

## First enantioselective synthesis of tetracyclic intermediates en route to madangamine D

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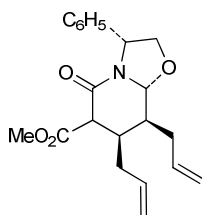
### Supporting Information Available

- I) Experimental procedures and spectroscopic data for all compounds: pages 1-16
- II) Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all compounds: pages 17-34

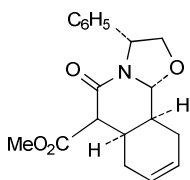
### Experimental procedures and spectroscopic data

**General Procedures:** All air sensitive manipulations were carried out under a dry argon or nitrogen atmosphere. THF and toluene were carefully dried and distilled from sodium/benzophenone prior to use.  $\text{CH}_2\text{Cl}_2$  was dried and distilled from  $\text{CaH}_2$ . Other solvents and all standard reagents were purchased from Aldrich, Fluka or Alfa Aesar and were used without further purification.

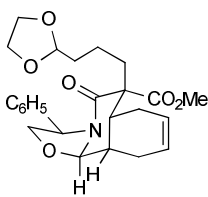
Analytical thin-layer chromatography was performed on  $\text{SiO}_2$  (Merck silica gel 60 F<sub>254</sub>), and the spots were located with 1% aqueous  $\text{KMnO}_4$ . Chromatography refers to flash chromatography and was carried out on  $\text{SiO}_2$  (SDS silica gel 60 ACC, 35-75 mm, 230-240 mesh ASTM). NMR spectra were recorded at 300 or 400 MHz ( $^1\text{H}$ ) and 75.4 or 100.6 MHz ( $^{13}\text{C}$ ), and chemical shifts are reported in  $\delta$  values downfield from TMS or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, integrated intensity, multiplicity, coupling constant ( $J$ ) in hertz (Hz), and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avantar 320 FT-IR and only noteworthy IR absorptions ( $\text{cm}^{-1}$ ) are listed. Optical rotations were measured on Perkin-Elmer 241 polarimeter.  $[\alpha]_D$  values are given in  $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$ . High resolution mass spectra (HMRS; LC/MSD TOF Agilent Technologies) were performed by Centres Científics i Tecnològics de la Universitat de Barcelona.



**(3R,7R,8S,8aR)-7,8-Diallyl-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,7,8,8a-hexahydro-5H-oxazolo[3,2-a]pyridine (2):** LiCl (1.2 g, 28.4 mmol) was dried at 80 °C for 1 h under vacuum (10–15 mmHg) in a three-necked, 250 mL round-bottomed flask. Then, CuI (5.4 g, 28.4 mmol) and THF (150 mL) were added under an inert atmosphere, and the mixture was stirred at room temperature for 5 min. The suspension was cooled to –78 °C, and allylmagnesium bromide (28.4 mL of a 1 M solution in Et<sub>2</sub>O, 28.4 mmol), TMSCl (3.6 mL, 28.4 mmol), and unsaturated lactam **1** (7.11 mmol) in THF (5 mL) were successively added. The resulting mixture was stirred at –78 °C for 18 h. The reaction was quenched with saturated aqueous NH<sub>4</sub>Cl, and the resulting mixture was filtered through Celite<sup>®</sup>. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 7:3 hexane–EtOAc) of the resulting oil gave **2** (2.05 g, 81% yield) as a mixture of C-6 epimers (ratio 2:1). (6*S*)-**2** (major): IR (film):  $\nu = 1665, 1736$  (CO) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.80 (1 H, ddd,  $J = 14.1, 12.0, 9.0$  Hz, CH<sub>2</sub> allyl), 2.16 (1 H, dt,  $J = 14.1, 9.3, 9.3$  Hz, CH<sub>2</sub> allyl), 2.34 (1 H, dm,  $J = 12.0$  Hz, H-7), 2.44–2.70 (3 H, m, H-8, CH<sub>2</sub> allyl), 3.43 (1 H, d,  $J = 1.5$  Hz, H-6), 3.60 (3 H, s, CH<sub>3</sub>O), 4.02 (1 H, dd,  $J = 9.3, 1.8$  Hz, H-2), 4.15 (1 H, dd,  $J = 9.3, 7.2$  Hz, H-2), 4.62 (1 H, d,  $J = 9.6$  Hz, H-8a), 4.91 (1 H, dd,  $J = 7.2, 1.8$  Hz, H-3), 5.14 (4 H, m, CH<sub>2</sub>=), 5.68 (1 H, dddd,  $J = 15.0, 10.2, 9.0, 4.8$  Hz, CH=), 5.84 (1 H, dddd,  $J = 15.3, 9.9, 8.7, 5.1$  Hz, CH=), 7.26–7.33 (5 H, m, C<sub>6</sub>H<sub>5</sub>);  $\delta_{\text{C}}$  (75.4 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 31.6, 31.8 (CH<sub>2</sub>), 36.9 (C-7), 38.5 (C-8), 51.5 (C-6), 52.3 (CH<sub>3</sub>O), 59.6 (C-3), 73.9 (C-2), 89.4 (C-8a), 117.4, 118.5 (CH<sub>2</sub>=), 126.4, 128.2 (C-*o*, *m*), 127.4 (C-*p*), 134.4, 134.8 (CH=), 140.5 (C-*i*), 162.3 (NCO), 170.6 (COO);  $m/z$  355 (M<sup>+</sup>, 1), 312 (21), 296 (13), 282 (8), 272 (8), 254 (5). (6*R*)-**2** (minor):  $\delta_{\text{C}}$  (75.4 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 32.8, 35.9 (CH<sub>2</sub>), 36.5 (C-7), 41.9 (C-8), 52.5 (CH<sub>3</sub>O), 53.7 (C-6), 59.2 (C-3), 73.8 (C-2), 89.8 (C-8a), 118.4, 119.6 (CH<sub>2</sub>=), 126.7–128.5 (C-*o*, *m*, *p*), 132.8, 133.4 (CH=), 140.6 (C-*i*), 162.5 (NCO), 170.8 (COO);  $m/z$  355 (M<sup>+</sup>, 2), 314 (5), 272 (8), 254 (4), 176 (6), 148 (11), 128 (7), 120 (17), 119 (12), 117 (20), 105 (13), 104 (100); HRMS (ESI) calcd for [C<sub>21</sub>H<sub>25</sub>NO<sub>4</sub> + H]<sup>+</sup>: 356.1783, found: 356.1779.

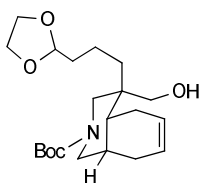


**(3R,6aR,10aS,10bR)-6-(Methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5H-oxazolo[2,3-a]isoquinoline (3):** Second-generation Grubbs catalyst (642 mg) was added to a solution of lactam **2** (3.58 g, 10.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.44 L). The mixture was stirred for 18 h at room temperature, and the resulting suspension was concentrated. Flash chromatography (4:1 to 3:2 hexane–EtOAc) of the residue gave tricyclic lactam **3** as a mixture of C-6 epimers (2.8 g, 85% yield). Compound (6*R*)-**3** (major): IR (film):  $\nu = 1667, 1738$  (CO) cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 2.00 (1 H, m, H-7), 2.20 (1 H, m, H-7), 2.43 (2 H, m, H-10), 2.50 (1 H, m, H-6a), 2.70 (1 H, m, H-10a), 3.18 (1 H, s, H-6), 3.60 (3 H, s, CH<sub>3</sub>O), 3.96 (1 H, dd,  $J = 9.0, 1.2$  Hz, H-2), 4.12 (1 H, dd,  $J = 9.0, 6.9$  Hz, H-2), 4.85 (1 H, d,  $J = 9.9$  Hz, H-10b), 4.92 (1 H, dd,  $J = 6.9, 1.2$  Hz, H-3), 5.69 (2 H, m, H-8, H-9), 7.22–7.35 (5 H, m, C<sub>6</sub>H<sub>5</sub>);  $\delta_{\text{C}}$  (75.4 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 25.1 (C-10), 28.0 (C-7), 32.6 (C-10a), 33.5 (C-6a), 52.2 (CH<sub>3</sub>O), 53.9 (C-6), 59.4 (C-3), 73.6 (C-2), 87.1 (C-10b), 124.4, 124.8 (C-8, C-9), 126.8, 128.0 (C-*o*, *m*), 127.2 (C-*p*), 140.6 (C-*i*), 162.0 (NCO), 170.2 (COO). Compound (6*S*)-**3** (minor):  $\delta_{\text{C}}$  (75.4 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si; selected resonances) 24.7 (C-10), 32.6 (C-10a), 36.7 (C-6a), 51.8 (CH<sub>3</sub>), 53.7 (C-6), 59.6 (C-3), 73.3 (C-2), 86.6 (C-10b), 140.9 (C-*i*), 162.4 (NCO), 169.1 (COO). Anal. Calcd for C<sub>19</sub>H<sub>21</sub>O<sub>4</sub>N· $\frac{1}{4}$  H<sub>2</sub>O: C, 68.76; H, 6.53; N, 4.22. Found: C, 68.82; H, 6.90; N, 4.20.



**(3R,6R,6aR,10aS,10bR)-6-[3-(1,3-Dioxolan-2-yl)propyl]-6-(methoxycarbonyl)-5-oxo-3-phenyl-2,3,6,6a,7,10,10a,10b-octahydro-5H-oxazolo[3,2-a]isoquinoline (4):** A solution of isoquinoline **3** (880 mg, 2.691 mmol) in DMF (2 mL) was added to a cooled (0 °C) suspension of NaH (161 mg of a 60% dispersion in mineral oil, 4.031 mmol) in anhydrous DMF (20 mL) under an inert atmosphere, and the resulting mixture was stirred at 0 °C for 1 h. 2-(3-Bromopropyl)-1,3-dioxolane (1.94 g, 13.4 mmol) and TBAI (198 mg, 0.538 mmol) were added at 0 °C, and the mixture was stirred overnight at room temperature. Saturated aqueous NH<sub>4</sub>Cl was added, and the mixture was extracted with diethyl ether and then with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Flash

chromatography (hexane to 6:4 hexane–EtOAc) of the resulting oil afforded lactam **4** (905 mg, 80%):  $[\alpha]_D^{22} = -29.7$  (*c* 2.1 in  $\text{CHCl}_3$ ); IR (film):  $\nu = 1668, 1737$  (CO)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.13–1.23 (2 H, m, H-2'), 1.40 (2 H, m, H-3'), 1.81–1.97 (3 H, m, 2H-1', H-7), 2.11–2.20 (2 H, 3m, H-7, H-10), 2.28 (1 H, ddd,  $J = 12.4, 6.0, 4.0$  Hz, H-6a), 2.45 (1 H, m, H-10), 2.54 (1 H, m, H-10a), 3.70 (3 H, s,  $\text{CH}_3\text{O}$ ), 3.77, 3.89 (4 H, 2m,  $\text{CH}_2\text{O}$ ), 4.07 (1 H, dd,  $J = 9.2, 1.6$  Hz, H-2), 4.15 (1 H, dd,  $J = 9.2$  Hz, H-2), 4.61 (1 H, t,  $J = 4.8$  Hz, H-4'), 4.91 (2 H, m, H-3, H-10b), 5.67 (2 H, m, H-8, H-9), 7.20–7.39 (5 H, m,  $\text{C}_6\text{H}_5$ );  $\delta_{\text{C}}$  (100.6 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 19.9 (C-2'), 25.6, 25.7 (C-7, C-10), 33.6 (C-10a), 34.1 (C-3'), 37.4 (C-1'), 39.5 (C-6a), 51.9 ( $\text{CH}_3\text{O}$ ), 58.9 (C-6), 59.8 (C-3), 64.6, 64.7 ( $2\text{CH}_2\text{O}$ ), 73.5 (C-2), 87.5 (C-10b), 104.4 (C-4'), 124.3, 124.7 (C-8, C-9), 126.8, 128.3 (C-*o*, *m*), 127.5 (C-*p*), 141.6 (C-*i*), 165.4 (NCO), 172.1 (CCO); HRMS calcd for  $[\text{C}_{25}\text{H}_{31}\text{NO}_6 + \text{H}]^+$ : 442.2224, found: 442.2227.

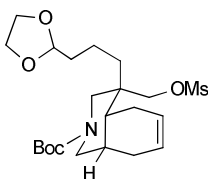


**(4R,4aR,8aS)-2-(tert-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-4-(hydroxymethyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (5):** *First step:* Liquid ammonia (15 mL) was condensed at  $-78$  °C in a three-necked 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, and then a solution of lactam **4** (200 mg, 0.452 mmol) in THF (10 mL) was added. The temperature was raised to  $-33$  °C and metal sodium was added in small portions until the blue color persisted. The mixture was stirred at  $-33$  °C for 2 min. The reaction was quenched by the addition of solid  $\text{NH}_4\text{Cl}$  until the blue colour disappeared, and the mixture was stirred at room temperature for 4 h. The residue was digested at room temperature with  $\text{CH}_2\text{Cl}_2$ , and the resulting suspension was filtered through Celite<sup>®</sup>. The solution was concentrated under reduced pressure.

*Second step:* Lithium aluminum hydride (257 mg, 6.78 mmol) was added under an argon atmosphere to a solution of the above residue in anhydrous dioxane (15 mL) and the mixture was stirred at reflux overnight. The resulting suspension was cooled to 0 °C, and the reaction was quenched with distilled water. The aqueous layer was extracted with  $\text{Et}_2\text{O}$ , and the combined organic extracts were dried, filtered, and concentrated to afford the crude amino alcohol as a yellow oil, which was used in the next step without purification.

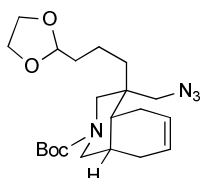
*Third step:* Di-*tert*-butyl dicarbonate (107 mg, 0.497 mmol) was added dropwise to a solution of the above crude amino alcohol in anhydrous  $\text{CH}_2\text{Cl}_2$  (8 mL) at room temperature under an inert atmosphere, and the resulting mixture was stirred for 20 h. The solution was then poured into

saturated aqueous  $\text{NH}_4\text{Cl}$  and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane–EtOAc) of the residue gave carbamate **5** (72 mg, 42%):  $[\alpha]_{\text{D}}^{22} = -14.4$  ( $c$  2.6 in  $\text{CHCl}_3$ ); IR (KBr):  $\nu = 3480$  (OH), 1688 (CO)  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.45 [11 H, s,  $(\text{CH}_3)_3\text{C}$ , H-2'], 1.50 (2 H, m, H-1'), 1.63 (2 H, m, H-3'), 1.81 (1 H, d,  $J = 18.0$  Hz, H-8), 1.90 (1 H, m, H-4a), 1.99 (1 H, dm,  $J = 18.8$  Hz, H-5), 2.09 (1 H, dm,  $J = 18.8$  Hz, H-5), 2.14 (1 H, m, H-8a), 2.23 (1 H, d,  $J = 18.0$  Hz, H-8), 2.70–2.97 (2 H, m, H-1, H-3), 3.42 (2 H, s,  $\text{CH}_2\text{OH}$ ), 3.52–3.63 (2 H, m, H-1, H-3), 3.85, 3.95 (4 H, 2m,  $\text{CH}_2\text{O}$ ), 4.87 (1 H, t,  $J = 4.8$  Hz, H-4'), 5.59 (2 H, m, H-6, H-7);  $\delta_{\text{C}}$  (100.6 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 17.6 (C-2'), 21.4 (C-5), 27.8 (C-8a), 28.3 [ $(\text{CH}_3)_3\text{C}$ ], 28.5 (C-8), 30.7 (C-1'), 34.2 (C-3', C-4a), 40.8 (C-4), 43.7–45.7 (C-1, C-3), 63.6, 64.2 ( $\text{CH}_2\text{OH}$ ), 64.7, 64.8 ( $2\text{CH}_2\text{O}$ ), 79.4 [ $(\text{CH}_3)_3\text{C}$ ], 104.4 (C-4'), 124.5 (C-6, C-7), 155.0 (NCOO); HRMS (ESI) calcd for  $[\text{C}_{22}\text{H}_{36}\text{NO}_5 + \text{H}]^+$ : 382.2588, found: 382.2585.

