Electronic Supplementary Material (ESI) for ChemComm.

Enantioselective Formal Synthesis of (+)-Madangamine A

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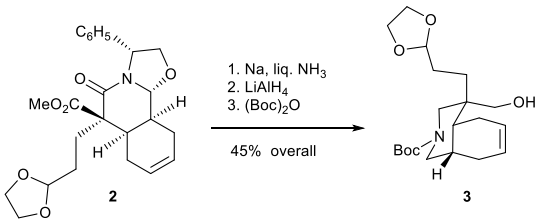
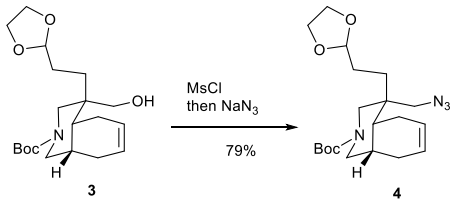
Supporting Information Available

General Experimental Information

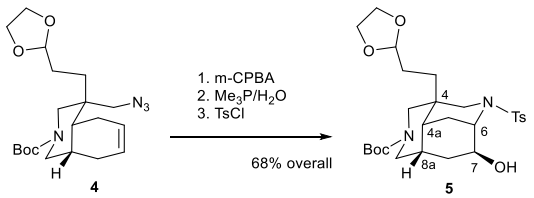
All air sensitive reactions were performed under a dry argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Evaporation of solvent was accomphished with a rotatory evaporator. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV light and a 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). Unless otherwise indicated, NMR spectra were recorded at 400 MHz (^1H) and 100.6 MHz (^{13}C), and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment (when possible). Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (*g*-HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on a Perlin-Elmer 241 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS) were performed by *Centres Científics i Tecnològics de la Universitat de Barcelona*.



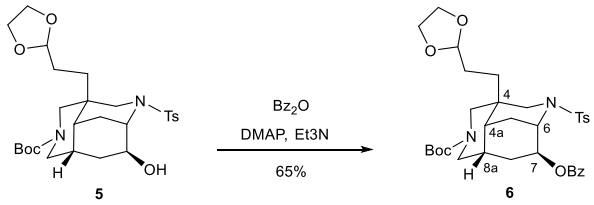
(4*R*,4a*R*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[2-(1,3-dioxolan-2-yl)ethyl]-4-(hydroxymethyl)-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (3): *First step:* Liquid ammonia (15 mL) was condensed at −78 °C in a three-necked, 100 mL round-bottomed flask equipped with a coldfinger condenser charged with dry ice-acetone, and then a solution of lactam **2** (214 mg, 0.50 mmol) in anhydrous THF (3 mL) was added. The temperature was raised to −33 °C and sodium metal 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 NH_4Cl until the blue color disappeared, and the mixture was stirred at room temperature for 4h. The residue was digested at room temperature with CH_2Cl_2, and the resulting suspension was filtered through Celite®. The solution was concentrated under reduced pressure. *Second step:* The resulting residue was added under an argon atmosphere to a solution of $LiAlH_4$ (278 mg, 7.35 mmol) in anhydrous dioxane (17 mL), and the mixture was stirred at reflux overnight. The reaction was quenched with water and 10% aqueous NaOH. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give a crude amino alcohol, which was used in the next step without purification. *Third step:* Boc_2O (119 mg, 0.55 mmol) was added dropwise under an inert atmosphere at room temperature to a solution of the above amino alcohol in anhydrous CH_2Cl_2 (8 mL), and the resulting mixture was stirred for 20 h. The solution was poured into saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue gave compound **3** (83 mg, 45% overall yield) as a white foam: $[\alpha]_D^{22}$ = – 8.34 (*c* 0.44 in $CHCl_3$); IR (film): ν = 3479 (OH), 1681 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.45 [9 H, s, $(CH_3)_3C$], 1.58-1.76 (4 H, m, H-1', H-2'), 1.78-1.96 (2 H, m, H-8, H-4a), 1.98-2.30 (4 H, m, H-5, H-8, H-8a), 2.67-2.77 (2 H, m, H-1, H-3), 3.42 (2 H, s, C*H*$_2$OH), 3.59-3.62 (2 H, m, H-1, H-3), 3.85-3.98 (4 H, 2m, OCH_2CH_2O), 4.87 (1 H, t, *J* = 4.8 Hz, H-3'), 5.60 (2 H, m, H-6, H-7); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.6 (C-5), 24.0 (C-1'), 27.2 (C-2'), 27.9 (c-8a), 28.4 [C-8, (*C*H_3)C], 34.2 (C-4a), 45.4 (C-1, C-3), 68.2 (CH_2OH), 64.9 (OCH_2CH_2O), 79.5 [(CH_3)*C*], 104.7 (C-3'), 124.8 (C-6, C-7); HRMS (ESI) calcd for $[C_{20}H_{33}NO_5 + Na]^+$: 390.2251, found: 390.2263.



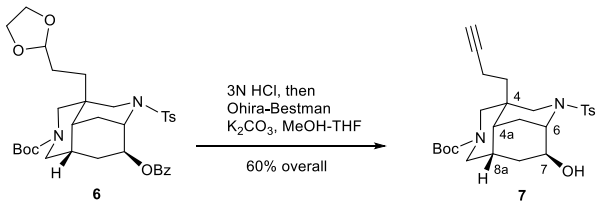
(4*R*,4a*R*,8a*S*)-4-(Azidomethyl)-2-(*tert*-butoxycarbonyl)-4-[2-(1,3-dioxolan-2-yl)ethyl]-1,2,3,4,4a,5,8,8a-octahydroisoquinoline (4): *First Step*: Anhydrous Et_3N (0.52 mL, 3.75 mmol) and methanesulfonyl chloride (0.29 mL, 3.75 mmol) were added at 0 °C under an inert atmosphere to a stirred solution of alcohol **3** (458 mg, 1.25 mmol) in anhydrous CH_2Cl_2 (21 mL), and the resulting mixture was stirred at room temperature for 4 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give the mesylate as a yellow oil, which was used in the next step without purification. *Second Step:* NaN_3 (471 mg, 7.25 mmol) was added under an inert atmosphere to a solution of the above mesylate in anhydrous DMF (3.6 mL) and the mixture was heated to 90 °C. After 48 h, more NaN_3 (471 mg, 7.25 mmol) was added and the resulting mixture was stirred at 90 °C for an additional 48 h. The reaction was quenched with distilled water and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 9:1 hexane-EtOAc) of the resulting oil gave azide **4** (387mg, 79%) as a pale yellow oil: $[\alpha]_D^{22} = -35.18$ (*c* 0.6 in $CHCl_3$); IR (film): ν = 2100 (N_3), 1693 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.42 [9 H, s, $(CH_3)_3C$], 1.49-1.59 (2 H, m, H-1', H-5), 1.64-1.71 (2 H, m, H-1', H-5), 1.75-1.85 (2 H, m, H-8), 1.90-1.98 (1 H, m, H-4a), 2.00-2.07 (1 H, m, H-2'), 2.11-2.24 (2 H, m, H-8a, H-2'), 2.59-2.70 (2 H, m, H-1, H-3), 3.17 (2 H, s, CH_2N_3), 3.53-3.61 (2 H, m, H-1, H-3), 3.81-3.92 (4 H, 2m, OCH_2CH_2O), 4.88 (1 H, t, *J* = 4.8 Hz, H-3'), 5.56 (2 H, m, H-6, H-7); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.5 (C-2'), 25.7 (C-1'), 27.7 (C-8a), 27.8 (C-5), 28.3 [(CH_3)$_3$C, C-8], 34.7 (C-4a), 39.7 (C-4), 43.3, 44.1, 44.4, 44.9 (C-3, C-1), 53.9 (CH_2N_3), 64.8 (OCH_2CH_2O), 79.6 [$(CH_3)_3C$], 104.6 (C-3'), 123.9, 124.5 (C-6, C-7), 154.9 (NCOO); HRMS (ESI) calcd for $[C_{20}H_{32}N_4O_4 + Na]^+$: 415.2316, found: 415.2334.



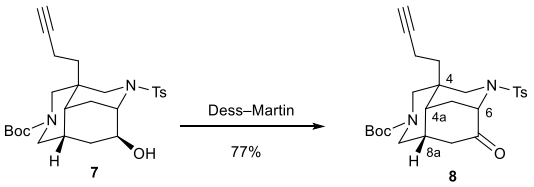
(4*R*,4a*R*,6*S*,7*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[2-(1,3-dioxolan-2-yl)ethyl]-7-hydroxy-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (5): *First step*: *m*-CPBA (317 mg, 1.41 mmol, ≤ 77% of purity) was added to a cold (0 ºC) solution of azide **4** (327 mg, 0.83 mmol) in CH_2Cl_2, and the mixture was allowed to warm slowly to room temperature. After 5 h, a solution of saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ (1:1) was added, and the resulting mixture was stirred for an additional 45 minutes. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with a 10% aqueous Na_2SO_3, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the azido epoxide intermediate, which was used in the next step without purification. *Second step*: Me_3P (1.33 mL of a 1 M solution in THF, 1.33 mmol) was added to a solution of the above azido epoxide in THF (16 mL) and water (1.6 mL), and the resulting mixture was stirred at room temperature overnight and concentrated to afford the diazatricyclic alcohol derivative. *Third step*: Et_3N (0.12 mL, 0.83 mmol) was added dropwise at 0 °C under an inert atmosphere to a stirring solution of the above aminoalcohol in anhydrous CH_2Cl_2 (14 mL). A solution of *p*-toluenesulfonyl chloride (158 mg, 0.83 mmol) in anhydrous CH_2Cl_2 (1.4 mL) was added, and the stirring was continued at 0 °C for 2.5 h. A saturated aqueous NH_4Cl solution was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue afforded the protected tricyclic compound **5** (302 mg, 68%) as a pale yellow oil: $[\alpha]_D^{22}$ = + 24.01 (*c* 3.15 in $CHCl_3$); IR (film): ν = 3444 (OH), 1693 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.35, 1.41 [13 H, m, $(CH_3)_3C$, H-1',H-2'], 1.45 (1 H, m, H-4a), 1.59-1.64 (3 H, m, 2H-8, H-5), 1.94 (1 H, dt, *J* = 13.6, 2.8 Hz, H-5), 1.97 (m, 1H, H-8a), 2.33 (3 H, s, CH_3-Ts), 2.60-2.78 (2 H, m, H-1, H-3), 3.03 (1 H, d, *J* = 12.8 Hz, H-10), 3.24 (1 H, d, *J* = 13.2 Hz, H-10), 3.76 (2 H, m, CH_2O), 3.83 (1 H, masked, H-7), 3.86 (2 H, m, CH_2O), 3.90 (2 H, masked, H-1, H-3), 3.96 (1 H, s, H-6), 4.60 (1 H, s, H-3'), 7.22 (2 H, d, *J* = 8.4 Hz, H-Ts), 7.64 (2 H, d, *J* = 8.4 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.1 (CH_3-Ts), 21.9 (C-5), 27.3 (C-1'), 28.2 [(*C*H_3)C], 29.4 (C-2'), 30.7 (8a), 32.3 (C-8), 32.4 (C-4), 35.2 (C-4a), 46.8 (C-10), 50.8 (C-6), 48.4-49.6 (C-1, C-3), 64.8 ($2CH_2O$), 67.3 (C-7), 80.0 [(CH_3)*C*], 104.4 (C-3'), 127.0 (CH-Ts), 129.9 (CH-Ts), 137.6 (C-Ts), 143.1 (C-Ts), 155.4 (NCOO); HRMS calcd for $[C_{27}H_{40}N_2O_7S + Na]^+$: 559.2448, found: 559.2435.



