 10.8 Hz), *3.09* (d, *J* = 10.9 Hz, 1 H), 2.76 (br s, 1 H), 2.34–2.28 (m, 1 H), 2.23–2.21 (m, 1 H), 2.18–2.16 (m, 1 H), 1.96 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 179.6, 179.3, 154.6, 154.1, 142.13, 142.07, 136.5, 128.7, 128.6, 127.8, 127.3, 127.2, 122.2, 122.1, 117.0, 116.9, 110.10, 110.06, 71.4, 66.3, 66.2, 62.4, 62.2, 56.7, 56.6, 56.3, 56.22, 56.15, 56.12, 54.2, 53.2, 52.6, 52.4, 52.3, 51.4, 51.3, 48.4, 33.3; IR (film) 3424 (br), 2952, 1713, 1610, 1468, 1401, 1354, 1250, 1132, 1084 cm$^{-1}$; MS (CI) *m/z* 477.1050 (MH, 477.1025 calcd for $C_{22}H_{25}BrN_2O_5$) 447, 445, 396, 365. Anal. Calcd for $C_{22}H_{25}BrN_2O_5$: C, 55.36; H, 5.28; N, 5.87. Found: C, 55.46; H, 5.44; N, 5.77.

**(1*R**,2*S**,3*R**,4*S**,6*S**,7*R**,8*S**)-7-Bromo-4-(1-ethoxyethoxy)-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (79)**. Pyridinium *p*-toluenesulfonate (58.0 mg, 0.230 mmol) was added to a solution of

alcohol **74** (100.0 mg, 0.209 mmol) and ethyl vinyl ether (1.05 mL) and $CH_2Cl_2$ (2.1 mL) at rt. The reaction mixture was allowed to stir for a period of 90 min and then concentrated to remove the solvent. The crude residue was purified by chromatography (30% EtOAc/petroleum ether) to afford 98 mg (85%) of **79** as a colorless foam: $^1$H NMR (500 MHz, $CDCl_3$, mixture of conformational isomers and diastereomers) δ 7.51–7.46 (m, 2 H), 7.25–7.20 (m, 2 H), 7.02–6.98 (m, 4 H), 5.92 (dd, *J* = 18.0, 11.0, 2 H), 5.38 (br d, *J* = 11.0 Hz, 2 H), 5.21–5.03 (m, 6 H), 4.84–4.76 (m, 3 H), 4.73–4.71 (m, 1 H), 4.53–4.47 (m, 1 H), 4.41–4.32 (m, 2 H), 4.14–4.10 (m, 1 H), 3.63 (s, 3 H), 3.62 (s, 3 H), 3.36–3.22 (m, 10 H), 3.08–2.97 (m, 3 H), 2.81–2.73 (m, 1 H), 2.70 (br s, 2 H), 2.34–2.27 (m, 4 H), 2.08 (br s, 2 H), 1.10 (t, *J* = 7.0 Hz, 3 H), 1.04–1.02 (m, 3 H), 0.93–0.88 (m, 3 H), 0.67–0.64 (m, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of conformational isomers and diastereomers) δ 180.0, 179.7, 179.5, 154.6, 154.1, 141.6, 141.5, 141.3, 141.2, 136.3, 136.2, 129.1, 129.0, 128.84, 128.80, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.94, 127.90, 121.9, 121.83, 121.77, 121.7, 117.2, 117.03, 116.99, 116.85, 109.5, 109.4, 99.4, 99.3, 98.8, 98.6, 71.6, 70.5, 70.4, 68.3, 62.7, 62.6, 62.4, 62.3, 61.0, 60.9, 60.6, 60.3, 57.42, 57.38, 57.3, 57.2, 56.5, 56.4, 55.3, 55.23, 55.16, 55.10, 54.4, 54.3, 53.1, 53.0, 52.43, 52.38, 52.2, 51.5, 51.4, 48.2, 31.8, 31.6, 31.5, 20.02, 19.96, 19.8, 19.7, 15.2, 14.8; IR (film) 2930, 1716, 1610, 1455, 1398, 1351, 1130, 1084 cm$^{-1}$; MS (CI) *m/z* 549.1589 (MH, 549.1600 calcd for $C_{26}H_{33}BrN_2O_6$), 478, 476, 447, 445, 429, 427, 396, 365.

**(1*R**,2*R**,3*S**,4*R**,6*R**,7*S**,8*R**)-4-(1-ethoxyethoxy)-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatetracyclo[4.4.0.0$^{2,8}$.0$^{7,9}$]decane (80)**. Sodium cyanide (85 mg, 1.73 mmol) was added to a solution of **79** (95.0 mg, 0.173 mmol) in DMSO (10.8 mL) and heated to 150 °C for 18 h resulting in an orange solution. The reaction mixture was cooled to rt, diluted with EtOAc (20 mL) and saturated aqueous $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with $H_2O$ (2×), brine and then dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (1:3:16 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc → 1:19 $CHCl_3$ (saturated with $NH_3$)/EtOAc) to afford 70 mg (99%) of aziridine **80** as a colorless foam:

$^1$H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.56 (d, *J* = 7.7 Hz, 2 H), 7.12 (d, *J* = 7.7 Hz, 2 H), 6.97–6.94 (m, 4 H), 5.79 (dd, *J* = 17.8, 10.9 Hz, 2 H), 5.20 (d, *J* = 10.9 Hz, 2 H), 5.18–5.13 (m, 4 H), 5.05 (d, *J* = 10.8 Hz, 1 H), 5.00 (d, *J* = 10.7 Hz, 1 H), 4.60 (t, *J* = 6.4 Hz, 1 H), 4.58 (t, *J* = 6.3 Hz, 1 H), 4.46 (q, *J* = 5.2 Hz, 1 H), 4.42 (q, *J* = 5.3 Hz, 1 H), 3.43–3.39 (m, 1 H), 3.32 (s, 3 H), 3.31–3.28 (m, 1 H), 3.30 (s, 3 H), 3.14–3.08 (m, 1 H), 3.05 (br s, 2 H), 2.91–2.85 (m, 1 H), 2.48 (d, *J* = 10.0 Hz, 2 H), 2.42 (br s, 4 H), 2.35–2.19 (m, 4 H), 2.22 (d, *J* = 10.1 Hz, 2 H), 1.82 (s, 2 H), 1.10 (t, *J* = 7.1 Hz, 3 H), 1.09 (d, *J* = 5.2 Hz, 3 H), 0.92 (t, *J* = 7.1 Hz, 3 H), 0.81 (d, *J* = 5.3 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ 179.8, 179.6, 141.8, 141.7, 135.4, 129.6, 128.2, 128.1, 127.8, 121.31, 121.27, 115.31, 115.29, 108.88, 108.85, 100.1, 98.6, 71.9, 71.38, 71.36, 69.1, 66.2, 60.8, 60.5, 56.18, 56.16, 55.6, 55.4, 49.9, 49.8, 46.1, 39.2, 39.1, 35.89, 35.87, 34.3, 27.2, 27.0, 20.3, 20.2, 15.2, 14.9; IR (film) 2936, 1716, 1612, 1488, 1467, 1349, 1085 cm$^{-1}$; MS (CI) *m/z* 410.2245 (M, 410.2205 calcd for $C_{24}H_{30}N_2O_4$), 338.

**(1*R**,2*R**,3*S**,4*R**,6*S**,7*R**,8*R**)-7-Cyano-4-(1-ethoxyethoxy)-9-methyl-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-aza-tricyclo[4.4.0.0$^{2,8}$]decane (81)**. Methyl trifluoromethanesulfonate (275 μl, 0.5 M in $CH_2Cl_2$ , 0.138 mmol) was added to a solution of aziridine **80** (56.0 mg, 0.136 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (30.8 mg, 0.150 mmol) in $CH_2Cl_2$ (2.7 mL) at 0 °C. After a period of 15 min, the reaction mixture was concentrated to remove the solvent and NaCN (67.0 mg, 1.36 mmol) and DMSO (2.7 mL) were added. The resulting mixture was heated at 90 °C for a period of 3 h. The reaction mixture was cooled and diluted with EtOAc (10 mL) and $H_2O$ (5 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with $H_2O$ (2×), brine and then dried ($Na_2SO_4$), filtered and concentrated. The resulting crude residue was purified by chromatography (1:3:16 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc) to afford 52.0 mg (85%) of nitrile **81** as a colorless foam: $^1$H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.56 (d, *J* = 7.4 Hz, 1 H), 7.27–7.24 (m, 2 H), 7.05–7.00 (m, 4 H), 5.93 (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.92 (dd, *J* = 17.8, 11.0 Hz, 1 H), 5.30 (d, *J* =

11.0 Hz, 2 H), 5.20–5.05 (m, 7 H), 4.95 (dd, *J* = 11.7, 6.7 Hz, 1 H), 4.36 (q, *J* = 5.1 Hz, 1 H), 4.33 (q, *J* = 5.2 Hz, 1 H), 3.96 (s, 1 H), 3.94 (s, 1 H), 3.52–3.46 (m, 1 H), 3.35 (s, 3 H), 3.34 (s, 3 H), 3.33–3.27 (m, 1 H), 3.06 (d, *J* = 7.6 Hz, 2 H), 3.03–2.97 (m, 1 H), 2.82–2.76 (m, 1 H), 2.74–2.72 (m, 2 H), 2.70 (d, *J* = 10.5 Hz, 1 H), 2.69 (d, *J* = 10.5 Hz, 1 H), 2.49–2.35 (m, 3 H), 2.30–2.25 (m, 1 H), 2.19 (s, 6 H), 2.07 (br s, 2 H), 1.99 (d, *J* = 10.5 Hz, 1 H), 1.98 (d, *J* = 10.5 Hz, 1 H), 1.16 (d, *J* = 5.1 Hz, 3 H), 1.11 (t, *J* = 7.0 Hz, 3 H), 0.89 (t, *J* = 7.1 Hz, 3 H), 0.74 (d, *J* = 5.2 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ 180.1, 180.0, 141.9, 141.7, 137.6, 137.5, 129.3, 129.2, 128.8, 128.6, 128.0, 127.9, 121.8, 120.0, 119.8, 115.74, 115.66, 109.34, 109.31, 100.2, 99.8, 71.6, 70.1, 68.5, 67.9, 63.9, 62.3, 62.2, 56.5, 56.4, 55.6, 55.44, 55.39, 55.36, 52.7, 40.8, 40.7, 38.61, 38.57, 30.2, 30.1, 28.0, 27.9, 20.7, 20.4, 15.2, 14.9; IR (film) 2932, 2231, 1717, 1611, 1488, 1468, 1353, 1084 cm$^{-1}$; MS (CI) *m/z* 451.2469 (M, 451.2471 calcd for $C_{26}H_{33}N_3O_4$), 378, 362, 347.

**(1*R**,2*R**,3*S**,4*R**,6*S**,7*R**,8*R**)-7-Cyano-4-hydroxy-9-methyl-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-aza-tricyclo[4.4.0.0$^{2,8}$]decane (82)**. *p*-Toluenesulfonic acid monohydrate (24.0 mg, 0.127 mmol) was added to a solution of **81** (52.0 mg, 0.115 mmol) in MeOH (5.8 mL) and $CH_2Cl_2$ (11.5 mL) at rt. The reaction was aged for a period of 1 h and then diluted with $CH_2Cl_2$ (10 mL) and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3×). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (1:3:16 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc → 1:1:18 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc gradient) to afford 43.1 mg (99%) of alcohol **82** as a colorless foam: $^1$H (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1 H), 7.30 (dd, *J* = 7.8, 1.0 Hz, 1 H), 7.09–7.06 (m, 2 H), 5.96 (dd, *J* = 18.0, 11.0 Hz, 1 H), 5.33 (d, *J* = 11.0 Hz, 1 H), 5.18 (d, *J* = 18.0 Hz, 1 H), 5.14 ($AB_q$, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 37.1 Hz, 2 H), 5.12–5.07 (m, 1 H), 4.02 (s, 1 H), 3.29 (s, 3 H), 3.06 (d, *J* = 7.6 Hz, 1 H), 2.75 (dt, *J* = 7.6, 4.8 Hz, 1 H), 2.70 (d, *J* = 10.6 Hz, 1 H), 2.38–2.29 (m, 2 H), 2.20 (s, 3 H), 2.13 (s, 1 H), 2.01 (d, *J* = 10.6 Hz, 1 H), 1.70 (br s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.8, 142.4, 137.8, 128.6, 128.2, 127.6, 122.0, 119.8, 115.7, 110.0,

71.5, 68.5, 65.3, 63.9, 56.4, 56.2, 54.7, 52.8, 40.9, 38.7, 32.0, 28.1; IR (film) 3456 (br), 2934, 2233, 1718, 1611, 1488, 1467, 1352, 1084 $cm^{-1}$; MS (CI) *m/z* 379.1882 (M, 379.1896 calcd for $C_{22}H_{25}N_3O_3$), 348.

**(±)-*N*-Methoxymethyl-17-oxogelsemine (83)**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (24 μL, 0.16 mmol) was added to a solution of alcohol **82** (20.0 mg, 53 μmol) and toluene (2.2 mL). The reaction mixture was heated to 110 °C for 6 h, and an additional 24 μL of DBU was added. Heating was continued for an additional 3 h, and then the reaction mixture was cooled to rt and diluted with $CH_2Cl_2$ (5 mL) and quenched with a saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic phases were concentrated and silica gel (100 mg) and $CH_2Cl_2$ (4 mL) were added to the resulting crude residue. The resulting mixture was allowed to stir for 15 h at rt, and then 1 mL of MeOH was added. Stirring was continued for an additional 1 hr and then the reaction mixture was filtered to remove the silica gel (wash with a 10% MeOH/$CH_2Cl_2$ solution). The filtrate was concentrated and the crude residue was purified by chromatography (1:3:16 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc) to afford 16.1 mg (80%) of lactone **83** as a white film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.25 (d, *J* = 7.7 Hz, 1 H), 7.09 (dd, *J* = 7.7, 1.1 Hz, 1 H), 7.02 (d, *J* = 7.7 Hz, 1 H), 6.25 (dd, *J* = 17.8, 11.0 Hz, 1 H), 5.19 (dd, *J* = 11.0, 0.8 Hz, 1 H), 5.11 ($AB_q$, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 51.2 Hz, 2 H), 5.00 (dd, *J* = 17.8, 0.8 Hz, 1 H), 4.37 (br s, 1 H), 3.59 (d, *J* = 1.2 Hz, 1 H), 3.34 (dd, *J* = 7.7, 1.1 Hz, 1 H), 3.32 (s, 3 H), 3.15 (dd, *J* = 14.5, 2.7 Hz, 1 H), 3.07 (d, *J* = 9.9 Hz, 1 H), 2.60 (ap t, *J* = 6.6 Hz, 1 H), 2.30 (s, 3 H), 2.15 (s, 1 H), 2.08 (d, *J* = 9.9 Hz, 1 H), 1.89 (ddd, *J* = 14.5, 5.8, 2.7 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.8, 172.2, 141.1, 137.4, 129.1, 128.7, 127.5, 123.3, 113.5, 109.6, 74.9, 71.3, 68.6, 65.3, 56.2, 53.9, 53.6, 52.6, 42.1, 38.4, 38.0, 26.4; IR (film) 2926, 1724, 1610, 1488, 1466, 1345, 1252, 1077 $cm^{-1}$; MS (CI) *m/z* 380.1722 (M, 380.1736 calcd for $C_{22}H_{24}N_2O_4$), 349, 337, 305.

**(±)-17-oxogelsemine (88)**. Concentrated HCl (0.68 mL) was added to a solution of lactone **83** (11.3 mg, 29.7 μmol) and ethylene glycol dimethyl ether (DME, 3.4 mL). The resulting mixture was heated at 55 °C for 3.25 h and then cooled to rt, diluted with $CH_2Cl_2$ (5

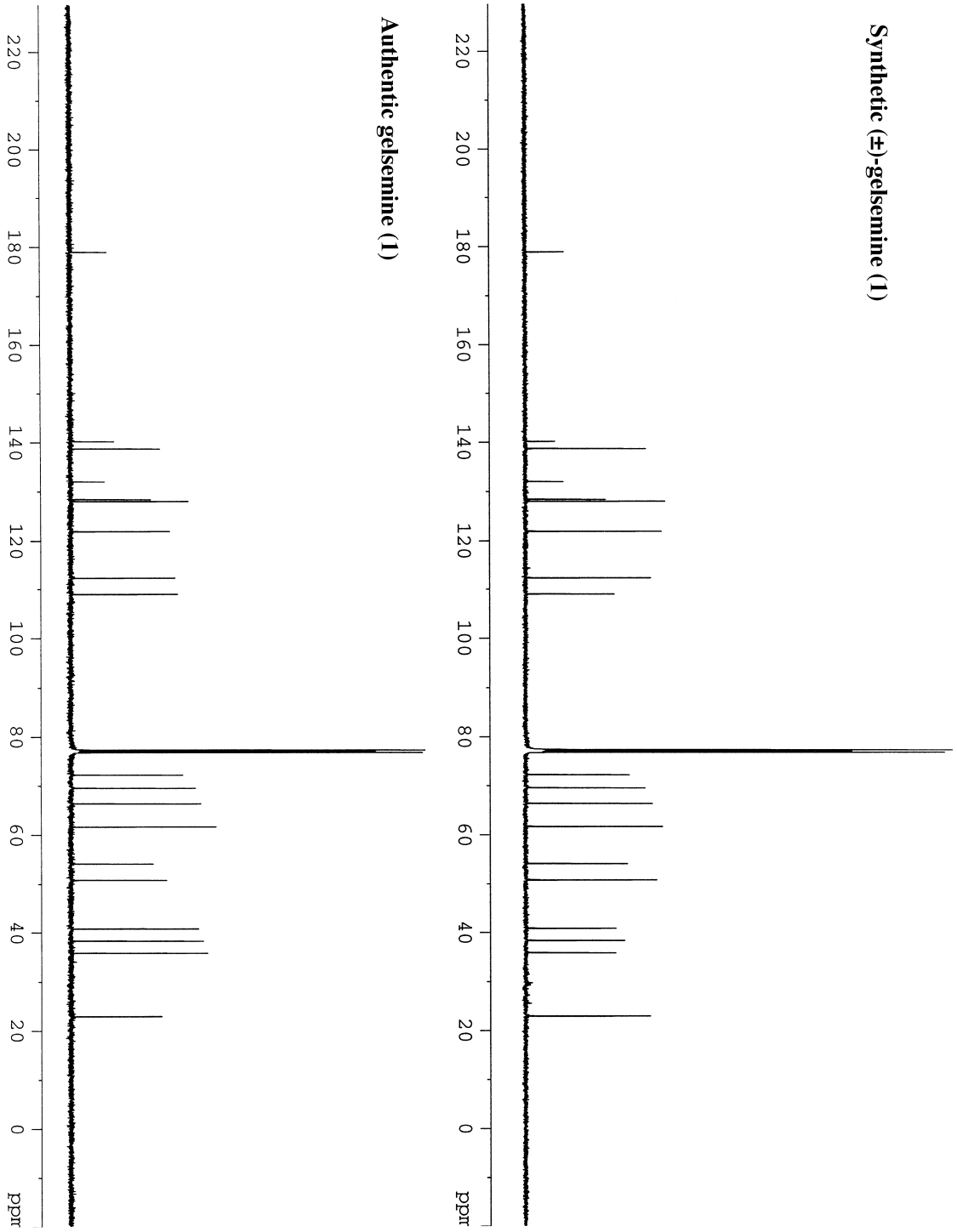
mL) and quenched with saturated aqueous $NaHCO_3$ (3 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic extracts were dried ($Na_2SO_4$), filtered, and concentrated. Methanol (3.4 mL) and *i*$Pr_2NEt$ (60 μL, 0.34 mmol) were added to the crude residue and the resulting mixture was heated at 55 °C for 20 h. The reaction mixture was then allowed to cool to rt and concentrated. The crude residue was purified by preperative TLC (1:1:18 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc) to afford 9.0 mg (90%) of oxindole **88** as a white solid: mp = 268–270 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.85–7.75 (m, 1 H), 7.23 (ap t, *J* = 7.1 Hz, 2 H), 7.02 (td, *J* = 7.7, 0.9 Hz, 1 H), 6.83 (d, *J* = 7.7 Hz, 1 H), 6.30 (dd, *J* = 17.8, 11.1 Hz, 1 H), 5.17 (d, *J* = 11.1 Hz, 1 H), 4.99 (dd, *J* =17.8, 0.7 Hz, 1 H), 4.40 (s, 1 H), 3.56 (d, *J* = 1.0 Hz, 1 H), 3.34 (d, *J* = 7.1 Hz, 1 H), 3.12 (dd, *J* = 14.5, 2.6 Hz, 1 H), 3.09 (d, *J* = 9.9 Hz, 1 H), 2.57 (t, *J* = 6.5 Hz, 1 H), 2.30 (s, 3 H), 2.19 (s, 1 H), 2.09 (d, *J* = 9.9 Hz, 1 H), 1.87 (ddd, *J* = 14.5, 5.8, 2.6 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 176.9, 172.3, 139.9, 137.3, 129.9, 129.0, 127.8, 122.7, 113.7, 109.6, 74.7, 68.6, 65.3, 53.8, 53.3, 52.5, 42.1, 38.4, 38.2, 26.4; IR (film) 3284 (br), 2924, 1720, 1618, 1473, 1325, 1255, 1165, 1078 $cm^{-1}$; MS (CI) *m*/*z* 336.1487 (M, 336.1474 calcd for $C_{20}H_{20}N_2O_3$), 309, 294.