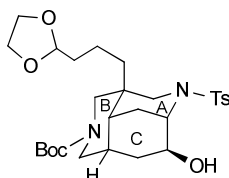


**(4R,4aR,8aS)-2-(tert-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-4-[(methanesulfonyl)oxy)methyl]-1,2,3,4,4a,5,8,8a-octahydroisoquinoline:** Anhydrous  $\text{Et}_3\text{N}$  (430  $\mu\text{L}$ , 3.11 mmol) and methanesulfonyl chloride (410  $\mu\text{L}$ , 5.3 mmol) were added at 0 °C under an inert atmosphere to a stirred solution of compound **5** (396 mg, 1.04 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  solution, and the mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 6:4 hexane–EtOAc) of the residue afforded the mesylate derivative (470 mg, 97%) as a yellow oil:  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.42 (2 H, m, H-2'), 1.45, 1.46 [9 H, s,  $(\text{CH}_3)_3\text{C}$ ], 1.64 (4 H, m, H-1', H-3'), 1.83 (1 H, d,  $J = 17.6$  Hz, H-8), 1.94 (1 H, m, H-4a), 1.99 (1 H, dm,  $J = 17.2$  Hz, H-5), 2.10 (1 H, dm,  $J = 17.2$  Hz, H-5), 2.16 (1 H, m, H-8a), 2.25 (1 H, dm,  $J = 17.6$  Hz, H-8), 2.78–2.81 (2 H, 2s, H-1, H-3), 3.03 (3 H, s,  $\text{CH}_3\text{S}$ ), 3.66–3.73 (2 H, 2m, H-1, H-3), 3.84, 3.95 (4 H, 2m,  $\text{CH}_2\text{O}$ ), 4.00 (2 H, s,  $\text{CH}_2\text{OS}$ ), 4.86 (1 H, t,  $J = 4.4$  Hz, H-4'), 5.60 (2 H, m, H-6, H-7);  $\delta_{\text{C}}$  (100.6 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 17.2 (C-2'), 21.4 (C-5), 27.8 (C-8a), 28.3 [ $(\text{CH}_3)_3\text{C}$ , C-8], 31.0 (C-1'), 33.5 (C-4a), 34.3 (C-3'), 37.1 ( $\text{CH}_3\text{SO}$ ), 39.8 (C-4), 43.4–44.6 (C-1, C-3), 64.7, 64.8 ( $2\text{CH}_2\text{O}$ ), 70.2 ( $\text{CH}_2\text{OS}$ ), 79.8 [ $(\text{CH}_3)_3\text{C}$ ], 104.1 (C-4'),

123.8, 124.5 (C-6, C-7), 155.0 (NCOO); HRMS calcd for  $[C_{22}H_{37}NO_7S + NH_4]^+$ : 477.2629, found: 477.2621.



**(4*R*,4*aR*,8*aS*)-4-(Azidomethyl)-2-(*tert*-butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-1,2,3,4,4*a*,5,8,8*a*-octahydroisoquinoline:** NaN<sub>3</sub> (404 mg, 6.22 mmol) was added to a solution of the above mesylate (476 mg, 1.04 mmol) in anhydrous DMF (2 mL), and the mixture was heated to 90 °C. After 48 h, more NaN<sub>3</sub> (404 mg, 6.22 mmol) was added, and the resulting mixture was stirred at 90 °C for an additional 24 h and quenched with distilled water. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic extracts were dried and concentrated under reduced pressure to give an oil. Flash chromatography (9:1 hexane–EtOAc) of the oil afforded the corresponding azide (335 mg, 70%):  $[\alpha]_D^{22} = -45.3$  (*c* 0.9 in CHCl<sub>3</sub>); IR (film):  $\nu = 2098$  (N<sub>3</sub>), 1688 (CO) cm<sup>-1</sup>;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.38 (2 H, m, H-2'), 1.42 [10 H, s, (CH<sub>3</sub>)<sub>3</sub>C], H-1'], 1.60 (1 H, m, H-1'), 1.65 (2 H, m, H-3'), 1.81 (1 H, d, *J* = 18.4 Hz, H-8), 1.86 (1 H, m, H-4*a*), 1.95 (1 H, dm, *J* = 17.6 Hz, H-5), 2.08 (1 H, dm, *J* = 17.6 Hz, H-5), 2.16 (1 H, m, H-8*a*), 2.24 (1 H, m, H-8), 2.61-2.74 (2 H, m, H-1, H-3), 3.22 (2 H, s, CH<sub>2</sub>N<sub>3</sub>), 3.62-3.73 (2 H, 2m, H-1, H-3), 3.85, 3.95 (4 H, 2m, CH<sub>2</sub>O), 4.82 (1 H, t, *J* = 4.4 Hz, H-4'), 5.60 (2 H, m, H-6, H-7);  $\delta_C$  (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 17.7 (C-2'), 21.5 (C-5), 27.8 (C-8*a*), 28.3 [(CH<sub>3</sub>)<sub>3</sub>C], C-8], 31.7 (C-1'), 34.5 (C-4*a*), 34.8 (C-3'), 42.2 (C-4), 43.5-45.0 (C-1, C-3), 54.0 (CH<sub>2</sub>N<sub>3</sub>), 64.8 (2CH<sub>2</sub>O), 79.7 [(CH<sub>3</sub>)<sub>3</sub>C], 104.3 (C-4'), 123.9, 124.6 (C-6, C-7), 155.0 (NCOO). HRMS calcd for  $[C_{21}H_{35}N_4O_4 + H]^+$ : 407.2653, found: 407.2645.

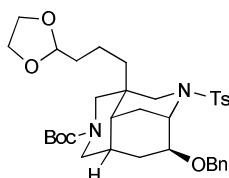


**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-2-(*tert*-Butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-7-hydroxy-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (7):** *First step:* *m*-Chloroperoxybenzoic acid (161 mg, 0.72 mmol) was added to a cold (0 °C) solution of the above azide (147 mg, 0.36 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.5 mL), and the mixture was allowed to warm slowly to room temperature. After 5 h, the reaction was quenched with saturated aqueous

NaHCO<sub>3</sub> and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated under reduced pressure to give azido epoxide **6**.

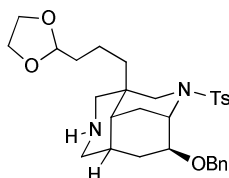
*Second step:* Me<sub>3</sub>P (540 μl of a 1 M solution in THF, 0.54 mmol) was added to a solution of the above azido epoxide **6** (0.36 mmol) in THF (6 mL), and the mixture was stirred at room temperature for 2 hours. Water (0.6 mL) was added, and the resulting mixture was stirred overnight at room temperature and concentrated under reduced pressure to afford a tricyclic amino derivative.

*Third step:* Et<sub>3</sub>N (55 μL, 0.397 mmol) was added dropwise to a stirring solution of the above tricyclic amine in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at 0 °C. A solution of *p*-toluenesulfonyl chloride (75 mg, 0.397 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was transferred via a cannula to the former solution, and the stirring was continued for 2.5 h at 0 °C. The reaction was then quenched with saturated aqueous NH<sub>4</sub>Cl, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to afford the protected compound **7** (80 mg, 40% overall yield from the azide) after flash chromatography (9:1 to 7:3 hexane–EtOAc): [α]<sub>D</sub><sup>22</sup> = + 36.1 (*c* 3.1 in CHCl<sub>3</sub>); IR (film): ν = 3500 (OH), 1689 (CO) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.19 (4 H, m, H-1', H-2'), 1.43 [9 H, s, (CH<sub>3</sub>)<sub>3</sub>C], 1.52 (1 H, m, H-4a), 1.60-1.71 (3 H, m, H-5, 2H-8), 1.94 (1 H, d, *J* = 14.4 Hz, H-5), 2.04 (1 H, m, H-8a), 2.43 (3 H, s, CH<sub>3</sub> Ts), 2.60-2.78 (2 H, m, H-1, H-3), 3.12 (1 H, m, H-10), 3.28 (1 H, d, *J* = 13.2 Hz, H-10), 3.84 (2 H, m, CH<sub>2</sub>O), 3.87 (1 H, m, H-7), 3.87 (2 H, m, CH<sub>2</sub>O), 3.80 (2 H, masked, H-3, H-1), 4.00 (1 H, s, H-6), 4.76 (1 H, m, H-4'), 7.27 (2 H, d, *J* = 8.0 Hz, H-*m* Ts), 7.69 (2 H, d, *J* = 8.0 Hz, H-*o* Ts); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 17.3 (C-2'), 21.4 (CH<sub>3</sub> Ts), 21.9 (C-5), 28.3 [(CH<sub>3</sub>)<sub>3</sub>C], 30.3 (C-8a), 32.5 (C-8), 32.8 (C-4), 34.0 (C-3'), 34.9 (C-4a), 36.1 (C-1'), 46.0-50.0 (C-10, C-1, C-3), 50.8 (C-6), 64.7, 64.8 (CH<sub>2</sub>O), 67.7 (C-7), 79.8 [(CH<sub>3</sub>)<sub>3</sub>C], 104.0 (C-4'), 126.8 (C-*o* Ts), 129.6 (C-*m* Ts), 136.5 (C-*i* Ts), 143.1 (C-*p* Ts), 155.5 (NCOO); HRMS calcd for [C<sub>28</sub>H<sub>42</sub>N<sub>2</sub>O<sub>7</sub>S + H]<sup>+</sup>: 551.2785, found: 551.2788.



**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-7-(Benzyloxy)-2-(*tert*-butoxycarbonyl)-4-[3-(1,3-dioxolan-2-yl)propyl]-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline:** NaH (17 mg of a 60% dispersion in mineral oil, 0.427 mmol) was added to a solution of tricyclic compound **7** (157 mg, 0.285 mmol) in anhydrous DMF (6 mL), and the mixture was stirred at 0 °C for 1 h. Then,

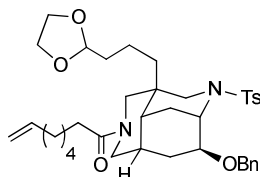
benzyl bromide (100  $\mu$ L, 0.855 mmol, previously filtered over a neutral alumina pad) and a solution of tetrabutylammonium iodide (21 mg, 0.057 mmol) were added at room temperature, and the resulting suspension was stirred overnight. The reaction was quenched by the addition of distilled water, and the aqueous layer was extracted with Et<sub>2</sub>O. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane–EtOAc) of the residue gave the corresponding benzyloxy derivative (137 g, 77%) as a colourless oil:  $[\alpha]_D^{22} = +38.8$  (*c* 0.75 in CHCl<sub>3</sub>); IR (film):  $\nu = 1689$  (CO) cm<sup>-1</sup>;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.25 (4 H, s, H-1', H-2'), 1.42 [11 H, s, H-3', (CH<sub>3</sub>)<sub>3</sub>C], 1.50 (2 H, m, H-4a, H-8), 1.70 (1 H, dm, *J* = 13.6 Hz, H-5), 1.75 (1 H, m, H-8), 1.92 (1 H, dt, *J* = 13.6, 2.4 Hz, H-5), 1.99 (1 H, m, H-8a), 2.37 (3 H, s, CH<sub>3</sub> Ts), 2.62-2.70 (2 H, 2m, H-1, H-3), 3.04 (1 H, d, *J* = 13.2 Hz, H-10), 3.32 (1 H, d, *J* = 13.2 Hz, H-10), 3.40 (1 H, br. s, H-7), 3.52-3.62 (2 H, 2m, H-1, H-3), 3.84, 3.95 (4 H, 2m, CH<sub>2</sub>O), 4.20 (1 H, m, H-6), 4.51 (2 H, m, CH<sub>2</sub> Bn), 4.78 (1 H, m, H-4'), 7.10-7.60 (9 H, m, C<sub>6</sub>H<sub>5</sub>, Ts);  $\delta_C$  (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 17.3 (C-2'), 21.4 (CH<sub>3</sub> Ts), 22.6 (C-5), 28.4 [(CH<sub>3</sub>)<sub>3</sub>C], 29.9 (C-8), 30.8 (C-8a), 31.9 (C-4), 34.2 (C-3'), 35.0 (C-4a), 36.1 (C-1'), 43.9 (C-3'), 47.0-49.9 (C-1, C-3), 48.2 (C-10), 51.0 (C-6), 64.8 (CH<sub>2</sub>O), 70.5 (CH<sub>2</sub> Bn), 73.4 (C-7), 79.8 [(CH<sub>3</sub>)<sub>3</sub>C], 104.1 (C-4'), 126.7-129.6 (C-*o*, *m* Ts, C-*o*, *m*, *p* C<sub>6</sub>H<sub>5</sub>), 137.4 (C-*i* Ts), 138.5 (C-*i* C<sub>6</sub>H<sub>5</sub>), 143.0 (C-*p* Ts), 155.5 (NCOO); HRMS calcd for [C<sub>35</sub>H<sub>48</sub>N<sub>2</sub>O<sub>7</sub>S + H]<sup>+</sup>: 641.3255, found: 641.3255.



**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-7-(Benzyloxy)-4-[3-(1,3-dioxolan-2-yl)propyl]-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline:** TFA (2 mL) was added to a solution of the above tricycle (137 mg, 0.213 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and the mixture was stirred for 30 minutes at room temperature. Toluene (2 mL) was added, and the resulting solution was concentrated under reduced pressure to give the corresponding secondary amine:  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.22 (2 H, m, H-2'), 1.36 (1 H, m, H-1'), 1.52 (3 H, m, 2H-3', H-1'), 1.65 (1 H, m, H-4a), 1.78 (2 H, dm, *J* = 13.6 Hz, H-4a, H-8), 1.90 (1 H, dm, *J* = 13.6 Hz, H-8), 1.98 (1 H, dm, *J* = 13.6 Hz, H-5), 2.25 (1 H, m, H-8a), 2.37 (3 H, s, CH<sub>3</sub> Ts), 2.78, 2.98-3.05 (4 H, 2m, H-1, H-3), 3.31 (1 H, br. s, H-7), 3.48 (1 H, d, *J* = 13.2 Hz, H-10), 3.53 (1 H, d, *J* = 13.2 Hz, H-10), 3.82, 3.94 (4 H, 2m, CH<sub>2</sub>O), 4.18 (1 H, br. s, H-6), 4.43 (2 H, m, CH<sub>2</sub> Bn), 4.79 (1 H, t, *J* = 4.4 Hz, H-4'), 7.15-7.57 (9 H, m, C<sub>6</sub>H<sub>5</sub>, Ts);  $\delta_C$  (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 17.0 (C-2'), 21.4



(CH<sub>3</sub> Ts), 22.5 (C-5), 27.7 (C-8a), 28.9 (C-8), 32.3 (C-4a), 33.1 (C-4), 33.6 (C-3'), 36.0 (C-1'), 46.2 (C-10), 47.6, 47.8 (C-1, C-3), 48.7 (C-6), 64.8 (CH<sub>2</sub>O), 70.7 (CH<sub>2</sub> Bn), 72.8 (C-7), 103.7 (C-4'), 126.6-129.8 (C-*o*, *m* Ts, C-*o*, *m*, *p* C<sub>6</sub>H<sub>5</sub>), 137.2 (C-*i* Ts), 138.0 (C-*i* C<sub>6</sub>H<sub>5</sub>), 143.4 (C-*p* Ts); HRMS calcd for [C<sub>30</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S + H]<sup>+</sup>: 541.2731, found: 541.2736.

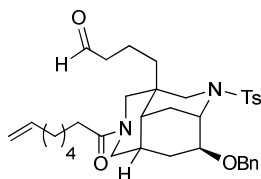


**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-7-(Benzyloxy)-4-[3-(1,3-dioxolan-2-yl)propyl]-6,4-(iminomethano)-2-(7-octenoyl)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (9):** Preparation of 7-octenoyl

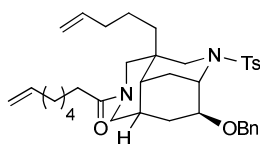
*chloride*: Oxalyl chloride (990 μL of a 2 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.98 mmol) was added to a solution of 7-octenoic acid (230 μL, 1.53 mmol) in 2 drops of DMF, and the resulting mixture was stirred at room temperature for 15 min. Ether was added, and the resulting mixture was filtered and concentrated under reduced pressure to give crude 7-octenoyl chloride.

*Acylation step*: Et<sub>3</sub>N (120 μL, 0.918 mmol) was added at 0 °C to a solution of the above secondary amine (0.306 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the resulting mixture was stirred at 0 °C for 10 min. A solution of 7-octenoyl chloride (1.53 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added at 0 °C, and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. Distilled water was added, and the resulting mixture was stirred for 20 minutes. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane–EtOAc) of the residue afforded amide **9** (116 mg, 57 %, overall yield from the Boc derivative): δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.20-1.50 (10 H, m, H-1', H-2', H-3', H-4'', H-5''), 1.59 (3 H, m, H-4a, 2H-3''), 1.64 (1 H, m, H-8), 1.69 (1 H, dm, *J* = 13.2 Hz, H-5), 1.78 (1 H, td, *J* = 14.8, 5.6 Hz, H-8), 1.93 (1 H, dt, *J* = 13.2, 2.8 Hz, H-5), 2.06 (3 H, m, H-8a, 2H-6''), 2.18-2.30 (3 H, m, H-2'', H-3ax), 2.39 (3 H, s, CH<sub>3</sub> Ts), 2.53, 3.06 (1 H, 2dd, *J* = 13.2, 2.8 Hz, H-1), 2.86 (1 H, d, *J* = 14.0 Hz, H-3), 3.00, 3.27 (1 H, 2d, *J* = 13.6 Hz, H-10), 3.05, 3.36 (1 H, 2d, *J* = 13.6 Hz, H-10), 3.37, 4.30 (1 H, 2d, *J* = 13.2 Hz, H-3), 3.40, 3.56 (1 H, 2br. s, H-7), 3.54, 4.43 (1 H, 2d, *J* = 13.2 Hz, H-1), 3.82, 3.93 (4 H, 2m, CH<sub>2</sub>O), 4.14, 4.22 (1 H, 2br. s, H-6), 4.50 (1 H, d, *J* = 12.4 Hz, CH<sub>2</sub> Bn), 4.56 (1 H, d, *J* = 12.0 Hz, CH<sub>2</sub> Bn), 4.73, 4.79 (1 H, 2t, *J* = 4.8 Hz, H-4'), 4.93-5.04 (2 H, m, CH<sub>2</sub>=), 5.80 (1 H, tdt, *J* = 13.2, 13.2, 10.0, 6.8, 6.8 Hz, CH=), 7.05-7.60 (9 H, m, Ts, C<sub>6</sub>H<sub>5</sub>); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 17.3, 17.4 (C-2'), 21.4 (CH<sub>3</sub> Ts), 22.3, 22.6 (C-5), 24.9 (C-3''), 28.6, 28.7, 28.8, 28.9 (C-4'', C-5''), 29.7, 30.0 (C-8), 30.4, 31.0 (C-

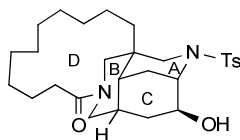
8a), 33.1, 33.2 (C-2''), 33.5 (C-6''), 34.4 (C-3'), 34.6, 34.8 (C-4a), 34.9, 35.3 (C-4), 36.1, 36.2 (C-1'), 43.9, 50.5 (C-1), 46.5, 46.8 (C-10), 47.8, 48.4 (C-6), 48.0, 52.2 (C-3), 64.7, 64.8 (2CH<sub>2</sub>O), 70.5, 70.8 (CH<sub>2</sub> Bn), 73.7, 74.7 (C-7), 103.9, 104.0 (C-4'), 114.3, 144.4 (CH<sub>2</sub>=), 126.6-129.6 (C-*o*, *m* Ts, C-*o*, *m*, *p* C<sub>6</sub>H<sub>5</sub>), 137.4-138.8 (C-*i* Ts, C<sub>6</sub>H<sub>5</sub>, CH=), 143.0, 143.2 (C-*p* Ts), 172.6, 172.7 (NCO); HRMS calcd for [C<sub>38</sub>H<sub>53</sub>N<sub>2</sub>O<sub>6</sub>S + H]<sup>+</sup>: 665.3619, found: 665.3608.