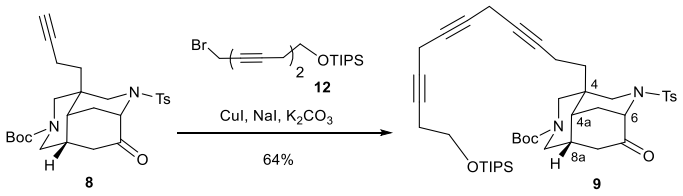
(4*R*,4a*R*,6*S*,7*S*,8a*S*)-7-(Benzoyloxy)-2-(*tert*-butoxycarbonyl)-4-[2-(1,3-dioxolan-2-yl)ethyl]-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (6): Triethylamine (40 μL, 0.296 mmol) and DMAP (2.4 mg, 0.02 mmol) were added under an inert atmosphere to a stirred solution of tricyclic compound **5** (56 mg, 0.099 mmol) in anhydrous CH_2Cl_2 (2.5 mL). After 30 minutes, benzoic anhydride (34 mg, 0.15 mmol) was added and the resulting mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue afforded tricyclic compound **6** (40 mg, 65%) as a white foam: IR (film): ν = 1714 (CO), 1682 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.37-1.54 [13 H, m, H-1', H-2', $(CH_3)_3C$], 1.56-1.70 (2 H, m, H-4a, H-8), 1.72-1.81 (1 H, m, H-8), 1.94 (2 H, s, H-5), 2.05 (1 H, s, H-8a), 2.42 (3 H, s, CH_3-Ts), 2.58-2.88 (2 H, m, H-1, H-3), 3.05 (1 H, d, *J* = 11.6 Hz, H-10), 3.51 (1 H, d, *J* = 13.2 Hz, H-10), 3.73-3.89 (2 H, masked, H-1, H-3), 3.85, 3.96 (4 H, 2m, $2CH_2O$), 4.28 (1 H, s, H-6), 4.76 (1 H, s, H-3'), 5.06 (1 H, s, H-7), 7.31 (2 H, d, *J* = 7.6 Hz, H-Ts), 7.45 (2 H, t, *J* = 7.6 Hz,C_6H_5), 7.57 (1 H, t, *J* = 7.2 Hz, C_6H_5), 7.81 (2 H, d, *J* = 8.0 Hz, H-Ts), 8.01 (2 H, d, *J* = 7.6 Hz, C_6H_5); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.5 (CH_3-Ts), 23.7 (C-5), 27.6 (C-1'), 28.3 [(*C*H_3)C, C-2'], 29.7 (C-8), 30.0 (C-8a), 31.1 (C-4), 34.8 (C-4a), 47.0 (C-10), 48.1 (C-6), 49.3-49.8 (C-1, C-3), 64.9 ($2CH_2O$), 69.2 (C-7), 79.9 [$(CH_3)C$], 104.3 (C-4'), 127.1 (CH-Ts), 128.4 (C_6H_5), 129.5 (C_6H_5), 129.7 (CH-Ts), 133.1 (C_6H_5), 137.0 (C-Ts), 143.2 (C-Ts), 155.3 (NCOO), 164.9 (COO); HRMS calcd for $[C_{34}H_{44}N_2O_8S + H]^+$: 641.2891, found: 641.2877.



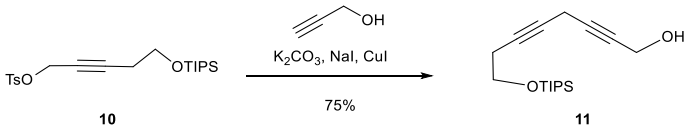
(4*R*,4a*R*,6*S*,7*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-(3-butynyl)-7-hydroxy-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)perhydroisoquinoline (7): *First step:* A 3 N aqueous solution of HCl (3.3 mL, 9.9 mmol) was added to a solution of compound **6** (122 mg, 0.19 mmol) in THF (3.3 mL) and the mixture was stirred at room temperature for 2 hours. Saturated aqueous K_2CO_3 was added until pH 8, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the intermediate aldehyde, which was used in the next step without purification. *Second step:* K_2CO_3 (50 mg, 0.36 mmol) and Bestmann reagent (34 μL, 0.22 mmol) were successively added under an inert atmosphere at room temperature to a solution of the above aldehyde in THF/MeOH (7 mL, 1:1), and the mixture was stirred at room temperature overnight. The mixture was then filtered through a Celite® pad, and the organic solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 and the resulting solution was washed with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 7:3 hexane-EtOAc) of the residue gave alkyne **7** (56 mg, 60%) as a pale yellow foam: $[\alpha]_D^{22}$ = + 32.56 (*c* 1.5 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.43 [9 H, m, $(CH_3)_3C$], 1.49-1.58 (4 H, m, H-8a, 2H-1', H-8), 1.68 (1 H, d, *J* = 12.0 Hz, H-5), 1.91-2.09 (5 H, m, H-4a, H-4', H-5, 2H-2'), 2.41 (3 H, s, CH_3-Ts), 2.45-2.56 (1 H, m, H-8), 2.62-2.85 (2 H, m, H-1, H-3), 3.11 (1 H, m, H-10), 3.32 (1 H, s, H-10), 3.70-3.94 (3 H, m, H-1, H-3, H-7), 4.00 (1 H, s, H-6), 7.28 (2 H, d, *J* = 8.1 Hz, H-Ts), 7.70 (2 H, d, *J* = 8.2 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 12.7 (C-2'), 21.5 (CH_3-Ts), 22.5 (C-5), 28.2 [(CH_3)C], 30.4 (C-4a), 32.2 (C-4), 34.9 (C-8), 35.3 (C-8a, C-1'), 46.5 (C-10), 48.8-49.6 (C-1, C-3), 50.9 (C-6), 67.5 (C-7), 69.0 (C-4'), 79.9 [(CH_3)*C*], 126.8 (CH-Ts), 129.8 (CH-Ts), 137.3 (C-Ts), 143.3 (C-Ts), 155.4 (NCOO); HRMS calcd for $[C_{26}H_{36}N_2O_5S + H]^+$: 489.2418, found: 489.2401.



(4*R*,4a*R*,6*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-(3-butynyl)-6,4-(iminomethano)-7-oxo-9-(*p*-toluenesulfonyl)perhydroisoquinoline (8): Dess–Martin periodinane (41 mg, 0.08 mmol) was added at 0 °C to a solution of tricyclic alcohol **7** in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at room temperature for 4 h. The solution was poured into a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1), and the mixture was stirred for an hour at room temperature. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue gave ketone **8** (30 mg, 77%) as a pale yellow foam: $[\alpha]_D^{22}$ = + 10.66 (*c* 1.5 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.28-1.45 [9 H, m, $(CH_3)_3C$], 1.70 (3 H, m, H-5, H-8a, H-8), 1.79-1.98 (2 H, m, H-1'), 2.09-2.18 (2 H, m, H-4a, H-4'), 2.19-2.27 (2 H, m, H-2'), 2.38 (3 H, s, CH_3-Ts), 2.37 (1 H, masked, H-8), 2.41-2.50 (1 H, m, H-5), 2.68-2.93 (3 H, m, H-1, H-3, H-10), 3.59 (1 H, d, *J* = 12.5 Hz, H-10), 3.71-4.01 (2 H, m, H-1, H-3), 4.37 (1 H, s, H-6), 7.24 (2 H, d, *J* = 8.1 Hz, H-Ts), 7.60 (2 H, d, *J* = 8.2 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 12.9 (C-2'), 21.5 (CH_3-Ts), 28.2 [(*C*H_3)C], 29.3 (C-5), 34.1 (C-8a, C-1'), 35.8 (C-4a), 36.5 (C-4), 43.3 (C-8), 46.9 (C-10), 56.8 (C-6), 48.4-50.1 (C-1, C-3), 69.5 (C-4'), 80.2 [(CH_3)*C*], 127.7 (CH-Ts), 129.5 (CH-Ts), 134.2 (C-Ts), 143.3 (C-Ts), 155.2 (NCOO), 204.9 (C-7); HRMS calcd for $[C_{26}H_{34}N_2O_5S + Na]^+$: 509.2081, found: 509.2086.



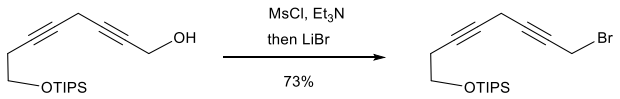
(4*R*,4a*R*,6*S*,8a*S*) Triyne intermediate (9): Alkyne **8** (31 mg, 0.063 mmol) and bromo derivative **12** (45 mg, 0.127 mmol) were added at room temperature under an inert atmosphere to a suspension of CuI (24 mg, 0.127 mmol), NaI (19 mg, 0.127), and K_2CO_3 (13 mg, 0.095 mmol) in anhydrous DMF (2 mL). The mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl and EtOAc were added, and the resulting mixture was filtered through a Celite® pad. The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue gave triyne **9** (31 mg, 64%) as an oil: $[\alpha]_D^{22}$ = + 5.59 (*c* 1.5 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.07 [21 H, s, $(CH_3)_2CH$], 1.37 [9 H, m, $(CH_3)_3C$], 1.67 (2 H, m, H-8, H-5), 1.77 (1 H, s, H-8a), 1.87 (2 H, m, H-1'), 2.11-2.23 (3 H, m, H-4a, H-2'), 2.36 (3 H, s, CH_3-Ts), 2.39-2.49 (4 H, m, H-5, H-8, H-11'), 2.71-2.82 (3 H, m, H-10, H-1, H-3), 3.13 (4 H, s, 2H-5', 2H-8'), 3.56 (1 H, d, *J* = 12.9 Hz, H-10), 3.78 (2 H, t, *J* = 8.2 Hz, H-12'), 3.75-3.93 (2 H, m, H-1, H-3), 4.37 (1 H, s, H-6), 7.24 (2 H, d, *J* = 8.1 Hz, H-Ts), 7.59 (2 H, d, *J* = 8.2 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 9.8 (C-5', C-8'), 12.0 [$(CH_3)_2CH$], 13.2 (C-2'), 17.9 [$(CH_3)_2CH$], 21.4 (CH_3-Ts), 23.1 (C-11'), 28.4 [$(CH_3)_3C$], 29.4 (C-5), 31.4 (C-4), 33.6 (C-8a), 34.1 (C-1'), 36.2 (C-4a), 43.1 (C-8), 47.0 (C-10), 48.1-51.0 (C-1, C-3), 56.9 (C-6), 62.2 (C-12'), 74.4, 74.8, 75.0, 75.3, 77.7, 79.5 (C-3', C-4', C-6', C-7', C-9', C-10'), 80.2 [$(CH_3)_3C$], 127.7 (CH-Ts), 129.5 (CH-Ts), 134.4 (C-Ts), 143.9 (C-Ts), 155.0 (NCOO), 204.9 (C-7); HRMS calcd for $[C_{43}H_{62}N_2O_6SSi + Na]^+$: 785.399, found: 785.3992.