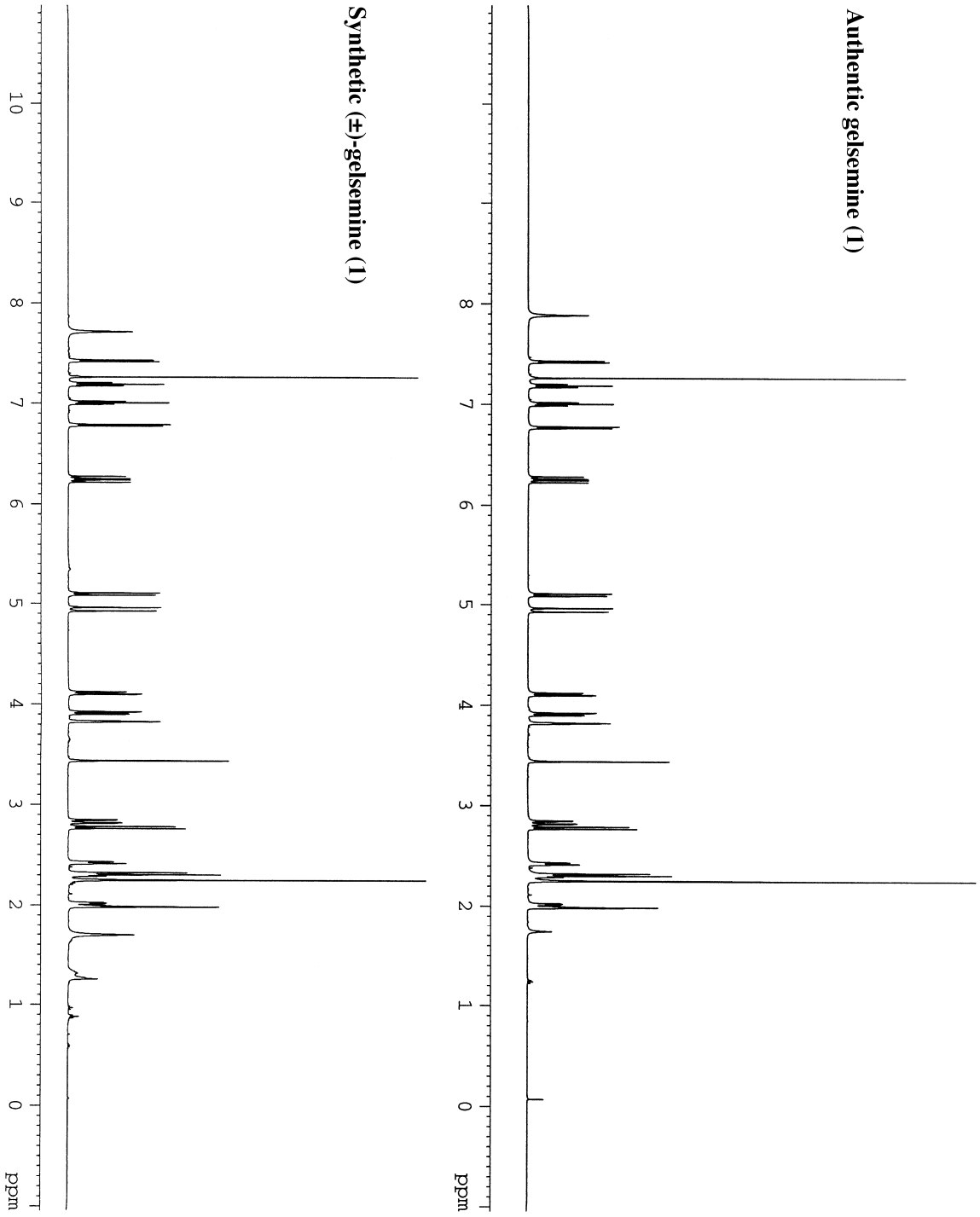
**Preparation of (±)-gelsemine (1)**. Diisobutylaluminum hydride (375 μL, 1 M in toluene, 0.375 mmol) was added to a solution of oxindole **88** (12.6 mg, 37.5 μg) and toluene (5.35 mL) at 0 °C. The reaction mixture was allowed to slowly warm to rt over a period of 3 h. The reaction was quenched with a saturated aqueous solution of Rochelle's salt and the resulting mixture was allowed to stir for 30 min. $CH_2Cl_2$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3×) and the combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated. The crude residue was used without purification. Data for crude lactol **89**: $^1$H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.93 (d, *J* = 7.5 Hz, 1 H), 7.38 (d, *J* = 7.7 Hz, 1 H), 7.34 (br s, 2 H), 7.23–7.15 (m, 2 H), 7.05-6.99 (m, 2 H), 6.78 (t, *J* = 7.0 Hz, 2 H), 6.24 (dd, *J* = 17.8, 11.0 Hz, 1 H), 6.23 (dd, *J* = 17.8, 11.0 Hz, 1 H), 5.55 (d, *J* = 2.0 Hz, 1 H), 5.48 (d, *J* = 2.4 Hz, 1 H), 5.12 (d, *J* = 11.0 Hz, 2 H), 4.97 (dd, *J* = 17.8, 1.1 Hz, 1 H), 4.96 (dd, *J* = 17.8, 1.0 Hz, 1 H), 3.95–3.92 (m, 2 H), 3.85 (br s, 1 H), 3.42 (s, 1 H), 2.86 (dd, *J* = 13.9, 2.9

Hz, 2 H), 2.83 (d, *J* = 10.3 Hz, 2 H), 2.69–2.65 (m, 2 H), 2.48 (dd, *J* = 13.8, 2.9 Hz, 2 H), 2.47 (dd, *J* = 13.8, 2.9 Hz, 2 H), 2.45–2.38 (m, 2 H), 2.30–2.26 (s, 6 H), 2.02 (s, 2 H), 1.91 (ddd, *J* = 14.4, 5.8, 2.9 Hz, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ 178.6, 178.4, 140.2, 140.0, 138.3, 138.2, 131.7, 131.6, 128.1, 128.0, 127.9, 122.1, 121.8, 112.6, 112.5, 109.2, 108.8, 92.5, 90.5, 71.5, 69.1, 67.9, 67.5, 66.0, 65.8, 54.3, 54.0, 53.6, 53.4, 51.1, 50.6, 41.24, 41.18, 40.3, 39.9, 34.1, 34.0, 23.0, 22.9; IR (film) 3274 (br), 2923, 1704, 1614, 1470, 1322, 1234, 1058 cm$^{-1}$; MS (CI) *m/z* 338.1636 (M, 338.1630 calcd for $C_{20}H_{22}N_2O_3$), 320, 249.

Trifluoroacetic acid (2.0 mL) and triethylsilane (2.0 mL) were added to a solution of the crude lactol **89** prepared above in $CH_2Cl_2$ (5.0 mL). The reaction mixture was heated to 45 °C in a sealable reaction vessel for 15 h and then allowed to cool to rt. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL) and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (5% $CHCl_3$ (saturated with $NH_3$)/EtOAc → 5% MeOH/$CH_2Cl_2$, gradient) to afford 7.8 mg (65% for 2 steps) of (±)-gelsemine **1** as a white solid: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.00 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 6.24 (dd, *J* = 17.8, 11.0 Hz, 1 H), 5.09 (dd, *J* = 11.0, 1.2 Hz, 1 H), 4.94 (dd, *J* = 17.8, 1.2 Hz, 1 H), 4.11 (dd, *J* = 11.0, 2.2 Hz, 1 H), 3.91 (dd, *J* = 11.0, 1.9 Hz, 1 H), 3.83 (s, 1 H), 3.43 (s, 1 H), 2.83 (dd, *J* = 14.4, 2.8 Hz, 1 H), 2.77 (d, *J* = 10.3, 1 H), 2.42 (br d, *J* = 8.3 Hz, 1 H), 2.31 (d, *J* = 10.3 Hz, 1 H), 2.30 (br d, *J* = 14.2 Hz, 1 H), 2.24 (s, 3 H), 2.00 (ddd, *J* = 14.4, 5.7, 2.8 Hz, 1 H), 1.98 (s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.9, 140.1, 138.7, 132.0, 128.4, 128.0, 121.9, 112.2, 108.9, 72.2, 69.5, 66.3, 61.6, 54.1, 50.7, 40.8, 38.3, 35.8, 22.9; IR (film) 3248, 3078, 2921, 2856, 1711, 1617, 1472, 1323, 1233, 1100 cm$^{-1}$; MS (CI) *m/z* 322.1669 (M, 322.1681 calcd for $C_{20}H_{22}N_2O_2$), 279, 251.

**B. $^1$H and $^{13}$C NMR Comparisons of Synthetic (±)-Gelsemine with an Authentic sample of Gelsemine.**


Synthetic (±)-gelsemine (1)
Authentic gelsemine (1)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Authentic gelsemine (1)
Synthetic (±)-gelsemine (1)
10
9
8
7
6
5
4
3
2
1
0
ppm

**C. Preliminary Studies.**

**(1*R**,2*R**,6*S**,7*R**,8*S**)-7-Bromo-3-trifluoromethanesulfonyloxy-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (8)**. *n*-BuLi (1.0 mL, 2.40 M in hexane, 2.40 mmol) was added to a solution of diisopropylamine (0.39 mL, 2.80 mmol) in dry THF (5 mL) at 0 °C. The solution was maintained at 0 °C for 10 min and then cooled to –78 °C. A solution of ketone **5** (617 mg, 1.96 mmol) in THF (5 mL) was added to the solution prepared above. The reaction was maintained at –78 °C for 1 h and then a solution of *N*-phenyltrifluoromethanesulfonimide **7** (1.05 g, 2.94 mmol) in THF (5 mL) was added dropwise. This solution was maintained at –78 °C for 10 min and then allowed to warm to 0 °C. After 1 h at 0 °C the reaction was quenched by the careful addition of saturated aqueous $NaHCO_3$ (20 mL). The resulting mixture was extracted with $CH_2Cl_2$ (3 × 30 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by chromatography (4:1:0.05 → 1:1:0.05 hexanes/$Et_2O$/$Et_3N$ gradient) afforded 680 mg (78%) of vinyl triflate **8** as a colorless oil, which was used immediately in the following steps: $^1$H NMR (300 MHz, $CDCl_3$)[5] δ 5.88 (dd, *J* = 17.7, 11.0 Hz, 1 H), *5.75* (br s, 1 H), 5.31 (d, *J* = 11.0 Hz, 1 H), *5.26* (d, *J* = 17.6 Hz, 1 H), 5.20 (d, *J* = 17.6 Hz), 4.86 (dd, *J* = 3.1, 1.8 Hz), *4.73* (dd, *J* = 3.2, 1.9 Hz, 1 H), 4.16–4.14 (m), *4.12–4.10* (m, 1 H), 3.75 (s), *3.74* (s, 3 H), 3.59 (d, *J* = 10.6 Hz), *3.54* (d, *J* = 11.3 Hz, 1 H), *3.38* (d, *J* = 11.0 Hz, 1 H), 3.36 (d, *J* = 10.6 Hz), *2.66* (s, 1 H), 2.64 (s), 2.54–2.52 (m), *2.49–2.47* (m, 1 H), *2.29–2.27* (m, 1 H), 2.22 (dd, *J* = 4.7, 3.0 Hz, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$)[5] δ 154.8, 154.5, 144.7, 132.6, 132.5, 120.5, 118.5, 118.3, 117.8, 117.6, 116.3, 66.9, 66.6, 53.8, 53.8, 52.7, 52.5, 52.3, 52.2, 52.1, 51.4, 51.2, 50.8, 49.9, 29.9; IR (film) 1705, 1702 cm$^{-1}$; MS (CI) *m*/*z* 445.9904 (MH, 445.9885 calcd for $C_{14}H_{15}BrF_3NO_5S$).

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-(2-bromophenylcarbamoyl)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (9)**. Carbon monoxide was bubbled through a solution of vinyl triflate **8** (530 mg, 1.19 mmol) and freshly distilled 2-bromoaniline (3.0 g, 17.8 mmol) in dry DMF (10 mL) at rt for a period of 5 min.

Tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) was added and the resulting mixture was heated to 80 °C for 1h. A second batch of tetrakis(triphenylphosphine)palladium (14 mg, 0.012 mmol) was then added and the resulting mixture was heated to 80 °C for 10 h with continuous bubbling of carbon monoxide through the solution. The reaction mixture was then allowed to cool to rt and partitioned between $CH_2Cl_2$ (20 mL) and brine (20 mL). The aqueous phase was extracted with $CH_2Cl_2$ (2 × 20 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by chromatography (2:1 → 1:1 hexanes/$Et_2O$ gradient) afforded 439 mg (74%) of the tricyclic amide **9** as a white solid: $^1$H NMR (300 MHz, $CDCl_3$)[5] δ 8.38 (d, *J* = 8.3 Hz, 1 H), *8.09* (br s, 1 H), 8.06 (br s), 7.55 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 7.83 Hz, 1 H), 7.02 (t, *J* = 7.7 Hz, 1 H), 6.61 (br s, 1 H), *5.86* (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.84 (dd, *J* = 17.5, 10.9 Hz), 5.24 (d, *J* = 10.9 Hz, 1 H), *5.16* (d, *J* = 17.6 Hz, 1 H), 5.15 (d, *J* = 17.7 Hz), 4.77 (br s), *4.66* (br s, 1 H), 4.12 (s), *4.09* (s, 1 H), 3.74 (s), *3.72* (s, 3 H), *3.60* (d, *J* = 10.0 Hz, 1 H), 3.56 (d, *J* = 12.5 Hz), *3.37* (d, *J* = 10.2 Hz, 1 H), 3.36 (d, *J* = 10.5 Hz), 3.20 (br s), *3.18* (br s, 1 H), 2.63–2.57 (m, 1 H), *2.42–2.41* (m, 1 H), 2.36–2.34 (m), 2.32 (br s, 1 H); $^{13}$C NMR (75 MHz, $CDCl_3$)[5] δ 164.3, 164.2, 154.9, 154.5, 135.2, 133.5, 133.4, 132.4, 132.2, 128.5, 128.3, 125.4, 125.3, 121.6, 121.5, 117.8, 117.7, 113.5, 104.1, 67.5, 67.1, 54.9, 52.9, 52.8, 52.5, 52.4, 50.7, 49.9, 47.4, 46.8, 32.9, 32.8; IR (KBr) 3400, 3319, 1676, 1683, 1700, 1704 $cm^{-1}$; MS (CI) *m/z* 496.9904 (MH, 496.9898 calcd for $C_{20}H_{20}Br_2N_2O_3$).

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-[(2-bromophenyl)methylcarbamoyl]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (10a).** Sodium hydride (20 mg, 60% in oil) was added to a solution of amide **9a** (36 mg, 73 μmol) in THF (2 mL) at rt. The reaction mixtrue was stirred for a period of 40 min at which time methyl iodide (50 μL, 0.8 mmol) was added. The reaction mixture was stirred for an additional 3 h and then diluted with $CH_2Cl_2$ and quenched with saturated aqueous $NaHCO_3$. The layers were partitioned and the aqueous phase was extracted with $CH_2Cl_2$ (3×). The combined organic phases were dried ($Na_2SO_4$), concentrated and purified by chromatography to afford 28.5 mg (77%) of product **10a** as a white solid: mp = 171–172 °C; $^1$H NMR (500 MHz, $CDCl_3$, mixtures of carbamate and

amide rotomers) δ 7.6–7.5 (m, 1 H), 7.3–7.2 (m, 2 H), 7.17–7.03 (m, 2 H), 5.7 and 5.55 (br s, 1 H), 5.53–5.30 (m, 1 H), 5.10–4.95 (m, 1 H), 4.4–4.2 (m, 1 H), 3.70–3.55 (m, 4 H), 3.45–3.35 (m, 1 H), 3.18–3.10 (m, 4 H), 2.9–2.65 (m, 1 H), 2.1–2.0 (m, 1 H), 1.96 (br s, 1 H), 1.9–1.7 (m, 1 H); IR ($CHCl_3$) 1693 $cm^{-1}$; MS (EI) *m/z* 507.9984 (M, 507.9998 calcd for $C_{21}H_{22}Br_2N_2O_3$), 433, 431, 429, 351.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-[(2-bromophenyl)-(2-trimethylsilylethoxymethyl)-carbamoyl]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (10b)**. Sodium hydride (52 mg, 60% in oil, 1.3 mmol) was added to a solution of amide **9a** (430 mg, 0.867 mmol) in dry THF (15 mL). The resulting mixture was stirred at rt for 1 h and 2–(trimethylsilyl)–ethoxymethyl chloride (0.31 mL, 1.75 mmol) was added. The mixture was stirred for an additional 4 h at rt and then quenched by the careful addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was then extracted with $Et_2O$ (20 mL) followed by $CH_2Cl_2$ (3 × 20 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by radial chromatography (1:1 hexanes/$Et_2O$, 4 mm plate) afforded 429 mg (79%) of **10b** as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$, mixture of amide and carbamate rotomers, intergration were omitted on purpose) δ 7.7–7.5 (m), 7.4–7.15 (m), 6.95–9.90 (m), 6.6–6.5 (m), 5.9–5.4 (m), 5.2–5.0 (m), 4.6–4.3 (m), 3.2–3.1 (m), 2.9–2.8 (m), 2.4–1.8 (m), 1.0–0.8 (m), 0.0 (s, 9H); IR (film) 1706 $cm^{-1}$; MS (CI) *m/z* 625.0724 (MH, 625.0732 calcd for $C_{26}H_{34}Br_2N_2O_4Si$), 511, 509, 507, 349.

**(1*R**,2*S**,3*S**,6*S**,7*R**,8*S**)-7-Bromo-3-(spiro-3-methyl-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (11a) and (1*R**,2*S**,3*R**,6*S**,7*R**,8*S**)-7-Bromo-3-(spiro-3-methyl-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (12a).** Cyclization was conducted exactly as described for **10b** and the product stereoisomers were separated on silica gel (4:1 hexane-EtOAc). Data for **11a**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.40–7.30 (m, 1 H), 7.15–7.05 (m, 1 H), 6.88 (d, *J* = 7.7 Hz, 1 H), 6.84 (d, *J* = 7.8 Hz, 1 H), 6.75 (ddd, *J* = 17.7, 11.1,

1.2 Hz, 1 H), *6.64* (dd, *J* = 9.1, 7.7 Hz, 1 H), 6.63 (dd, *J* = 9.1, 7.6 Hz), 5.40 (dd, *J* = 9.1, 2.5 Hz, 1 H), 5.26 (dd, *J* = 11.1, 5.2 Hz, 1 H), 5.04 (t, *J* = 18.3 Hz, 1 H), 4.67 (d, *J* = 3.4 Hz), *4.65* (d, *J* = 3.4 Hz, 1 H), 4.53 (dd, *J* = 3.6, 1.5 Hz), *4.37* (dd, *J* = 3.5, 1.5 Hz, 1 H), *3.76* (d, *J* = 10.7 Hz, 1 H), 3.70 (d, *J* = 10.3 Hz), 3.70 (s), 3.69 (s, 3 H), *3.39* (d, *J* = 10.9 Hz, 1 H), 3.37 (d, *J* = 10.8 Hz), 3.19 (s, 3 H), 3.18 (dd, *J* = 7.5, 2.2 Hz, 1 H), 2.72 (dd, *J* = 7.5, 2.2 Hz), *2.46* (d, *J* = 1.1 Hz, 1 H), 2.44 (d, *J* = 1.0 Hz); IR ($CDCl_3$) 1703 $cm^{-1}$; MS (CI) *m/z* 429 (MH), 152. Data for **12a**: $^1H$ NMR (500 MHz, $CDCl_3$)[5] δ *7.38* (d, *J* =7.4 Hz, 1 H), 7.34 (d, *J* = 7.3 Hz), 7.29–7.24 (m, 1 H), 7.02–6.98 (m, 1 H), *6.84* (d, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 6.3 Hz), 6.63 (t, *J* = 8.3 Hz, 1 H), *6.15* (dd, *J* = 17.8, 11.2 Hz, 1 H), 6.12 (dd, *J* = 16.9, 11.0 Hz), 5.43 (d, *J* = 10.9 Hz), *5.42* (d, *J* = 11.0 Hz, 1 H), 5.30 (d, *J* = 8.2 Hz), *5.29* (d, *J* = 8.9 Hz, 1 H), *5.21* (d, *J* = 17.8 Hz, 1 H), 5.18 (d, *J* = 17.5 Hz), 5.08 (d, *J* = 3.5 Hz), *5.04* (d, *J* = 3.5 Hz, 1 H), 4.83 (d, *J* = 3.3 Hz), *4.72* (d, *J* = 3.2 Hz, 1 H), 3.69 (s, 3 H), *3.64* (d, *J* = 10.8 Hz, 1 H), 3.58 (d, *J* = 10.6 Hz), *3.32* (d, *J* = 10.8 Hz, 1 H), 3.29 (d, *J* = 10.7 Hz), *3.23* (s, 3 H), 3.20 (s), 2.70 (dd, *J* = 7.4, 1.7 Hz, 1 H), *2.39* (s, 1 H), 2.34 (s); IR ($CDCl_3$) 1707 $cm^{-1}$; MS (CI) *m/z* 429 (MH).

**(1*R**,2*S**,3*S**,6*S**,7*R**,8*S**)-7-Bromo-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (11b) and (1*R**,2*S**,3*R**,6*S**,7*R**,8*S**)-7-Bromo-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (12b)**. Tetrakis(triphenylphosphine)palladium (153 mg, 0.13 mmol) was added to a solution of **10b** (415 mg, 0.663 mmol) and triethylamine (2.77 mL, 19.9 mmol) in THF (10 mL), in a thick walled resealable tube, under an argon atmosphere. The tube was sealed and heated to 110 °C for 2.25 h. The reaction was then allowed to cool to rt and poured into brine (10 mL) and extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($K_2CO_3$), filtered and concentrated. Purification of the residue by chromatography (2:1 hexane/$Et_2O$) afforded 298 mg (83%) of oxindoles **11b** and **12b** as a 1:1 mixture, which could not be separated; IR ($CHCl_3$) 1700, 1698 $cm^{-1}$; MS (CI) *m/z* 547.1442 (MH, 547.1450 calcd for $C_{26}H_{33}BrN_2O_4Si$), 429, 427,

349, 263; NMR spectra were too complex to analyze as two stereoisomers and two amide conformational isomers were present.

**(1*R**,2*R**,3*R**,6*R**,7*S**,8*R**)-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatetracyclo[4.4.0.0$^{2,8}$.0$^{7,9}$]dec-4-ene (15) and (1*R**,2*R**,3*S**,6*R**,7*S**,8*R**)-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatetracyclo[4.4.0.0$^{2,8}$.0$^{7,9}$]dec-4-ene (16)**. NaCN (285 mg, 5.85 mmol) was added to a solution of **11b/12b** (319 mg, 0.585 mmol) in dry DMSO (5 mL). This mixture was heated to 140 °C for 20 h and the resulting solution was allowed to cool to rt. The solvent was removed *in vacuo* and the residue partitioned between EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic phases were washed with brine, dried ($K_2CO_3$) and concentrated. The residue was purified by radial chromatography (1:1 hexanes/EtOAc, 4mm plate) to give 106.7 mg (45%) of the desired oxindole **15** (high Rf) and 94.8 mg (40%) of the oxindole epimer **16** (low Rf). Data for **15**: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.28 (dt, *J* = 7.7, 1.2 Hz, 1 H), 7.18 (dd, *J* = 7.3, 0.5 Hz, 1 H), 7.07 (dt, *J* = 7.7, 0.7 Hz, 1 H), 7.05 (d, *J* = 7.7 Hz, 1 H), 6.62 (dd, *J* = 17.7, 10.8 Hz, 1 H), 6.20 (dd, *J* = 9.5, 6.9 Hz, 1 H), 5.35 (dd, *J* = 9.5, 1.6 Hz, 1 H), 5.19 (dd, J = 10.8, 1.5 Hz, 1 H), 5.13 ($AB_q$, $J_{AB}$ = 10.9 Hz, $\Delta\nu_{AB}$ = 20.2 Hz, 2 H), 5.00 (dd, *J* = 17.6, 1.4 Hz, 1 H), 3.56 (ddd, *J* = 10.4, 7.3, 1.7 Hz, 2 H), 2.83 (d, *J* = 10.2 Hz, 1 H), 2.79 (br s, 1 H), 2.69 (d, *J* = 10.2 Hz, 1 H), 2.44 (dd, *J* = 6.8, 1.1 Hz, 1 H), 2.39 (br s, 1 H), 2.03 (s, 1 H), 0.92–0.88 (m, 2 H), –0.03 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 177.7, 141.9, 134.6, 130.3, 128.8, 128.6, 125.7, 125.4, 122.4, 114.2, 109.7, 69.4, 65.9, 62.6, 52.6, 48.4, 47.8, 43.7, 42.3, 37.8, 17.7, –1.5; IR ($CHCl_3$) 1720 cm$^{-1}$; MS (CI) *m/z* 407.2165 (MH, 407.2154 calcd for $C_{24}H_{30}N_2O_2Si$), 289. Characterization data for oxindole epimer **16**: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1 H), 7.21 (dt, *J* = 7.6, 1.0 Hz, 1 H), 7.03 (d, *J* = 7.7 Hz, 1 H), 7.00 (dt, *J* = 7.6, 0.8 Hz, 1 H), 6.26 (dd, *J* = 9.5, 6.7 Hz, 1 H), 6.06 (dd, *J* = 17.6, 10.7 Hz, 1 H), 5.35 (dd, *J* = 9.7, 1.1 Hz, 1 H), 5.32 (dd, J = 9.5, 1.6 Hz, 1 H), 5.18 (dd, *J* = 17.7, 0.9 Hz, 1 H), 5.15 ($AB_q$, $J_{AB}$ = 11.0 Hz, $\Delta\nu_{AB}$ = 59.5 Hz, 2 H), 3.61–3.56 (m, 2 H), 2.85 (br s, 1 H), 2.77 (d, *J* = 10.2 Hz, 1 H), 2.71 (dd, *J* = 3.8, 1.8 Hz, 1 H), 2.55 (dd, *J* = 1.8, 1.7 Hz, 1 H), 2.52 (d, *J* = 10.2 Hz, 1 H), 2.07 (s,

1 H), 0.95–0.87 (m, 2 H), –0.03 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 177.6, 141.0, 134.5, 131.9, 129.0, 128.3, 126.7, 125.2, 122.2, 117.5, 109.3, 69.5, 65.8, 64.0, 53.9, 49.2, 48.0, 43.6, 39.9, 36.8, 17.6, –1.6; IR ($CHCl_3$) 1717 cm$^{-1}$; MS (CI) *m/z* 407 (MH), 289, 117, 101, 91.