**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-7-(Benzyloxy)-6,4-(iminomethano)-2-(7-octenoyl)-9-(*p*-toluenesulfonyl)-4-perhydroisoquinolinebutyraldehyde:** TFA (2 mL) was added to a solution of amide **9** (100 mg, 0.15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and water (4 mL), and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous NaHCO<sub>3</sub>, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure to give a yellow oil, which was used in the next step without further purification: δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.25-1.49 (8 H, m, H-1', H-2', H-4'', H-5''), 1.58-1.65 (4 H, m, H-8, H-4a, 2H-3''), 1.74 (1 H, dm, *J* = 14.0 Hz, H-5), 1.79 (1 H, dd, *J* = 14.0, 6.4 Hz, H-8), 1.96 (1 H, dm, *J* = 14.0 Hz, H-5), 2.07 (3 H, m, H-8a, 2H-6''), 2.26 (4 H, t, *J* = 7.6 Hz, H-2'', H-3'), 2.35, 2.90 (1 H, d, *J* = 13.2 Hz, H-3), 2.39 (3 H, s, CH<sub>3</sub> Ts), 2.55, 3.08 (1 H, dd, *J* = 13.2, 3.2 Hz, H-1), 2.98, 3.03 (1 H, 2d, *J* = 13.6 Hz, H-10), 3.29, 3.38 (1 H, 2d, *J* = 13.6 Hz, H-10), 3.33, 3.50 (1 H, 2br. s, H-7), 3.41, 4.34 (1 H, 2d, *J* = 13.2 Hz, H-3), 3.55, 4.45 (1 H, 2d, *J* = 13.2 Hz, H-1), 4.14, 4.22 (1 H, 2br. s, H-6), 4.48 (1 H, d, *J* = 12.0 Hz, CH<sub>2</sub> Bn), 4.55 (1 H, d, *J* = 12.0 Hz, CH<sub>2</sub> Bn), 7.13-7.60 (9 H, m, Ts, C<sub>6</sub>H<sub>5</sub>), 9.67, 9.75 (1 H, 2s, CHO); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 15.3, 15.5 (C-2'), 21.0, 21.4 (CH<sub>3</sub> Ts), 22.4, 22.5 (C-5), 24.9 (C-3''), 28.6, 28.7, 28.8, 28.9 (C-4'', C-5''), 29.7, 30.0 (C-8), 30.5, 31.0 (C-8a), 31.5 (C-4), 33.1, 33.2 (C-2''), 33.5 (C-6''), 34.6, 34.9 (C-4a), 35.4, 35.5 (C-1'), 43.9 (C-3'), 46.5, 50.1 (C-1), 46.6 (C-10), 47.8, 52.1 (C-3), 47.9, 48.4 (C-6), 70.4, 70.7 (CH<sub>2</sub> Bn), 73.2, 74.2 (C-7), 114.3, 144.4 (CH<sub>2</sub>=), 126.6-129.6 (C-*o*, *m* Ts, C-*o*, *m*, *p* C<sub>6</sub>H<sub>5</sub>), 137.3-138.9 (C-*i* Ts, C<sub>6</sub>H<sub>5</sub>, CH=), 143.0 (C-*p* Ts), 172.5, 172.7 (NCO), 201.4, 201.5 (CHO); HRMS (malDI) calcd for [C<sub>36</sub>H<sub>48</sub>N<sub>2</sub>O<sub>5</sub>S + Na]<sup>+</sup>: 643.32, found: 643.30.

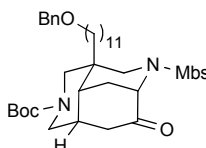


**(4*R*,4*aR*,6*S*,7*S*,8*aS*)-7-(Benzyloxy)-6,4-(iminomethano)-2-(7-octenoyl)-4-(4-pentenyl)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (**10**):** KO<sup>t</sup>Bu (750 μL of a 1 M solution in THF, 0.75 mmol) was added dropwise to a solution of Ph<sub>3</sub>PCH<sub>3</sub>Br (375 mg, 1.05 mmol) in THF (4 mL), and the solution was stirred at room temperature for 1h. The resulting mixture was added to a solution of the above aldehyde (0.150 mmol) in THF (4 mL), and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated aqueous NH<sub>4</sub>Cl, and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure.. Flash chromatography (hexane to 6:4 hexane–EtOAc) of the resulting oil afforded diene **10** (73 mg, 80%): δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.08-1.43 (8 H, m, 2H-1', 2H-2', 2H-4'', 2H-5''), 1.55 (1 H, m, H-4a), 1.61 (3 H, m, 2H-3'', H-8), 1.71 (1 H, dm, *J* = 14.8 Hz, H-5), 1.80 (2 H, m, H-3', H-8), 1.91 (1 H, m, H-3'), 1.94 (1 H, dm, *J* = 14.8 Hz, H-5), 2.06 (3 H, m, H-6'', H-8a), 2.20, 2.84 (1 H, 2d, *J* = 14.0 Hz, H-3), 2.26 (2 H, t, *J* = 8.0 Hz, H-2''), 2.40 (3 H, s, CH<sub>3</sub> Ts), 2.54, 3.07 (1 H, 2dd, *J* = 12.8, 2.8 Hz, H-1), 2.98, 3.04 (1 H, 2d, *J* = 13.6 Hz, H-10), 3.26, 3.36 (1 H, 2d, *J* = 13.8 Hz, H-10), 3.36, 4.31 (1 H, 2d, *J* = 14.0 Hz, H-3), 3.40, 3.57 (1 H, 2br. s, H-7), 4.14, 4.23 (1 H, 2d, *J* = 12.8 Hz, H-1), 4.51 (1 H, d, *J* = 12.0 Hz, CH<sub>2</sub> Bn), 4.56 (1 H, d, *J* = 12.0 Hz, CH<sub>2</sub> Bn), 4.95 (4 H, m, CH<sub>2</sub>=), 5.61-5.90 (2 H, m, CH=), 7.08-7.60 (9 H, m, Ts, C<sub>6</sub>H<sub>5</sub>); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 21.0, 21.4 (CH<sub>3</sub> Ts), 22.2, 22.3, 22.4, 22.6 (C-2', C-5), 24.7, 25.0 (C-3''), 28.7, 28.8, 28.9 (C-4'', C-5''), 30.1, 30.6 (C-8), 31.1, 31.5 (C-8a), 33.2, 33.3 (C-2''), 33.6 (C-6''), 34.0 (C-3'), 34.8, 35.3 (C-4a), 35.7, 35.8 (C-1'), 36.6 (C-4), 46.5, 50.6 (C-1), 46.7, 46.8 (C-10), 47.9, 48.4 (C-6), 48.2, 52.3 (C-3), 70.5, 70.9 (CH<sub>2</sub> Bn), 73.7, 74.7 (C-7), 114.3, 114.4, 114.8, 115.1 (2CH=), 126.7-129.6 (C-*o*, *m* Ts, C-*o*, *m*, *p* C<sub>6</sub>H<sub>5</sub>), 137.4, 138.0, 138.1, 138.4, 138.5 (2CH=, C-*i* Ts, C<sub>6</sub>H<sub>5</sub>), 143.1, 143.3 (C-*p* Ts), 172.6, 172.7 (NCO).



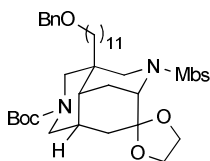
**ABCD system 11:** *First step:* A solution of diene **10** (72 mg, 0.116 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was slowly added via syringe pump (3 h) to a refluxed solution of second generation Grubbs catalyst (20 mg, 0.023 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (580 mL). The resulting mixture was heated to reflux

for 12 h and then concentrated under reduced pressure. Flash chromatography (hexane to 1:1 hexane–EtOAc) of the residue afforded the corresponding tetracyclic compound (37 mg, 54%) as a mixture of *E/Z* isomers. HRMS (malldi) calcd for  $[C_{35}H_{46}N_2O_4S + Na]^+$ : 613.3, found: 613.3  
*Second step*:  $PtO_2$  (5.3 mg, 40% in weight) was added to a solution of the above lactam (12 mg, 0.02 mmol) in MeOH (2 mL), and the resulting mixture was stirred under a hydrogen atmosphere at room temperature for 2 h to afford alcohol **11** (8 mg, 78%) as a single product:  $\delta_H$  (400 MHz;  $CDCl_3$ ;  $Me_4Si$ , selected resonances) 1.38 (1 H, m, H-4a), 1.63-1.79 (3 H, m, 3H-8, H-5), 1.86 (1 H, dm,  $J = 13.2$  Hz, H-5), 2.04 (1 H, m, H-8a), 2.13 (2 H, m,  $CH_2$ ), 2.43 (3 H, s,  $CH_3$  Ts), 2.75 (1 H, dd,  $J = 13.6, 4.4$  Hz, H-1), 2.95 (1 H, d,  $J = 13.2$  Hz, H-3), 3.12 (1 H, d,  $J = 12.8$  Hz, H-10), 3.37 (1 H, d,  $J = 12.8$  Hz, H-10), 3.41 (1 H, br. s, H-7), 3.59 (1 H, d,  $J = 13.2$  Hz, H-3), 3.88 (1 H, br. s, H-6), 4.10 (1 H, d,  $J = 13.6$  Hz, H-1), 7.31 (2H, d,  $J = 8.4$  Hz, H-*m* Ts), 7.68 (2 H, d,  $J = 8.4$  Hz, H-*o* Ts);  $\delta_C$  (100.6 MHz;  $CDCl_3$ ;  $Me_4Si$ ) 20.7 ( $CH_2$ ), 21.5 ( $CH_3$  Ts), 22.1 (C-5), 22.7-27.4 ( $CH_2$ ), 30.0 (C-8,  $CH_2$ ), 30.1 (C-8a), 33.8, 35.2 ( $CH_2$ ), 37.0 (C-4a), 37.1 (C-4), 45.5 (C-10), 46.8 (C-1), 48.9 (C-6), 51.5 (C-3), 75.2 (C-7), 126.9 (C-*o* Ts), 129.5 (C-*m* Ts), 136.8 (C-*i* Ts), 143.4 (C-*p* Ts), 173.9 (NCO); HRMS (malldi) calcd for  $[C_{28}H_{42}N_2O_4S + Na]^+$ : 525.2, found: 525.2.

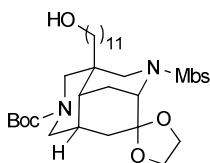


**(4*R*,4*aR*,6*S*,8*aS*)-4-(11-Benzyloxyundecyl)-2-(*tert*-butoxycarbonyl)-6,4-(iminomethano)-9-(*p*-methoxybenzenesulfonyl)-7-oxoperhydroisoquinoline**: Dess-Martin periodinane (82 mg, 0.19 mmol) was added under an inert atmosphere at room temperature to a solution of tricyclic compound **8** (0.08 mmol) in  $CH_2Cl_2$  (3 mL). After 4 h of stirring at room temperature, a saturated aqueous solution of  $NaHCO_3$ - $Na_2S_2O_3$  (1:1) was slowly added. The resulting mixture was stirred vigorously for 1 h and extracted with  $CH_2Cl_2$ . The combined organic extracts were dried over anhydrous  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 4:6 hexane–EtOAc) of the residue afforded the corresponding ketone (43 mg, 78%) as a colourless oil:  $[\alpha]_D^{22} = +13.3$  ( $c$  1.7 in  $CHCl_3$ ); IR (film):  $\nu = 3408, 3279$  (OH, NH),  $1692$  (C=O) $cm^{-1}$ ;  $\delta_H$  (400 MHz;  $CDCl_3$ ;  $Me_4Si$ ) 1.27 (18 H, m,  $CH_2$ ), 1.35 [9 H, s,  $(CH_3)_3C$ ], 1.62 (3 H, m,  $CH_2$ , H-5), 1.65 (1 H, m, H-8a), 1.74 (1 H, dd,  $J = 16.8, 11.6$  Hz, H-8), 2.10 (1 H, m, H-4a), 2.32 (1 H, m, H-8), 2.43 (1 H, d,  $J = 14.0$  Hz, H-5), 2.88-2.60 (3 H, m, H-3, H-1, H-10), 3.47 (2 H, t,  $J = 6.4$  Hz, 2H-11'), 3.57, 3.66-4.00 (3 H, m, H-3, H-1, H-10), 3.82

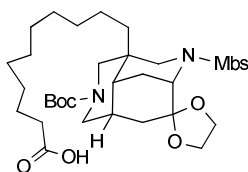
(3 H, s, CH<sub>3</sub>O Mbs), 4.38 (1 H, s, H-6), 4.50 (2 H, s, CH<sub>2</sub> Bn), 6.89 (2 H, d, *J* = 10.0 Hz, H-*m* Mbs), 7.29 (3 H, m, C<sub>6</sub>H<sub>5</sub>), 7.34 (2 H, m, C<sub>6</sub>H<sub>5</sub>), 7.65 (2 H, d, *J* = 10.0 Hz, H-*o* Mbs); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 23.0 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 28.3 [(CH<sub>3</sub>)<sub>3</sub>C], 29.3 (C-5), 29.5-30.1 (CH<sub>2</sub>), 33.7 (C-8a), 34.4 (C-4), 35.6, 35.8 (CH<sub>2</sub>), 36.6 (C-4a), 43.2 (C-8), 47.4-49.9 (C-1, C-3, C-10), 55.4 (CH<sub>3</sub>O Mbs), 56.9 (C-6), 70.5 (C-11'), 72.8 (CH<sub>2</sub> Bn), 80.1 [(CH<sub>3</sub>)<sub>3</sub>C], 113.9 (C-*m* Mbs), 127.4 (C-*p* C<sub>6</sub>H<sub>5</sub>), 127.6, 128.3 (C-*o*, *m* C<sub>6</sub>H<sub>5</sub>), 129.1 (C-*i* Mbs), 129.8 (C-*o* Mbs), 138.7 (C-*i* C<sub>6</sub>H<sub>5</sub>), 155.0 (NCOO), 163.8 (C-*p* Mbs), 205.6 (C=O); HRMS (ESI) calcd for [C<sub>40</sub>H<sub>59</sub>N<sub>2</sub>O<sub>7</sub>S + Na]<sup>+</sup>: 733.3857, found: 733.3867.