10 11

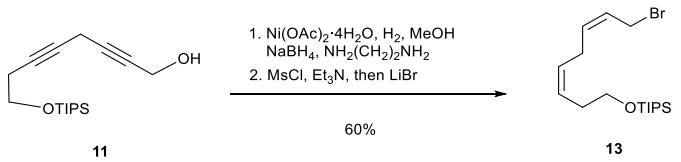
8-[(Trisopropylsilyl)oxy]-2,5-octadiyn-1-ol (11): Potassium carbonate (506 mg, 3.66 mmol) was added at room temperature under an inert atmosphere to a suspension of tosylate **10**[1] (1 g, 2.44 mmol), 2-propyn-1-ol (148 µL, 2.54 mmol), CuI (465 mg, 2.44 mmol), and NaI (366 mg, 2.44 mmol) in anhydrous DMF (12 mL). The mixture was stirred at 40 °C for 12 h and quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was filtered through a Celite® pad. After the organic layer was separated, the resulting aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to hexane-EtOAc 9:1) of the residue gave 1,4-diyne **11** (538 mg, 75%) as a colorless oil: IR (film): 3332 (OH) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC) 1.03, 1.04 [21 H, 2s, $(CH_3)_2CH$], 2.39 (2 H, tt, *J* = 7.6, 2.4 Hz, H-7), 3.15 (2 H, m, H-4), 3.76 (2 H, t, *J* = 7.6 Hz, H-8), 4.23 (2 H, t, *J* = 2.4 Hz, H-1); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 9.5 (C-4), 11.9 [$(CH_3)_2CH$], 17.9 [$(CH_3)_2CH$], 23.1 (C-7), 51.1 (C-1), 62.1 (C-8), 74.5 (C-5), 77.9 (C-3), 78.5 (C-2), 80.3 (C-6); HRMS (ESI) calcd for $[C_{17}H_{30}O_2Si + H]^+$: 295.2088, found: 295.2090.

[1] T. Suto, Y. Yanagita, Y. Nagashima, S. Takikawa, Y. Kurosu, N. Matsuo, T. Sato and N. Chida, *J. Am. Chem. Soc.* 2017, **139**, 2952.



11 12

1-Bromo-8-[(triisopropylsilyl)oxy]-2,5-octadiyne (12): *First step*: Triethylamine (610 µL, 4.38 mmol), and methanesulfonyl chloride (454 µL, 5.84 mmol) were added dropwise at 0 °C under an inert atmosphere to a solution of alcohol **11** (860 mg, 2.92 mmol) in anhydrous CH_2Cl_2 (50 mL). The mixture was stirred at 0 °C for 15 min and between 10 and 20 °C for 1.5 h. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford the mesylate, which was used in the next step without purification. *Second step:* A solution of LiBr (2.5 g, 4.38 mmol) in anhydrous THF (20 mL) was added under an inert atmosphere at 0 °C to a solution of the above mesylate (2.92 mmol) in anhydrous CH_2Cl_2 (15 mL). The mixture was stirred at room temperature overnight. Water was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 7:3 hexane-EtOAc) of the residue afforded bromo derivative **12** (760 mg, 73%) as an oil: δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC) 1.05, 1.06 [21 H, 2s, $(CH_3)_2CH$], 2.41 (2 H, m, *J* = 6.8, 2.4 Hz, H-7), 3.20 (2 H, t, *J* = 2.4 Hz, H-4), 3.78 (2 H, t, *J* = 7.2 Hz, H-8), 3.90 (2 H, t, *J* = 2.4 Hz, H-1); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 10.1 (C-5), 12.0 [$(CH_3)_2CH$], 14.7 (C-8), 17.9 [$(CH_3)_2CH$], 23.1 (C-7), 62.1 (C-8), 74.0 (C-5), 75.3 (C-3), 78.3 (C-2), 81.8 (C-6); HRMS (ESI) calcd for $[C_{17}H_{29}BrOSi + H]^+$: 357.1244, found: 357.1232.

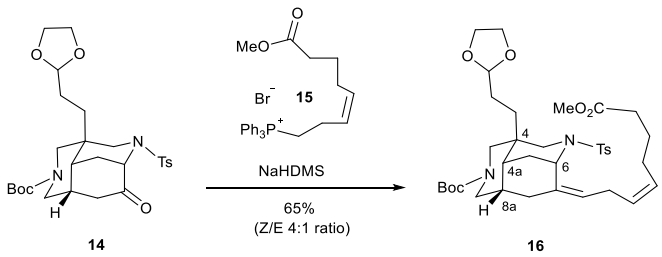


11 13

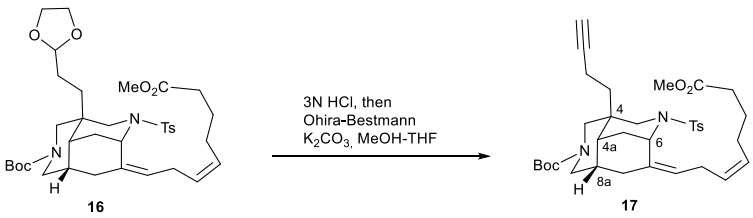
(2*Z*,5*Z*)-1-Bromo-8-[(triisopropylsilyl)oxy]-2,5-octadiene (13): *First step*: Ethylenediamine (0.83 mL, 12.42 mmol) was added at room temperature under an argon atmosphere to a solution of $Ni(OAc)_2{\cdot}4H_2O$ (2.31 g, 9.28 mmol) and $NaBH_4$ (413 mg, 10.9 mmol) in anhydrous MeOH (185 mL). Then, diyne **11** (1.68 g, 5.45 mmol) in anhydrous MeOH (20 mL) was added and the argon atmosphere was replaced with hydrogen. The mixture was vigorously stirred for one hour and filtered through a Celite® pad. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding diene, which was used in the next step without purification. *Second step:* Methanesulfonyl chloride (0.51 mL, 6.55 mmol) and Et_3N (1.1 mL, 7.64 mmol) were added under an inert atmosphere at 0 °C to a solution of the above diene in anhydrous CH_2Cl_2 (14 mL), and the mixture was stirred at room temperature for 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to give the mesylate, which was used in the next step without further purification. *Third step:* A solution of LiBr (4.73 g, 54.5 mmol) in anhydrous THF (23 mL) was added at 0 °C under an inert atmosphere to a solution of the above mesylate in anhydrous CH_2Cl_2 (17 mL). The resulting mixture was stirred at room temperature overnight. Distilled water was added, and the mixture was then extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. Flash chromatography (hexane to 98:2 hexane-EtOAc) of the residue afforded bromo derivative **13** (1.18 g, 60%) as an oil: δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC) 1.06, 1.07 [21 H, 2s, $(CH_3)_2CH$], 2.36 (2 H, m, H-2), 2.85 (2 H, t, *J* = 6.8 Hz, H-5), 3.70 (2 H, t, *J* = 6.4 Hz, H-1), 4.04 (2 H, d, *J* = 6.8 Hz, H-8), 5.40-5.80 (4 H, m, H-5, H-6, H-2, H-3); δ_C (100.6 MHz; $CDCl_3$; Me_4Si) 12.0 [$(CH_3)_2CH$], 18.0 [$(CH_3)_2CH$], 25.4 (C-4), 27.0 (C-1), 31.3 (C-7), 63.0 (C-8), 125.5, 127.5, 127.8, 133.9 (CH=).

5 14

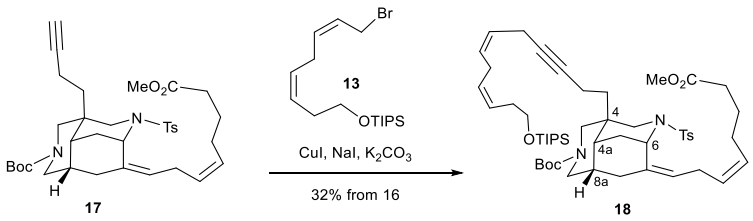
(4*R*,4a*R*,6*S*,8a*S*)-2-(*tert*-Butoxycarbonyl)-4-[2-(1,3-dioxolan-2-yl)ethyl]-6,4-(iminomethano)-9-(*p*-toluenesulfonyl)-7-oxoperhydroisoquinoline (14): Dess–Martin periodinane (1.36 g, 3.21 mmol) was added to an ice-cold solution of alcohol **5** (574 mg, 1.08 mmol) in CH_2Cl_2 (11 mL), and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with the addition of a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$ (1:1), and the resulting mixture was stirred for an hour. The mixture was then extracted with CH_2Cl_2, and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (9:1 to 1:1 hexane-EtOAc) of the residue gave ketone **14** (538 mg, 94%) as a white foam: $[\alpha]_D^{22}$ = + 11.5 (*c* 0.59 in $CHCl_3$); IR (film): ν = 1685 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.32-1.41 [11 H, m, $(CH_3)_3C$, H-1'], 1.54-1.58 (2 H, m, H-2'), 1.63-1.72 (3 H, m, H-4a, H-8, H-5), 2.11 (1 H, s, H-8a), 2.29-2.35 (1 H, m, H-8), 2.37 (3 H, s, CH_3-Ts), 2.42-2.48 (1 H, m, H-5), 2.59, 2.78 (3 H, br. s, H-1, H-3, H-10), 3.55, 3.76 (3 H, br.s, H-1, H-3, H-10), 3.86 (2 H, m, CH_2O), 3.98 (2 H, m, CH_2O), 4.35 (1 H, s, H-6), 4.85 (1 H, s, H-3'), 7.23 (2 H, d, *J* = 8.0 Hz, H-Ts), 7.59 (2 H, d, *J* = 8.0 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.4 (CH_3-Ts), 27.5, 28.2, 29.1, 29.4 [C-5, C-2', C-1', (CH_3)$_3$C], 34.1 (C-4a), 36.3 (8a), 43.1 (C-8), 47.0 (C-10), 56.9 (C-6), 47.2-50.8 (C-1, C-3), 64.9 ($2CH_2O$), 80.1 [(CH_3)*C*], 104.1 (C-3'), 127.0 (CH-Ts), 129.8 (CH-Ts), 134.4 (C-Ts), 143.5 (C-Ts), 155.0 (NCOO), 205.1 (C-7); HRMS calcd for $[C_{27}H_{38}N_2O_7S + NH_4]^+$: 552.2738, found: 552.2736.