**(1*R**,2*R**,3*R**,6*S**,7*R**,8*R**)-7-Cyano-9-methyl-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (18) and (1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-7-Cyano-9-methyl-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (30)**. Methyl triflate (30 μL, 0.265 mmol) was added to a solution of aziridine **15** (106 mg, 0.261 mmol) in $CH_2Cl_2$ (1.5 mL) at rt. After 5 min the solvent was removed under a flow of argon, and the solid residue was dissolved in DMSO (5 mL). NaCN (64 mg, 1.31 mmol) was then added and the resulting suspension was heated to 90 °C with stirring for 1.5 h. The mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The residue was suspended in EtOAc and filtered through a plug of silica. The filtrate was concentrated and purified by radial chromatography (1:1 hexanes/EtOAc, 2mm plate) to afford ~2 mg of epimer **30**, diagnostic data $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29–7.22 (m, 1 H), 7.05 (t, *J* = 7.1 Hz, 1 H), 7.02 (t, *J* = 7.4 Hz, 1 H), 6.90 (d, *J* = 7.7 Hz, 1 H), 6.62 (d, *J* = 8.3 Hz, 1 H), 6.59 (dd, *J* = 17.9, 10.9 Hz, 1 H), 5.41 (d, *J* = 9.2 Hz, 1 H), 5.21 (d, *J* = 11.0 Hz, 1 H), 5.25–5.15 (m, 2 H), 4.97 (d, *J* = 17.7, 1 H), 3.6–3.5 (m, 2 H) 3.45 (s, 1 H), 3.32 (d, *J* = 4.2 Hz, 1 H), 3.18 (d, *J* = 11.3 Hz, 1 H), 2.75 (d, *J* = 7.2 Hz, 1 H), 2.68 (d, *J* = 11.3 Hz, 1 H), 2.37 (s, 1 H), 2.21 (s, 3 H) 0.95–0.86 (m, 2 H), –0.03 (s, 9 H); IR ($CDCl_3$) 1722 cm$^{-1}$, MS (EI) *m/z* 447.2340 (M, 447.2342 calcd for $C_{26}H_{33}N_3O_2Si$), and 98 mg (84%) of nitrile **18** as a white solid: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 1 H), 7.30 (t, *J* = 7.7 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 6.64 (dd, *J* = 17.8, 11.1 Hz, 1 H), 6.43 (dd, *J* = 9.4, 7.3 Hz, 1 H), 5.62 (dd, *J* = 9.6, 1.3 Hz, 1 H), 5.21 (d, *J* = 11.0 Hz, 1 H), 5.13 ($AB_q$, $J_{AB}$ = 10.1 Hz, $\Delta\nu_{AB}$ = 20.7 Hz, 2 H), 4.95 (d, J = 17.7 Hz, 1 H), 3.6–3.5 (m, 2 H), 3.53 (s, 1 H), 3.22 (d, *J* = 7.2 Hz, 1 H), 3.17 (d, *J* = 10.2 Hz, 1 H), 2.78 (dt, *J* = 7.2, 1.6 Hz, 1 H), 2.35 (s, 1 H), 2.23 (s, 3 H), 2.16 (d, *J* = 10.2 Hz, 1 H), 0.95–0.86 (m, 2 H), –0.03 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 177.5, 142.1, 137.9, 133.6, 129.1, 128.8, 126.7, 126.0, 123.2, 120.9, 114.3, 109.8, 70.7, 69.6, 66.1, 61.4, 54.8, 53.5,

53.4, 43.2, 38.5, 33.6, 17.7, –1.4; IR ($CHCl_3$) 1722 $cm^{-1}$; MS (EI) *m/z* 447.2313 (M, 447.2342 calcd for $C_{26}H_{33}N_3O_2Si$), 108.

**(1*R**,2*R**,3*R**,6*S**,7*R**,8*R**)-7-Cyano-9-methyl-3-(spiro-3-indoline)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (20)**. $LiAlH_4$ (0.5 mL, 1 M in $Et_2O$ , 0.5 mmol) was added to a solution of nitrile **18** (10 mg, 0.023 mmol) in $Et_2O$ (2.0 mL) at –78 °C. The solution was maintained at –78 °C for a period of 1 h and then quenched with excess MeOH. The mixture was allowed to warm to rt and 1 N HCl (0.5 mL) was added. The resulting mixture was allowed to stir for a period of 1 h and then basified by the addition of saturated aqueous $NaHCO_3$. The layers were partitioned and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($K_2CO_3$), filtered and concentrated to afford 5.5 mg (80%) of **19** as a white film. This material was homogeneous by TLC and capillary GC analysis and was not further purified: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.86 (d, *J* = 7.3 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 6.44 (dd, *J* = 9.2, 7.1 Hz, 1 H), 6.18 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.42 (d, *J* = 10.9 Hz, 1 H), 5.24 (d, *J* = 17.6 Hz, 1 H), 5.20 (d, *J* = 9.4 Hz, 1 H), 3.64 (s, 1 H), 3.27 (d, *J* = 7.3 Hz, 1 H), 3.09 (d, *J* = 10.3 Hz, 1 H), 2.79 (dt, *J* = 7.1, 1.4 Hz, 1 H), 2.25 (s, 3 H), 2.22 (d, *J* = 10.2 Hz, 1 H), 2.03 (s, 1 H); IR ($CHCl_3$) 1731 $cm^{-1}$; MS (CI) *m/z* 302 (MH), 279, 149, 108.

$LiAlH_4$ (0.3 mL, 1 M in $Et_2O$ , 0.3 mmol) was added to a solution of indolenine **19** (3.8 mg, 12 μmol) in $Et_2O$ (0.5 mL) at –20 °C. The solution was maintained at –20 °C for 1.5 h and then MeOH (0.5 mL) was added. The mixture was allowed to warm to rt and 1 N HCl (1.0 mL) was added. The resulting mixture was allowed to stir for a period of 1 h and then basified by the addition of saturated aqueous $NaHCO_3$. The layers were partitioned and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic phases were dried ($K_2CO_3$), filtered and concentrated. The residue was purified by chromatography (EtOAc) to afford 2 mg (53%) of **20** as a white film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.4 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 6.79 (t, *J* = 7.4 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 6.18 (dd, *J* = 9.4, 7.1 Hz, 1 H), 6.05 (dd, *J* = 17.7, 11.0 Hz, 1 H), 5.81 (d, *J* = 9.3 Hz, 1 H), 5.21 (d, *J* = 10.9 Hz, 1 H), 5.07 (d, *J* = 17.6 Hz,

1 H), 3.59 (d, *J* = 9.1 Hz, 1 H), 3.22 (d, *J* = 9.1 Hz, 2 H), 3.18 (s, 1 H), 3.16 (d, *J* = 10.1 Hz, 1 H), 3.11 (d, *J* = 6.8 Hz, 1 H), 2.70 (s, 1 H), 2.60 (t, *J* = 7.1 Hz, 1 H), 2.20 (s, 3 H), 2.06 (d, *J* = 10.1 Hz, 1 H); MS (CI) *m/z* 304 (MH), 108.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-7-Aminomethyl-9-methyl-3-(spiro-3-methyl-3-indoline)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (21)**. $AlH_3$ (0.40 mL, 0.65 M in THF, 0.26 mmol) was added to a solution of nitrile **18** (12.3 mg, 27 μmol) in THF (1 mL) at –78 °C. The solution was maintained at –78 °C for a period of 1 h and then the reaction mixture was allowed to warm to rt. After a period of 3.5 h at rt, the reaction was quenched by careful addition of MeOH (0.5 mL) followed by 1 N HCl (0.5 mL). The resulting mixture was then basified by the addition of saturated aqueous $NaHCO_3$. The layers were partitioned and the aqueous layer was extracted with $CH_2Cl_2$ (3×). The combined organic phases were dried ($K_2CO_3$), filtered and concentrated to afford 10 mg (93%) of **21**, which was not further purified: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J* = 7.6 Hz, 1 H), 6.99 (d, *J* = 7.4 Hz, 1 H), 6.65 (t, *J* = 7.5 Hz, 1 H), 6.48 (d, *J* = 7.8 Hz, 1 H), 6.09 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.88 (dd, *J* = 9.3, 7.0 Hz, 1 H), 5.68 (d, *J* = 9.3 Hz, 1 H), 5.15 (d, *J* = 10.9 Hz, 1 H), 5.07 (d, *J* = 17.6 Hz, 1 H), 3.41 (d, *J* = 8.8 Hz, 1 H), 3.12 (dd, *J* = 12.0, 9.5 Hz, 1 H), 2.99–2.95 (m, 1 H), 2.96 (d, *J* = 9.8 Hz, 1 H), 2.91 (d, *J* = 8.8 Hz, 1 H), 2.86 (s, 1 H), 2.69 (s, 3 H), 2.52 (s, 1 H), 2.44 (t, *J* = 6.8 Hz, 1 H), 2.29 (d, *J* = 10.1 Hz, 1 H), 2.24 (s, 3 H), 2.21–2.17 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.3, 138.7, 134.5, 132.1, 128.0, 127.9, 124.4, 117.5, 115.9, 107.7, 68.9, 67.8, 62.1, 55.2, 54.7, 49.3, 47.7, 43.6, 42.5, 39.6, 35.7. MS (CI) *m/z* 322.2262 (MH, 322.2283 calcd for $C_{21}H_{28}N_3$).

**(1*R**,2*R**,3*R**,6*S**,7*R**,8*R**)-7-Cyano-9-methyl-3-(spiro-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (22)**. A suspension of nitrile **18** (47.4 mmol, 0.106 mmol) in 6 N HCl (3 mL) was stirred at rt for 20 h. The resulting solution was cooled to 0 °C and basified to pH 14 with 5 N KOH. The resulting cold mixture was extracted with $CH_2Cl_2$ (3 × 15 mL) and the combined organic phases dried ($K_2CO_3$), filtered and concentrated. Purification of the residue by chromatography (2:1 EtOAc/hexanes) afforded 26.5 mg (80%) of **22** as a white solid: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.78 (d, *J* = 7.5 Hz, 1 H), 7.25 (dt, *J* = 7.7, 1.1, Hz, 1 H),

7.09 (dt, *J* = 7.7, 1.0 Hz, 1 H), 6.86 (dd, *J* = 7.7, 0.5 Hz, 1 H), 6.64 (dd, *J* = 17.7, 11.0 Hz, 1 H), 6.43 (dd, *J* = 9.4, 7.2 Hz, 1 H), 5.67 (dd, *J* = 9.4, 1.4 Hz, 1 H), 5.19 (dd, *J* = 11.0, 0.9 Hz, 1 H), 4.96 (dd, *J* = 17.7, 1.0 Hz, 1 H), 3.51 (s, 1 H), 3.22 (d, *J* = 7.2 Hz, 1 H), 3.19 (d, *J* = 10.2 Hz, 1 H), 2.77 (dt, *J* = 7.3, 1.7 Hz, 1 H), 2.44 (s, 1 H), 2.24 (s, 3 H), 2.17 (d, *J* = 10.2 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.4, 140.8, 137.9, 133.7, 130.3, 128.8, 126.5, 126.3, 122.8, 121.0, 114.4, 109.8, 70.7, 61.4, 54.7, 53.6, 53.0, 43.2, 38.6, 33.7; IR ($CHCl_3$) 3434, 1725 cm$^{-1}$; MS (CI) *m/z* 318.1594 (MH, 318.1606 calcd for $C_{20}H_{19}N_3O$).

**(1*R**,2*R**,3*R**,6*S**,7*R**,8*R**)-7-Cyano-9-methyl-3-(spiro-3-triispopropylsilyl-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (23)**. Triisopropylsilyl triflate (49 μL, 0.18 mmol) was added to a solution of nitrile **22** (29 mg, 91 μmol) and Hünig's base (48 μL, 0.27 mmol) in $CH_2Cl_2$ (2 mL) at rt. The resulting solution was maintained at rt for 2.5 h, then poured into saturated aqueous $NaHCO_3$ (5 mL), and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($K_2CO_3$), filtered and concentrated. Purification of the residue by chromatography (4:1 hexanes/$Et_2O$) afforded 32 mg (80%) of **23** as a clear oil: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.76 (d, *J* = 7.5 Hz), *7.73* (d, *J* = 7.5 Hz, 1 H), 7.19 (t, *J* = 8.1 Hz, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 7.04 (d, *J* = 7.5 Hz, 1 H), 6.56 (dd, *J* = 17.6, 11.0 Hz), *6.55* (dd, *J* = 17.7, 10.9 Hz, 1 H), *6.41* (dd, *J* = 9.3, 7.2 Hz, 1 H), 6.34 (dd, *J* = 9.3, 7.2 Hz), *5.66* (dd, *J* = 9.5, 1.1 Hz, 1 H), 5.48 (dd, *J* = 9.2, 0.9 Hz), *5.15* (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 11.0 Hz), *4.94* (d, *J* = 18.2 Hz, 1 H), 3.60 (s), *3.43* (s, 1 H), 3.20 (d, *J* = 6.5 Hz), *3.17* (d, *J* = 7.3 Hz, 1 H), *3.14* (d, *J* = 10.2 Hz, 1 H), *2.74* (td, *J* = 7.3, 1.4 Hz, 1 H), 2.70 (td, *J* = 7.3, 1.4 Hz), *2.36* (s, 1 H), 2.24 (s), *2.22* (s, 3 H), 2.20 (s), 2.16–2.14 (m), *2.13–2.10* (m, 1 H), *1.79–1.75* (m, 3 H), 1.52–1.48 (m), *1.16* (d, *J* = 7.5 Hz, 9 H), *1.13* (d, *J* = 7.5 Hz, 9 H), 1.09 (d, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 184.7, 180.0, 146.3, 137.9, 137.7, 133.3, 132.5, 132.1, 128.5, 128.4, 127.8, 127.0, 125.9, 124.9, 123.5, 122.2, 121.1, 118.5, 114.9, 114.4, 112.6, 71.4, 70.8, 61.6, 61.3, 57.1, 54.6, 54.4, 53.9, 52.5, 43.7, 43.3, 38.6, 38.5, 33.6, 33.5, 18.6, 18.4, 17.9, 17.8, 12.3; MS (CI) *m/z* 474.2922 (MH, 474.2940 calcd for $C_{29}H_{39}N_3OSi$), 318, 175, 108.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-9-methyl-3-(spiro-2-oxindole)-7-[(*N*-trifluoroacetyl)aminomethyl]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (25)**. $AlH_3 \cdot Me_2NEt$ (0.12 mL, 0.8 M in toluene, 96 μmol) was added to a solution of **23** (9.1 mg, 19 μmol) in THF (1 mL) at 0 °C. The resulting solution was allowed to warm to rt, and maintained at this temperature for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with $CH_2Cl_2$ (4 × 5 mL), the combined organic extracts were dried ($K_2CO_3$), filtered and concentrated. The residue was dissolved in $CH_2Cl_2$ (1 mL), cooled to 0 °C and triethylamine (0.01 mL) and *N*–(trifluoroacetoxy)succinimide (32 μL, 1 M in benzene) were added. After 5 h at 0 °C, the reaction was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic extracts were dried ($K_2CO_3$), filtered and concentrated. Purification of the residue by chromatography (10:1 $CHCl_3$/MeOH) afforded 4 mg (50%) of amide **25** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.21 (td, *J* = 7.6, 0.8 Hz, 1 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 6.99 (td, *J* = 7.5, 0.6 Hz, 1 H), 6.81 (d, *J* = 7.7 Hz, 1 H), 6.61 (dd, *J* = 17.4, 10.7 Hz, 1 H), 6.15 (dd, *J* = 9.4, 7.1 Hz, 1 H), 5.61 (d, *J* = 9.4 Hz, 1 H), 5.14 (d, *J* = 10.9 Hz, 1 H), 4.95 (d, *J* = 17.6 Hz, 1 H), 3.96–3.92 (m, 1 H), 3.72–7.65 (m, 1 H), 3.12 (s, 1 H), 2.93 (d, *J* = 10.7 Hz, 1 H), 2.62 (t, *J* = 7.0 Hz, 1 H), 2.57–2.50 (m, 2 H), 2.35 (s, 1 H), 2.26 (s, 3 H), 2.00–1.90 (br s, 1 H); MS (CI) *m/z* 418.1743 (MH, 418.1742 calcd for $C_{22}H_{22}N_3O_2F_3$), 167, 134, 108.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-7-(acetylaminomethyl)-9-methyl-3-(spiro-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (26)**. $AlH_3 \cdot Me_2NEt$ (0.15 mL, 0.8 M in toluene, 120 μmol) was added to a solution of **23** (7.0 mg, 15 μmol) in THF (1 mL) at 0 °C. The resulting solution was allowed to warm to rt, and maintained at this temperature for 12 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with $CH_2Cl_2$ (4 × 5 mL). The combined organic extracts were dried ($K_2CO_3$), filtered and concentrated. The residue was dissolved in DMF (0.5 mL) and triethylamine (8 μL) and pentafluorophenylacetate (5 μL, 30 μmol) were added. After 4.5 h at rt, the reaction was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried ($K_2CO_3$),

filtered and concentrated. Purification of the residue by chromatography (15:1 → 10:1 $CHCl_3$/MeOH gradient) afforded 2 mg (40%) of amide **26** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.66 (br s, 1 H),7.21 (dt, *J* = 7.7, 0.9 Hz, 1 H), 7.15 (d, *J* = 7.6 Hz, 1 H), 7.00 (dt, *J* = 7.7, 0.9 Hz, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 6.61 (dd, *J* = 17.7, 10.9 Hz, 1 H), 6.15 (dd, *J* = 9.4, 7.2 Hz, 1 H), 5.57 (dd, *J* = 9.4, 1.4 Hz, 1 H), 5.15 (dd, *J* = 10.9, 1.0 Hz, 1 H), 4.95 (dd, *J* = 17.7, 1.0 Hz, 1 H), 3.89–3.80 (m, 1 H), 3.51–3.43 (m, 1 H), 3.24 (s, 1 H), 2.94 (d, *J* = 10.9 Hz, 1 H), 2.65–2.60 (m, 2 H), 2.52–2.48 (m, 1 H), 2.34 (s, 1 H), 2.32 (s, 3 H), 2.06 (s, 3 H); MS (CI) *m/z* 364.2022 (MH, 364.2025 calcd for $C_{22}H_{25}N_3O_2$), 134, 108.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-9-methyl-3-(spiro-3-benzoyl-2-oxindole)-7-[(*N*-trifluoroacetyl)aminomethyl]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (27)**. DMAP (ca. 0.5 mg) was added to a solution of trifluoroacetamide **25** (6.8 mg, 16 μmol), triethylamine (23 μL, 0.16 mmol) and benzoic anhydride (37 mg, 0.16 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C. After 4 h at 0 °C the reaction mixture was poured into saturated aqueous $NaHCO_3$ (2 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were dried ($K_2CO_3$), filtered and concentrated. The residue was purified by chromatography (40:3 $CHCl_3$/MeOH) to give 6.0 mg (72%) of **27** as a white film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 1 H), 7.69 (d, *J* = 7.3 Hz, 2 H), 7.58 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.37 (t, *J* = 8.5 Hz, 1 H), 7.20–7.12 (m, 2 H), 6.51 (br s, 1 H), 6.33 (dd, *J* = 17.6, 10.9 Hz, 1 H), 6.19 (dd, *J* = 9.4, 7.1 Hz, 1 H), 5.71 (dd, *J* = 9.4, 1.5 Hz, 1 H), 5.03 (dd, *J* = 11.0, 0.9 Hz, 1 H), 4.96 (dd, *J* = 17.6, 0.9 Hz, 1 H), 3.94–3.88 (m, 1 H), 3.80–3.75 (m, 1 H), 3.12 (d, *J* = 10.4 Hz, 1 H), 3.08 (s, 1 H), 2.61 (t, *J* = 7.0 Hz, 1 H), 2.52 (ap q, *J* = 7.7 Hz, 1 H), 2.48 (s, 1 H), 2.36 (d, *J* = 10.5 Hz, 1 H), 2.27 (s, 3 H); MS (CI) *m/z* 522.1977 (MH, 522.2004 calcd for $C_{29}H_{26}N_3O_3F_3$), 494, 418, 123, 107.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-7-(acetylaminomethyl)-9-methyl-3-(spiro-3-benzoyl-2-oxindole)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene (28)**. DMAP (ca. 0.2 mg) was added to a solution of acetamide **26** (2.5 mg, 6.9 μmol), triethylamine (10 μL) and benzoic anhydride (12 mg, 53 μmol) in $CH_2Cl_2$ (1 mL) at rt. After 3 h at rt the reaction mixture was poured into saturated aqueous $NaHCO_3$ (1 mL) and extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic

extracts were dried ($K_2CO_3$), filtered and concentrated. The residue was purified by chromatography (10:1 $CHCl_3$/MeOH) to give 2.0 mg (62%) of **28** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 7.5 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 7.3 Hz, 1 H), 6.33 (dd, *J* = 17.6, 10.9 Hz, 1 H), 6.18 (dd, *J* = 9.5, 7.3 Hz, 1 H), 5.66 (dd, *J* = 10.0, 0.9 Hz, 1 H), 5.02 (d, *J* = 11.0 Hz, 1 H), 4.96 (d, *J* = 17.7 Hz, 1 H), 3.85–3.79 (m, 1 H), 3.61–3.53 (m, 1 H), 3.11 (d, *J* = 10.3 Hz, 1 H), 3.07 (s, 1 H), 2.58 (t, *J* = 7.1 Hz, 1 H), 2.50–2.42 (m, 2 H), 2.33 (d, *J* = 10.3 Hz, 1 H), 2.27 (s, 3 H), 2.22 (s, 1 H), 2.05 (s, 3 H); MS (CI) *m/z* 467.2208 (M, 467.2209 calcd for $C_{29}H_{29}N_3O_3$), 408, 304, 251, 202, 151, 108.