**(4*R*,4*aR*,6*S*,8*aS*)-4-(11-Benzyloxyundecyl)-2-(*tert*-butoxycarbonyl)-6,4-(iminomethano)-9-(*p*-methoxybenzenesulfonyl)perhydroisoquinolin-7-one ethylene acetal (12):** 1,2-Bis(trimethylsilyloxy)ethane (47 μL, 0.19 mmol) was added to a cooled (-78 °C) solution of trimethylsilyl triflate (2.3 μL, 0.01 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL). A solution of the above ketone (91 mg, 0.13 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added, and the mixture was stirred at 0 °C for 30 min, heated to reflux for 1 h, and poured into saturated sodium bicarbonate aqueous solution. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, and the organic extracts were dried, filtered, and concentrated under reduced pressure to give an oil. Flash chromatography (CH<sub>2</sub>Cl<sub>2</sub> to 9:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH) of the residue gave acetal **12** (55 mg, 57%) as an oil: [α]<sub>D</sub><sup>22</sup> = +45.3 (*c* 1.8 in CHCl<sub>3</sub>); IR (film): ν = 1689 (C=O) cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.27 (18 H, m, CH<sub>2</sub>), 1.40 [9 H, s, (CH<sub>3</sub>)<sub>3</sub>C], 1.56 (1 H, m, H-8a), 1.62 (2 H, m, H-10'), 1.74 (1 H, m, H-8), 1.78 (1 H, dt, *J* = 13.6, 2.8, 2.8 Hz, H-5), 1.97 (3 H, m, H-4a, H-8, H-5), 2.40-2.60 (3 H, 3m, H-3, H-1), 3.08 (1 H, d, *J* = 14.0 Hz, H-10), 3.14 (1 H, d, *J* = 14.0 Hz, H-10), 3.47 (2 H, t, *J* = 6.4 Hz, 2H-11'), 3.83 (3 H, s, CH<sub>3</sub>O Mbs), 3.87 (2 H, m, CH<sub>2</sub>O), 4.02 (5 H, m, H-6, H-3, H-1, CH<sub>2</sub>O), 4.50 (2 H, s, CH<sub>2</sub> Bn), 6.92 (2 H, d, *J* = 10.0 Hz, H-*m* Mbs), 7.29 (3 H, m, C<sub>6</sub>H<sub>5</sub>), 7.34 (2 H, m, C<sub>6</sub>H<sub>5</sub>), 7.79 (2 H, d, *J* = 10.0 Hz, H-*o* Mbs); δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 22.8 (CH<sub>2</sub>), 25.1 (C-5), 26.2 (CH<sub>2</sub>), 28.4 [(CH<sub>3</sub>)<sub>3</sub>C], 29.5-30.2 (CH<sub>2</sub>), 33.5 (C-4a), 34.7 (C-4), 35.6 (C-8a), 35.9 (CH<sub>2</sub> C-8), 48.8-50.9 (C-1, C-3, C-10), 51.0 (C-6), 55.4 (CH<sub>3</sub>O Mbs), 64.3, 65.0 (CH<sub>2</sub>O), 70.5 (C-11'), 72.8 (CH<sub>2</sub> Bn), 80.0 [(CH<sub>3</sub>)<sub>3</sub>C], 107.8 (CO<sub>2</sub>), 113.7 (C-*m* Mbs), 127.4 (C-*p* C<sub>6</sub>H<sub>5</sub>), 127.6, 128.3 (C-*o*, *m* C<sub>6</sub>H<sub>5</sub>), 129.5 (C-*o* Mbs), 132.5 (C-*i* Mbs), 138.7 (C-*i* C<sub>6</sub>H<sub>5</sub>), 155.0 (NCOO), 162.5 (C-*p* Mbs); HRMS (ESI) calcd for [C<sub>42</sub>H<sub>62</sub>N<sub>2</sub>O<sub>8</sub>S + H]<sup>+</sup>: 755.4300, found: 755.4304.

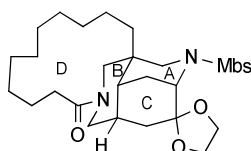


**(4*R*,4*aR*,6*S*,8*aS*)-2-(*tert*-Butoxycarbonyl)-4-(11-hydroxyundecyl)-6,4-(iminomethano)-9-(*p*-methoxybenzenesulfonyl)perhydroisoquinoline-7-one ethylene acetal:** A solution of acetal **12** (54 mg, 0.07 mmol) in MeOH (2 mL) containing Pd/C (6 mg) was hydrogenated at room temperature for 96 h. The catalyst was removed by filtration, and the solvent was evaporated. Flash chromatography (9:1 to 6:4 hexane–EtOAc) of the residue afforded the corresponding alcohol (35 mg, 73%):  $[\alpha]_D^{22} = +60.2$  (*c* 2.1 in CHCl<sub>3</sub>); IR (film):  $\nu = 3490$  (OH), 1686 (C=O) cm<sup>-1</sup>;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 1.27 (18 H, m, CH<sub>2</sub>), 1.40 [9 H, s, (CH<sub>3</sub>)<sub>3</sub>C], 1.48 (1 H, m, H-8a), 1.57 (2 H, m, CH<sub>2</sub>), 1.71 (1 H, m, H-8), 1.78 (1 H, dt, *J* = 13.6, 2.8, 2.8 Hz, H-5), 1.97 (3 H, m, H-4a, H-8, H-5), 2.40–2.80 (2 H, 3m, H-3, H-1), 3.08 (1 H, d, *J* = 14.0 Hz, H-10), 3.16 (1 H, d, *J* = 14.0 Hz, H-10), 3.64 (2 H, t, *J* = 6.4 Hz, 2H-11'), 3.84 (3 H, s, CH<sub>3</sub>O Mbs), 3.86 (2 H, m, CH<sub>2</sub>O), 3.87 (2 H, masked, H-3, H-1), 4.00 (2 H, m, CH<sub>2</sub>O), 4.03 (1 H, s, H-6), 6.92 (2 H, d, *J* = 8.8 Hz, H-*m* Mbs), 7.79 (2 H, d, *J* = 8.8 Hz, H-*o* Mbs);  $\delta_C$  (100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si) 22.8 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 25.9 (C-5), 28.4 [(CH<sub>3</sub>)<sub>3</sub>C], 29.4–30.2 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 33.5 (C-4a), 34.7 (C-4), 35.9 (C-8a), 36.0 (CH<sub>2</sub>, C-8), 45.9–49.9 (C-1, C-3, C-10), 50.3 (C-6), 55.4 (CH<sub>3</sub>O Mbs), 63.0 (C-11'), 64.3, 65.0 (CH<sub>2</sub>O), 79.8 [(CH<sub>3</sub>)<sub>3</sub>C], 107.8 (C-7), 113.7 (C-*m* Mbs), 129.5 (C-*o* Mbs), 132.3 (C-*i* Mbs), 156.0 (NCOO), 162.5 (C-*p* Mbs); HRMS (ESI) calcd for [C<sub>35</sub>H<sub>56</sub>N<sub>2</sub>O<sub>8</sub>S + H]<sup>+</sup>: 665.3830, found: 665.3828.



**(4*R*,4*aR*,6*S*,8*aS*)-2-(*tert*-Butoxycarbonyl)-7,7-(ethylenedioxy)-6,4-(iminomethano)-9-(*p*-methoxybenzenesulfonyl)-4-perhydroisoquinolineundecanoic acid (**13**):** PDC (483 mg, 1.26 mmol) was added to a solution of the above alcohol (56 mg, 0.084 mmol) in DMF (2.5 mL), and the resulting mixture was stirred overnight at room temperature. The reaction was quenched with water, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. Flash

chromatography (8:2 to 3:7 hexane–EtOAc) of the residue afforded carboxylic acid **13** (36 mg, 63%):  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.20-1.25 (16 H, m,  $\text{CH}_2$ ), 1.42 [9 H, s,  $(\text{CH}_3)_3\text{C}$ ], 1.49 (1 H, s, H-8a), 1.63 (2 H, m, H-9'), 1.72 (1 H, m, H-8), 1.78 (1 H, dt,  $J = 13.6, 2.8, 2.8$  Hz, H-5), 1.95 (3 H, m, H-4a, H-5, H-8), 2.35 (2 H, t,  $J = 7.6$  Hz, H-10'), 2.53-2.82 (2 H, m, H-1, H-3), 3.08 (1 H, d,  $J = 14.8$  Hz, H-10), 3.16 (1 H, d,  $J = 14.8$  Hz, H-10), 3.60 (2 H, m, H-1, H-3), 3.84 (3 H, s,  $\text{CH}_3\text{O}$  Mbs), 3.90 (1 H, m, H-6), 4.04 (4 H, m,  $\text{CH}_2\text{O}$ ), 6.92 (2 H, d,  $J = 8.8$  Hz, H-*m* Mbs), 7.79 (2 H, d,  $J = 8.8$  Hz, H-*o* Mbs);  $\delta_{\text{C}}$  (100.6 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 22.7 ( $\text{CH}_2$ ), 24.6 (C-9'), 25.6 (C-5), 25.8 ( $\text{CH}_2$ ), 28.4 [ $(\text{CH}_3)_3\text{C}$ ], 29.0-30.1 ( $\text{CH}_2$ ), 33.5 (C-4a), 33.8 (C-10'), 34.6 (C-4), 35.5 (C-8a), 35.9 (C-8), 45.9-48.8 (C-1, C-3, C-10), 50.3 (C-6), 55.4 ( $\text{CH}_3\text{O}$  Mbs), 64.3, 65.0 ( $\text{CH}_2\text{O}$ ), 79.9 [ $(\text{CH}_3)_3\text{C}$ ], 107.8 (C-7), 113.7 (C-*m* Mbs), 129.5 (C-*o* Mbs), 132.5 (C-*i* Mbs), 155.6 (NCOO), 162.4 (C-*p* Mbs), 178.6 (COOH); HRMS (ESI) calcd for  $[\text{C}_{35}\text{H}_{55}\text{N}_2\text{O}_9\text{S} + \text{H}]^+$ : 679.3623, found: 679.3613.

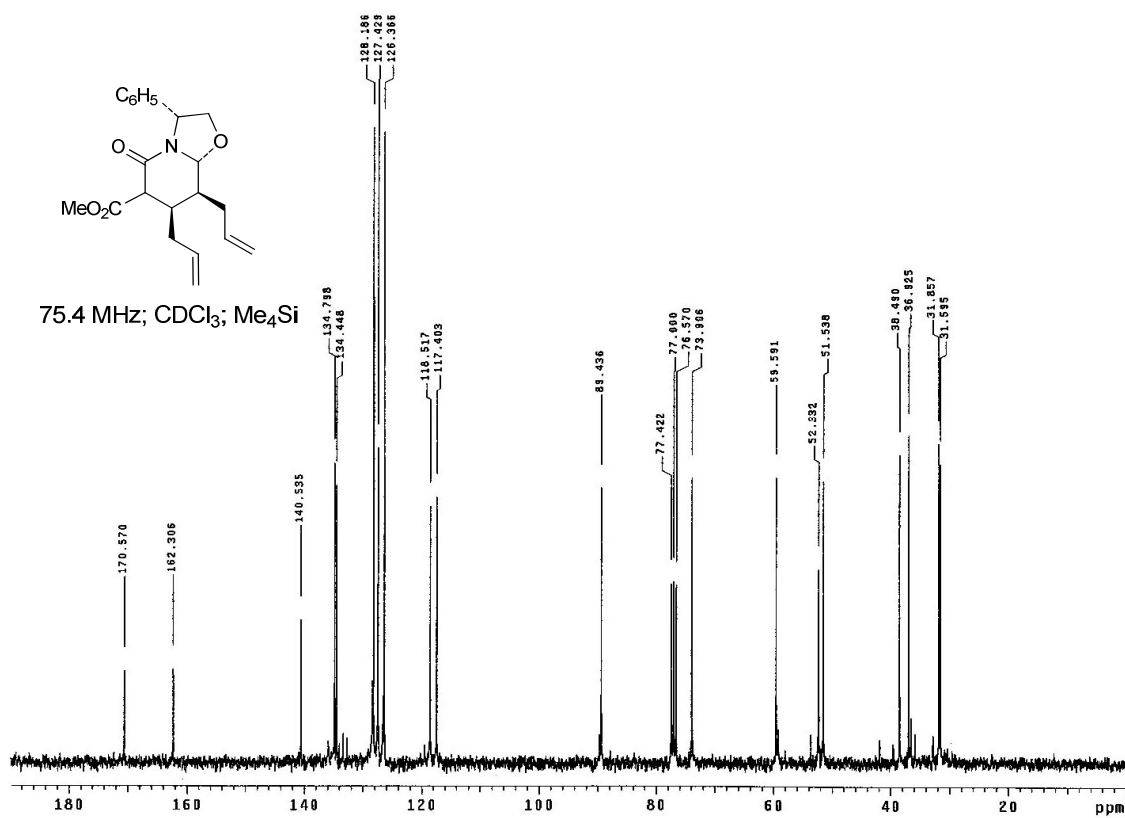
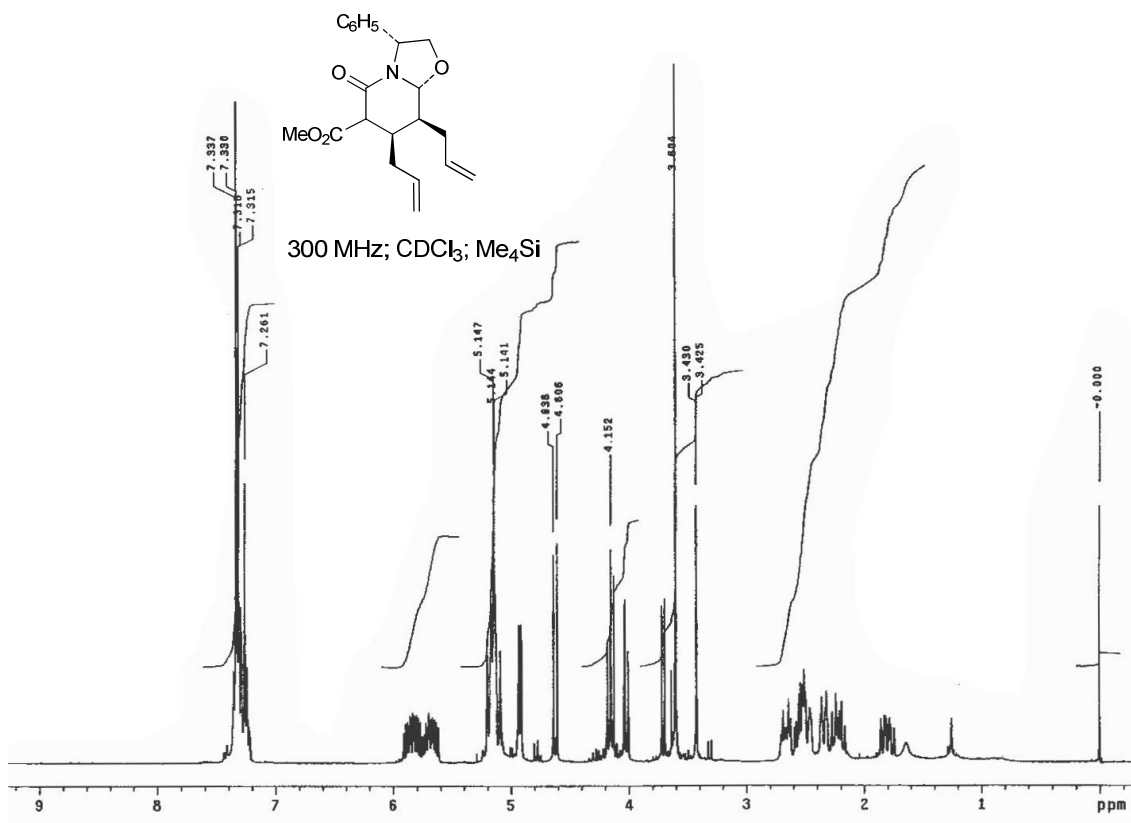