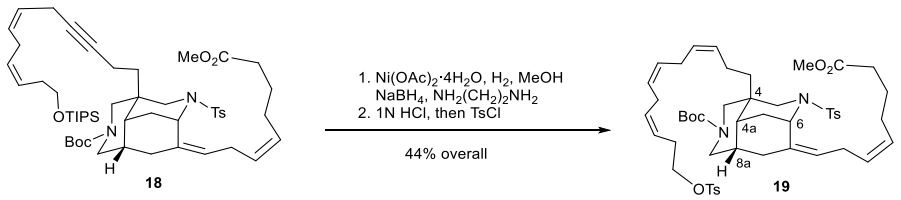
(4*R*,4a*R*,6*S*,8a*S*) Tricyclic derivative (16): Phosphonium salt **15** was dried by repeated dilution with anhydrous 1:1 THF-toluene and concentration under reduced pressure using a rotary evaporator with a dry ice condenser. Sodium bis(trimethylsilyl)amide (1.4 mL of a 1 M solution in THF, 1.4 mmol) was added under an inert atmosphere at 0 °C to a solution of the dry phosphonium salt **15** (548 mg, 1.1 mmol) in anhydrous THF (2.0 mL). After 1 h of stirring at this temperature, a solution of tricyclic ketone **14** (227 mg, 0.43 mmol) in anhydrous THF (3.0 mL) was added, and the resulting mixture was stirred at 0 °C for 1 h, at room temperature for 90 min, and at 60 °C for 3 h. The reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc, and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 6:4 hexane-EtOAc) of the residue gave an inseparable mixture of *Z*/*E* isomers of compound **16** (171 mg, *Z*/*E* 8:2 ratio, 65%): IR (film): ν = 1737, 1693 (CO) cm^{-1}; Major isomer (spectral data from a mixture of isomers) δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, rotamers) 1.32-1.38 [10 H, m, H-5, $(CH_3)_3C$], 1.47-1.73 (7 H, m, H-2',H-1', H-6", H-4a), 1.77-1.88 (1 H, m, H-8a), 1.92-1.99 (2 H, m, H-8), 2.02-2.05 (1 H, m, H-5"), 2.11-2.16 (1 H, m, H-5"), 2.22-2.33 (3 H, m, H-7", H-5), 2.34 (3 H, s, CH_3-Ts), 2.64 (2 H, br. s, H-1, H-3), 2.86 (2 H, m, H-10, H-2"), 2.98-3.05 (1 H, m, H-2"), 3.24-3.37 (1 H, m, H-10), 3.65 (3 H, s, OCH_3), 3.83, 3.94 (6 H, 2s, $2CH_2O$, H-1, H-3 masked), 4.42, 4.95 (1 H, s,H-6), 4.79 (1 H, s, H-3'), 5.06 (1 H, t, *J* = 7.6 Hz, H-1"), 5.28-5.29 (2 H, m, H-3", H-4"), 7.16-7.20 (2 H, m, H-Ts), 7.57-7.61 (2 H, m, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, rotamers) 21.4 (CH_3-Ts), 24.7 (C-6"), 25.1 (C-2"), 25.8 (C-5"), 26.6 (C-2'), 28.3 (CH_3)$_3$C), 29.7 (C-1'), 31.0 (C-5), 33.4 (C-7"), 35.1, 35.2 (C-4a,C-8a), 36.1 (C-8), 46.9, 55.0 (C-6), 48.1 (C-10), 49.8, 50.9 (C-1, C-3), 51.5 (OCH_3), 64.9 (CH_2O), 79.7 [$(CH_3)_3C$], 104.3 (C-3'), 127.7, 128.2, 128.5, 129.1 (C-3",C-4", CH-Ts), 135.7 (C-Ts), 155.15 (NCOO), 174.0 (COO); HRMS (ESI) calcd for $[C_{36}H_{52}N_2O_8S + NH_4]^+$: 690.3783, found: 690.3777.



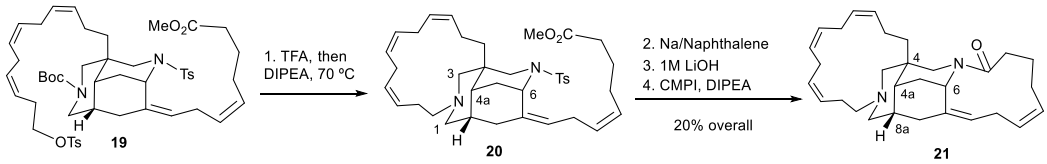
(4*R*,4a*R*,6*S*,8a*S*) Alkyne derivative (17): *First step:* A 3 N aqueous solution of HCl (2.4 mL, 7.2 mmol) was added to a solution of the tricyclic compound **16** (89 mg, 0.13 mmol) in THF (2.4 mL) and the mixture was stirred for 2 hours at room temperature. Saturated aqueous K_2CO_3 was added until pH 8 and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the intermediate aldehyde, which was used in the next step without purification. *Second step:* K_2CO_3 (50 mg, 0.23 mmol) and Bestmann reagent (20 µL, 0.14 mmol) were added under an inert atmosphere at room temperature to a solution of the aldehyde in anhydrous THF/MeOH (4 mL, 1:1), and the resulting mixture was stirred at room temperature overnight. The mixture was filtered through a Celite® pad, and the organic solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give alkyne **17**, which was used in the next step without purification. A sample was purified by flash column chromatography (hexane to 7:3 hexane-EtOAc) to give pure alkyne **17**: $[\alpha]_D^{22}$ = + 79.6 (*c* 0.43 in $CHCl_3$); IR (film): ν = 1732, 1682 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, selected resonances, rotamers) 1.32-1.48 [11 H, m, H-5, H-4a, $(CH_3)_3C$], 1.62-1.75 (3 H, m, H-6", H-8a), 1.78-1.89 (2 H, m, H-8), 2.00 (1 H, s, H-4'), 2.05-2.18 (4 H, m, H-5", H-2'), 2.22-2.27 (1 H, m, H-5), 2.30-2.34 (2 H, m, H-7''), 2.36 (3 H, s, CH_3-Ts), 2.80-3.07 (3 H, m, H-2'', H-1, H-10), 3.29-3.43 (1 H, m, H-10), 3.67 (3 H, s, OCH_3), 4.46, 4.95 (1 H, s, H-6), 5.09 (1 H, t, *J* = 7.2 Hz, H-1"), 5.18-5.40 (2 H, m, H-3", H-4"), 7.16-7.24 (2 H, d, *J* = 7.6 Hz, H-Ts), 7.57-7.62 (2 H, d, *J* = 7.6 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, selected resonances, rotamers) 12.9 (C-2'), 21.4 (CH_3-Ts), 24.7 (C-6''), 25.8 (C-2"), 26.6 (C-5"), 28.3 [(CH_3)$_3$C], 31.2 (C-5), 33.5 (C-7"), 34.0 (C-8a), 35.5 (C-8), 46.9, 55.0 (C-6), 51.4 (OCH_3), 69.5 (C-4'), 79.7 [$(CH_3)_3C$], 128.2, 128.4, 129.2 (C-3",C-4", CH-Ts, CH-Ts), 155.1 (NCOO). HRMS (ESI) calcd for $[C_{35}H_{48}N_2O_6S + NH_4]^+$: 642.3571, found: 642.3568.



(4*R*,4a*R*,6*S*,8a*S*) Dienyne intermediate (18): The above alkyne **17** and bromo derivative **13** (94 mg, 0.26 mmol) were added at room temperature under an inert atmosphere to a suspension of CuI (49 mg, 0.26 mmol), NaI (39 mg, 0.26 mmol), and K_2CO_3 (27 mg, 0.20 mmol) in anhydrous DMF (0.3 mL). The mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl and EtOAc were added, and the resulting mixture was filtered through a Celite® pad. The layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 8:2 hexane-EtOAc) of the residue gave compound **18** (38 mg, 32% from **16**) as an oil: $[\alpha]_D^{22}$ = + 56.9 (*c* 0.35 in $CHCl_3$); IR (film): *v* = 1739, 1694 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, selected resonances, rotamers) 1.06 [21 H, m, $(CH_3)_2CH$], 1.31-1.40 [10 H, m, H-5, $(CH_3)_3C$], 1.65-1.74 (4 H, m, H-6", H-8a, H-4a), 2.03-2.17 (2 H, m, H-5"), 2.23-2.34 (5 H, m, H-11', H-7", H-5), 2.36 (3 H, s, CH_3-Ts), 2.77-2.82 (2 H, m, H-8'), 2.84-2.93 (4 H, m, H-2'', 2H-5', H-10), 2.99-3.08 (1 H, m, H-2"), 3.25-3.37 (1 H, m, H-10), 3.66-3.70 (5 H, m, H-12', OCH_3), 4.45, 4.94 (1 H, s, H-6), 5.04-5.10, 5.19-5.54, 5.59-5.67, 5.70-5.79 (7 H, 4 m, H-1", H-3", H-4", H-6', H-7', H-9', H-10'), 7.15-7.20 (2 H, m, H-Ts), 7.56-7.60 (2 H, m, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, selected resonances, rotamers) 12.0 [$(CH_3)_2$*C*H], 13.3 (C-2'), 18.0 [(*C*$H_3)_2$CH], 21.4 (CH_3-Ts), 22.0 (C-5'), 24.7, 24.8 (C-6''), 25.8 (C-2"), 26.6 (C-5"), 28.3 [(*C*$H_3)_3$C], 30.2 (C-8'), 31.2 (C-5), 33.5 (C-7"), 35.0, 35.5, 35.7 (C-4a, C-8a, C-8), 46.9, 55.0 (C-6), 48.1-50.3 (C-1, C-3, C-10), 51.5 (OCH_3), 63.1 (C-12"), 79.7 [$(CH_3)_3$*C*], 125.0, 127.8, 128.8, 129.1, 129.2, 129.9 (C-3",C-4",C-6', C-7', C-9', C-10', C-Ts), 155.1 (NCOO), 174.1 (COO); HRMS (ESI) calcd for $[C_{52}H_{80}N_2O_7SSi + NH_4]^+$: 922.5794, found: 922.5786.