**(1*R**,2*R**,3*R**,6*S**,7*S**,8*R**)-9-methyl-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-7-carboxylic acid methyl ester (32)**. 5 N KOH (0.73 mL, 3.65 mmol) was added to a suspension of nitrile **18** (142 mg, 0.317 mmol) in ethylene glycol (1.5 mL) in a sealable tube. The tube was flushed with argon, sealed, and placed in a 150 °C bath for 6 h. The reaction was then poured into 4:1 $CHCl_3$/isopropanol and $H_2O$, acidified with 1 N HCl, and adjusted to pH 8 with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with 4:1 $CHCl_3$/isopropanol (3×). The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated to a pale yellow foam. The crude amino acid **31** was used in the next reaction without further purification. Diagnostic data: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 1 H), 7.19 (d, *J* = 7.8 Hz, 1 H), 7.10–7.07 (m, 2 H), 6.76 (dd, *J* = 8.9, 7.6 Hz, 1 H), 6.69 (dd, *J* = 17.8, 11.1 Hz, 1 H), 5.34 (d, *J* = 8.9 Hz, 1 H), 5.26 (d, *J* = 11.1 Hz, 1 H), 5.13 (ap d, *J* = 0.9 Hz, 2 H), 4.97 (d, *J* = 17.8 Hz, 1 H), 3.61–3.58 (m, 1 H), 3.57 (t, *J* = 8.1 Hz, 2 H), 3.40 (d, *J* = 11.7 Hz, 1 H), 3.35 (dd, *J* = 3.4, 1.1 Hz, 1 H), 2.81 (d, *J* = 11.7 Hz, 1 H), 2.70 (d, *J* = 7.2 Hz, 1 H), 2.56 (s, 3 H), 2.46 (br s, 1 H), 0.91 (t, *J* = 8.1 Hz, 2 H), –0.04 (s, 9 H).

An ethereal solution of diazomethane was prepared by adding 5 N KOH (1 mL, 5.0 mmol) to a 0 °C solution of 1-methyl-3-nitro-1-nitrosoguanidine (100 mg, 0.68 mmol) and $Et_2O$ (1.0 mL). After warming to rt, the yellow diazomethane solution was transferred by fire polished

pipette to a 0 °C solution of the crude amino acid prepared above (~0.3 mmol) in THF (1.0 mL). After 1 h, repeat diazomethane generation and addition. The reaction was then quenched with aqueous citric acid and adjusted to pH 8 with saturated aqueous $NaHCO_3$. The mixture was extracted with 4:1 $CHCl_3$/isopropanol (3×). The combined extracts were dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (1:4 → 1:1 EtOAc/hexanes) to furnish 96 mg (63% for two steps) of amino ester **32** as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.23 (d, *J* = 7.2 Hz, 1 H), 7.11 (dt, *J* = 7.6, 1.2 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 6.61 (dd, *J* = 17.5, 10.7 Hz, 1 H), 6.57 (dd, *J* = 9.1, 7.6 Hz, 1 H), 5.29 (d, *J* = 9.1 Hz, 1 H), 5.18 (dd, *J* = 11.1, 1.2 Hz, 1 H), 5.14 (s, 2 H), 4.98 (dd, *J* = 17.5, 1.2 Hz, 1 H), 3.73 (s, 3 H), 3.57 (t, *J* = 8.2 Hz, 2 H), 3.38 (dd, *J* = 4.8, 1.2 Hz, 1 H), 3.30 (dd, *J* = 4.8, 1.2 Hz, 1 H), 3.03 (d, *J* = 10.7 Hz, 1 H), 3.05–3.01 (m, 1 H), 2.46 (d, *J* = 10.7 Hz, 1 H), 2.29 (d, *J* = 0.8 Hz, 1 H), 2.19 (s, 3 H), 0.91 (ap dt, *J* = 8.2, 3.1 Hz, 2 H), –0.05 (s, 9 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 172.7, 142.1, 139.1, 138.9, 130.2, 128.7, 125.1, 124.4, 123.1, 114.2, 110.1, 71.1, 69.6, 66.1, 63.1, 59.1, 57.3, 53.4, 51.6, 49.7, 44.5, 39.3, 17.8, -1.4; IR (film) 2950, 1732, 1609, 1486, 1468, 1339, 1248, 1178 cm$^{-1}$; MS (CI) *m/z* 481.2518 (MH, 481.2522 calcd for $C_{27}H_{36}N_2O_4Si$), 363, 154.

**Acidic Hydrolysis of 22 to Form Pentacyclic Amide 33**. Nitrile **22** (20 mg, 63 μmol) was dissolved in concentrated $H_2SO_4$ (0.3 mL) and the resulting solution was maintained at rt for 14 h. The solution was then cooled to 0 °C and diluted with 1 mL of ice water, basified with 5 N KOH, and extracted with $CHCl_3$ (4 x 5 mL). The combined organic phases were dried ($K_2CO_3$), filtered and concentrated to afford 8.4 mg (40%) of amide **33** as a colorless single crystals, homogeneous by TLC analysis: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.9 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 7.2 Hz, 1 H), 6.15 (dd, *J* = 9.3, 6.6 Hz, 1 H), 5.43–5.30 (br s, 2 H), 5.03 (d, *J* = 9.0 Hz, 1 H), 4.80 (q, *J* = 6.6 Hz, 1 H), 3.91 (s, 1 H), 3.08 (d, *J* = 8.3 Hz, 1 H), 2.76 (t, *J* = 7.2 Hz, 1 H), 2.63 (d, *J* = 9.7 Hz, 1 H), 2.44 (d, *J* = 9.7 Hz, 1 H), 2.29 (s, 3 H), 2.14 (s, 1 H), 1.58 (d, *J* = 6.6 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 180.8, 173.1, 153.7, 138.6, 129.5, 128.7, 128.6, 124.9, 123.9, 119.1, 83.2, 68.4, 62.7, 55.4, 51.9, 50.2,

50.1, 42.4, 39.6, 19.2; MS (CI) *m/z* 336 (MH), 319, 236, 222, 134. Structure established by X-ray analysis.[6]

**(1*R**,2*R**,6*S**,7*R**,8*S**)-7-Bromo-3-(oxo-ethylene acetal)-1-vinyl-9-aza-tricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (46)**. A mixture of benzene (22 mL), ethylene glycol (85 μL, 1.53 mmol), TsOH (36 mg, 190 μmol) and ketone **5** (300 mg, 0.96 mmol) was fitted with a Dean Stark trap and heated at reflux. The reflux was continued for 18 h and then the reaction mixture was allowed to cool to rt. The reaction mixture was poured into a saturated aqueous $NaHCO_3$ and the resultant mixture was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by chromatography (2:1 hexane/EtOAc containing 5% $Et_3N$) to yield 257 mg (75%) of ketal **46** as white crystals: mp = 114.5–116 °C; $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *6.19* (dd, *J* = 17.9, 11.1 Hz, 1 H), 6.17 (dd, *J* = 17.9, 11.1 Hz), *5.20* (d, *J* = 11.1 Hz, 1 H), 5.19 (d, *J* = 11.1 Hz) *5.08* (d, *J* = 17.9 Hz, 1 H), 5.06 (d, *J* = 17.9 Hz), 4.44–4.42 (m, 1 H), 4.40–4.39 (m), *4.30* (dd, *J* = 3.5, 1.6 Hz, 1 H) 3.95–3.80 (m, 4 H), 3.68 (s), *3.67* (s, 3 H), *3.44* (d, *J* = 10.4 Hz, 1 H), 3.38 (d, *J* = 10.3 Hz) *3.24* (d, *J* = 10 Hz, 1 H), 3.22 (d, *J* = 10 Hz), 2.26–2.22 (m, 2 H), 1.91–1.84 (m, 1 H), 1.76–1.66 (m, 2 H), 1.66–1.62 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 154.8, 154.6, 135.7, 135.6, 116.7, 116.6, 108.1, 108.0, 64.4, 64.3, 62.2, 61.9, 57.4, 57.1, 53.5, 53.4, 53.2, 53.1, 52.5, 52.4, 52.2, 51.8, 50.6, 50.5, 23.3, 23.2; IR (film) 2952, 2880, 1706, 1456, 1399 cm$^{-1}$; MS (EI) *m/z* 357.0594 (M, 357.0577 calcd for $C_{15}H_{20}NO_4Br$).

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Cyano-9-methyl-3-(oxo-ethylene acetal)-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane (48)**. NaCN (351 mg, 7.17 mmol) was added to a solution of ketal **46** (257 mg, 0.717 mmol) in DMSO (7.2 mL). The mixture was heated at 150 °C for 3 h, then cooled, diluted with $H_2O$ and extracted with EtOAc (4×). The combined organic extracts were washed with $H_2O$ and brine, then dried ($Na_2SO_4$), filtered and concentrated. The resulting crude oil was purified by chromatography (1:19 MeOH/EtOAc) to afford 124 mg (79%) of aziridine **47** as a pale yellow oil, which was used immediately in the next step. Diagnostic data: $^1$H NMR (500 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 17.5, 11.0 Hz, 1 H), 5.08 (d, *J* = 11.0 Hz, 1 H), 4.95 (d, *J* =

17.5 Hz, 1 H), 3.97–3.80 (m, 4 H), 2.50 (d, *J* = 9.8 Hz, 1 H), 2.45 (d, *J* = 9.8 Hz, 1 H), 2.29 (br s, 1 H), 2.15 (br s, 1 H), 1.90 (br s, 1 H), 1.84 (br s, 1 H), 1.81–1.68 (m, 3 H), 1.49–1.44 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 134.1, 114.7, 109.1, 64.5, 63.7, 63.2, 50.1, 46.5, 40.7, 36.0, 35.4, 28.1, 19.4; IR (film) 2941, 2879, 1637, 1113 cm$^{-1}$; MS (CI) *m/z* 220.1339 (MH, 220.1337 calcd for $C_{13}H_{17}NO_2$).

Methyl triflate (230 μL, 2.03 mmol) was added dropwise to a solution of aziridine **47** (321 mg, 1.46 mmol) and $CH_2Cl_2$ (8.6 mL) at rt. After 5 min, the reaction was concentrated. The resulting white solid was dissolved in DMSO (14.5 mL), and NaCN (725 mg, 14.8 mmol) was added. The mixture was heated at 100 °C for 30 min. The homogeneous brown solution was then allowed to cool, diluted with saturated aqueous $NaHCO_3$ and extracted with $CH_2Cl_2$ (4×). The organic extracts were combined and washed with $H_2O$ (2×) and brine. The aqueous washes were back-extracted once with $CH_2Cl_2$, then the organic extracts were combined and dried ($Na_2SO_4$), filtered and concentrated. The resulting brown residue was purified by chromatography ($Et_2O$ → 1:19 MeOH/$Et_2O$ gradient) to afford 318 mg (83%) of the nitrile **48** as a colorless solid: mp = 110–111 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.29 (dd, *J* = 17.9, 11.1 Hz, 1 H), 5.19 (d, *J* = 11.1 Hz, 1 H), 4.99 (d, *J* = 17.9 Hz, 1 H), 4.00–3.90 (m, 4 H), 3.41 (s, 1 H), 3.00 (d, *J* = 7.6 Hz, 1 H), 2.96 (d, *J* = 10.0 Hz, 1 H), 2.33–2.25 (m, 2 H), 2.29 (s, 3 H), 2.22 (s, 1 H), 2.10 (d, *J* = 10.0 Hz, 1 H), 2.03 (dddd, *J* = 15.4, 13.2, 7.4, 2.2 Hz, 1 H), 1.81–1.74 (m, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.6, 120.2, 115.9, 107.9, 68.6, 64.5, 64.2, 62.3, 55.6, 52.6, 43.4, 38.5, 28.9, 27.5, 21.7; IR ($CHCl_3$) 2942, 2233, 1636, 1457, 1217, 1106 cm$^{-1}$; MS (CI) *m/z* 261.1603 (MH, 261.1603 calcd for $C_{15}H_{20}N_2O_2$), 152, 108. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.94; N, 10.76. Found: C, 69.33; H, 7.80; N, 10.77.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Hydroxymethyl-9-methyl-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decan-3-one (45).** A freshly prepared solution of DIBALH (0.69 mL, 1.4 M in toluene, 0.96 mmol) was added dropwise to a solution of nitrile **48** (50 mg, 0.19 mmol) and toluene (0.96 mL) at –78 °C. After a period of 1 h at –78 °C, excess DIBALH was quenched with acetone (0.1 mL), and the reaction was allowed to warm to 0 °C. Acetic acid (2.5 mL, 5%

v/v in $H_2O$) was added and the resulting opaque mixture was vigorously stirred at 0 °C for 1.5 h. The cooling bath was removed and vigorous stirring was continued for another 30 min before the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (~3 mL). The resulting mixture was extracted with $CH_2Cl_2$ (4×), then the combined extracts were briefly dried ($Na_2SO_4$), filtered and concentrated to a pale yellow oil. Crude aldehyde **49** was carried into the next reaction without further purification.

The resulting oily residue was dissolved in THF (1.0 mL) and ethanol (1.0 mL). The solution was cooled to 0 °C, and then $NaBH_4$ (80 mg, 2.1 mmol) was added in two portions before the cooling bath was removed. The mixture was heated at 50 °C for 10 h, then allowed to cool. Excess $NaBH_4$ was quenched with $H_2O$ (2 mL) and the resulting mixture was stirred at rt for 2 h. The organic solvents were removed by concentration and the remaining aqueous mixture was extracted with $CH_2Cl_2$ (4×). The combined extracts were dried ($Na_2SO_4$), filtered and concentrated to afford ketal alcohol **50** (as a 4:1 mixture of diastereomers), which was used without further purification. Diagnostic data: $^1$H NMR (500 MHz, $CDCl_3$) δ 6.18 (dd, *J* = 17.7, 11.1 Hz, 1 H), 5.14 (d, *J* = 11.1 Hz, 1 H), 5.10 (d, *J* = 17.7 Hz, 1 H), 3.97–3.88 (m, 5H), 3.85 (d, *J* = 7.6 Hz, 1H), 2.98 (s, 1H), 2.84 (d, *J* = 9.8 Hz, 1H), 2.31 (s, 3H), 2.30–2.25 (m, 3H), 2.13 (br s, 1H), 1.85–1.80 (m, 2H), 1.70–1.55 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.9, 115.2, 109.3, 67.4, 64.1, 63.9, 63.7, 61.8, 55.0, 53.5, 42.6, 42.3, 39.4, 29.9, 18.7.

The crude hydroxy ketals **50** (~55 mg, prepared as above from **48**, 0.19 mmol) were dissolved in a solution of 1 N HCl/acetic acid/THF (1:2:3, 1.9 mL) and heated at 50 °C for 8 h. The reaction was allowed to cool to rt and was concentrated. The resulting mixture was made strongly basic with 5 N KOH, then extracted with $CH_2Cl_2$ (4×). The combined extracts were dried ($Na_2SO_4$), filtrered and concentrated. The residue was purified by chromatography (15% $H_2O$ w/w was added to deactivate the silica gel, $CHCl_3$ → 1:9 MeOH/$CHCl_3$ gradient) to afford 24 mg (56% from **48**) of slightly impure hydroxy ketone **45**: $^1$H NMR (500 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 17.6, 10.9 Hz, 1 H), 5.19 (d, *J* = 11.0 Hz, 1 H), 5.12 (d, *J* = 17.6 Hz, 1 H), 3.61 (dd, *J* = 10.8, 7.2 Hz, 1 H), 3.44 (dd, *J* = 10.8, 8.0 Hz, 1 H), 3.08 (d, *J* = 1.5 Hz, 1 H), 2.86 (d, *J* = 1.0

Hz, 1 H), 2.81 (d, *J* = 10.5 Hz, 1 H), 2.49 (d, *J* = 10.5 Hz, 1 H), 2.36 (s, 3 H), 2.38–2.22 (m, 3 H), 1.97–1.90 (m, 3 H), 1.79 (dddd, *J* = 14.3, 9.9, 4.5, 1.4 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 212.3, 136.3, 116.1, 70.0, 64.8, 61.7, 57.1, 55.6, 46.4, 42.4, 41.6, 35.4, 17.4; IR (film) 3376 (br), 2929, 1705, 1458, 1218 cm$^{-1}$; MS (CI) *m/z* 222.1491 (MH, 222.1494 calcd for $C_{13}H_{19}NO_2$).

**(1*R**,2*R**,6*S**,7*R**,8*S**)-7-Bromo-4,4-bismethylsulfanyl-3-oxo-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (55)**. Potassium bis(trimethylsilyl)amide (4.5 mL, 0.5 M in toluene, 2.3 mmol) was added dropwise to a solution of ketone **5** (340 mg, 1.08 mmol) in THF (15 mL) at 0 °C. After a period of 30 min, freshly distilled methyl methanethiolsulfonate (450 μL, 4.4 mmol) was added and the reaction mixture was maintained at 0 °C for 1 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was partitioned between $Et_2O$ (5 mL). The aqueous layer was extracted with $Et_2O$ (2×) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by chromatography (1:1 → 1:3 hexanes/$Et_2O$ gradient) afforded 226 mg (52%) of dithioketal **55** as a thick oil and 125 mg (37%) of recovered ketone **5**. Data for **55**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 6.18–6.09 (m, 1 H), *5.34* (d, *J* = 10.8 Hz, 1 H), *5.16* (d, *J* = 17.9 Hz, 1 H), 5.14 (d, *J* = 17.6 Hz), 5.04 (br s), *4.97* (br s, 1 H), 4.69 (br s), *4.56* (br s, 1 H), 3.73 (s), *3.72* (s, 3 H), *3.52* (d, *J* = 10.5 Hz, 1 H), 3.46 (d, *J* = 10.5 Hz), 3.38 (d, *J* = 10.5 Hz, 1 H), 3.08–3.04 (m, 1 H), 2.50 (br s, 1 H), *2.41* (s, 1 H), 2.10 (s, 1 H), 2.08 (s, 3 H), 2.02 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 197.7, 155.3, 134.8, 119.7, 65.4, 65.1, 62.2, 61.8, 61.3, 56.0, 55.1, 54.1, 53.3, 52.2, 40.5, 40.3, 32.3, 23.3, 14.8, 13.4; IR (film) 2953, 1713, 1688, 1455, 1397 cm$^{-1}$; MS (CI) *m/z* 408.0109 (MH, 408.0146 calcd for $C_{15}H_{20}NO_3S_2$), 358, 326, 278.

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-4-methylsulfanyl-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-3,9-dicarboxylic acid dimethyl ester (57)**. Sodium thiomethoxide (65 mg, 0.93 mmol) was added to a solution of dithioketal **55** (73 mg, 0.18 mmol) in THF (1.5 mL) at 0 °C. After 1 h at 0 °C, the mixture was cooled to –78 °C and a solution of *N*-phenyltriflimide (320 mg, 0.190 mmol) in THF (1 mL) was added via cannula. After an additional 10 min at –78 °C, the reaction was warmed to 0 °C for 1.5 h. The mixture was diluted

with $CH_2Cl_2$ (5 mL) and quenched with saturated aqueous $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2×). The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated. The residue was normally taken on crude in the next reaction. However, a pure sample could be obtained after chromatography (2:1 → 1:3 hexanes/$Et_2O$ gradient) to give **56** as an oil. Diagnostic data: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *5.86* (dd, *J* = 17.8, 11.0 Hz, 1 H), 5.33–5.30 (m, 1 H), 5.22–5.18 (m, 1 H), 4.81 (br s), *4.67* (br s, 1 H), 4.14 (br s), *4.11* (br s, 1 H), 3.74 (s), *3.73* (s, 3 H), *3.56* (d, *J* = 10.4 Hz, 1 H), 3.52 (d, *J* = 10.3 Hz), 3.35–3.32 (m, 1 H), 2.68–2.67 (m, 1 H), 2.62 (br d, *J* = 17.0 Hz, 1 H), 2.44 (br d, *J* = 17.0 Hz, 1 H), 2.34 (s, 1 H), 2.28 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 154.9, 154.4, 137.7, 137.5, 132.6, 132.5, 128.5, 128.4, 118.7, 118.6, 66.6, 66.3, 53.5, 52.6, 52.0, 51.8, 51.4, 50.6, 34.1, 13.3; IR (film) 1708, 1458, 1418, 1399, 1208, 1137 cm$^{-1}$; MS (CI) *m/z* 493.9741 (MH, 493.9741 calcd for $C_{15}H_{17}BrF_3NO_5S_2$).

A solution of crude triflate **56** prepared above (~0.18 mmol) and $Et_3N$ (250 mL, 1.8 μmol) in methanol (2 mL) and DMF (1 mL) was transferred via cannula to a Fisher-Porter tube containing tetrakis(triphenylphosphine)palladium (42 mg, 0.04 mmol, 20 mol%). An additional portion of methanol (2 mL) was used to wash in the remaining substrate. The solution was degassed by evacuation and back filling with CO and then placed under a CO atmosphere at 30 psi. The reaction mixture was heated to 80 °C for 16 h, and then allowed to cool to rt. The mixture was partioned between $Et_2O$ and brine and the aqueous layer was extracted with $Et_2O$ (2×). The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by chromatography (2:3 → 1:3 hexanes/$Et_2O$ gradient) to afford 58 mg (80% from **5**) of ester **57** as an oil: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 5.85–5.78 (m, 1 H), 5.23 (d, *J* = 10.8 Hz, 1 H), 5.22 (d, *J* = 10.7 Hz), 5.12 (d, *J* = 10.8 Hz, 1 H), 5.09 (d, *J* = 10.7 Hz), 4.61–4.59 (m), 4.44–4.42 (m, 1 H), 4.07–4.05 (m), 4.03–4.01 (m, 1 H), 3.78 (s), *3.75* (s, 3 H), 3.74 (s), *3.73* (s, 3 H), 3.56 (d, *J* = 10.3 Hz, 1 H), 3.52 (d, *J* = 10.3 Hz), 3.35 (d, *J* = 10.5 Hz, 1 H), 3.32 (d, *J* = 10.3 Hz), 3.21 (t, *J* = 2.1 Hz, 1 H), 3.18 (t, *J* = 2.2 Hz), 2.74 (dt, *J* = 18.5, 4.1 Hz, 1 H), 2.59 (dt, *J* = 18.5, 3.0 Hz, 1 H), 2.33 (s, 1 H), 2.30 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 166.4, 166.3,

155.0, 154.7, 153.8, 153.6, 140.2, 138.2, 133.7, 133.6, 118.1, 118.0, 116.5, 66.8, 66.6, 54.5, 54.4, 52.6, 52.5, 51.7, 50.5, 49.7, 49.2, 49.1, 48.8, 37.0, 14.3; IR (film) 1688, 1455, 1435, 1245 $cm^{-1}$; MS (CI) *m/z* 404.0306 (MH, 404.0353 calcd for $C_{16}H_{20}BrNO_4S$).

**(1*R**,2*S**,6*S**,7*R**,8*S**)-7-Bromo-3-[(2-bromophenyl)-(2-trimethylsilylethoxymethyl)-carbamoyl]-4-methylsulfanyl-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-3-ene-9-carboxylic acid methyl ester (58)**. Trimethylaluminum (95 mL, 0.99 mmol) was added to a solution of freshly distilled 2-bromoaniline (180 mg, 1.05 mmol) in benzene (6 mL) at 0 °C. After 5 min, the cooling bath was removed and the reaction was maintained at rt for 45 min. An aliquot of the above solution (310 mL, 0.17 M, 53 μmol) was added to a solution of ester **57** (19 mg, 50 μmol) in benzene (0.5 mL) in a sealable vial. The vial was sealed and heated to 85 °C for 4 h. Upon cooling to rt, the reaction was quenched with 1 M HCl and partioned between $Et_2O$ and $H_2O$. The aqueous layer was extracted with $Et_2O$ (2×) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by chromatography (7:3 → 2:3 hexanes/$Et_2O$ gradient) gave 17 mg (63%) of the corresponding bromoamide: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ *8.43* (d, *J* = 9.5 Hz, 1 H), 8.42 (d, *J* = 8.3 Hz), *8.38* (br s, 1 H), 8.30 (br s), 7.55 (br d, *J* = 8.1 Hz, 1 H), 7.32 (br t, *J* = 8.0 Hz, 1 H), 6.99 (br t, *J* = 8.0 Hz, 1 H), 5.92–5.85 (m, 1 H), 5.30–5.27 (m, 1 H), 5.24–5.19 (m, 1 H), 4.83 (br s), *4.71* (br s, 1 H), 4.18 (br s), *4.13* (br s, 1 H), 3.74 (s), *3.72* (s, 3 H), *3.60* (d, *J* = 10.3 Hz, 1 H), 3.55 (d, *J* = 10.3 Hz), 3.38–3.35 (m, 1 H), 3.10 (br s, 1 H), 2.78–2.72 (m, 1 H), *2.60* (br s, 1 H), 2.56 (br s), 2.36 (br s, 1 H), *2.34* (s, 3 H), 2.32 (s); IR (film) 1704, 1689, 1579, 1456, 1303 $cm^{-1}$; MS (CI) *m/z* 546, 545, 544, 543, 542, 541.