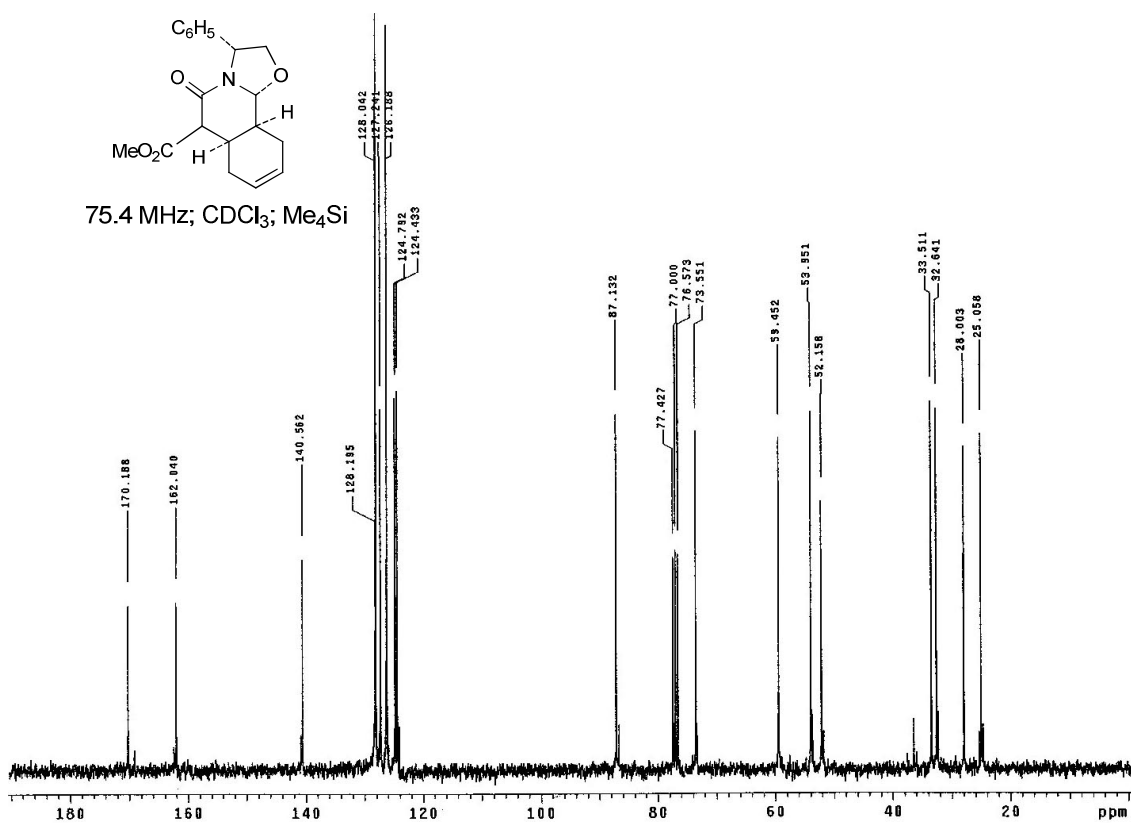
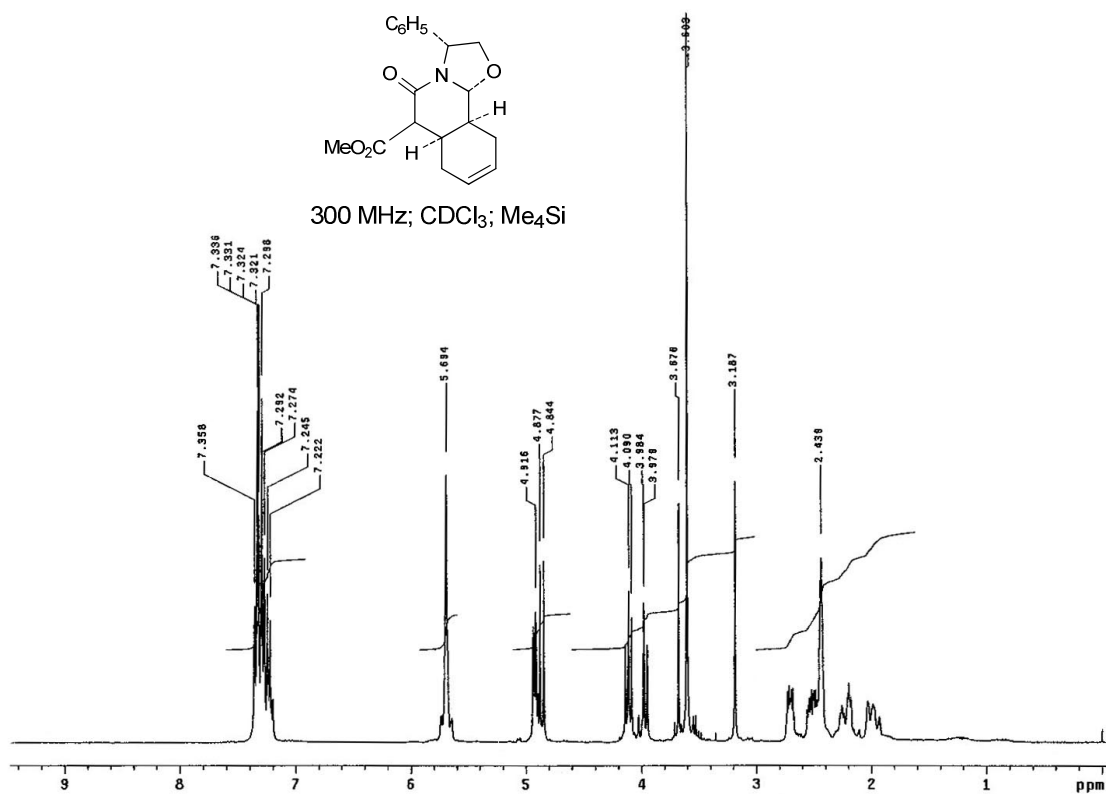
**ABCD system 14.** *First step:* TFA (600  $\mu\text{L}$ , 0.058 mmol) was added to a solution of acid **13** (39 mg, 0.058 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1.6 mL), and the mixture was stirred for 30 minutes at room temperature. Toluene (2 mL) was added to the resulting solution, and the mixture was concentrated under reduced pressure.

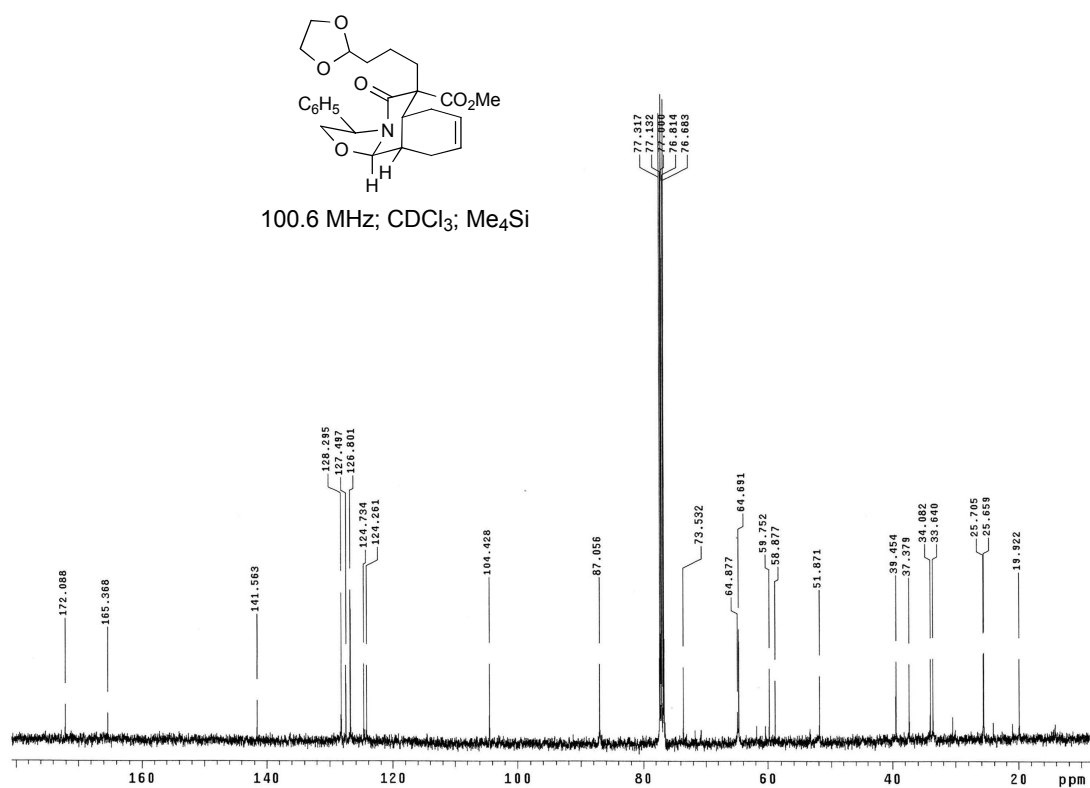
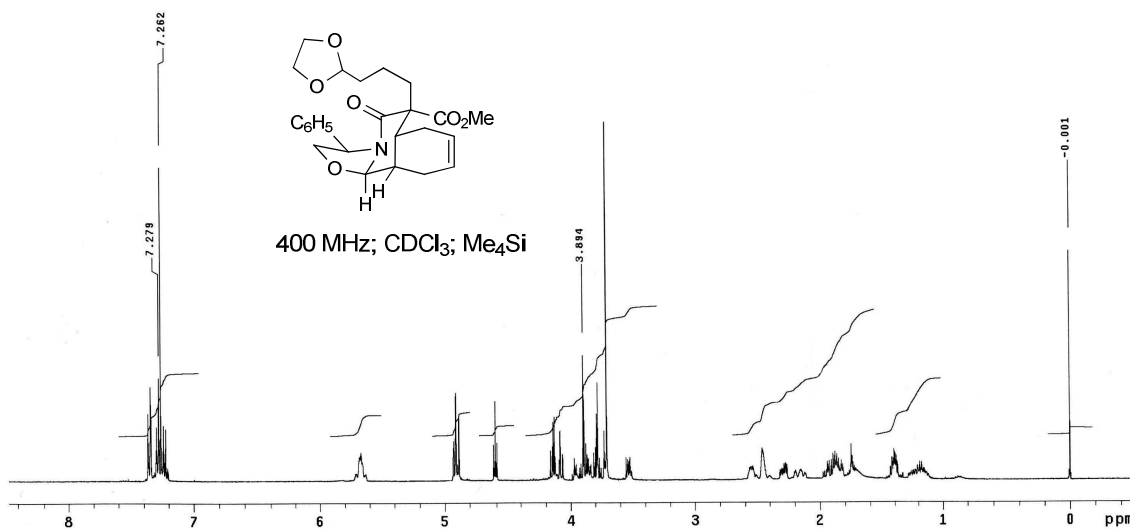
*Second step:* A solution of the above residue in DMF/ $\text{CH}_2\text{Cl}_2$  (9:1, 16 mL) was added over 6 h to a solution of HOBT (40 mg, 0.29 mmol) and EDCI (56 mg, 0.29 mmol) in  $\text{CH}_2\text{Cl}_2$ /DMF (9:1, 116 mL) cooled to 0 °C. The resulting solution was stirred overnight at this temperature and concentrated under reduced pressure. A 1 N aqueous HCl solution was added to the residue, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. Flash chromatography ( $\text{CH}_2\text{Cl}_2$  to 6:4  $\text{CH}_2\text{Cl}_2$ –EtOAc) of the residue afforded tetracyclic compound **14** (14 mg, 43%):  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ;  $\text{Me}_4\text{Si}$ ) 1.25 (12 H, m,  $\text{CH}_2$ ), 1.42 (1 H, m, H-4a), 1.59 (2 H, m,  $\text{CH}_2$ ), 1.80 (3 H, m, H-1', H-5), 2.02 (3 H, m,  $\text{CH}_2$ , H-5), 2.10 (2 H, m, H-8, H-8a), 2.34 (2 H, t,  $J = 7.2$  Hz, H-10'), 2.40 (1 H, m, H-8), 2.61 (1 H, dd,  $J = 13.2, 2.8$  Hz, H-1), 2.78 (1 H, d,  $J = 13.6$  Hz, H-3), 3.16 (1 H, d,  $J = 14.0$  Hz, H-10), 3.46 (1 H, d,  $J = 14.0$  Hz, H-10), 3.56 (1 H, d,  $J = 13.6$  Hz, H-3), 3.87 (3 H, s,  $\text{CH}_3\text{O}$  Mbs), 3.82-3.96 (5 H, m,  $\text{CH}_2\text{O}$ , H-6), 4.38 (1 H, d,  $J = 13.2$  Hz, H-1), 6.95 (2 H, d,  $J = 8.8$  Hz, Mbs), 7.79 (2 H, d,  $J = 8.4$  Hz, Mbs);  $\delta_{\text{C}}$  (100.6 MHz;

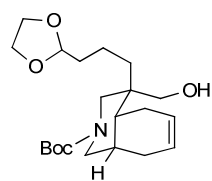
CDCl<sub>3</sub>; Me<sub>4</sub>Si) 20.8-24.9 (CH<sub>2</sub>), 25.4 (C-5), 26.6 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 29.5 (C-8a), 31.9 (CH<sub>2</sub>), 33.2 (C-10'), 33.4 (C-8), 36.6 (C-1'), 36.5 (C-4), 37.6 (C-4a), 43.8 (C-10), 46.3 (C-1), 50.8 (C-6), 53.5 (C-3), 55.6 (OCH<sub>3</sub> Mbs), 64.4, 65.0 (CH<sub>2</sub>O), 107.4 (C-7), 113.8 (C-*m* Mbs), 129.5 (C-*o* Mbs), 131.2 (C-*i* Mbs), 162.4 (C-*p* Mbs), 164.7 (NCO). (CI) *m/z* (%): 560 (M<sup>+</sup>, 1), 391 (5), 390 (27), 342 (8), 389 (100), 346 (4), 317 (8), 248 (6), 246 (4), 170 (8), 123 (8), 112 (5), 108 (8), 107 (14); HRMS (ESI) calcd for [C<sub>30</sub>H<sub>45</sub>N<sub>2</sub>O<sub>6</sub>S + H]<sup>+</sup>: 561.2993, found: 561.2988.



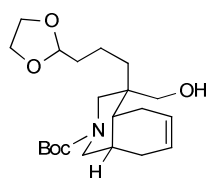
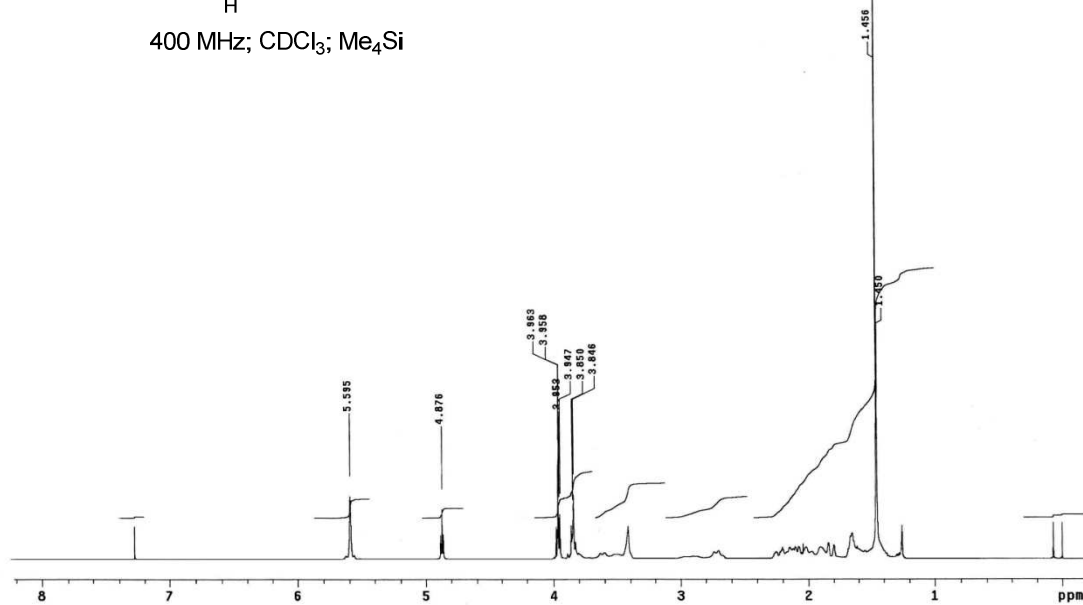