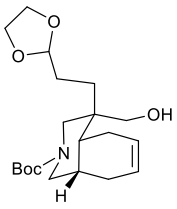


(4*R*,4a*R*,6*S*,8a*S*) Tosylate derivative (19): *First step*: Ethylenediamine (5 µL, 0.07 mmol) was added at room temperature under an argon atmosphere to a solution of $Ni(OAc)_2{\cdot}4H_2O$ (15 mg, 0.06 mmol) and $NaBH_4$ (3 mg, 0.07 mmol) in anhydrous MeOH (1.2 mL). Then, dienyne **18** (31 mg, 0.03 mmol) in anhydrous MeOH (20 mL) was added and the argon atmosphere was replaced with hydrogen. The mixture was vigorously stirred for one hour, filtered through Celite®, and concentrated. The resulting residue was dissolved in CH_2Cl_2, and the solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding triene, which was used in the next step without purification. HRMS (ESI) calcd for $[C_{52}H_{82}N_2O_7SSi + NH_4]^+$: 924.5950, found: 924.5938. *Second step:* A 2 N aqueous solution of HCl (0.4 mL, 0.8 mmol) was added to a solution of the above triene in MeOH (3 mL), and the mixture was stirred for 20 minutes at room temperature. Saturated aqueous $NaHCO_3$ was added until pH 7, and the methanol was evaporated. The aqueous phase was extracted with CH_2Cl_2, and the organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude alcohol. *Third step: p*-Toluenesulfonyl chloride (11 mg, 0.06 mmol) was added at room temperature under an inert atmosphere to a solution of the above alcohol, Et_3N (17 µL, 0.12 mmol), and DMAP (0.7 mg, 6 µmol) in anhydrous CH_2Cl_2 (0.6 mL), and the mixture was stirred for 15 hours. Saturated aqueous NH_4Cl was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (hexane to 7:3 hexane-EtOAc) of the residue afforded tosylate **19** (12 mg, 44%) as an oil: $[\alpha]_D^{22}$ = + 47.3 (*c* 0.23 in $CHCl_3$); IR (film): ν = 1738, 1693 (CO) cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si, COSY, HSQC, selected resonances, rotamers) 1.31-1.45 [10 H, m, H-5, $(CH_3)_3C$], 1.57-1.63 (3 H, m, H-6", H-4a), 2.03-2.17 (2 H, m, H-5"), 2.22-2.48 (5 H, m, H-11', H-7", H-5), 2.36 (3 H, s, CH_3-Ts), 2.45 (3 H, s, CH_3-Ts), 2.67-2.96 (6 H, m, H-8', H-2'', H-5'), 3.02 (1 H, m, H-10), 3.35 (1 H, m, H-10), 3.67 (3 H, s, OCH_3), 4.01 (2 H, m, H-12'), 4.45, 4.94 (1 H, s, H-6), 5.08 (1 H, m, H-12), 5.25-5.53 (9 H, m, H-1'', H-3", H-4", H-3', H-4', H-6', H-7', H-9', H-10'), 7.16-7.20 (2 H, m, H-Ts), 7.34 (2 H, d, *J* = 8.0 Hz, H-Ts), 7.57-7.61 (2 H, m, H-Ts), 7.79 (2 H, d, *J* = 8.0 Hz, H-Ts); δ_C (100.6 MHz; $CDCl_3$; Me_4Si, selected resonances, rotamers) 21.4, 21.6 (CH_3-Ts), 22.7 (C-5'), 24.7, 24.8 (C-6''), 25.8 (C-2"), 26.6 (C-5"), 28.3 [(CH_3)$_3$C], 33.5 (C-7"), 35.5, 35.8 (C-4a, C-8a), 46.9, 55.1 (C-6), 47.5-50.0 (C-1, C-3, C-10), 51.5 (OCH_3), 69.7 (C-12"), 79.6 [(CH_3)$_3$*C*], 127.9, 128.3, 128.5, 129.2, 129.6, 129.8 (C-3",C-4",C-3', C-4', C-6', C-7', C-9', C-10', C-Ts), 155.2 (NCOO), 174.1 (COO); HRMS (ESI) calcd for $[C_{50}H_{68}N_2O_9S_2 + H]^+$: 905.3720, found: 905.3710.



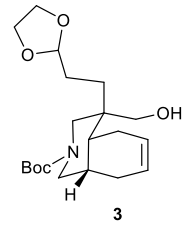
(4*R*,4a*R*,6*S*,8a*S*) Pentacyclic lactam (21): *First step*: TFA (0.12 mL, 1.4 mmol) was added under an inert atmosphere to a solution of tosylate **19** (20 mg, 0.022 mmol) in anhydrous CH_2Cl_2 (0.4 mL), and the mixture was stirred at room temperature for 30 minutes. The solvent was removed, and the resulting residue was dissolved in toluene and evaporated (two times) to give the crude secondary amine, which was taken in anhydrous MeCN (20 mL). *N*,*N*-Diisopropylethylamine (0.02 mL, 0.12 mmol) was added at room temperature under an inert atmosphere to the above solution and the mixture was stirred overnight at 70 °C. The solvent was evaporated under reduced pressure. Flash chromatography (hexane to 1:1 hexane-EtOAc) of the residue afforded crude tetracycle **20** (6 mg), which was purified by semipreparative HPLC: δ_H (500 MHz, 1.7 mm microcryoprobe, toluene-d8, HSQC, selected resonances) 1.75 (1 H, m, H-4a), 2.08-2.20 (4 H, m, CH_2CO, CH_2N), 2.36 (3 H, s, CH_3-Ts), 3.44 (3 H, s, OCH_3), 3,75 (2 H, m, H-1, H-3), 4.60 (1 H, s, H-6), 5.15-5.53 (9 H, m, =CH), 7.00-7.10 (2 H, m, H-Ts), 7.80-7.88 (2 H, m, H-Ts); HRMS (ESI) calcd for $[C_{38}H_{52}N_2O_4S + H]^+$: 633.3721, found: 633.3720. *Second step*: Sodium metal (11 mg, 0.43 mmol) was added at room temperature to a solution of naphthalene (29 mg, 0.22 mmol) in anhydrous THF (1 mL). After stirring for 2 h, part of the mixture (0.4 mL) was added at –78 °C to a solution of sulfonamide **20** (5 mg, 0.007 mmol) in anhydrous THF (0.8 mL), and the resulting mixture was stirred for 10 min. A few drops of saturated aqueous NH_4Cl were carefully added, and the resulting solution was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a sensitive crude amino ester. *Third step*: A solution of LiOH (0.6 mL of a 1 M solution in water, 0.6 mmol) was added to a stirred solution of the above amino ester in THF (0.5 mL), and the mixture was stirred at room temperature for 3.5 h. The solution was concentrated under reduced pressure to give the crude amino acid. *Four step*: *N*,*N*-Diisopropylethylamine (6 μL, 0.035 mmol) and 2-chloro-1-methylpyridinium iodide (9 mg, 0.035 mmol) were added at room temperature under an inert atmosphere to a solution of the above amino acid in anhydrous CH_2Cl_2 (7 mL), and the mixture was stirred overnight at room temperature. Saturated aqueous NH_4Cl was added and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (hexane to 1:1 hexane-EtOAc) of the residue afforded pentacyclic lactam **21**[2] (1.5 mg, 20% from **19**): HRMS (ESI) calcd for $[C_{30}H_{42}N_2O + H]^+$: 447.3370, found: 447.3376.

[2] T. Suto, Y. Yanagita, Y. Nagashima, S. Takikawa, Y. Kurosu, N. Matsuo, T. Sato and N. Chida, *J. Am. Chem. Soc.* 2017, **139**, 2952.



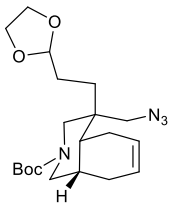
3

400 MHz; $CDCl_3$; Me_4Si



3

100.6 MHz; $CDCl_3$; Me_4Si



4

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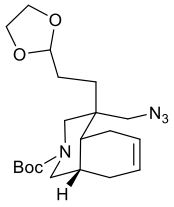
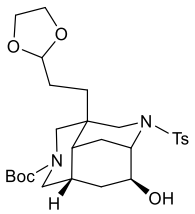