Sodium hydride (5 mg, 60% dispersion, 0.13 mmol) was added in one portion to a solution of the amide prepared above (50 mg, 0.09 mmol) in THF at 0 °C. After 1 h 2-(trimethylsilyl)ethoxymethyl chloride (50 μL, 0.28 mmol) was added and stirring continued for 16 h as the reaction warmed to rt. The mixture was diluted with $Et_2O$ (5 mL) and quenched with saturated aqueous $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (2×). The combined organic layers were dried ($Na_2SO_4$), filtered and

concentrated. Purification of the residue by chromatography (4:1 → 2:3 hexanes/$Et_2O$ gradient) afforded 43 mg (71%) of amide **58** as and oil: $^1$H NMR (500 MHz, $CDCl_3$, complex mixture of 2 sets of conformational isomers, integration ommitted) δ 7.75–7.55 (m), 5.85–5.75 (m), 5.35–5.2 (m), 4.85–4.6 (m), 4.55–4.4 (m), 4.15–3.95 (m), 3.75–3.65 (m), 3.5–3.35 (m), 3.15–3.05 (m), 2.65–2.5 (m), 2.4–2.1 (m); IR (film) 1708, 1658, 1478, 1455, 1397, 1062 cm$^{-1}$; MS (CI) *m/z* 673.5542 (MH, 673.5512 calcd for $C_{27}H_{36}Br_2N_2O_4SSi$), 594, 592.

**(1*R**,2*S**,3*R**,6*S**,7*R**,8*S**)-7-Bromo-4-methylsulfanyl-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (59) and (1*R**,2*S**,3*S**,6*S**,7*R**,8*S**)-7-Bromo-4-methylsulfanyl-3-[spiro-3-(2-trimethylsilylethoxymethyl)-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (60)**. A solution of **58** (10 mg, 15 μmol) and $Et_3N$ (20 μL, 0.14 mmol) in acetonitrile (1.0 mL) was transferred via cannula to a resealable vial containing tetrakis(triphenylphosphine)palladium (4 mg, 3 μmol). The solution was degassed (evac, fill with $N_2$, 5×) and the vial was sealed and heated to 150 °C for 16 h. After cooling to rt, the mixture was partioned between $Et_2O$ and brine. The aqueous layer was extracted with $Et_2O$ (2×) and the combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Purification of the residue by chromatography (4:1 → 1:1 hexanes/$Et_2O$ gradient) afforded 2 mg (23%) of **59** and 4 mg (46%) of **60** as films. Data for **59**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.40–7.30 (m, 1 H), 7.25–7.22 (m, 1 H), 7.12–7.08 (m, 2 H), 6.20 (d, *J* = 8.2 Hz, 1 H), 6.10–6.04 (m, 1 H), 5.22–5.03 (m, 4 H), 4.92 (br s, 1 H), *4.39* (br s, 1 H), 4.25 (br s), *4.02* (d, *J* = 10.2 Hz, 1 H), 3.97 (d, *J* = 10.2 Hz, 1 H), 3.76 (s), *3.72* (s, 3 H), 3.68–3.52 (m, 3 H), 2.42–2.40 (m, 1 H), 2.15 (s, 3 H), 0.95–0.83 (m, 2 H), –0.05 (s, 9 H); MS (CI) *m/z* 591 (MH), 547, 429. Data for **60**: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.31–7.26 (m, 1 H), 7.16–6.97 (m, 3 H), 6.18 (d, *J* = 7.9 Hz, 1 H), 5.62–5.58 (m, 1 H), 5.30–5.20 (m, 2 H), 5.40–5.01 (m, 2 H), 4.88 (s), *4.81* (s, 1 H), 4.58 (s, 1 H), 3.95–3.85 (m, 1 H), 3.75–3.45 (m, 5 H), 3.10–2.94 (m, 2 H), 2.21 (br s, 1 H), 2.11 (s, 3 H), 1.15–1.10 (m, 1 H), 0.97–0.84 (m, 1 H), –0.06 (s, 9 H); MS (EI) *m/z* 590.1243, (590.1270 calcd for $C_{27}H_{35}BrN_2O_4SSi$, (CI) *m/z* 591 (MH), 547, 429.

**(1*R**,2*R**,6*S**,7*R**,8*S**)-7-Bromo-4-methoxy-3-oxo-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]dec-4-ene-9-carboxylic acid methyl ester (65)**. Triflate **64** was subjected to the general carbonylation procedure described for the formation of **9a** to afford 28 mg (58%) of enone **65** as a colorless solid: mp = 150-154 °C; $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 6.28 (ap t, *J* = 8.4 Hz, 1 H), 5.88–5.80 (m, 1 H), *5.23* (d, *J* = 10.9 Hz, 1 H), 5.22 (d, *J* = 10.8 Hz), *5.06* (d, *J* = 17.6 Hz, 1 H), 5.05 (d, *J* = 17.6 Hz), 4.59–4.58 (m), *4.46–4.45* (m, 1 H), 4.15 (d, *J* = 3.5 Hz), *4.10* (d, *J* = 3.6 Hz, 1 H), 3.71 (br s, 3 H), *3.60* (s, 3 H), 3.59 (s), *3.46* (d, *J* = 11.0 Hz, 1 H), 3.41 (d, *J* = 10.9 Hz), 3.30 (d, *J* = 11.0 Hz, 1 H), 3.13–3.12 (m, 1 H), 2.92–2.89 (m, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 189.6, 154.7, 153.1, 133.5, 133.4, 120.2, 119.9, 119.0, 118.9, 63.6, 62.9, 62.5, 58.9, 58.8, 57.1, 55.3, 52.6, 52.5, 52.2, 51.5; IR ($CHCl_3$) 2958, 1694, 1621, 1459, 1399, 1160, 1124 cm$^{-1}$; MS (EI) *m/z* 341.0255 (MH, 341.0263 calcd for $C_{14}H_{16}BrNO_4$), 262, 152.

**(1*R**,2*R**,3*S**,5*R**,6*R**,7*R**,8*S**)-4-oxo-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatetracyclo[4.4.0.0$^{2,8}$.0$^{5,7}$]decane carboxylic acid methyl ester (71)**. Oxalic acid (21 mg, 0.17 mmol) was added to a solution of enol ether **69** (10 mg, 17 mmol) and MeOH/$H_2O$ (0.15 mL/0.05 mL). The reaction mixture was heated to 50 °C for 12 h, cooled to rt, and diluted with $CH_2Cl_2$ (2 mL) and $H_2O$ (2 mL). The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (2×). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. The resulting crude residue was purified by chromatography (40% EtOAc/petroleum ether) to afford 6.0 mg (90%) of cyclopropane ketone **71** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.53 (br d, *J* = 6.8 Hz, 1 H), 7.28 (ap t, *J* = 7.7 Hz, 1 H), 7.03–6.99 (m, 2 H), 6.11 (dd, *J* = 17.2, 10.6 Hz, 1 H), 5.72 (d, *J* = 17.4 Hz, 1 H), 5.55 (d, *J* = 10.6 Hz, 1 H), 5.44 (s, 1 H), 5.07 ($AB_q$, $J_{AB}$ = 10.9 Hz, $Dn_{AB}$ = 15.3 Hz, 2 H), 3.73–3.68 (m, 3 H), 3.37–3.32 (m, 1 H), 3.28 (s, 3 H), 3.23–3.13 (m, 1 H), 2.49–2.42 (m, 1 H), 2.20 (t, *J* = 6.5 Hz, 1 H), 2.09 (br s, 1 H), 2.02 (ap t, *J* = 7.1 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 201.6, 173.7, 155.5, 142.5, 137.0, 129.2, 128.0, 127.5, 123.0, 119.5, 109.8, 71.6, 60.3, 57.7, 56.3, 55.4, 55.3, 52.5, 48.9, 28.1, 24.5, 24.1; IR (film) 2954, 1722, 1694, 1611, 1489, 1456, 1394 cm$^{-1}$; MS (CI) *m/z* 394.1531 (M, 394.1529 calcd for $C_{22}H_{22}N_2O_5$) 363, 334.

**Preparation of Furan 75**. 1,8-Diazabicyclo[5.4.0]undec-7-ene (26 mL, 0.17 mmol) was added to a solution of alcohols **73/74** (25.7 mg, 54 mmol, 1:1) in toluene (2.0 mL) and heated to 110 °C for 4 h. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL), and washed with 1 M HCl (2×) and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatography (1:1 EtOAc/petroleum ether) to afford 12 mg (57%) of furan **75** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$)[5] δ 7.91 (d, *J* = 7.5 Hz, 1 H), 7.87 (d, *J* = 7.5 Hz), 7.34–7.28 (m, 1 H), 7.16–7.11 (m, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 6.98 (d, *J* = 7.9 Hz), 6.43 (dd, *J* = 17.8, 10.7 Hz, 1 H), 6.40 (dd, *J* = 17.8, 10.7 Hz), 5.26 (d, *J* = 10.7 Hz, 1 H), 5.25 (d, *J* = 10.7 Hz), 5.16–5.11 (m, 1 H), 5.09 ($AB_q$, $J_{AB}$ = 10.9 Hz, $Dn_{AB}$ = 37.6 Hz, 2 H), 4.71 (br s, 1 H), 4.67 (br d, *J* = 3.9 Hz, 1 H), 4.60 (br d, *J* = 3.9 Hz), 4.57 (br s), 4.06 (d, *J* = 4.2 Hz, 1 H), 3.71 (s, 3 H), 3.66 (s), 3.38–3.31 (m, 1 H), 3.30 (s, 3 H), 3.27 (d, *J* = 10.3 Hz, 1 H), 3.03 (d, *J* = 10.4 Hz, 1 H), 2.97 (d, *J* = 10.3 Hz), 2.75–2.73 (m, 1 H), 2.06–2.01 (m, 1 H), 1.75 (ddd, *J* = 12.1, 7.1, 4.8 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$)[5] δ 175.2, 175.1, 154.9, 154.7, 140.8, 140.6, 137.3, 137.1, 131.1, 130.9, 128.6, 127.8, 127.5, 123.2, 123.0, 114.9, 114.6, 109.2, 109.0, 79.8, 79.6, 77.4, 77.3, 71.2, 59.0, 58.9, 56.6, 56.5, 56.2, 52.7, 52.5, 52.4, 52.0, 51.9, 51.8, 51.4, 45.1, 30.2; IR (film) 2954, 1710, 1707, 1610, 1456, 1398, 1344, 1123 cm$^{-1}$; MS (CI) *m/z* 396.1687 (M, 396.1685 calcd for $C_{22}H_{24}N_2O_5$) 365.

**(1*R**,2*S**,3*R**,4*R**,6*S**,7*R**,8*S**)-7-Bromo-4-(1-ethoxyethoxy)-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatricyclo[4.4.0.0$^{2,8}$]decane-9-carboxylic acid methyl ester (76)**. Pyridinium *p*-toluenesulfonate (10.0 mg, 40 mmol) was added to a solution of alcohol **73** (9.0 mg, 19 mmol) and ethyl vinyl ether (0.1 mL) and $CH_2Cl_2$ (0.2 mL) at rt. The reaction mixture was allowed to stir for a period of 60 min and then concentrated to remove the solvent. The crude residue was purified by chromatography (40% EtOAc/petroleum ether) to afford 9.0 mg (90%) of **76** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$, mixture of conformational isomers and diastereomers) δ 7.31–7.23 (m, 4 H), 7.13–7.07 (m, 2 H), 6.98–6.95 (m, 2 H), 6.38–6.31 (m, 2 H), 5.73–5.67 (m, 2 H), 5.49–5.43 (m, 4 H), 5.21–5.15 (m, 2 H), 5.06–5.00 (m, 2 H), 4.47 (q, *J* = 5.3 Hz, 1 H), 4.45–4.30 (m, 4 H), 4.04–3.99 (m, 1 H), 3.66 (s, 3 H), 3.64 (s, 3 H),

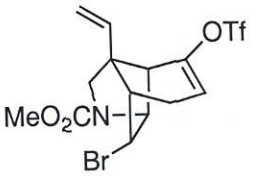
3.44 (d, *J* = 10.9 Hz, 1 H), 3.43 (d, *J* = 10.9 Hz, minor isomer), 3.39 (d, *J* = 10.7 Hz, 1 H), 3.38 (d, *J* = 10.9 Hz, minor isomer), 3.36 (s, 3 H), 3.34 (s, 3 H), 3.32 (s, minor isomer), 3.22–3.14 (m, 2 H), 3.10–3.01 (m, 2 H), 2.74–2.62 (m, 5 H), 2.57–2.51 (m, 1 H), 2.41–2.35 (m, 2 H), 2.07–1.85 (m, 2 H), 0.99 (td, *J* = 7.0, 0.5 Hz, 3 H), 0.91 (dd, *J* = 5.4, 0.5 Hz, 3 H), 0.84 (t, *J* = 7.1 Hz, 3 H), 0.83 (d, *J* = 5.3 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of conformational isomers and diastereomers) δ 176.12, 176.06, 175.97, 175.89, 154.7, 154.3, 141.41, 141.38, 141.35, 136.43, 136.39, 136.31, 136.27, 135.44, 135.37, 135.14, 135.08, 128.6, 128.4, 123.6, 123.5, 123.4, 123.3, 123.13, 123.08, 123.0, 122.9, 117.7, 117.6, 117.5, 117.4, 109.3, 109.2, 100.8, 100.7, 97.6, 97.5, 73.5, 73.2, 71.4, 71.2, 70.5, 70.2, 63.9, 63.6, 59.8, 59.7, 58.9, 58.8, 58.7, 58.4, 56.6, 56.3, 55.93, 55.85, 54.3, 53.95, 53.90, 53.84, 53.79, 53.7, 53.23, 53.17, 52.5, 52.3, 48.1, 48.0, 47.93, 47.86, 35.8, 35.7, 34.5, 34.4, 20.00, 19.98, 15.7, 15.2, 15.0; IR (film) 2932, 1716, 1612, 1490, 1456, 1398, 1343, 1303, 1249, 1185 cm$^{-1}$; MS (ES) *m/z* 571.1414 (MNa, 571.1420 calcd for $C_{26}H_{33}BrN_2O_6$), 519, 517, 505, 478, 476, 446, 444, 365.

**(1*R**,2*R**,3*S**,4*S**,6*R**,7*S**,8*R**)-4-(1-ethoxyethoxy)-3-[spiro-3-methoxymethyl-2-oxindole]-1-vinyl-9-azatetracyclo[4.4.0.0$^{2,8}$.0$^{7,9}$]decane (77)**. Sodium cyanide (6.2 mg, 0.13 mmol) was added to a solution of **76** (7.0 mg, 13 mmol) in DMSO (0.8 mL) and heated to 150 °C for 18 h, resulting in an orange solution. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL), and saturated aqueous $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with $H_2O$ (2×), brine and then dried ($Na_2SO_4$), filtered and concentrated. The crude residue was purified by chromatography (1:3:16 $CHCl_3$ (saturated with $NH_3$)/petroleum ether/EtOAc) to afford 4.0 mg (80%) of aziridine **77** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ 7.36 (d, *J* = 7.5 Hz, 2 H), 7.28-7.23 (m, 2 H), 7.09 (td, *J* = 7.0, 0.9 Hz, 1 H), 7.07 (td, *J* = 7.0, 0.9 Hz, 1 H), 6.97 (d, *J* = 7.7 Hz, 1 H), 6.96 (d, *J* = 7.7 Hz, 1 H), 6.39 (dd, *J* = 17.7, 10.7 Hz, 2 H), 5.44–5.39 (m, 4 H), 5.17 (d, *J* = 16.2 Hz, 1 H), 5.14 (d, *J* = 16.2 Hz, 1 H), 5.07 (d, *J* = 11.0 Hz, 1 H), 5.06 (d, *J* = 11.0 Hz, 1 H), 4.49–4.42 (m, 3 H), 4.03 (q, *J* = 5.3 Hz, 1 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.24–3.17 (m, 2 H), 3.03 (dq, *J* = 9.2, 7.1 Hz, 1 H), 2.61 (d, *J* =

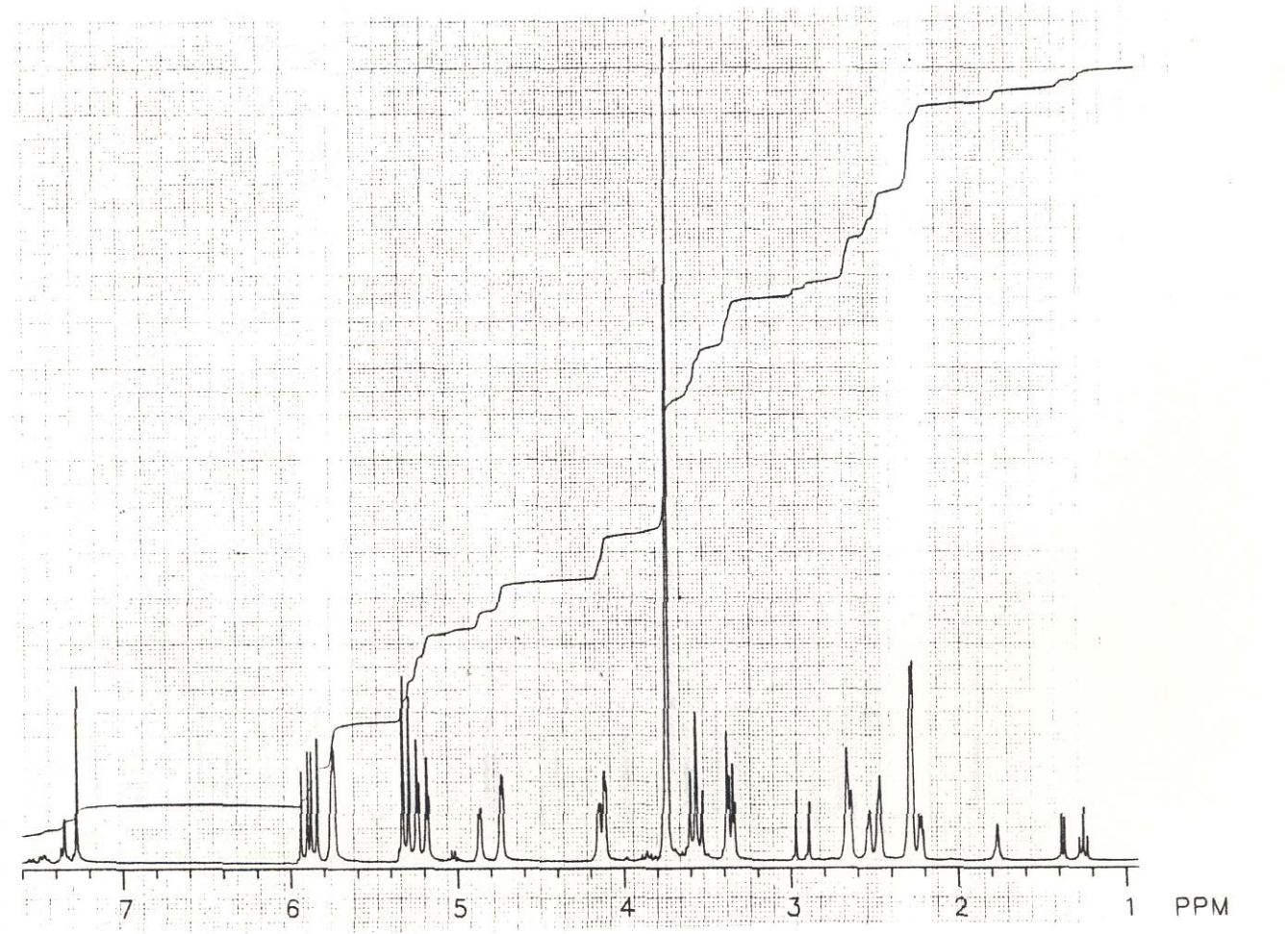
10.0 Hz, 2 H), 2.58–2.52 (m, 3 H), 2.43–2.33 (m, 7 H), 2.28–2.17 (m, 3 H), 2.07 (dd, *J* = 5.4, 1.3 Hz, 2 H), 1.03 (t, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 5.4 Hz, 3 H), 0.85 (t, *J* = 7.0 Hz, 3 H), 0.79 (d, *J* = 5.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$, mixture of diastereomers) δ 176.1, 142.0, 136.1, 136.0, 134.8, 134.5, 128.2, 128.1, 123.42, 123.37, 123.0, 122.9, 116.72, 116.67, 109.0, 100.8, 97.6, 73.9, 71.1, 71.0, 70.6, 65.0, 59.7, 58.9, 56.4, 56.1, 53.6, 53.3, 49.5, 47.2, 40.0, 39.9, 37.99, 37.97, 37.4, 37.2, 24.3, 23.0, 20.2, 20.0, 15.2, 15.0; IR (film) 3055, 2936, 1724, 1612, 1489, 1468, 1336, 1249, 1187, 1088 cm$^{-1}$; MS (ES) *m/z* 433.2087 (MNa, 433.2103 calcd for $C_{24}H_{30}N_2O_4$), 410, 364, 338.

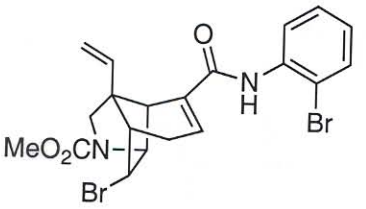
**Preparation of Furan 78**. Methyl trifluoromethanesulfonate (19 ml, 0.5 M in $CH_2Cl_2$ , 9.8 mmol) was added to a solution of aziridine **77** (4.0 mg, 9.7 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.0 mg, 11 mmol) in $CH_2Cl_2$ (0.2 mL) at 0 °C. After a period of 15 min, the reaction mixture was concentrated to remove the solvent and NaCN (4.8 mg, 98 mmol) and DMSO (0.2 mL) were added. The resulting mixture was heated at 90 °C for a period of 3 h. The reaction mixture was cooled to rt and diluted with EtOAc (4 mL) and $H_2O$ (2 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with $H_2O$ (2×), brine and then dried ($Na_2SO_4$), filtered and concentrated. The resulting crude residue was purified by chromatography (1:19 $CHCl_3$ (saturated with $NH_3$)/EtOAc) to afford 2.7 mg (80%) of hexacyclic furan **78** as a colorless film: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1 H), 7.29 (td, *J* = 7.7, 0.8 Hz, 1 H), 7.04 (td, *J* = 7.7, 0.9 Hz, 1 H), 7.02 (d, *J* = 7.7 Hz, 1 H), 6.17 (dd, *J* = 17.9, 10.9 Hz, 1 H), 5.37 (dd, *J* = 10.9, 0.9 Hz, 1 H), 5.33 (dd, *J* = 17.9, 0.9 Hz, 1 H), 5.15 ($AB_q$, $J_{AB}$ =10.8 Hz, $Dn_{AB}$ = 10.4 Hz, 2 H), 4.69 (br d, *J* = 5.2 Hz, 1 H), 4.40 (s, 1 H), 3.89 (d, *J* = 4.6 Hz, 1 H), 3.33 (s, 3 H), 2.77–2.75 (m, 1 H), 2.73 (d, *J* = 12.4 Hz, 1 H), 2.45 ($AB_q$, $J_{AB}$ =10.3 Hz, $Dn_{AB}$ = 21.9 Hz, 2 H), 2.38 (s, 3 H), 2.24 (br s, 1 H), 1.83 (ddd, *J* = 12.3, 7.1, 4.9 Hz, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) d 177.2, 142.0, 139.9, 128.6, 128.0, 127.4, 122.1, 116.0, 109.2, 80.0, 77.4, 71.3, 67.1, 65.7, 56.3, 55.5, 53.7, 48.9, 42.7, 42.6, 31.6; IR (film) 2936, 1720, 1611, 1488, 1467, 1345 cm$^{-1}$; MS (CI) *m/z* 352.1772 (M, 352.1787 calcd for $C_{21}H_{24}N_2O_3$), 321, 309, 277.