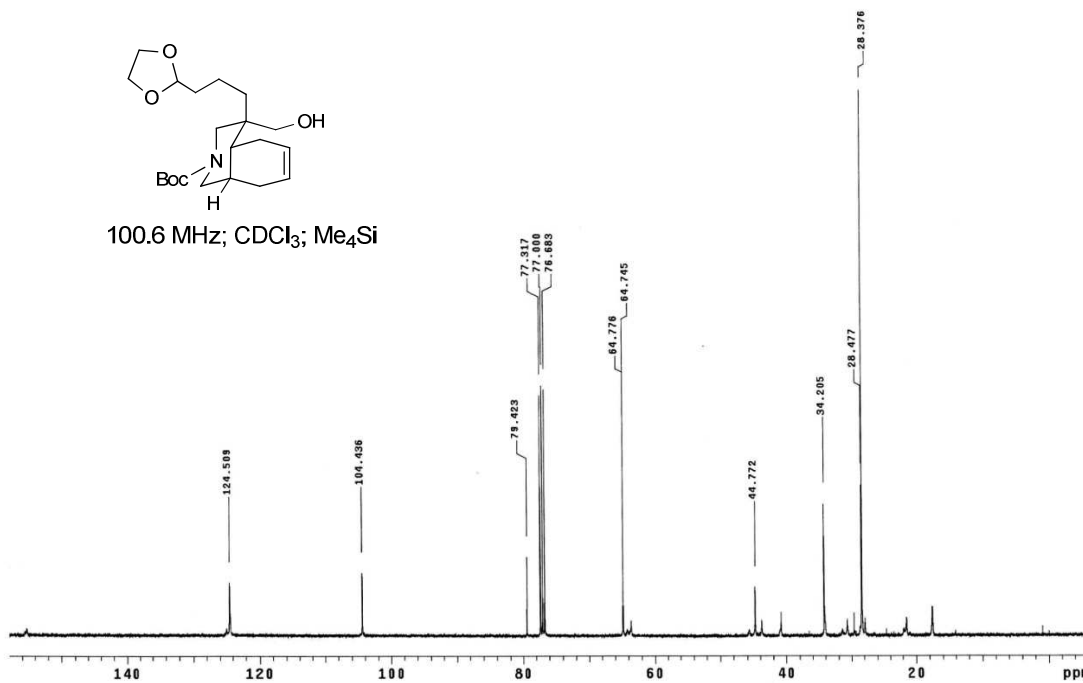


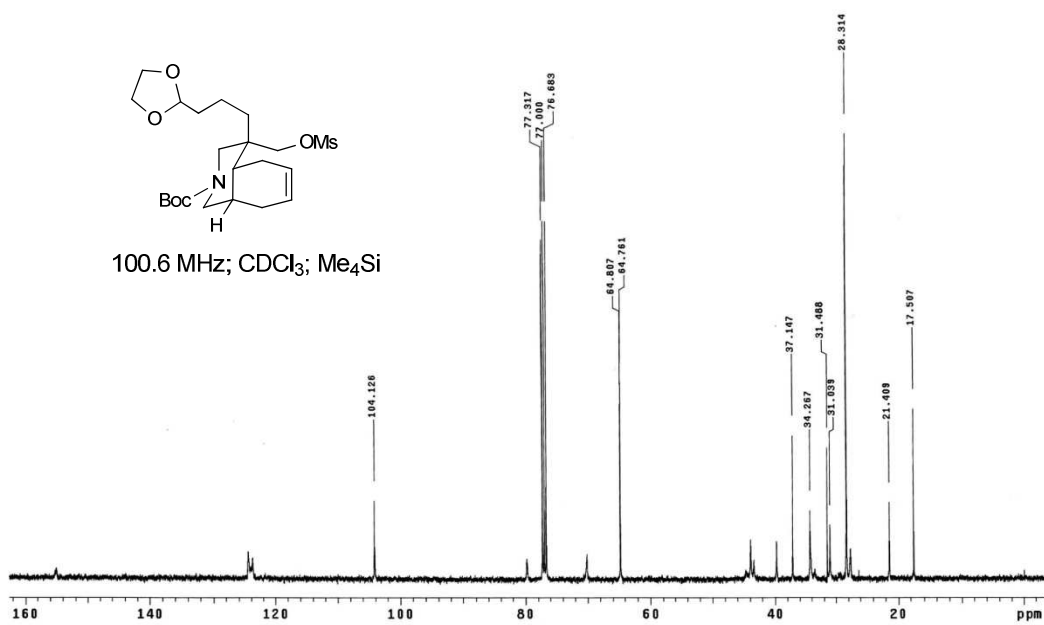
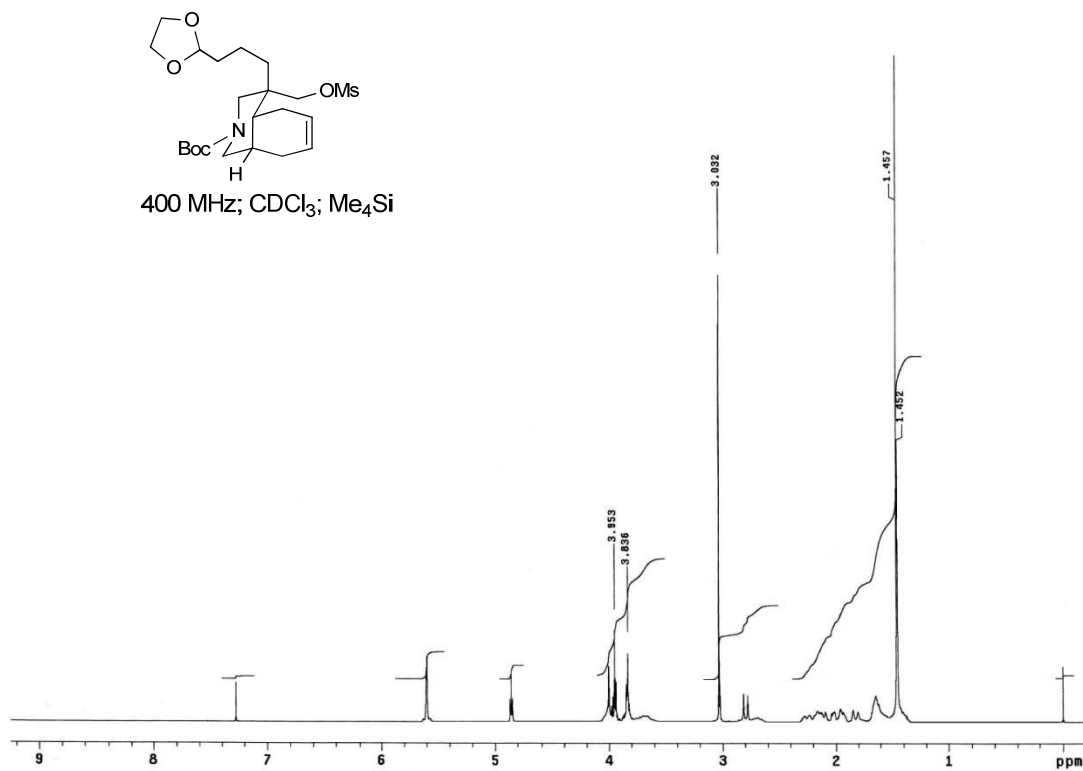


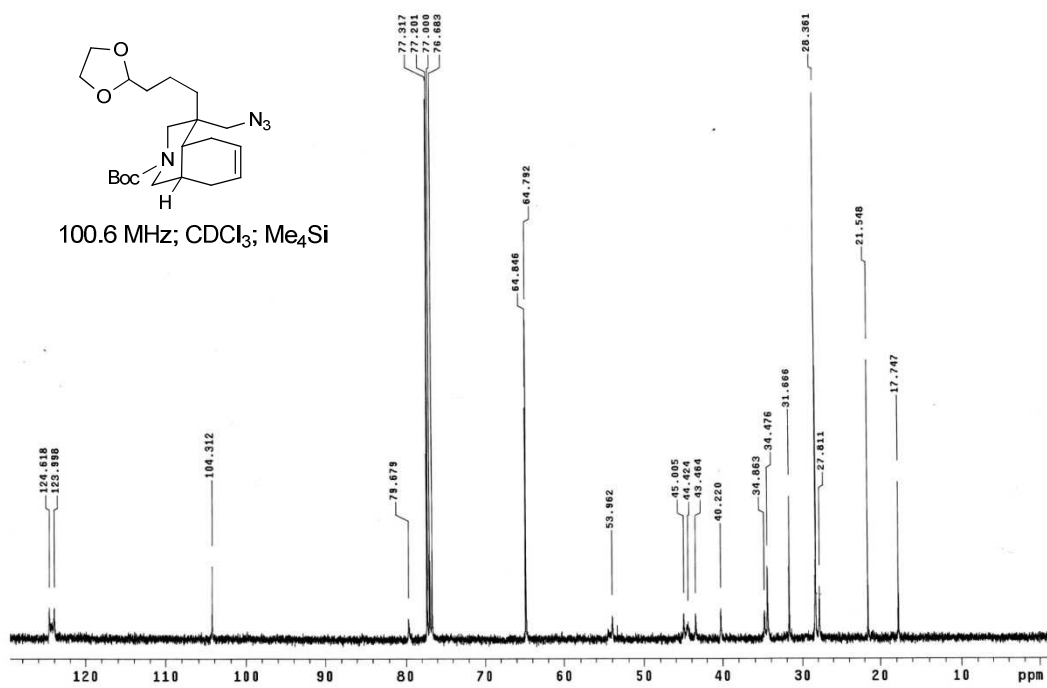
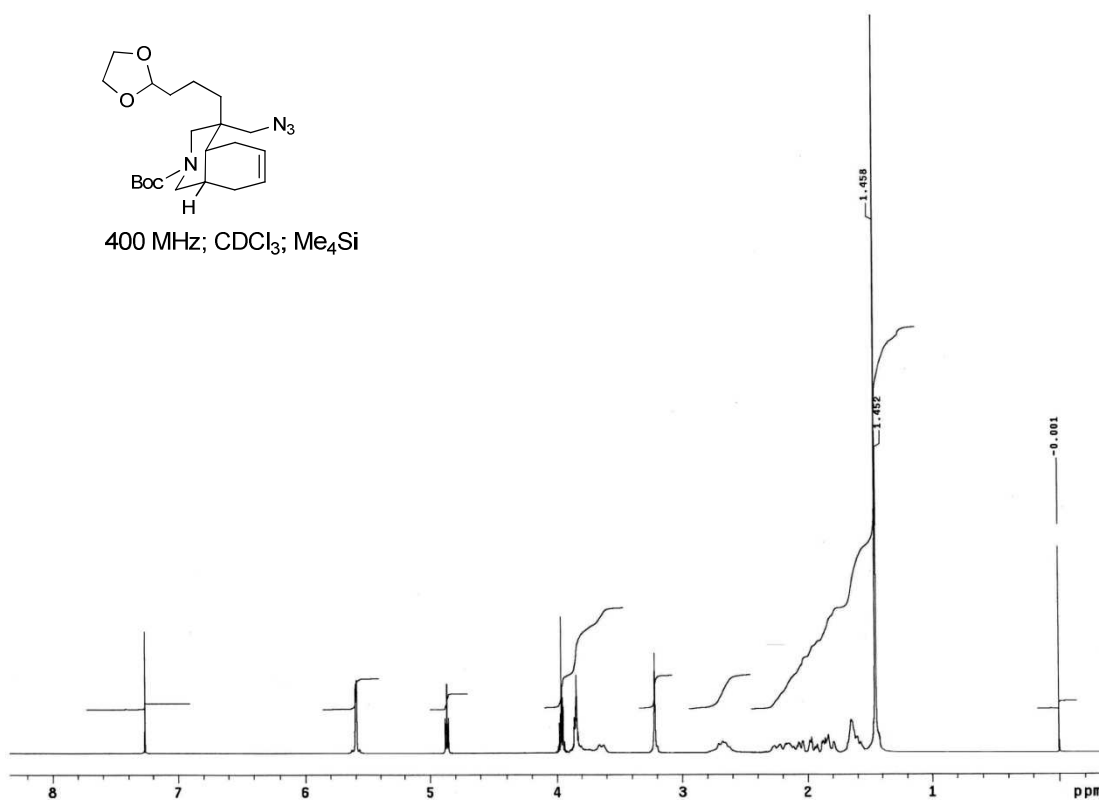
400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

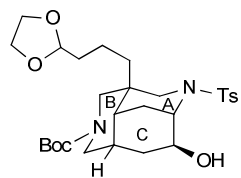


100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

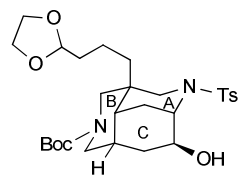
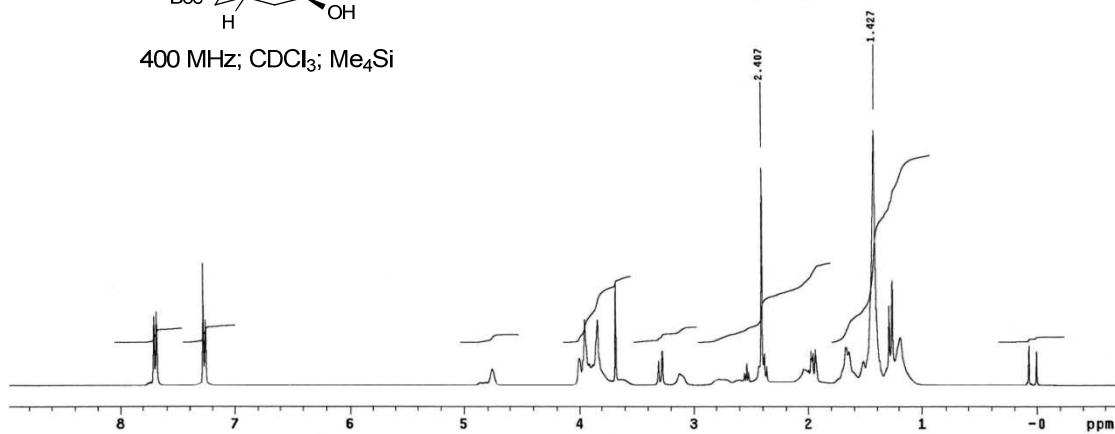




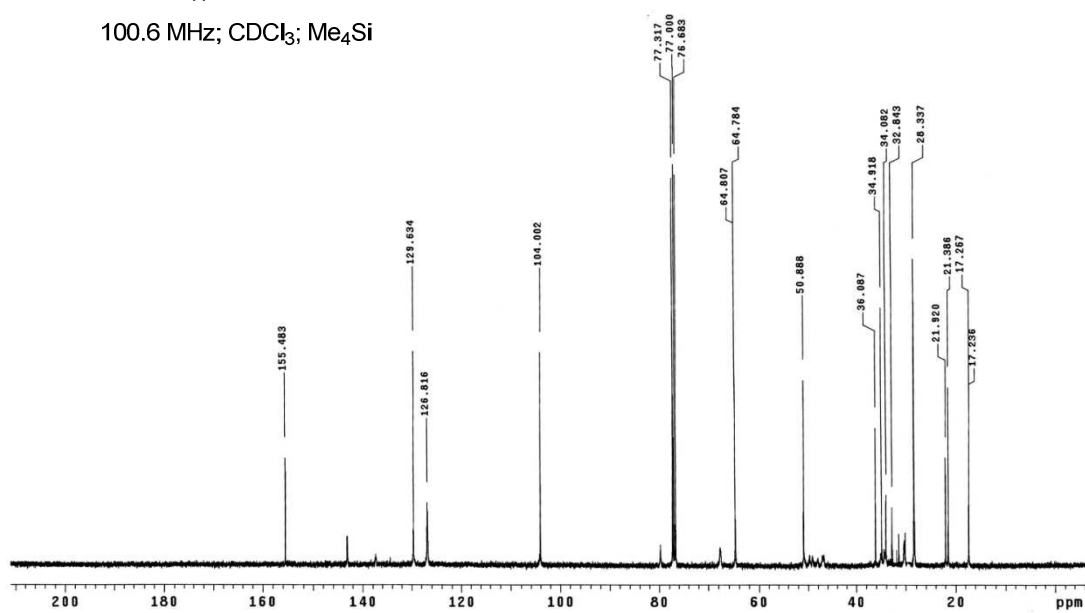


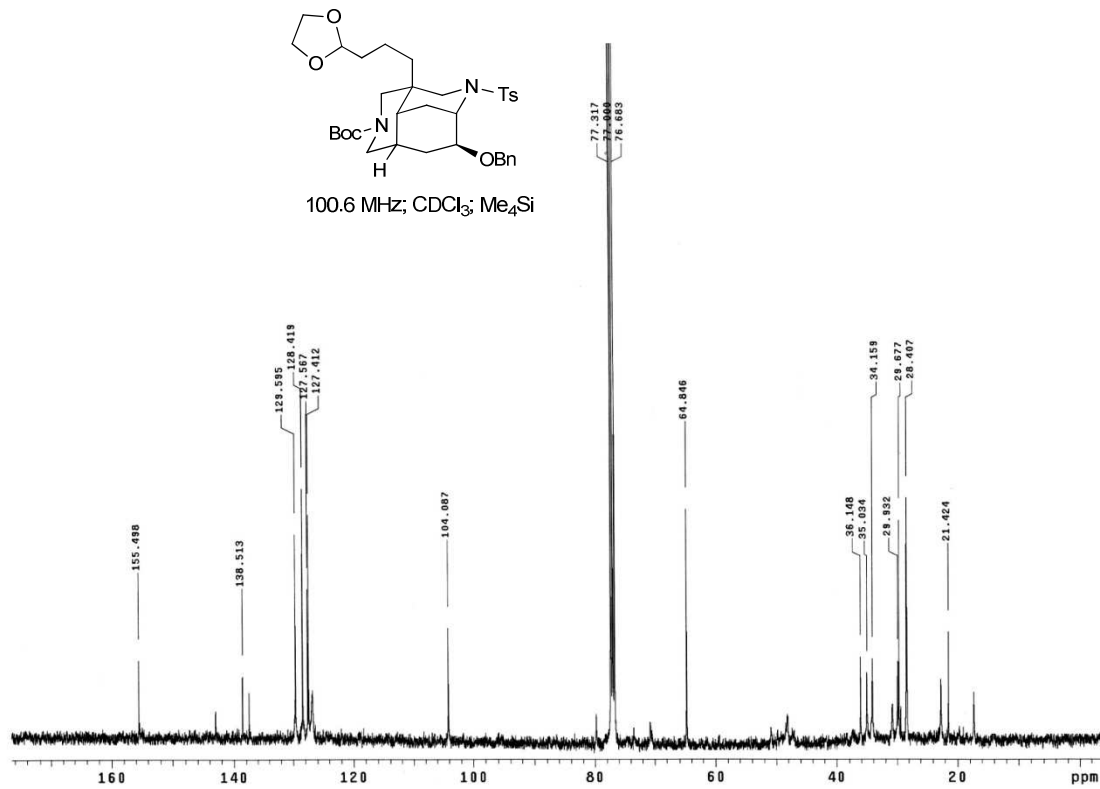
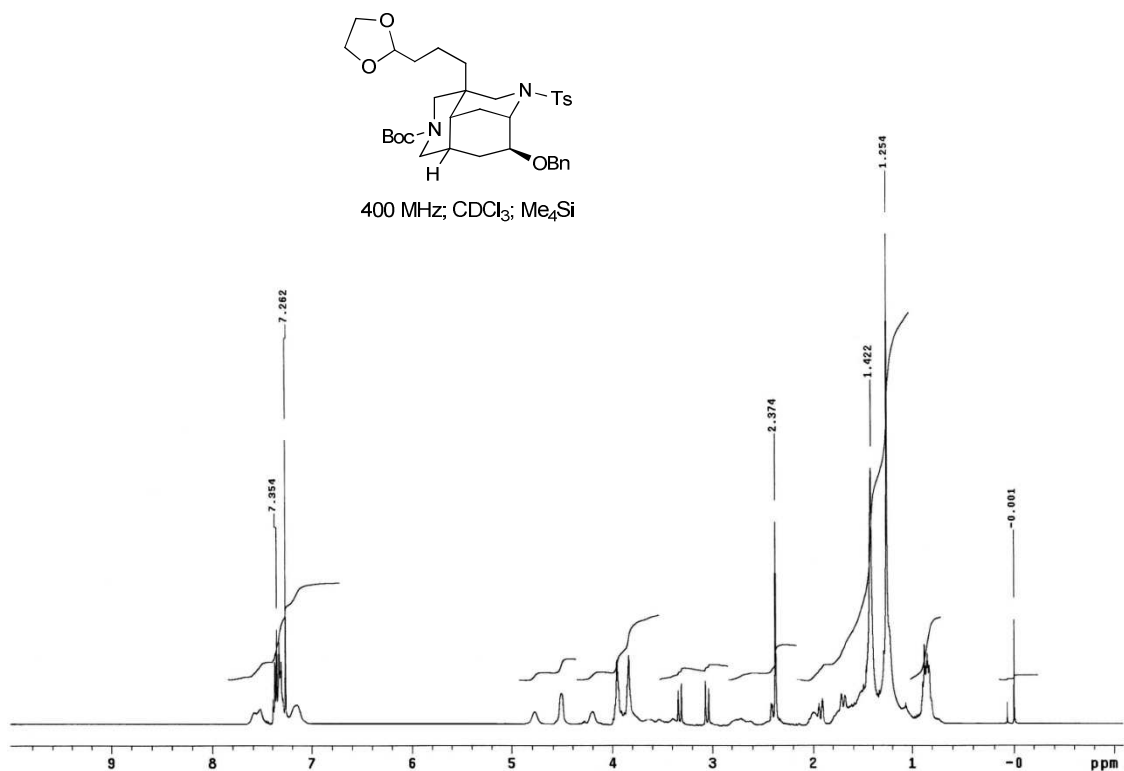