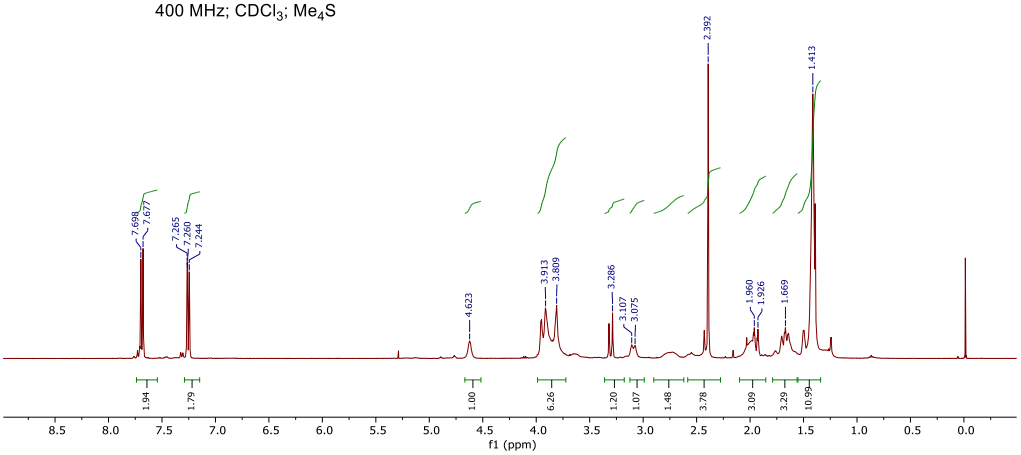
4

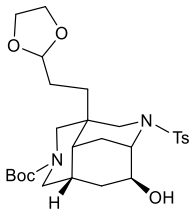
100.6 MHz; $CDCl_3$; Me_4Si



5

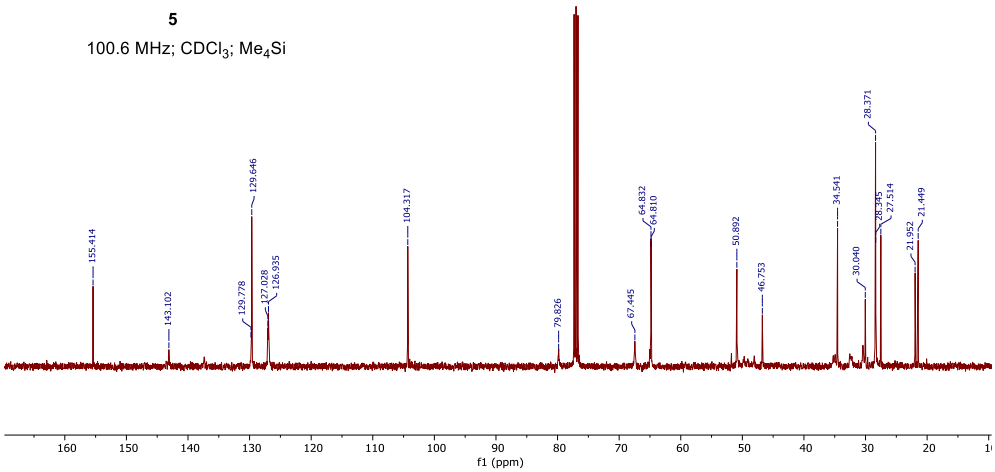
400 MHz; $CDCl_3$; Me_4S

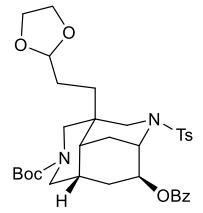




5

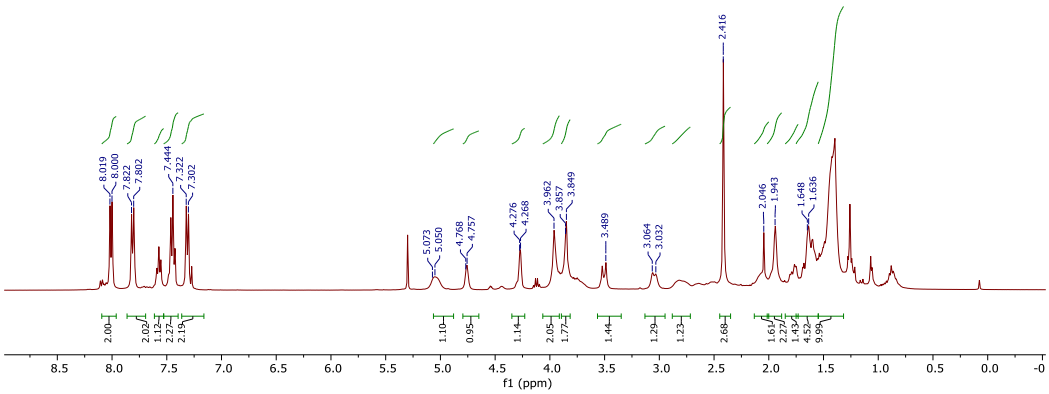
100.6 MHz; $CDCl_3$; Me_4Si

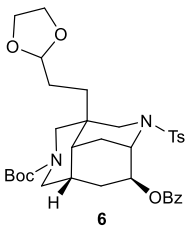




6

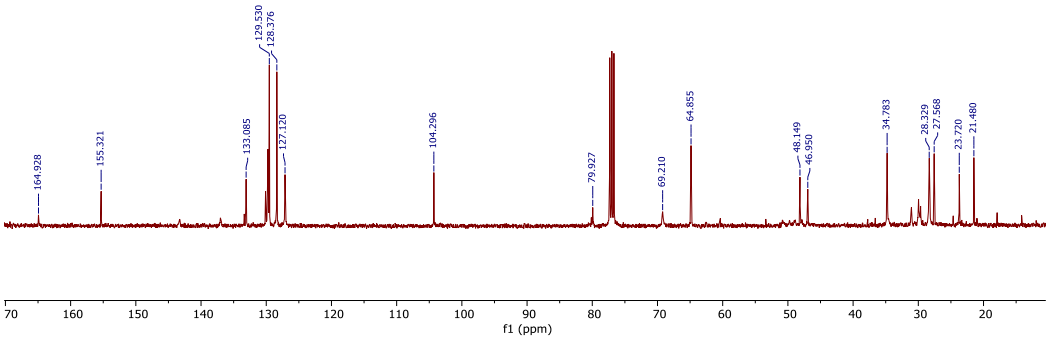
400 MHz; $CDCl_3$; Me_4S

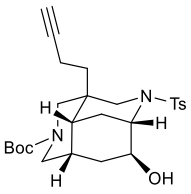




6

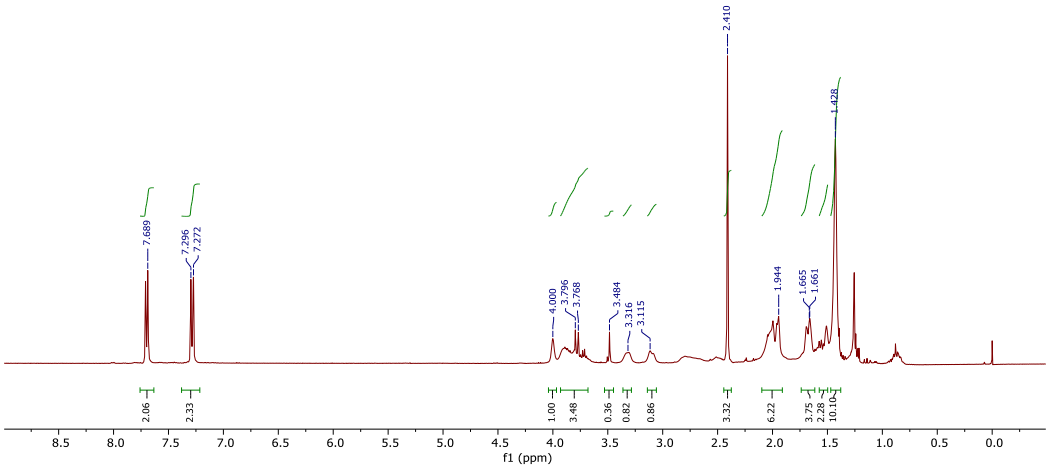
100.6 MHz; $CDCl_3$; Me_4Si

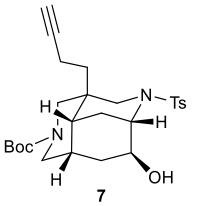




7

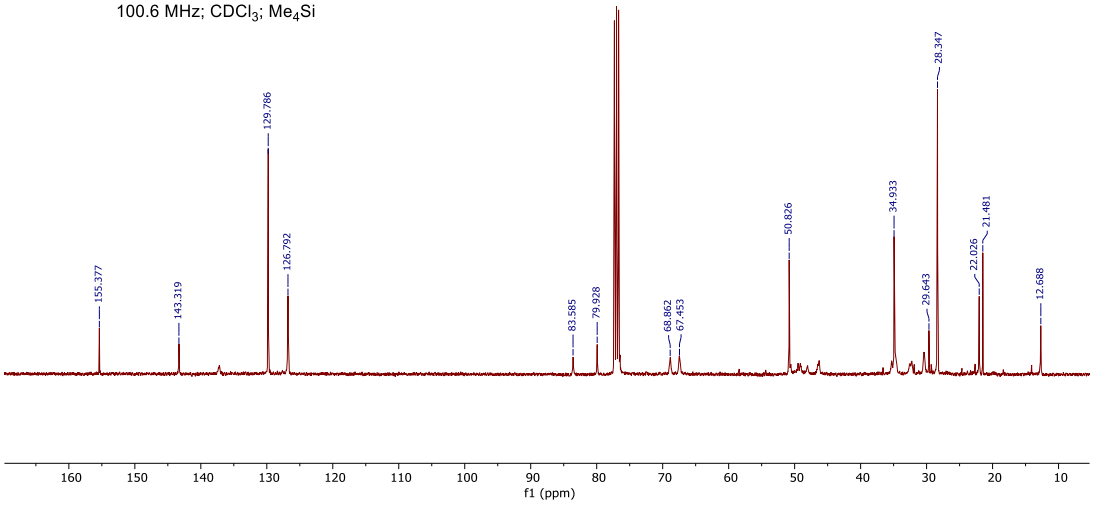
400 MHz; $CDCl_3$; Me_4S

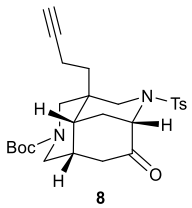




7

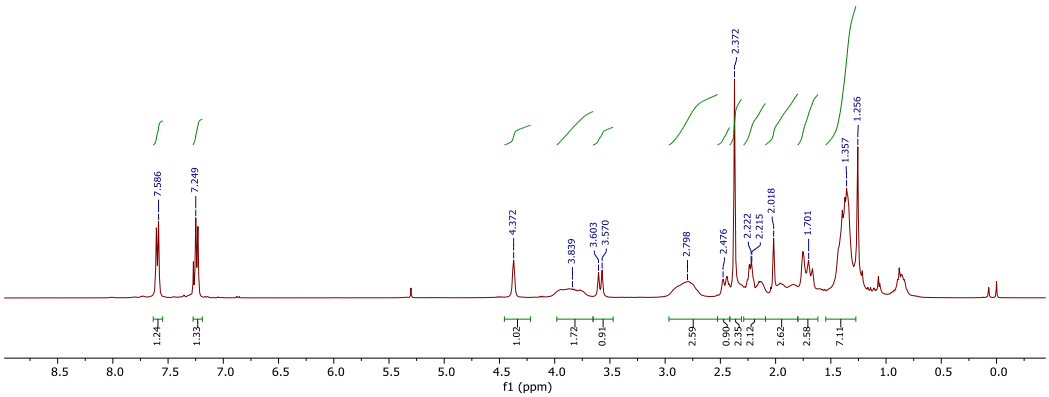
100.6 MHz; $CDCl_3$; Me_4Si

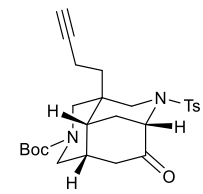




8