(1) The procedure we employed to purify THF, $Et_2O$, $CH_2Cl_2$, and toluene has been described: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. Triethylamine, pyridine, and diisopropylethylamine were distilled from $CaH_2$ at atmospheric pressure. Other general experimental details have been described: Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241-11250.
(2) Experimental details for the transformations summarized in Scheme 6 have been reported: Overman, L. E.; Sharp, M. J. *J. Org. Chem.* **1992**, *57*, 1035–1038.
(3) $^1$H NMR spectra of compounds prepared during preliminary studies that were not characterized by elemental analysis. Most intermediates gave highly complex spectra as they were mixtures of 2–4 carbamate conformational isomers.
(4) See the preceding paper in this journal.
(5) A mixture of conformational isomers. When signals for the two isomers are clearly separated and assignable, the absorption for the major isomer is noted in italics font and the total hydrogen count is specified with the signal of the major isomer.
(6) Sharp, M. J. Ph.D. Application of New Cyclization Strategies to Alkaloid Synthesis, *Ph.D. Dissertation*, University of California, Irvine 1991.

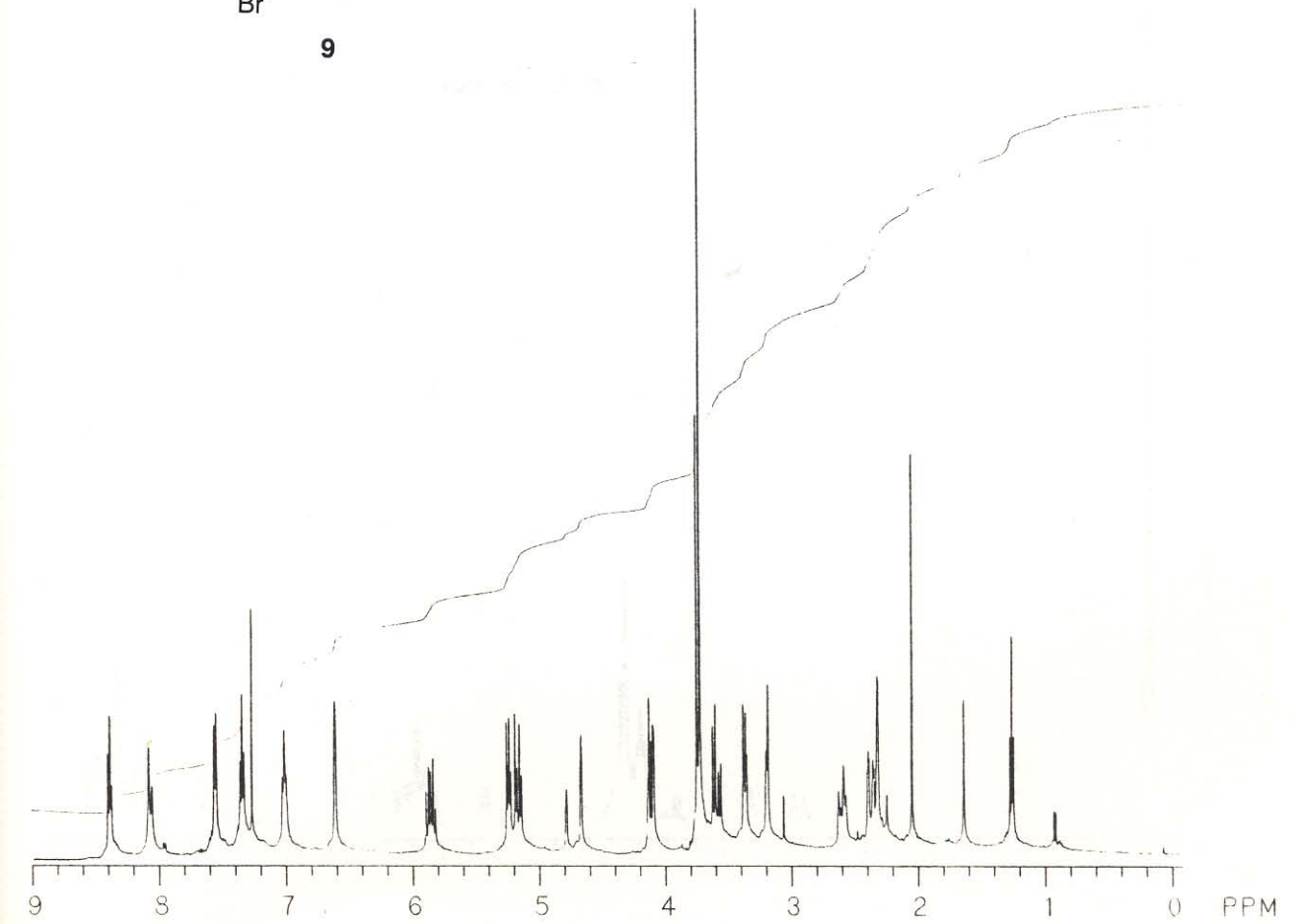


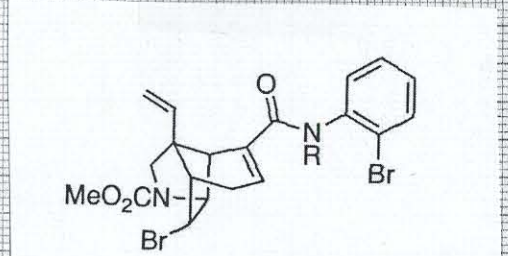

**8**



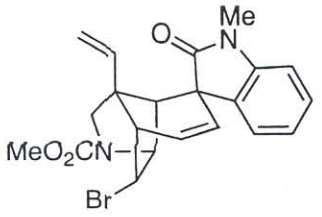



**9**

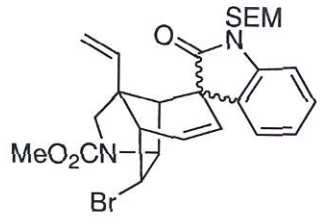




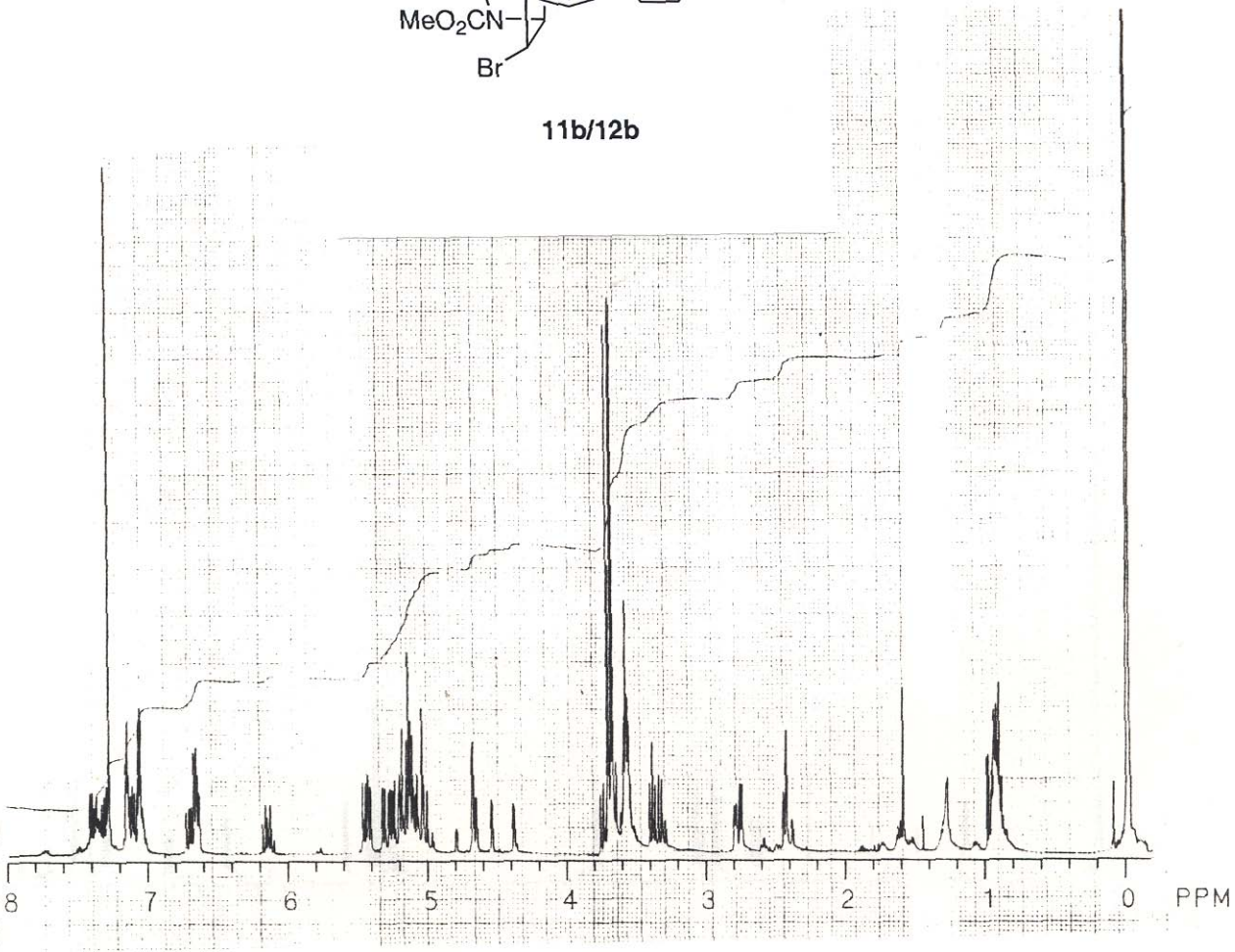

**10b** R = SEM

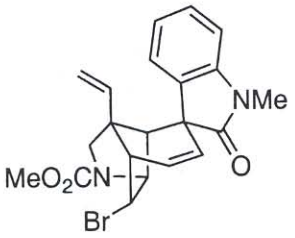



**11a**




**11b/12b**




NMe
O
MeO2CN
Br

**12a**


0.54
7
6
5
4
3
2
H9
H14
H19
H18
H3
H18
H15
H6
CH3O
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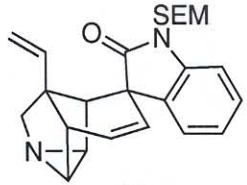
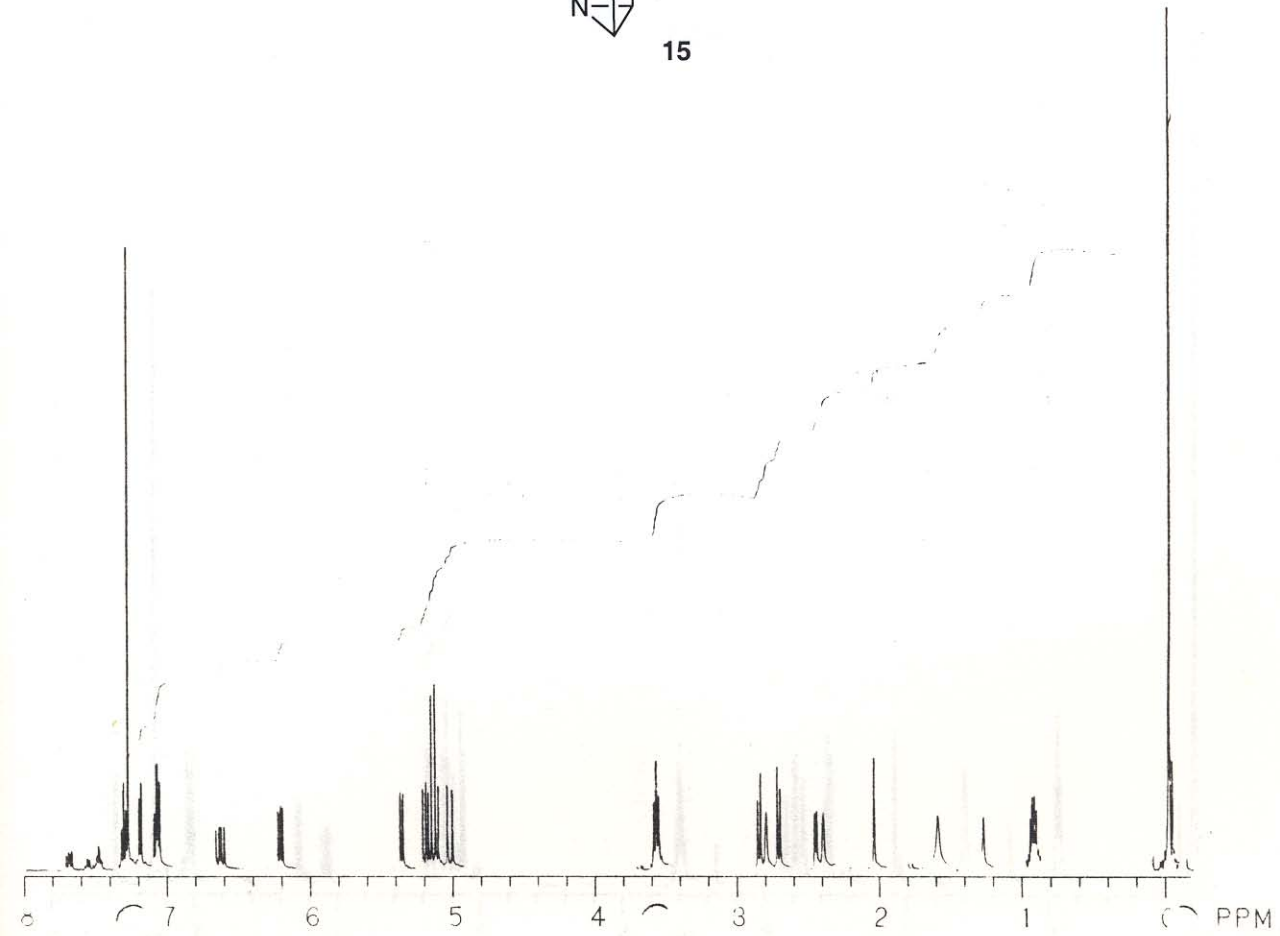
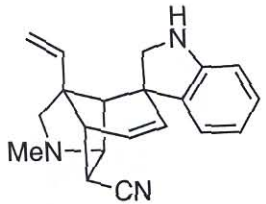