400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

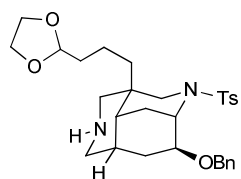


100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

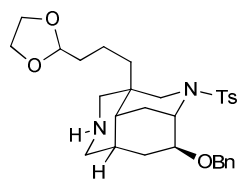
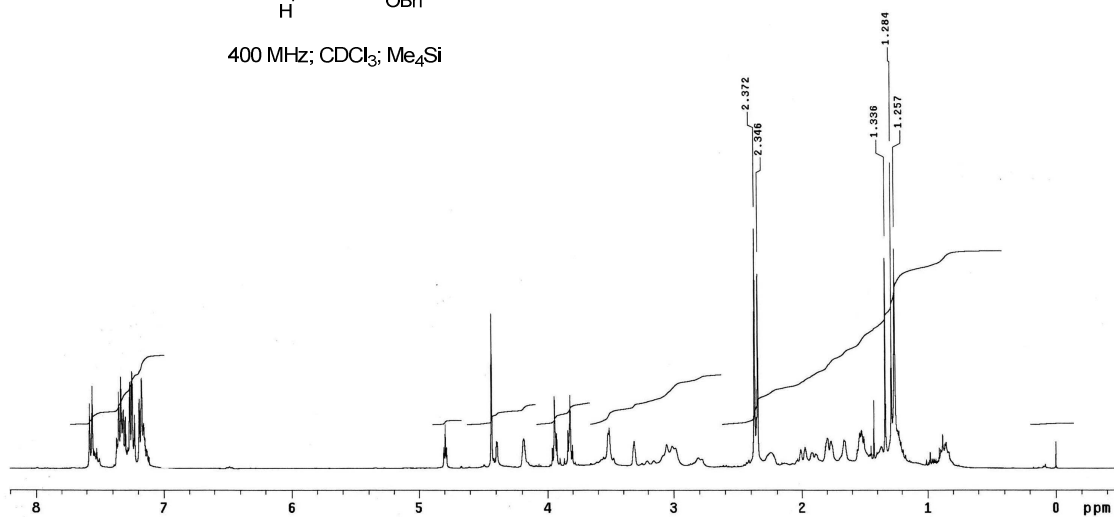




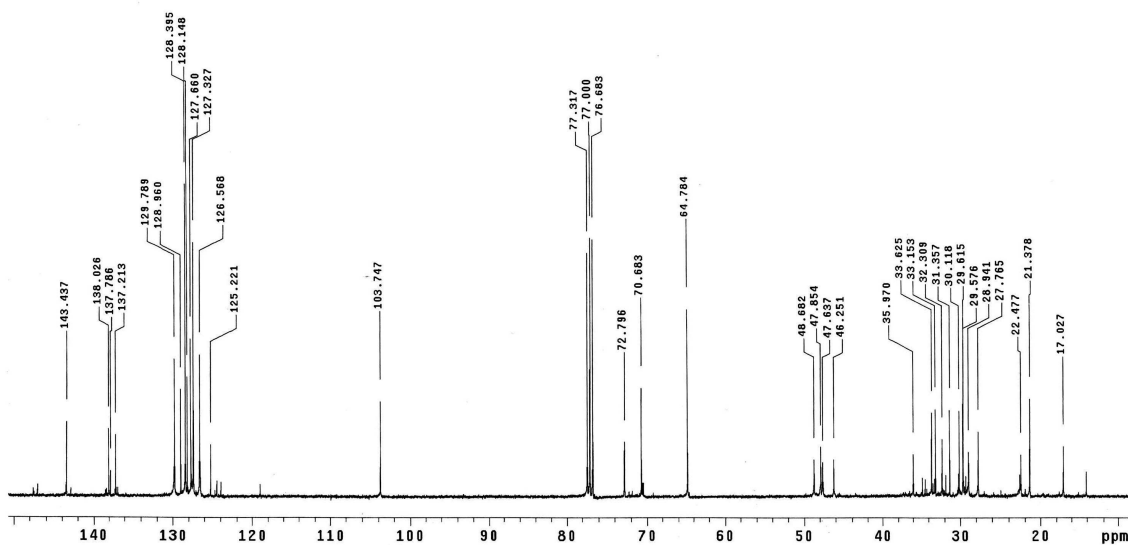


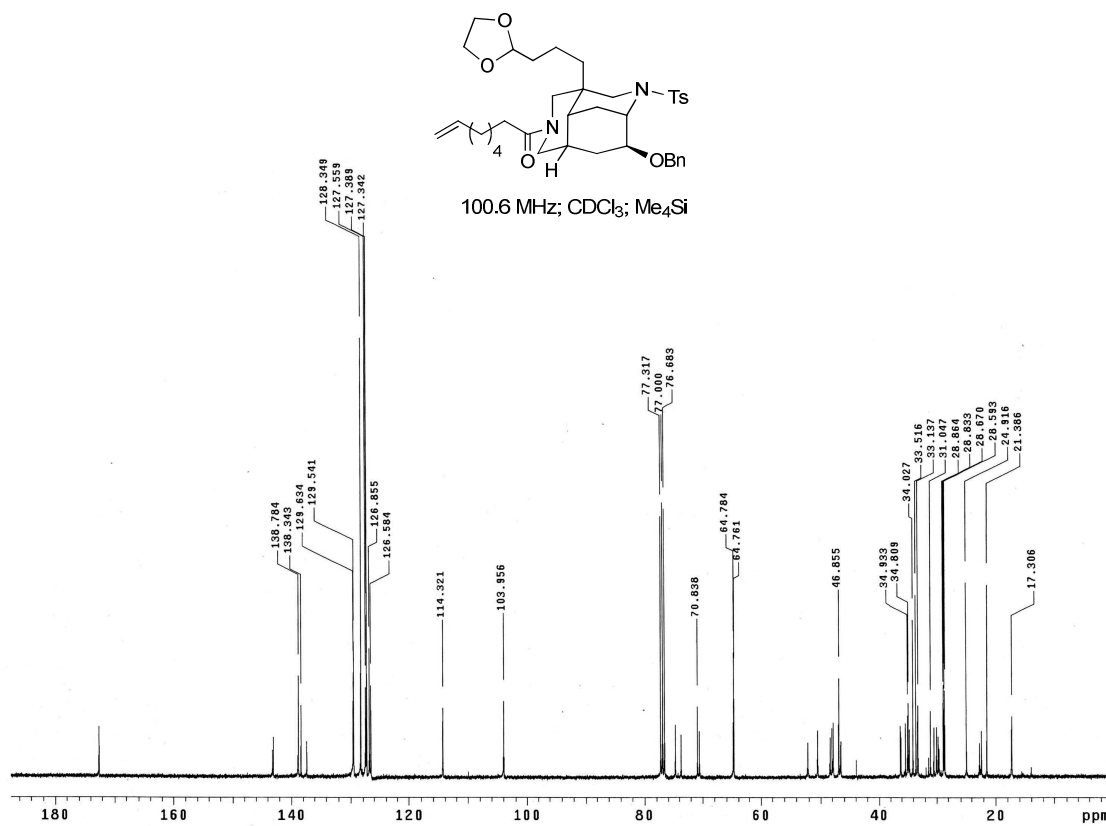
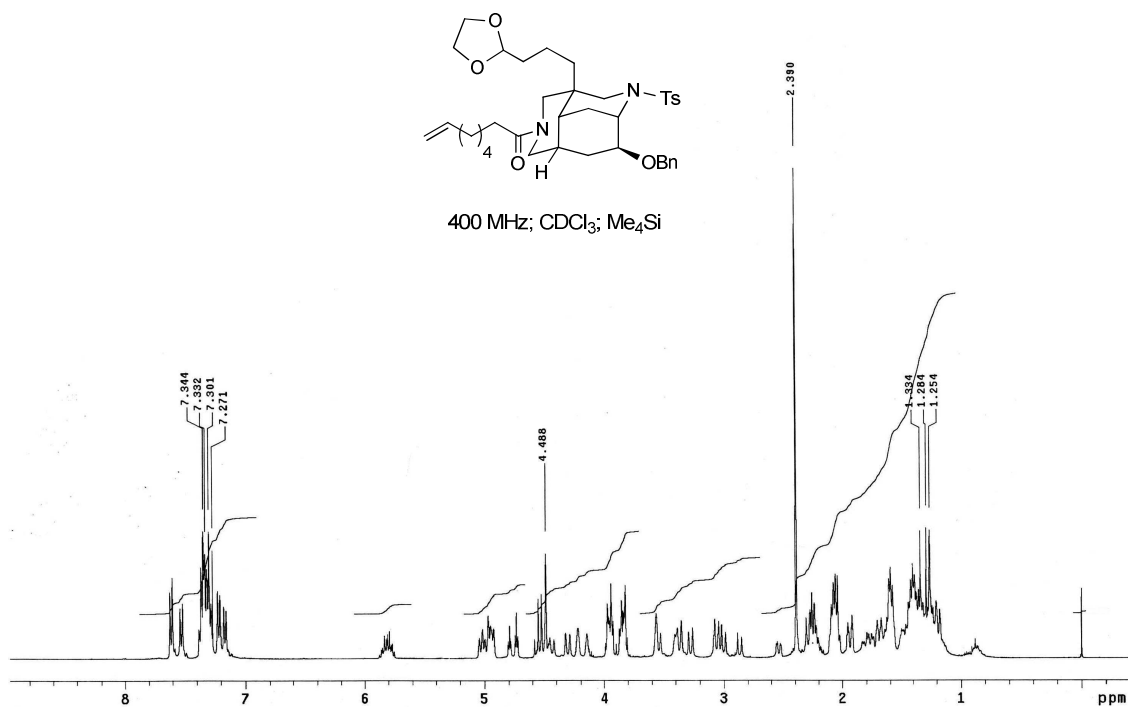


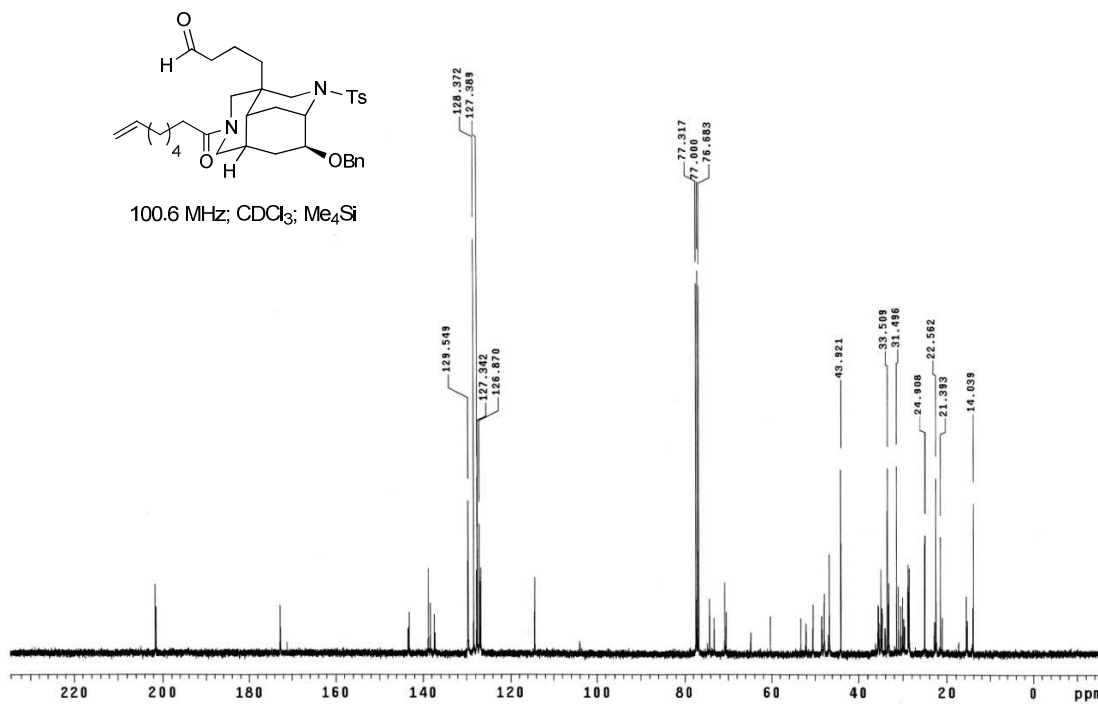
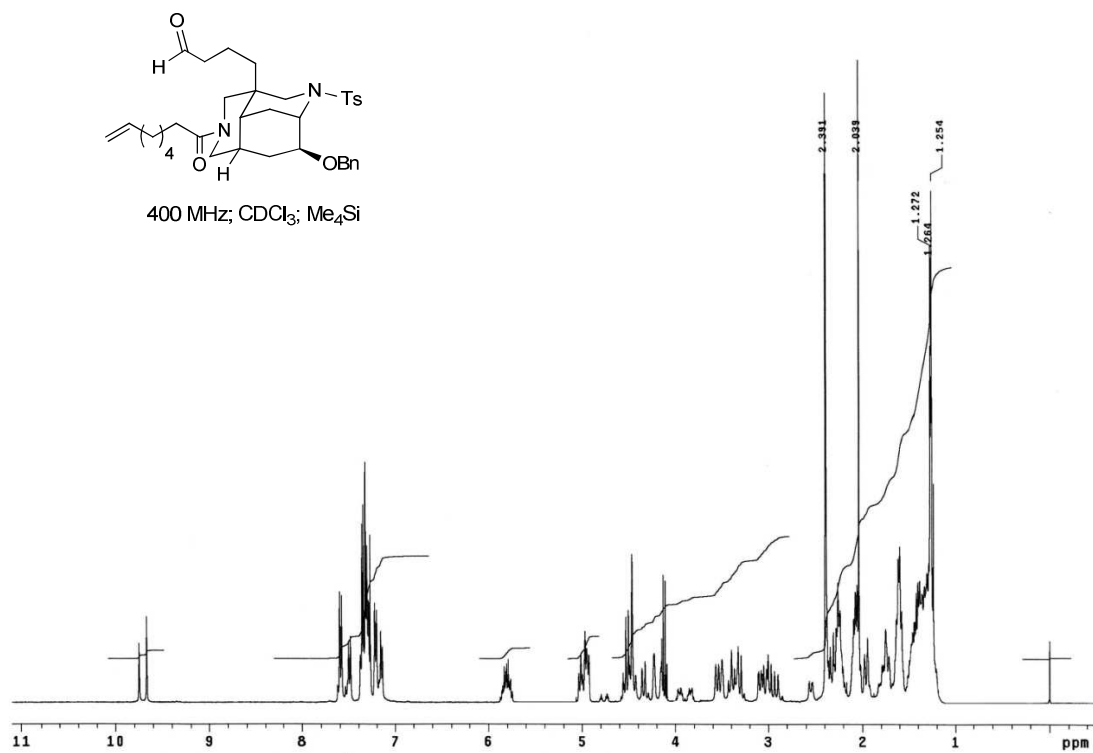
400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