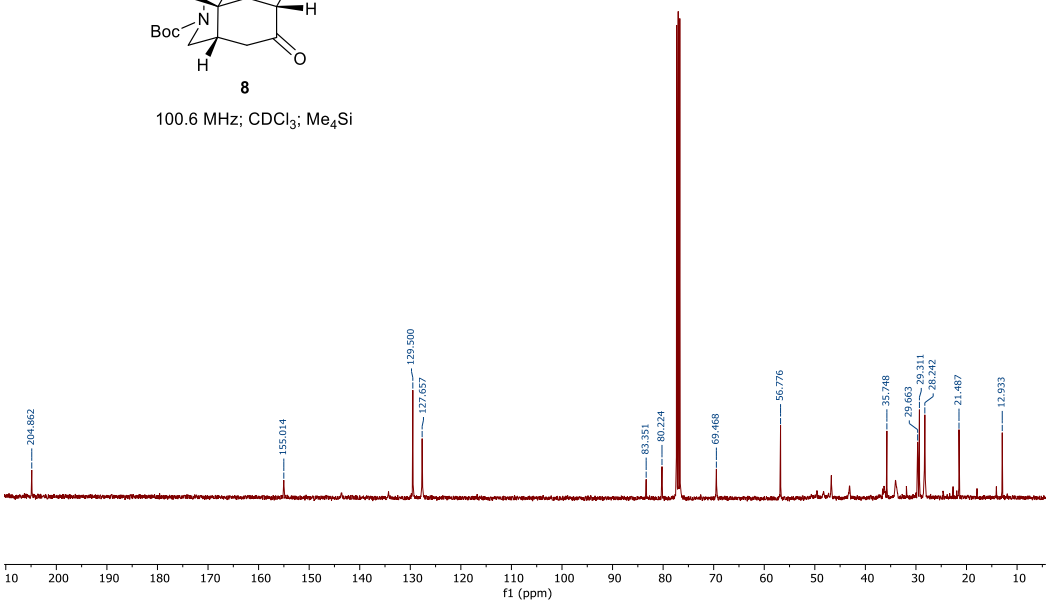
400 MHz; $CDCl_3$; Me_4S

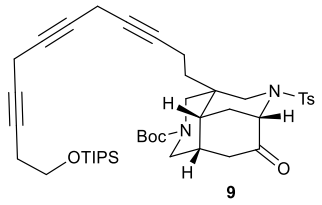




8

100.6 MHz; $CDCl_3$; Me_4Si





9

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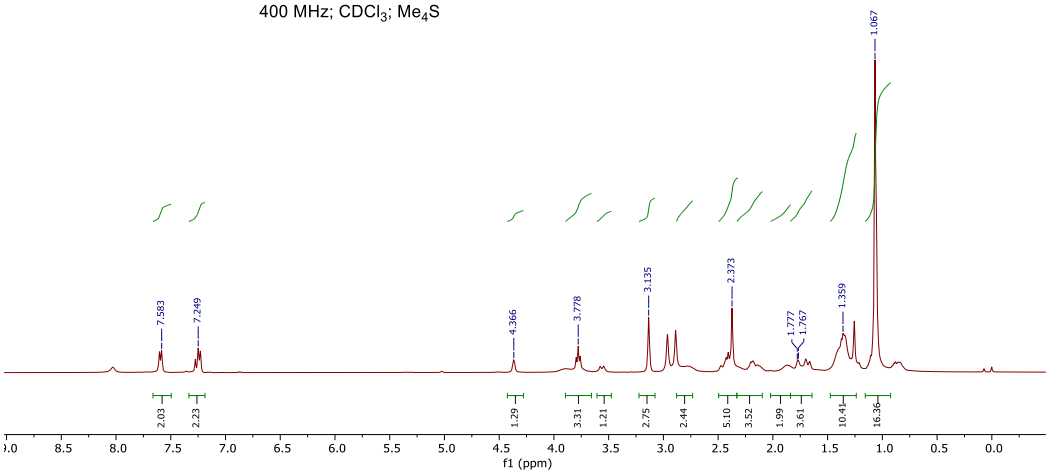

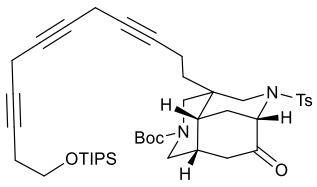

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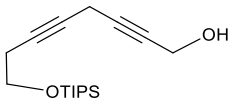
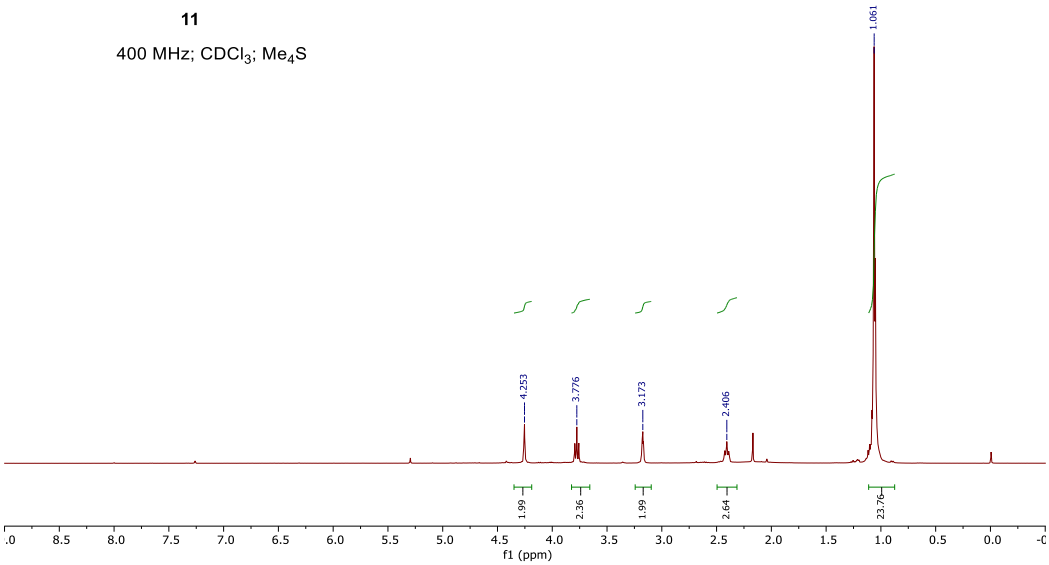
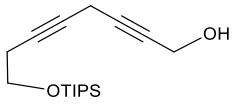


11

400 MHz; $CDCl_3$; Me_4S





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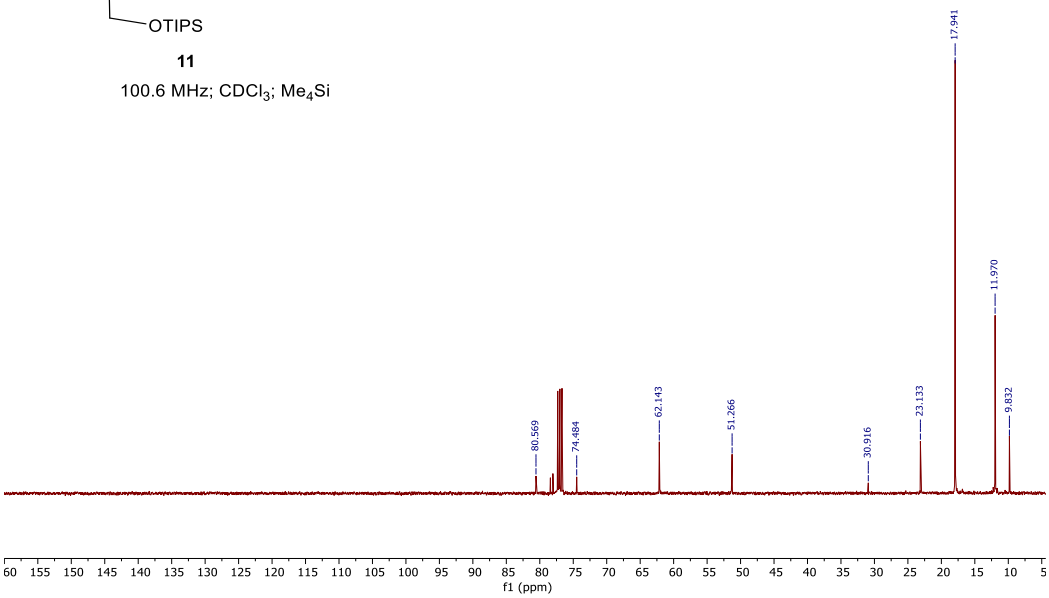
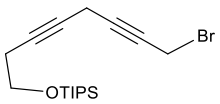
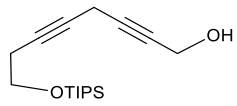
100.6 MHz; $CDCl_3$; Me_4Si





12

400 MHz; $CDCl_3$; Me_4S



12

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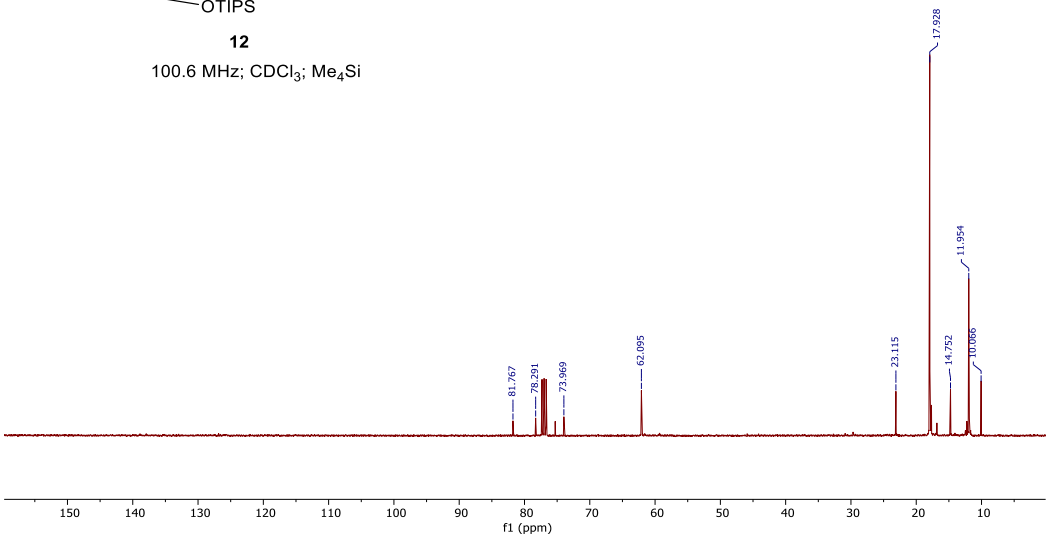