**15**

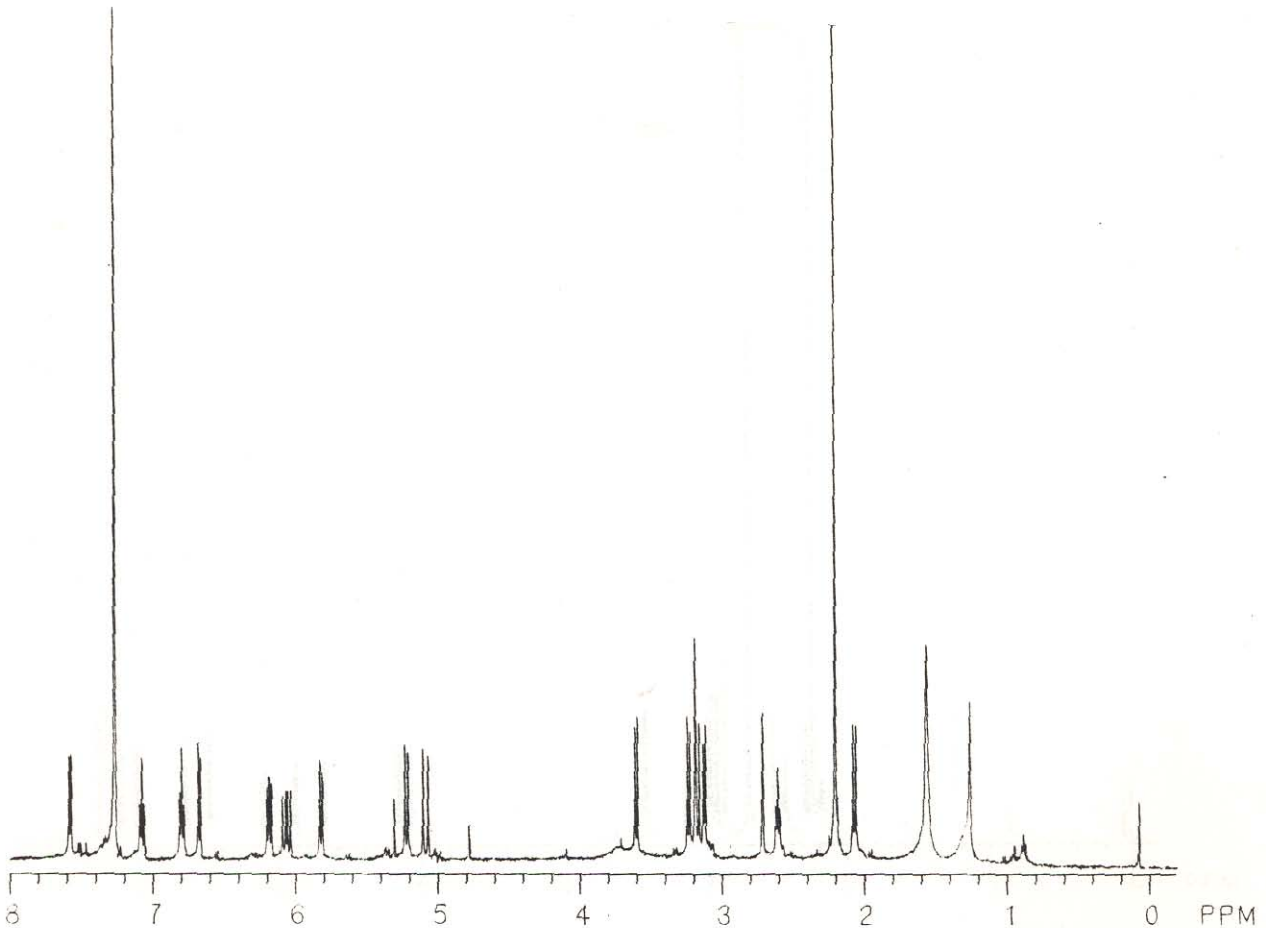


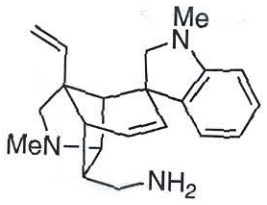

**16**


**18**

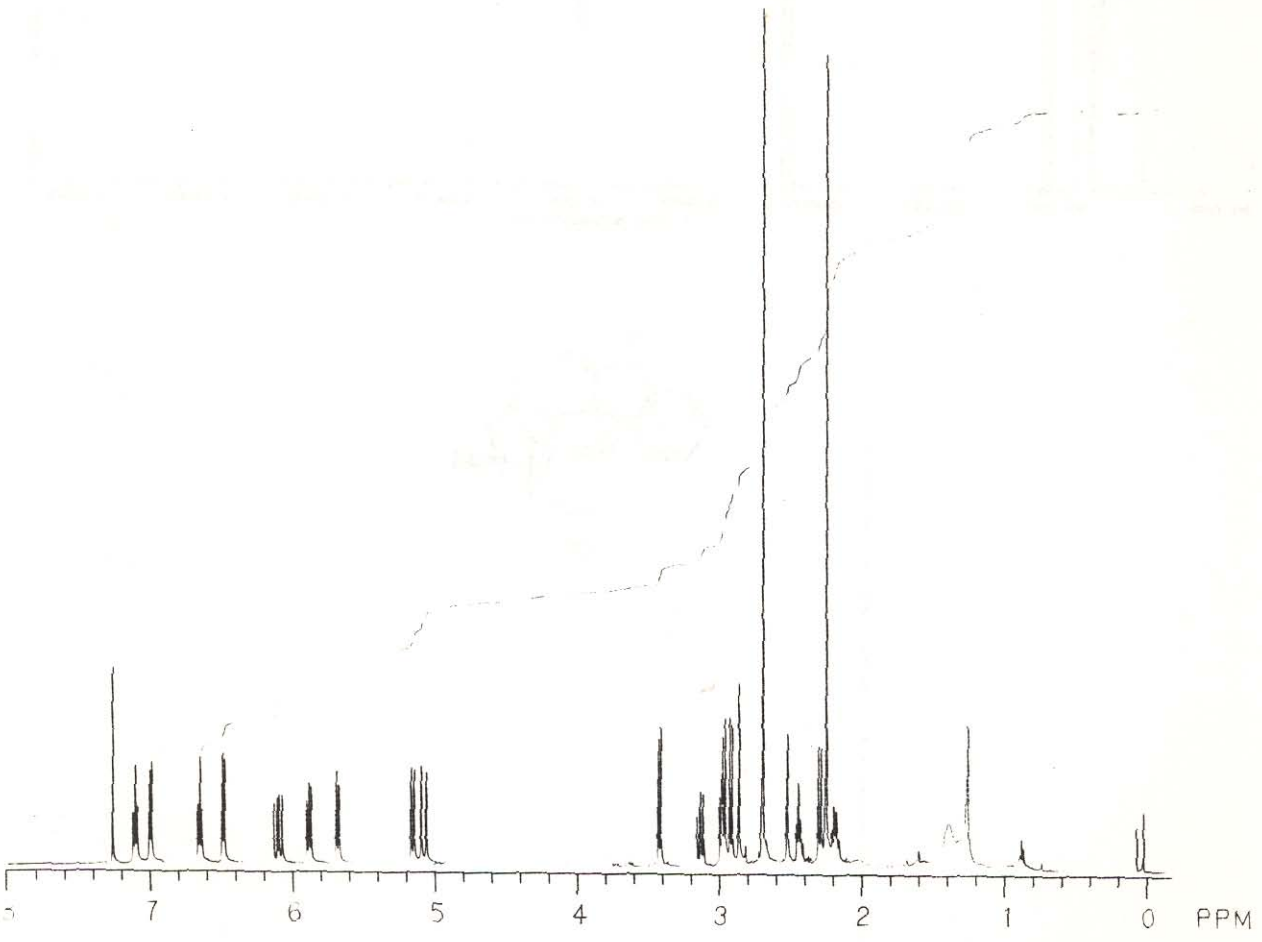


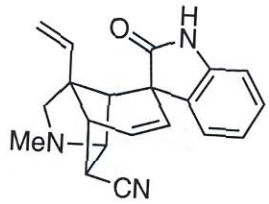

**20**



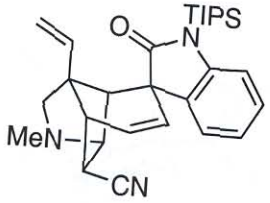



**21**

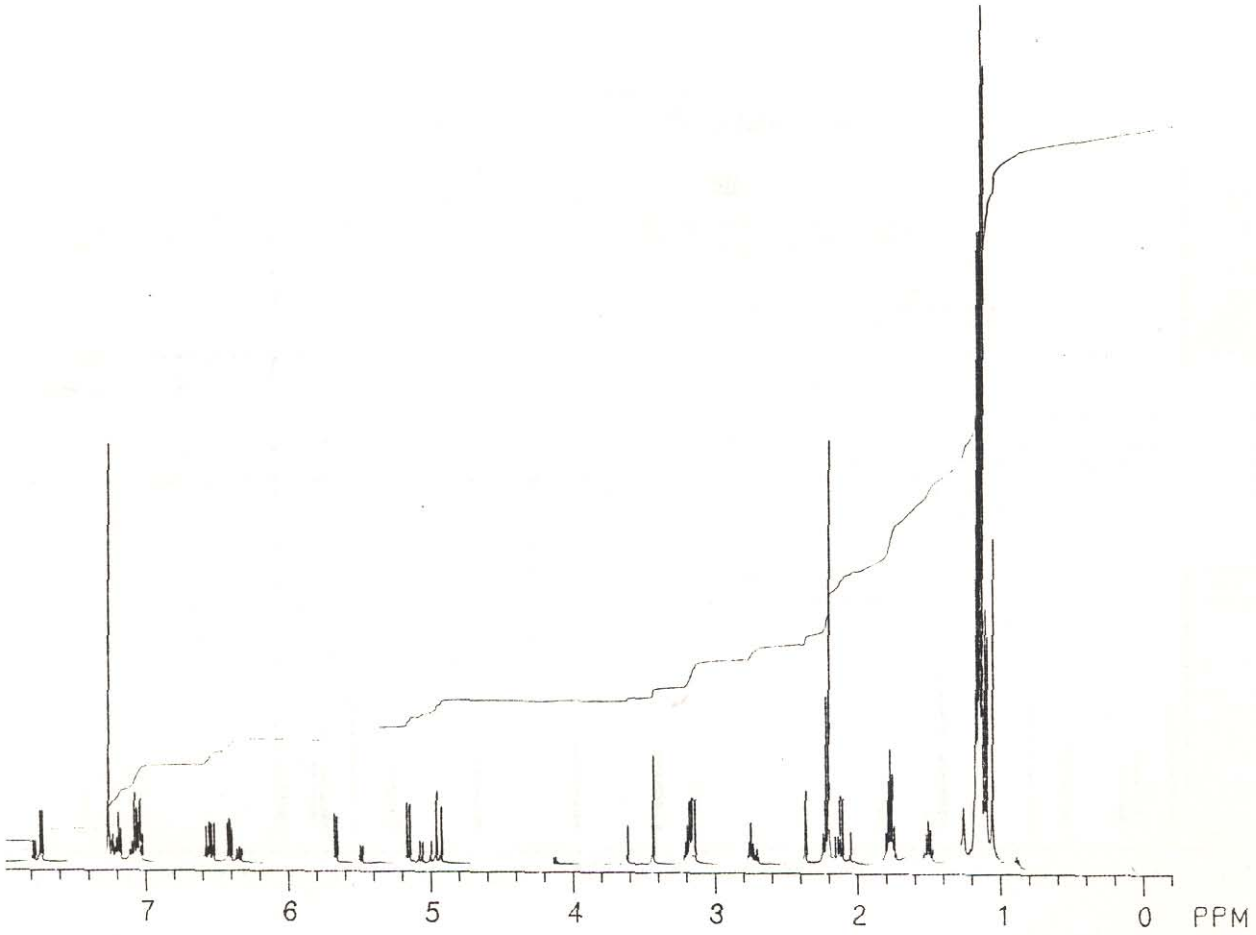




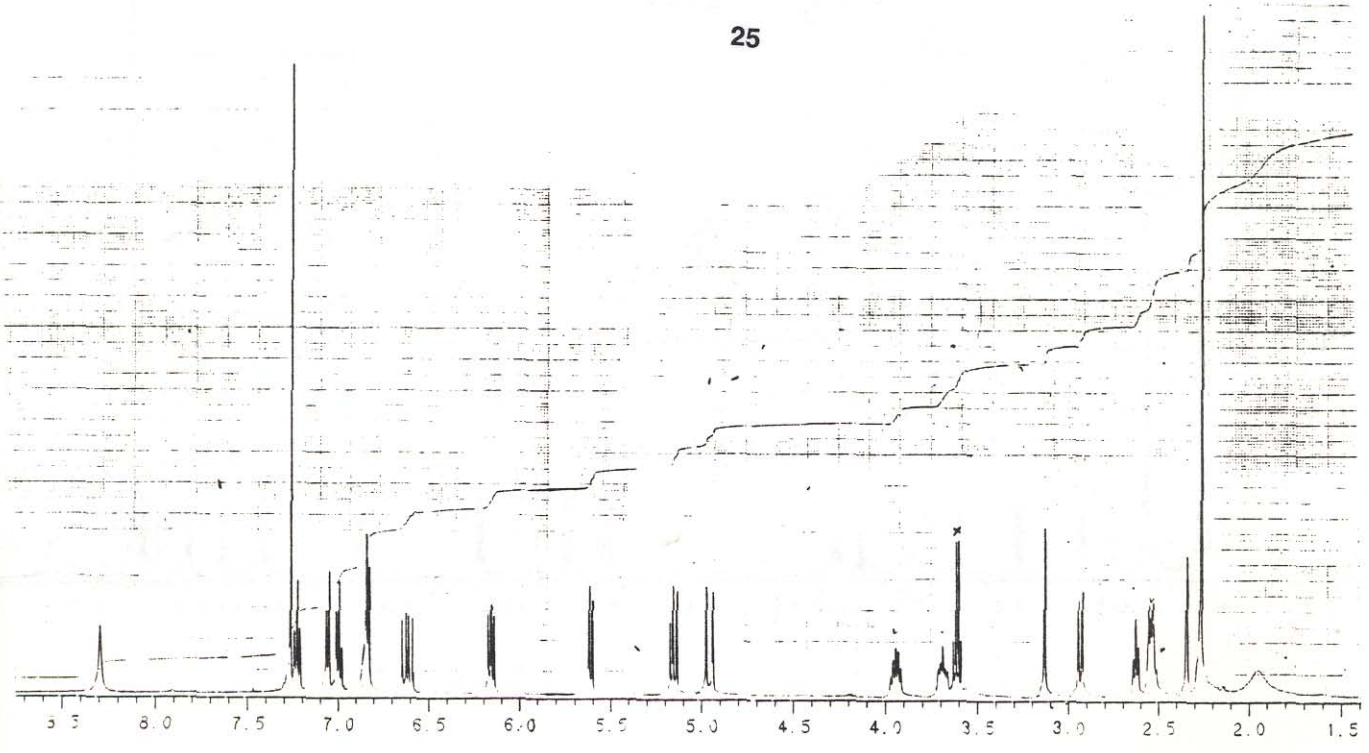

**22**

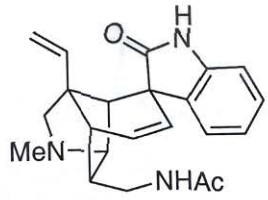



**23**

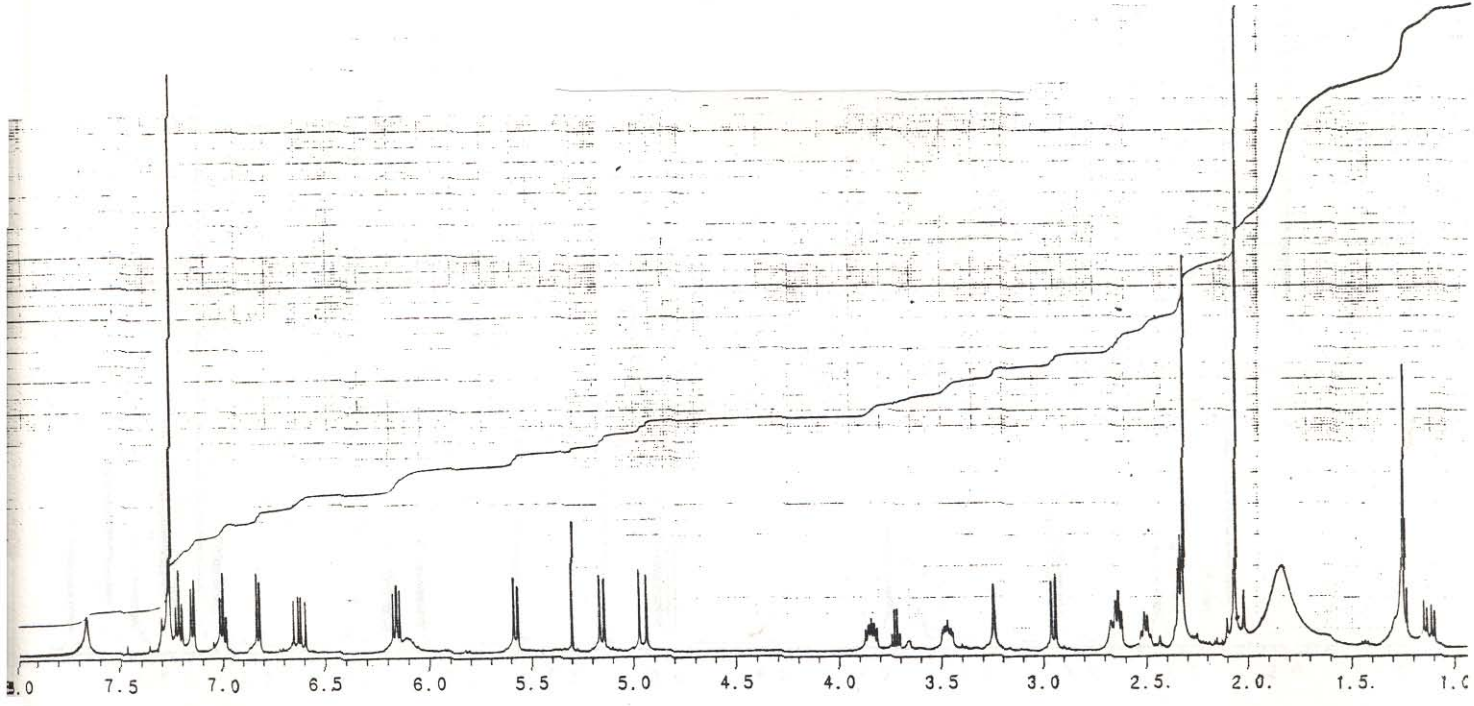



**25**

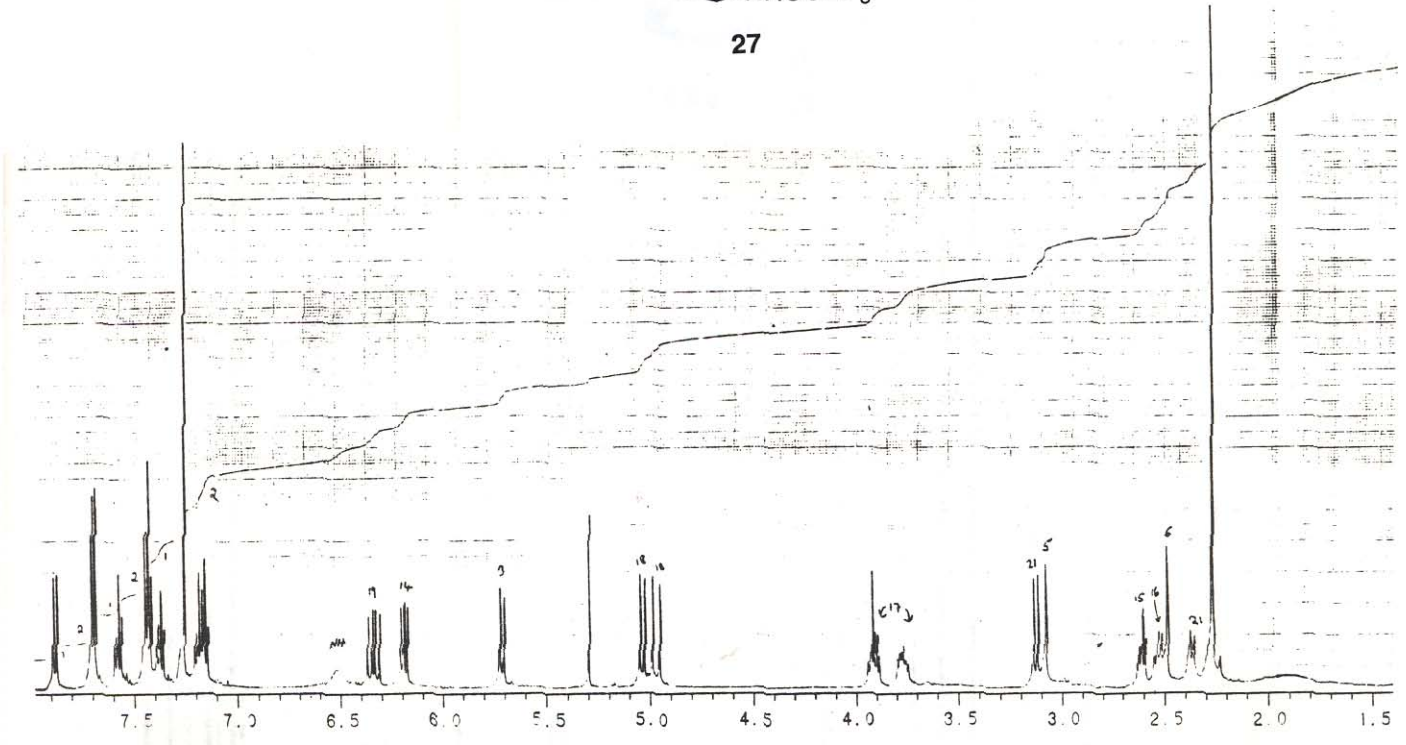


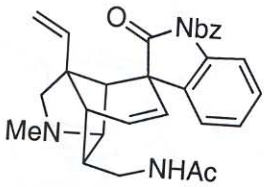



**26**

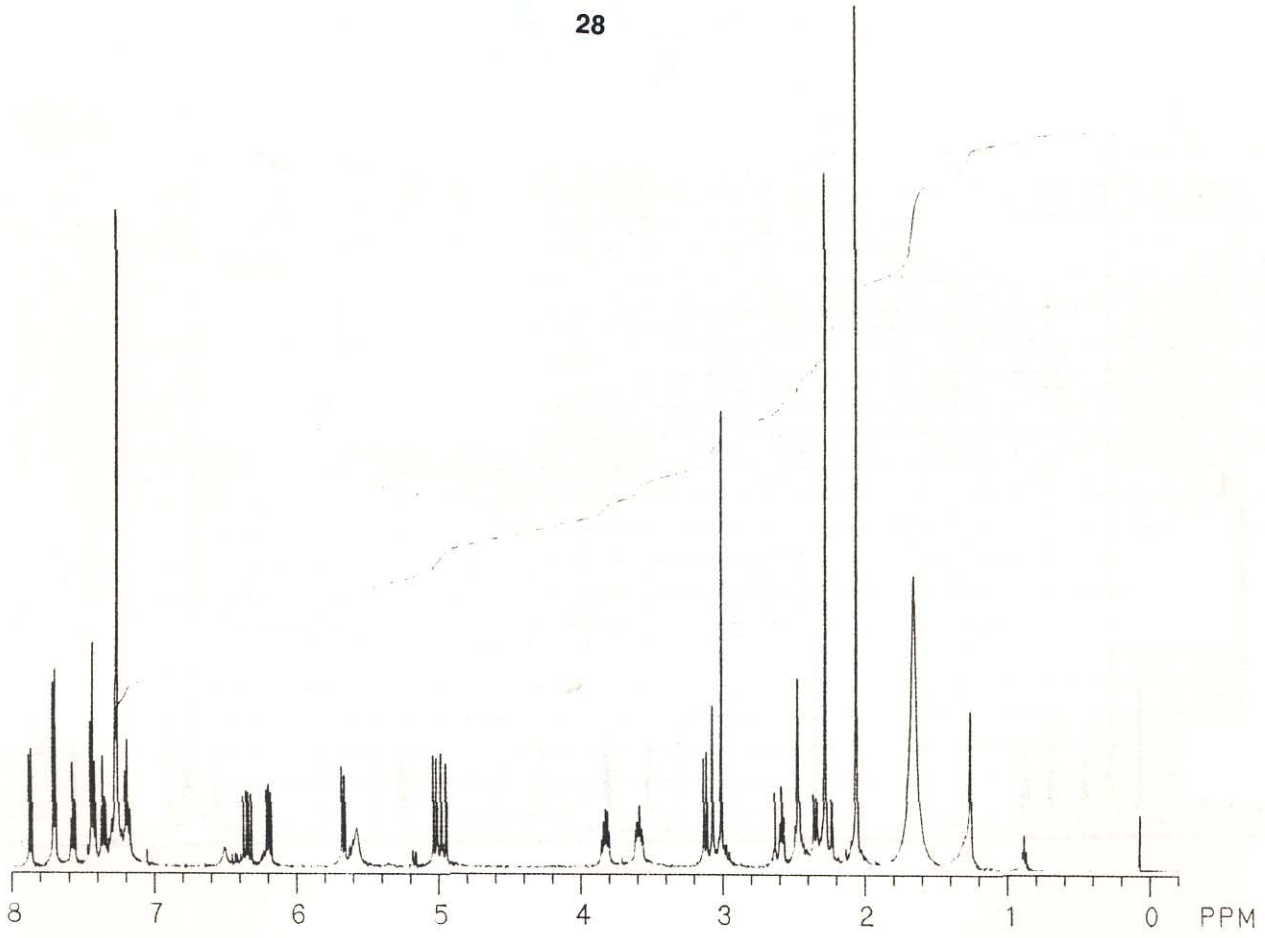


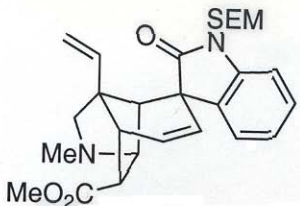

**27**






**28**



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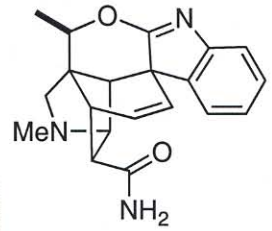
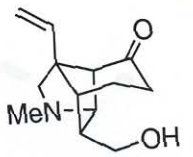
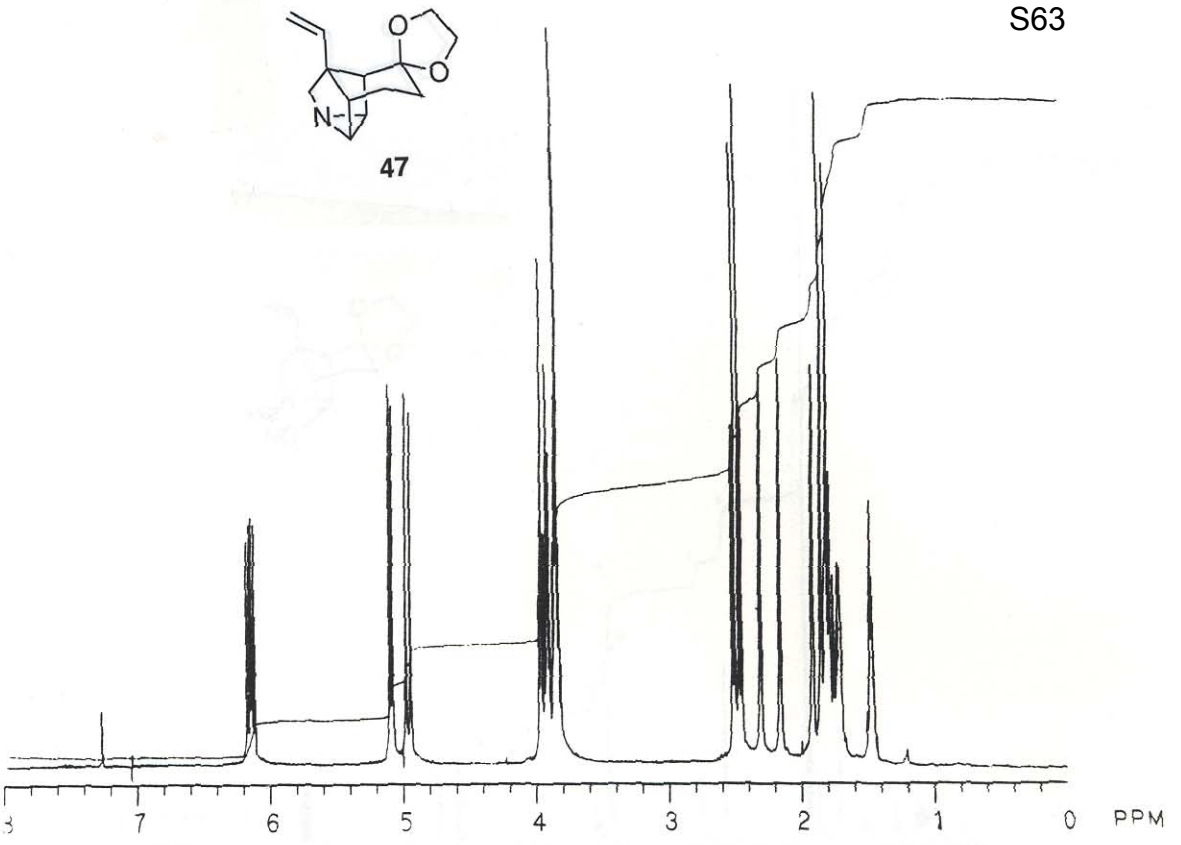


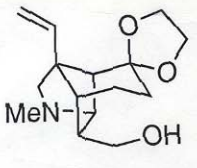

33



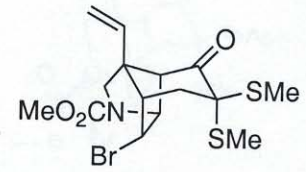

**45**




47




**50**




**55**

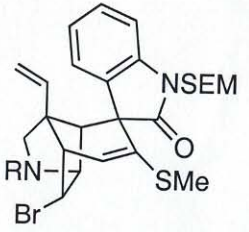
AM-II-287-1 (500)