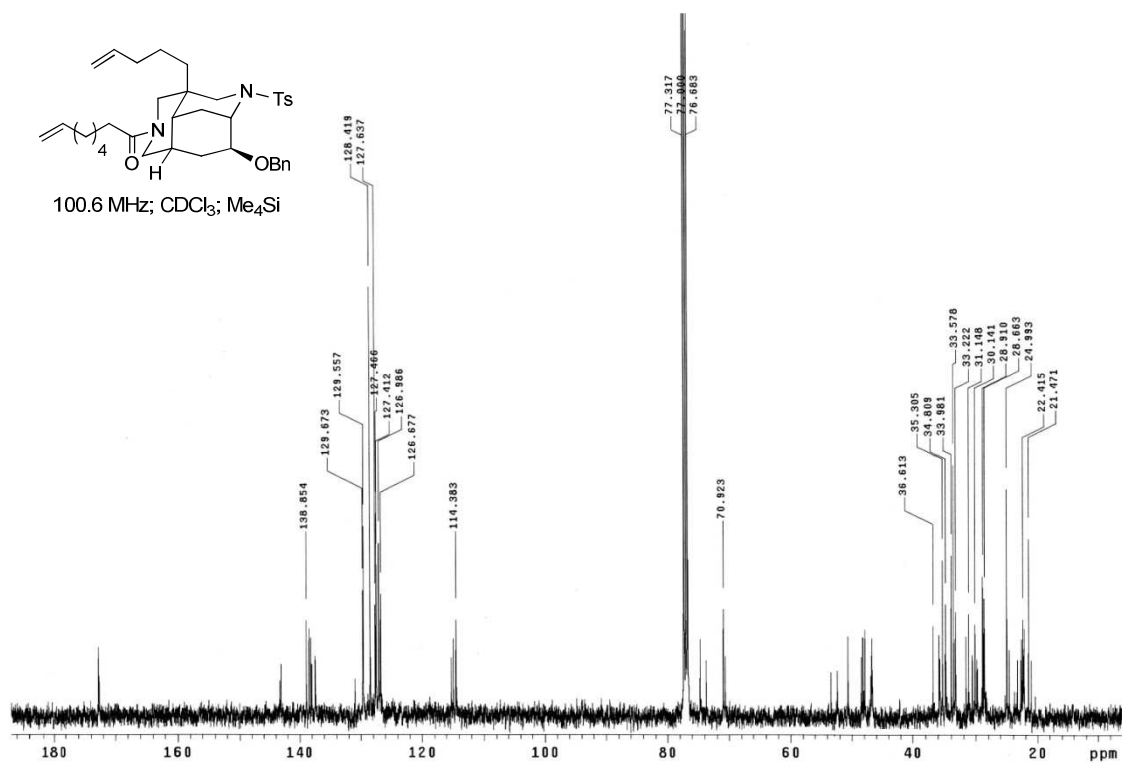
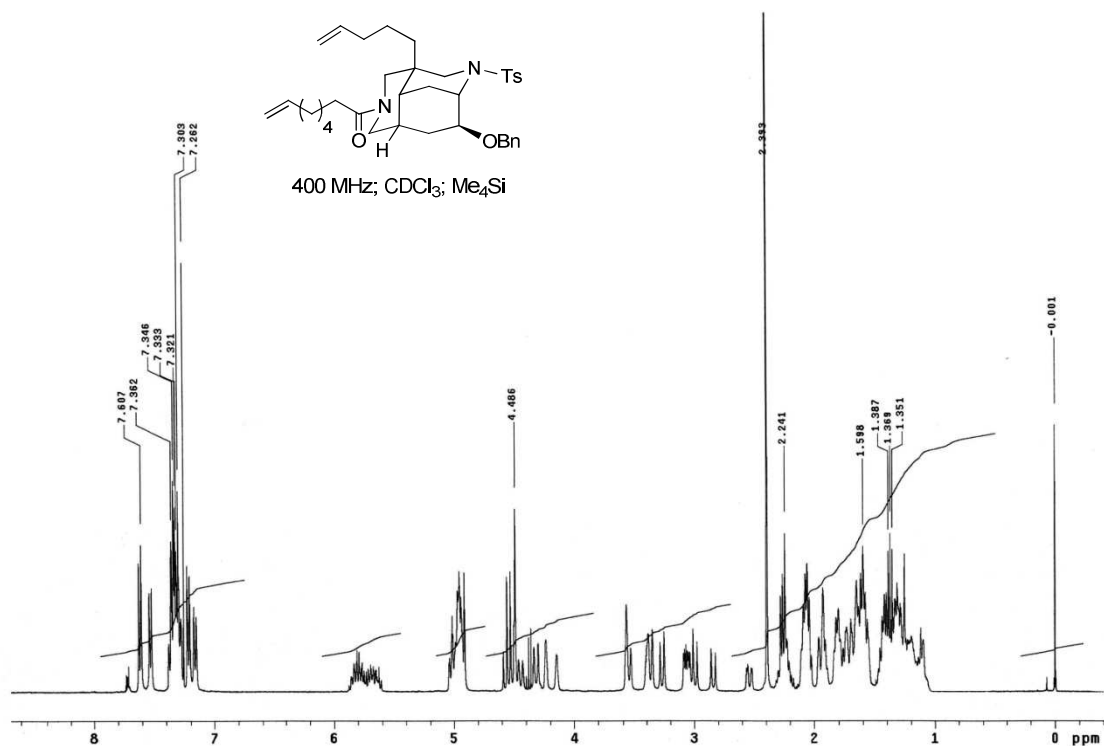


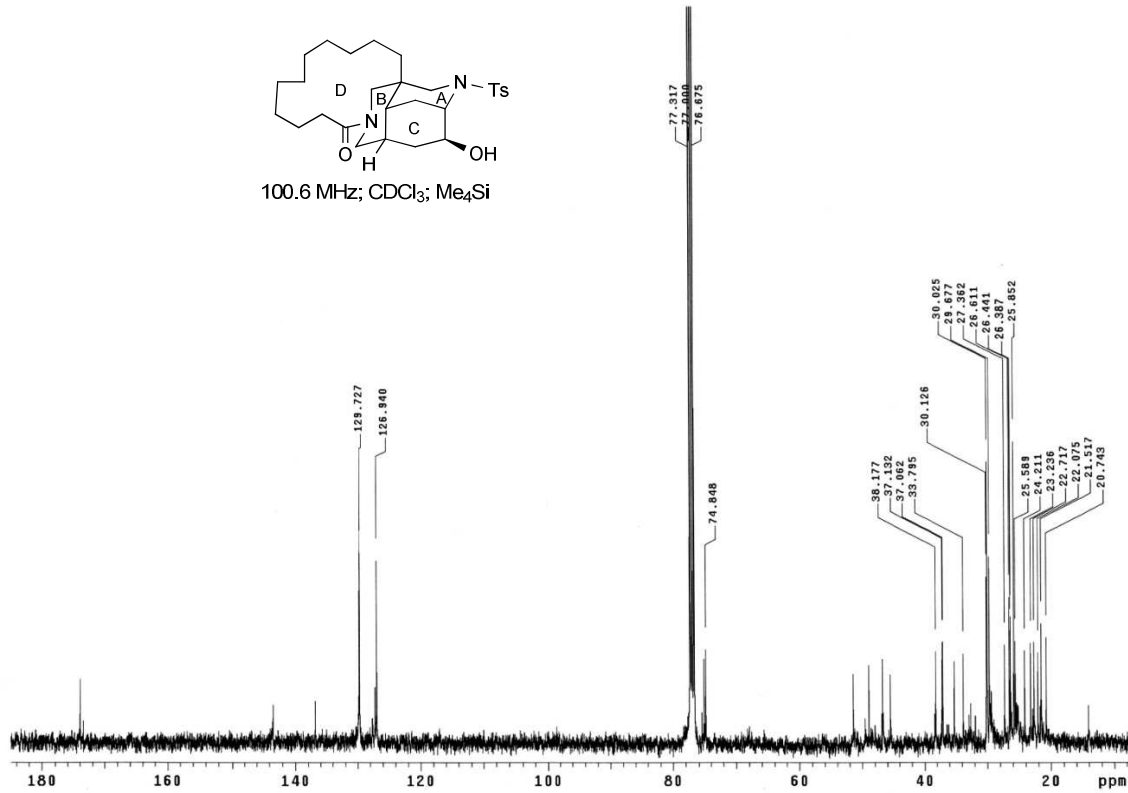
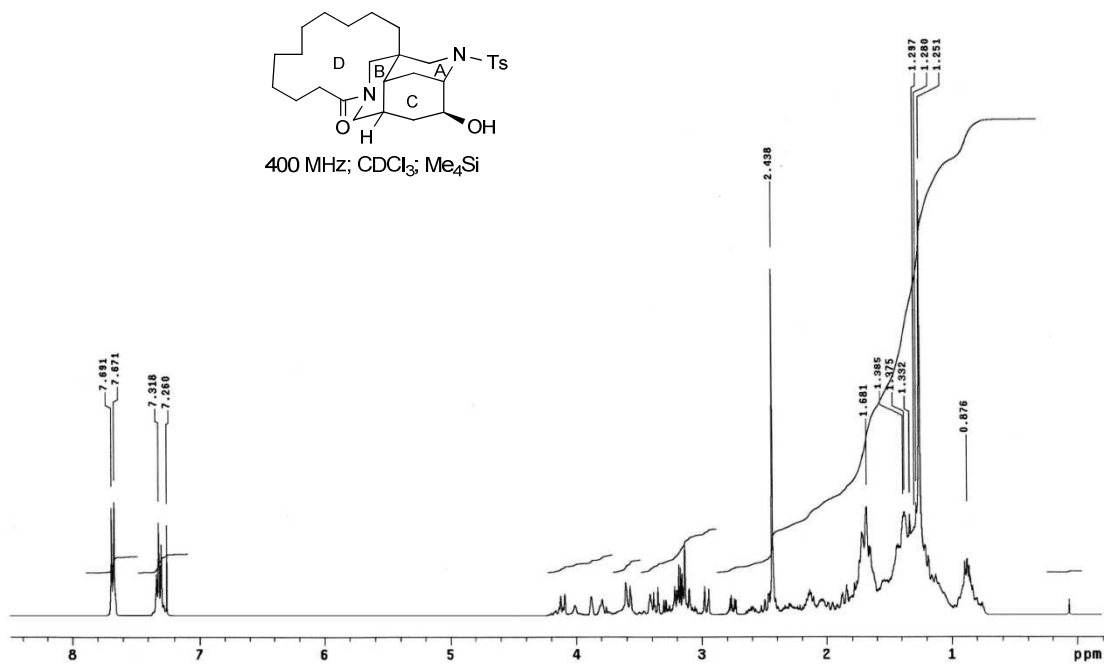
100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

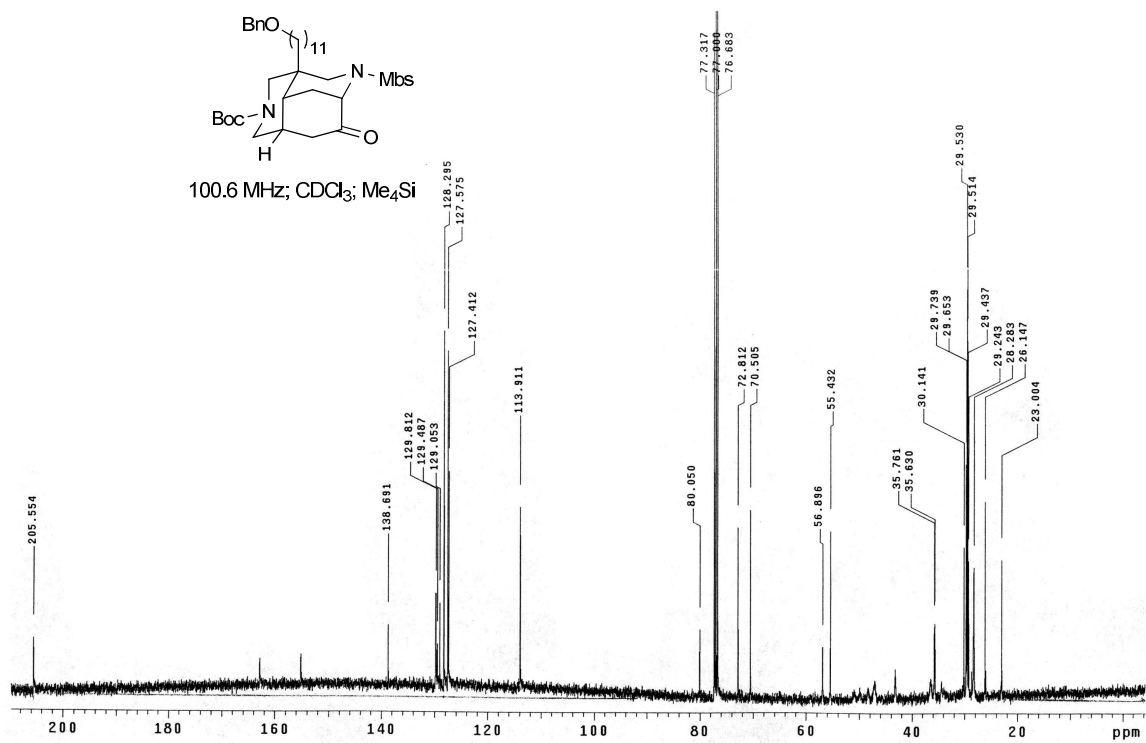
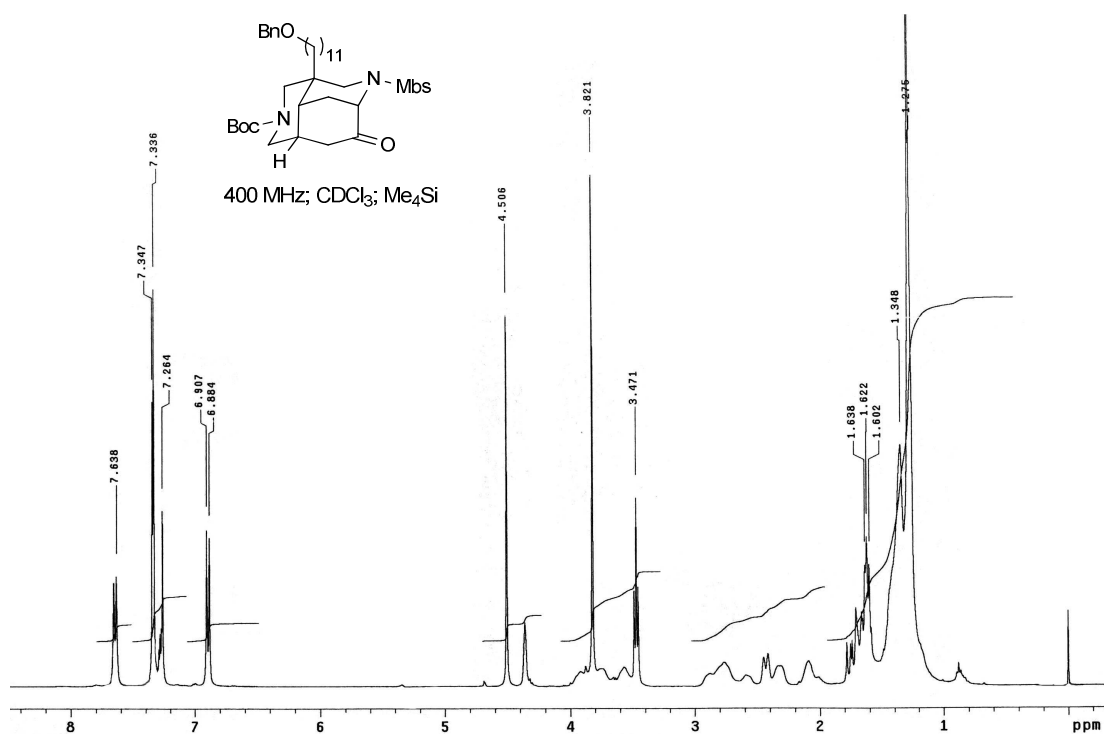


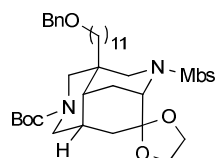




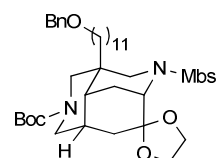
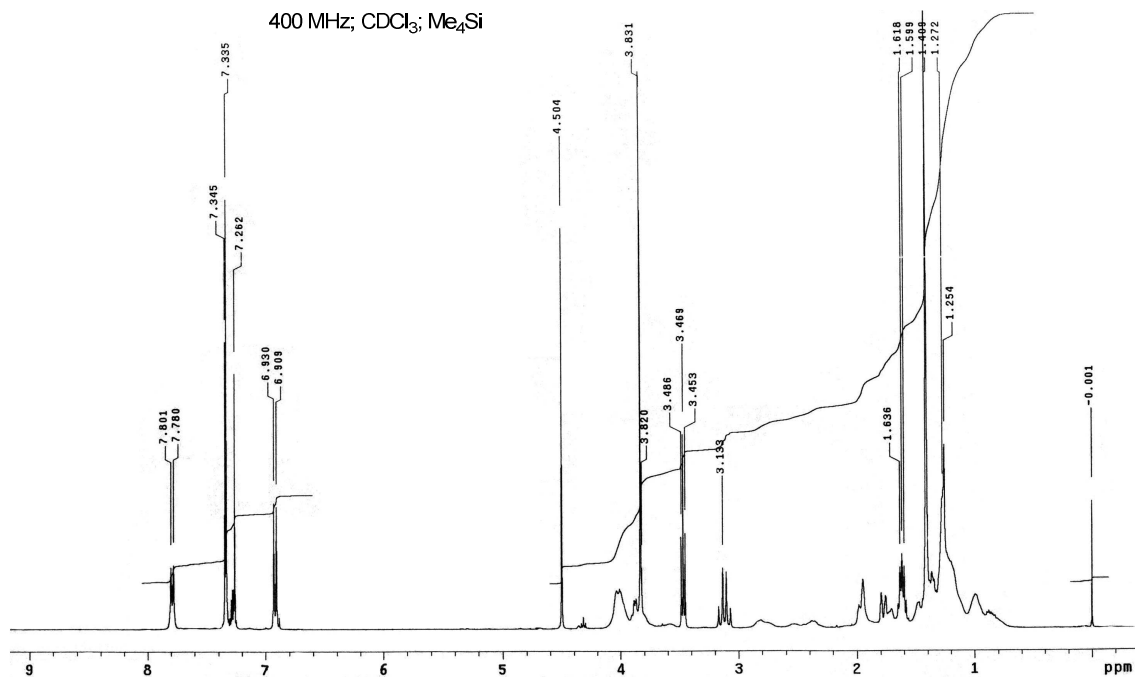








400 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si



100.6 MHz; CDCl<sub>3</sub>; Me<sub>4</sub>Si