57

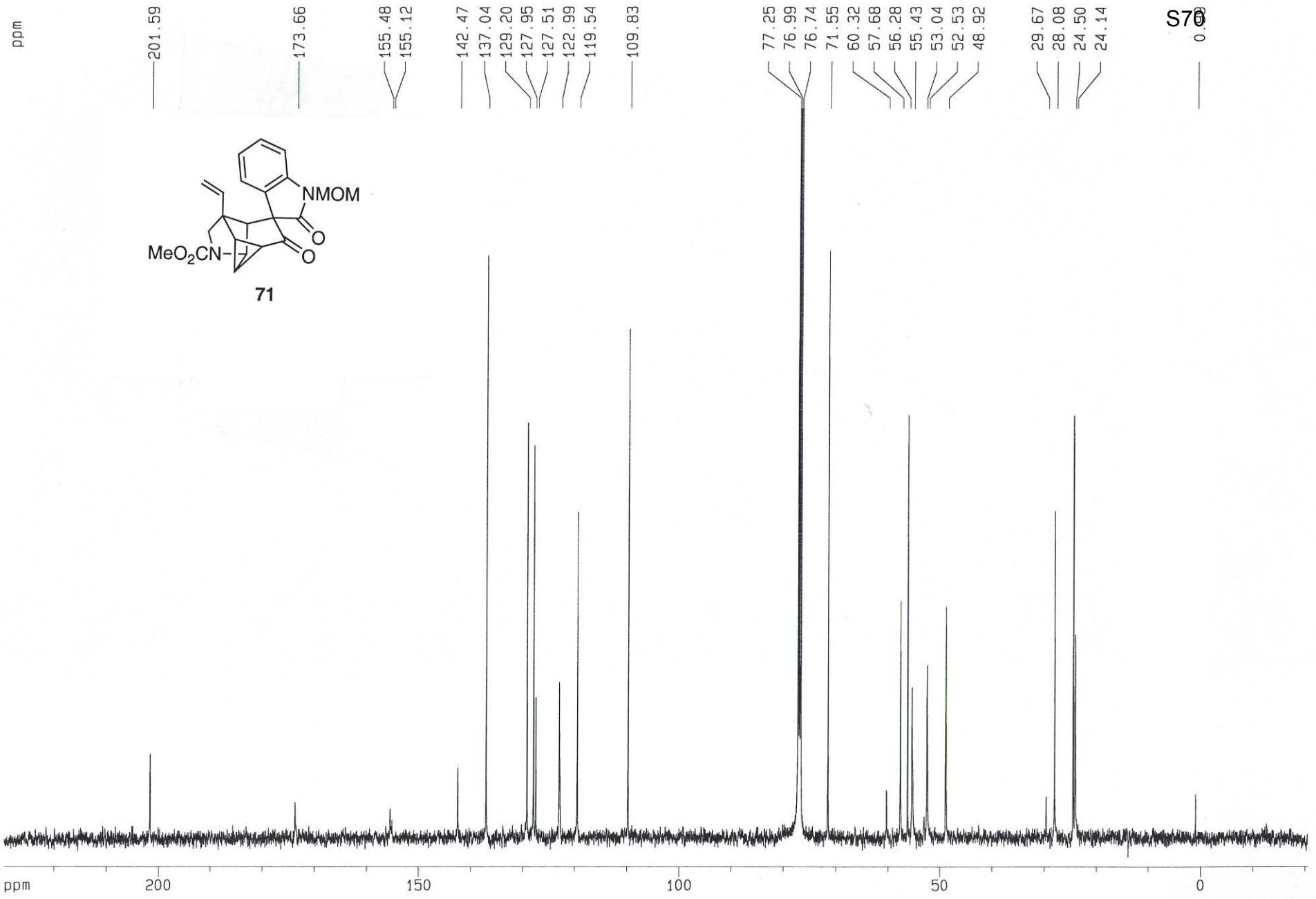

58

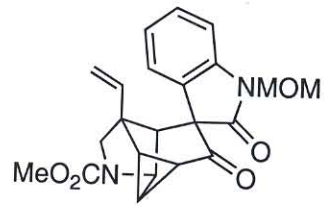
Am-III-101-1 (500)


**59** R = $CO_2Me$

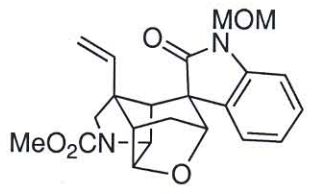



**60** R = $CO_2Me$

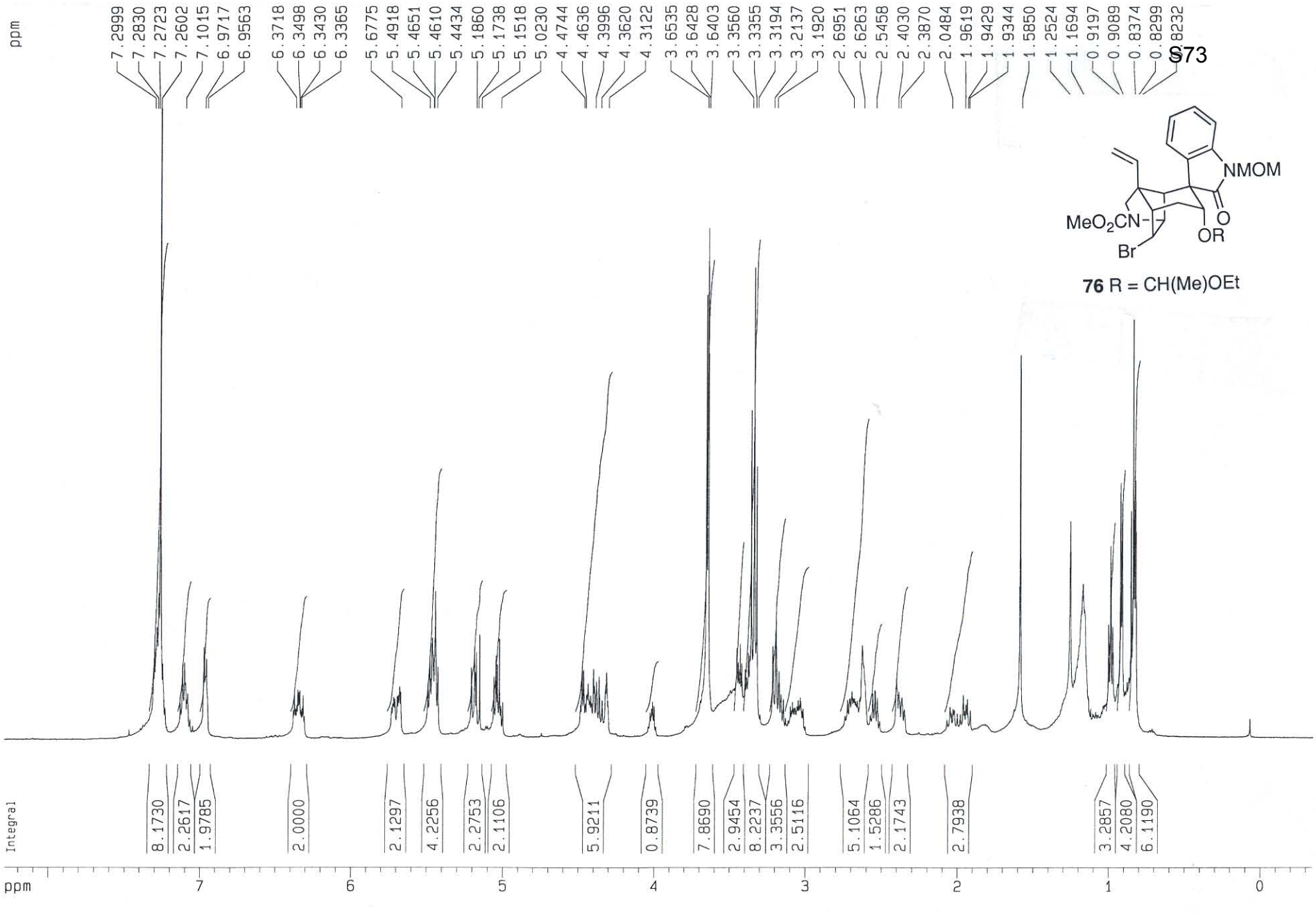

ppm
201.59
173.66
155.48
155.12
142.47
137.04
129.20
127.95
127.51
122.99
119.54
109.83
77.25
76.99
76.74
71.55
60.32
57.68
56.28
55.43
53.04
52.53
48.92
29.67
28.08
24.50
24.14
0.00
NMOM
O
O
MeO2CN
71
ppm
200
150
100
50
0



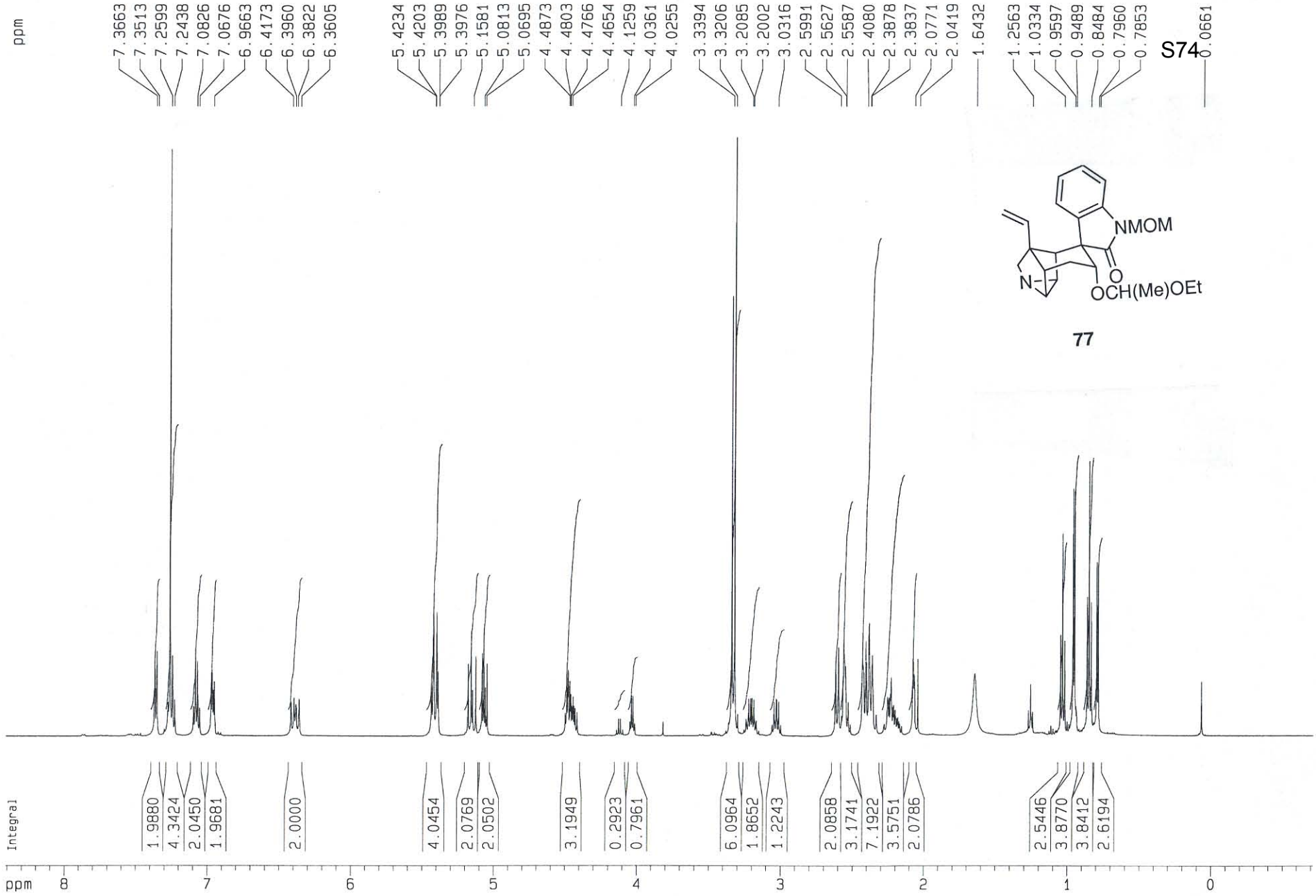

71



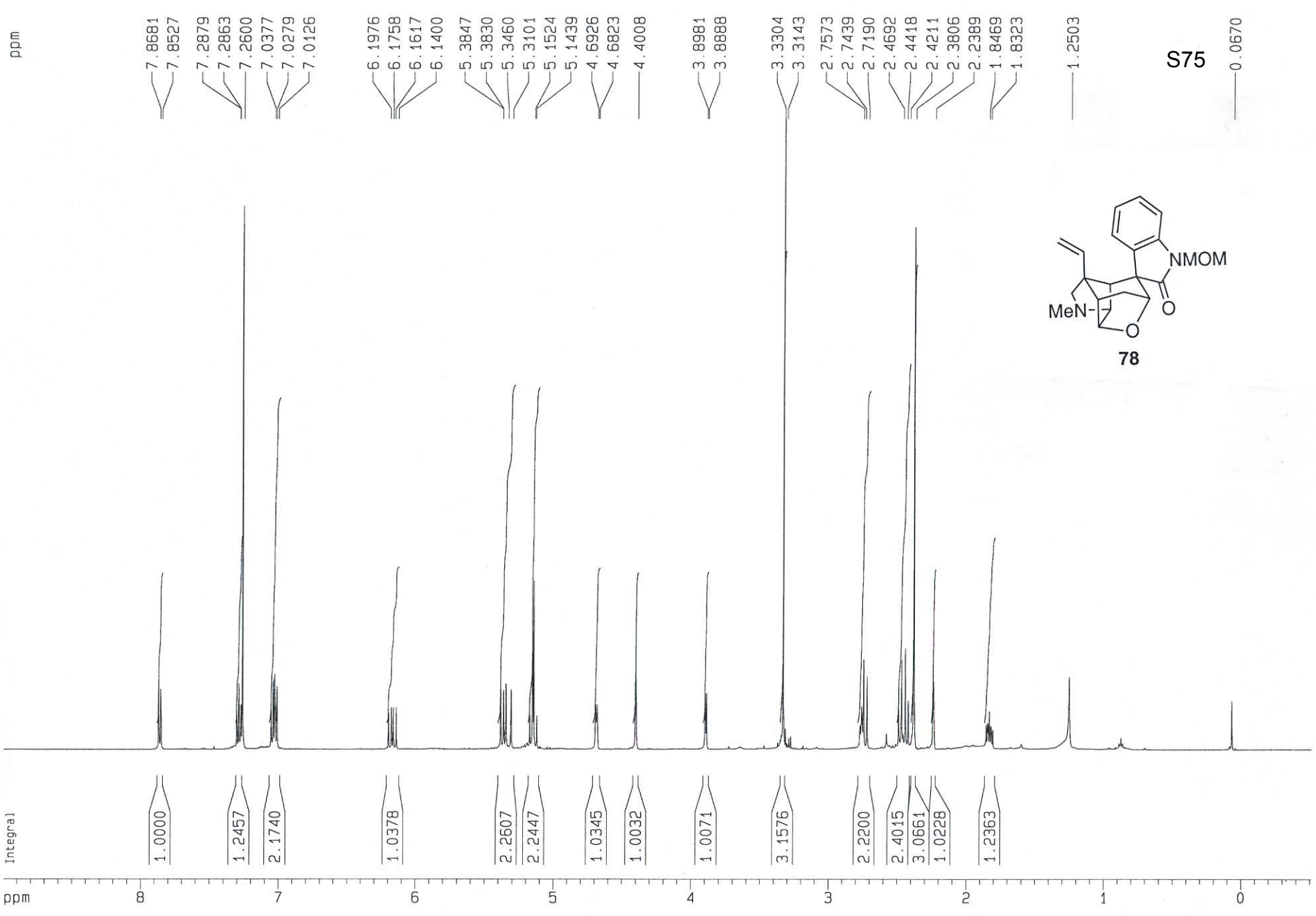

**75**


ppm
7.2999
7.2830
7.2723
7.2602
7.1015
6.9717
6.9563
6.3718
6.3498
6.3430
6.3365
5.6775
5.4918
5.4651
5.4610
5.4434
5.1860
5.1738
5.1518
5.0230
4.4744
4.4636
4.3996
4.3620
4.3122
3.6535
3.6428
3.6403
3.3560
3.3355
3.3194
3.2137
3.1920
2.6951
2.6263
2.5458
2.4030
2.3870
2.0484
1.9619
1.9429
1.9344
1.5850
1.2524
1.1694
0.9197
0.9089
0.8374
0.8299
0.8232
NMOM
MeO2CN-
O
OR
Br
Integral
8.1730
2.2617
1.9785
2.0000
2.1297
4.2256
2.2753
2.1106
5.9211
0.8739
7.8690
2.9454
8.2237
3.3556
2.5116
5.1064
1.5286
2.1743
2.7938
3.2857
4.2080
6.1190
ppm
7
6
5
4
3
2
1
0

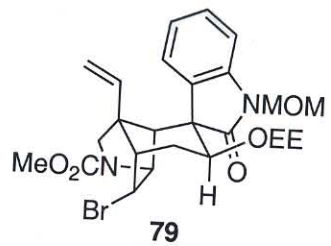
**76** R = CH(Me)OEt


ppm
7.3663
7.3513
7.2599
7.2438
7.0826
7.0676
6.9663
6.4173
6.3960
6.3822
6.3605
5.4234
5.4203
5.3989
5.3976
5.1581
5.0813
5.0695
4.4873
4.4803
4.4766
4.4654
4.1259
4.0361
4.0255
3.3394
3.3206
3.2085
3.2002
3.0316
2.5991
2.5627
2.5587
2.4080
2.3878
2.3837
2.0771
2.0419
1.6432
1.2563
1.0334
0.9597
0.9489
0.8484
0.7960
0.7853
0.0661
NMOM
O
N
OCH(Me)OEt
Integral
1.9880
4.3424
2.0450
1.9681
2.0000
4.0454
2.0769
2.0502
3.1949
0.2923
0.7961
6.0964
1.8652
1.2243
2.0858
3.1741
7.1922
3.5751
2.0786
2.5446
3.8770
3.8412
2.6194
ppm
8
7
6
5
4
3
2
1
0

77

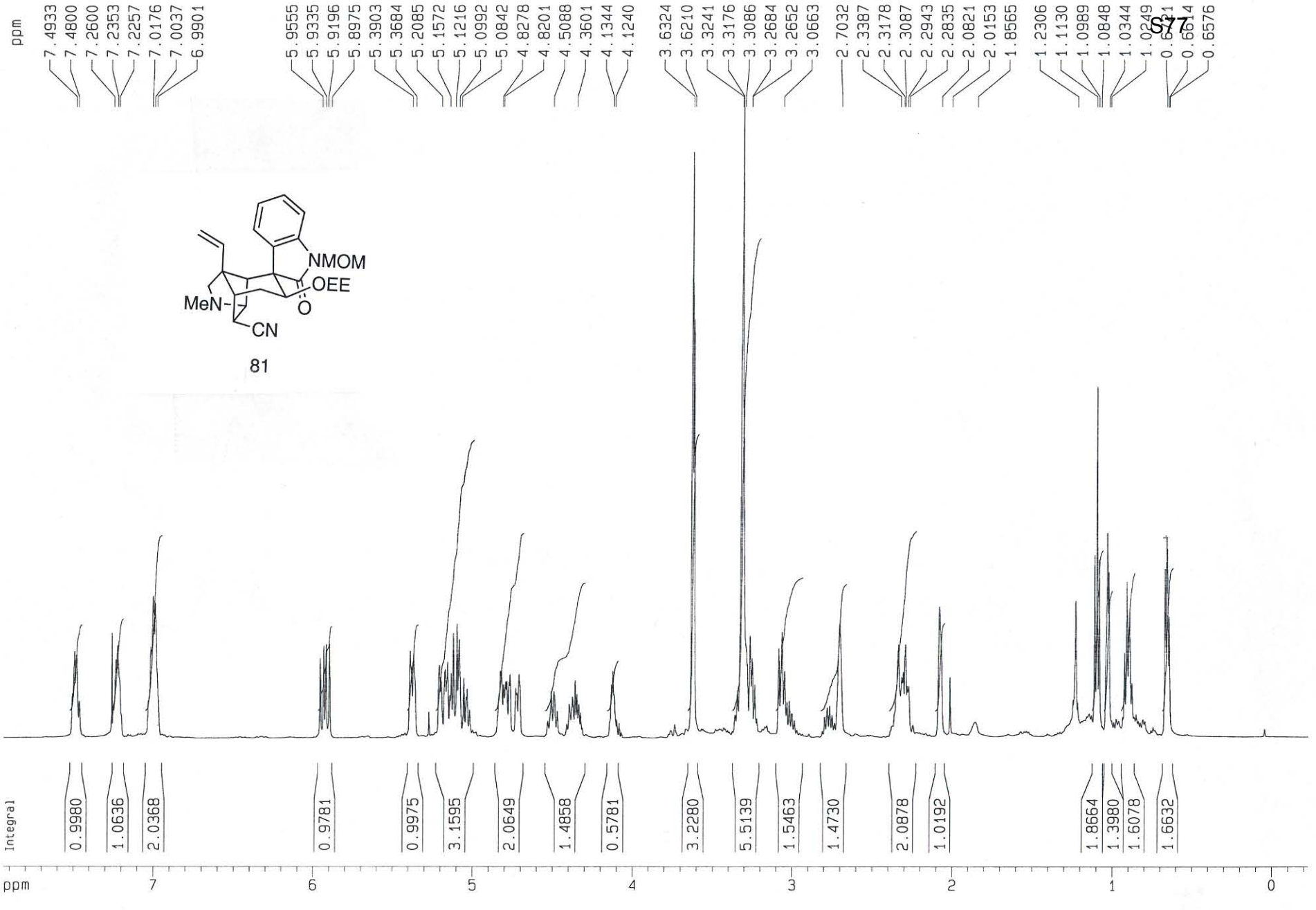

ppm
7.8681
7.8527
7.2879
7.2863
7.2600
7.0377
7.0279
7.0126
6.1976
6.1758
6.1617
6.1400
5.3847
5.3830
5.3460
5.3101
5.1524
5.1439
4.6926
4.6823
4.4008
3.8981
3.8888
3.3304
3.3143
2.7573
2.7439
2.7190
2.4692
2.4418
2.4211
2.3806
2.2389
1.8469
1.8323
1.2503
0.0670
NMOM
MeN
O
O
Integral
1.0000
1.2457
2.1740
1.0378
2.2607
2.2447
1.0345
1.0032
1.0071
3.1576
2.2200
2.4015
3.0661
1.0228
1.2363
ppm
8
7
6
5
4
3
2
1
0

**78**

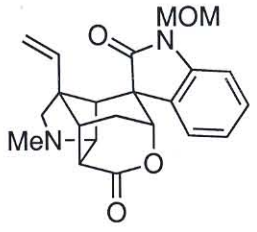

NMOM
OEE
MeO2CN
O
H
Br

79


ppm
7.5660
7.5516
7.2600
7.2543
7.2483
7.0469
7.0315
7.0165
5.9500
5.9274
5.9140
5.8920
5.3114
5.2894
5.1756
5.1664
5.1397
5.1073
4.9584
4.3704
4.3602
4.3370
4.3265
4.3162
3.9646
3.9392
3.4914
3.3514
3.3429
3.0654
3.0503
2.9819
2.7088
2.7025
2.6877
2.1936
2.0734
2.0024
1.9987
1.9813
1.9776
1.2518
1.1619
1.1517
1.1237
1.1095
0.8903
0.8417
0.7312
Integral
1.9473
2.7714
4.0804
2.0032
2.0345
7.6705
0.8825
1.9577
1.9213
1.1937
6.1383
1.2903
2.0020
1.0750
1.2352
4.1055
3.4623
1.3339
6.1083
2.0835
2.0540
3.0408
3.5091
3.2147
3.2905
ppm
7
6
5
4
3
2
1
0


ppm
7.4933
7.4800
7.2600
7.2353
7.2257
7.0176
7.0037
6.9901
5.9555
5.9335
5.9196
5.8975
5.3903
5.3684
5.2085
5.1572
5.1216
5.0992
5.0842
4.8278
4.8201
4.5088
4.3601
4.1344
4.1240
3.6324
3.6210
3.3241
3.3176
3.3086
3.2684
3.2652
3.0663
2.7032
2.3387
2.3178
2.3087
2.2943
2.2835
2.0821
2.0153
1.8565
1.2306
1.1130
1.0989
1.0848
1.0344
1.0249
0.6611
0.6614
0.6576
NMOM
OEE
O
MeN-
CN
81
Integral
0.9980
1.0636
2.0368
0.9781
0.9975
3.1595
2.0649
1.4858
0.5781
3.2280
5.5139
1.5463
1.4730
2.0878
1.0192
1.8664
1.3980
1.6078
1.6632
ppm
7
6
5
4
3
2
1
0


82




**83**