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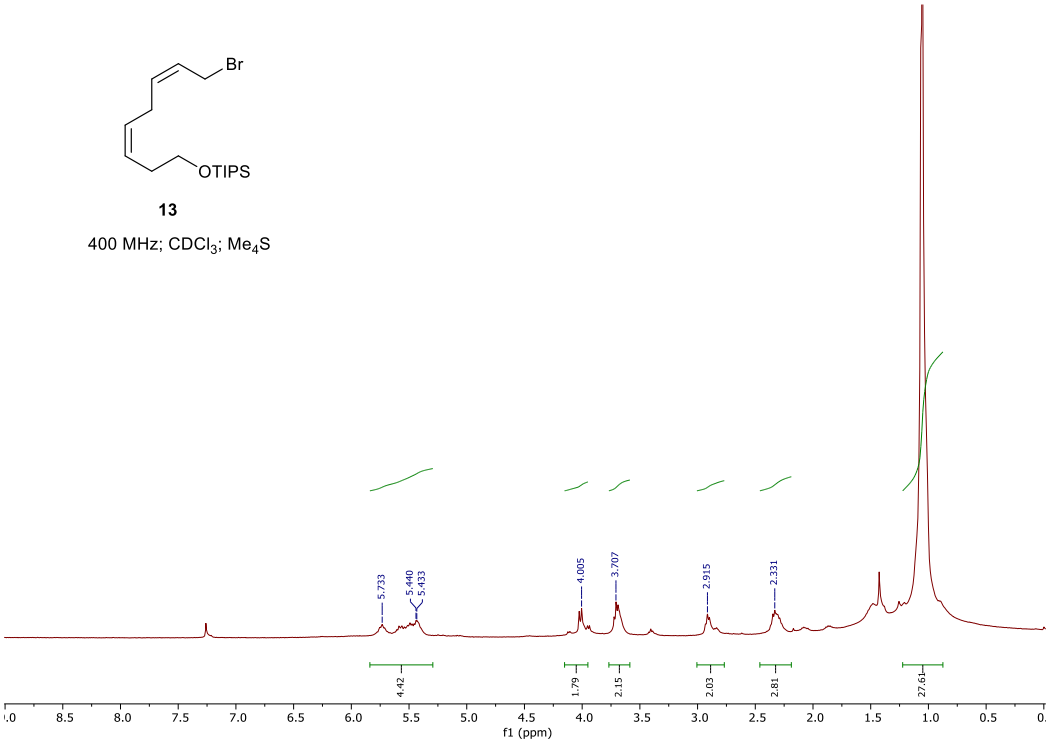
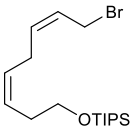
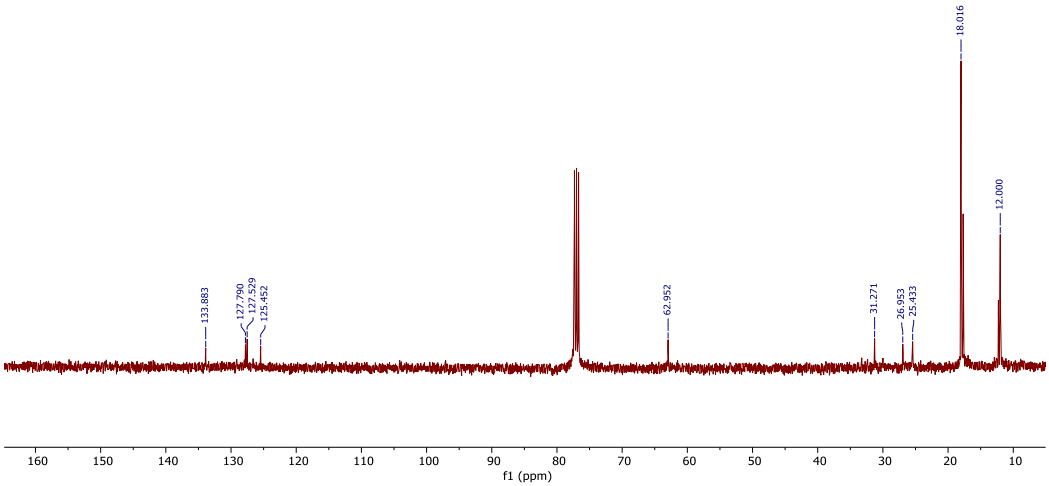
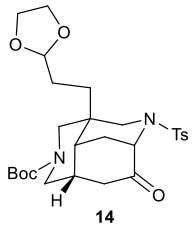




13

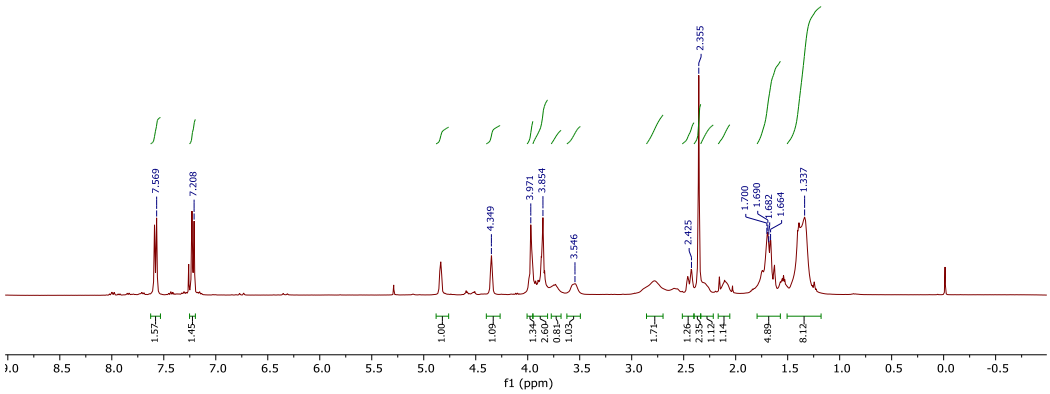
100.6 MHz; $CDCl_3$; Me_4Si

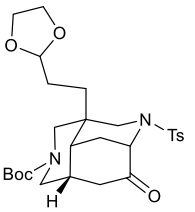




14

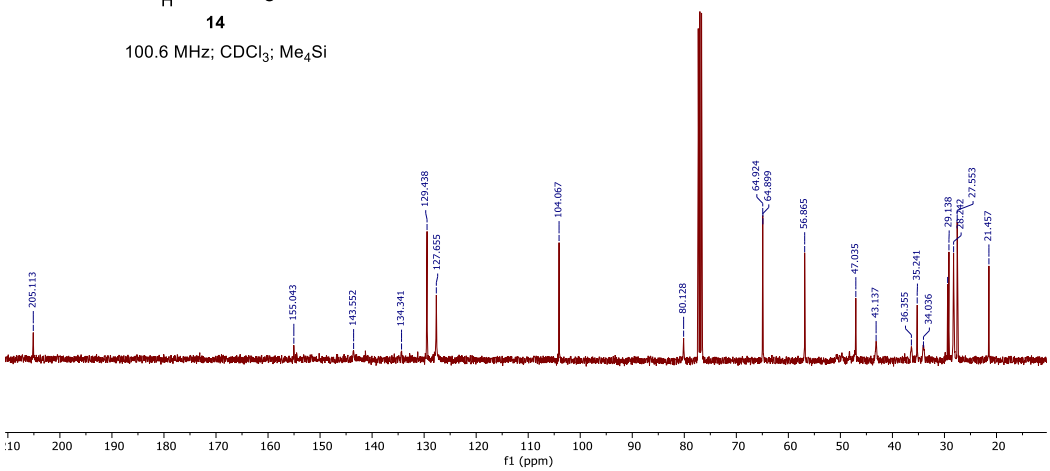
400 MHz; $CDCl_3$; Me_4S

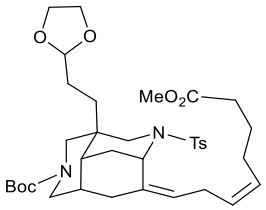




14

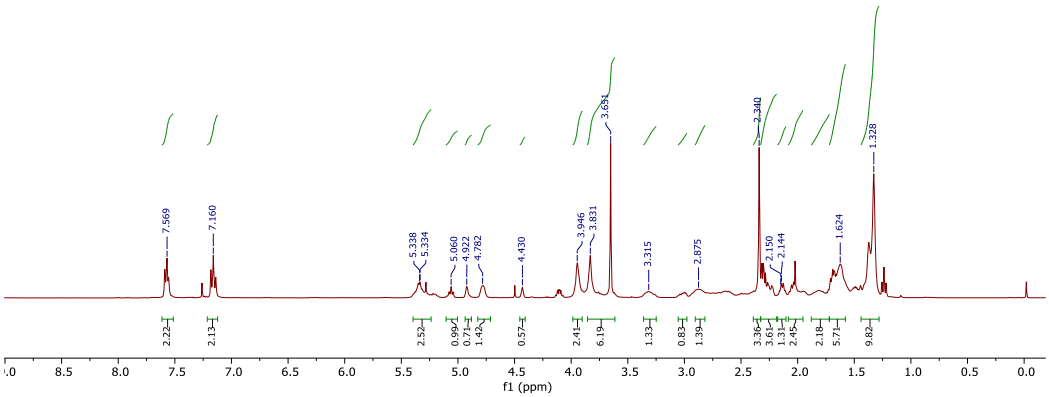
100.6 MHz; $CDCl_3$; Me_4Si

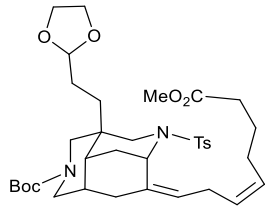




16

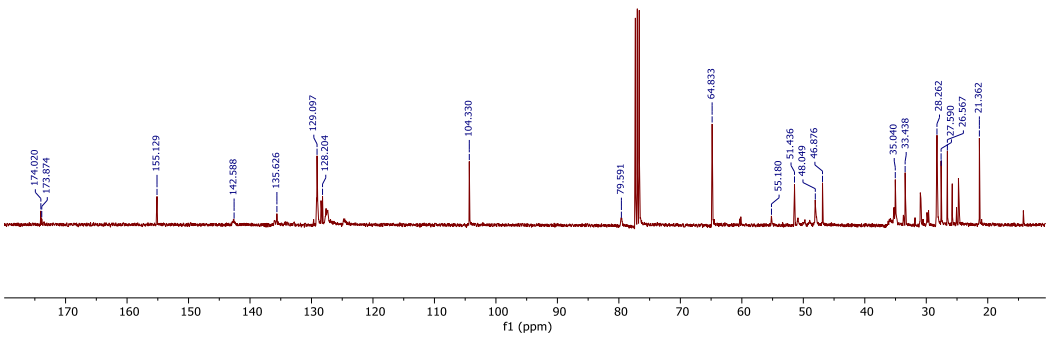
400 MHz; $CDCl_3$; Me_4S

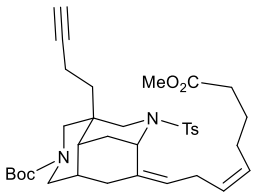




16

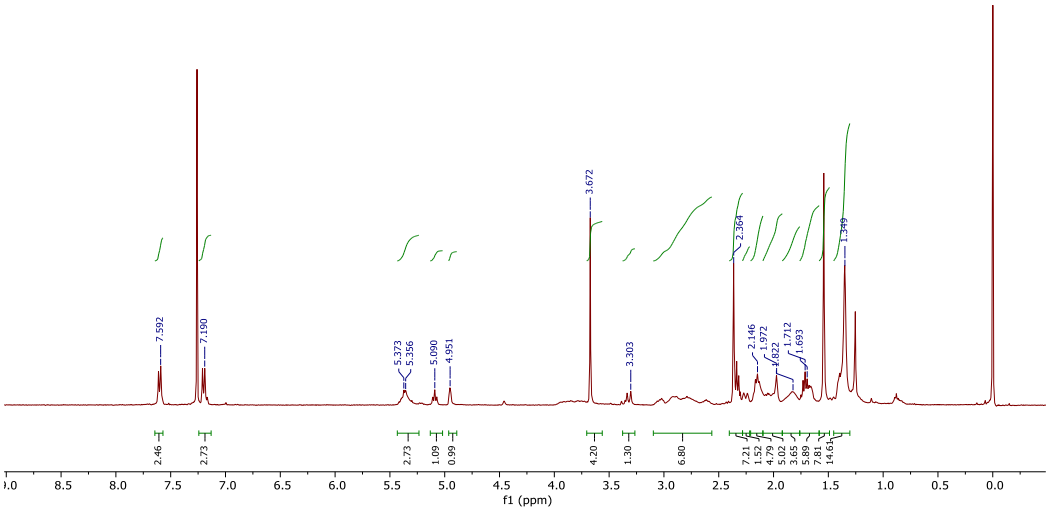
100.6 MHz; $CDCl_3$; Me_4Si

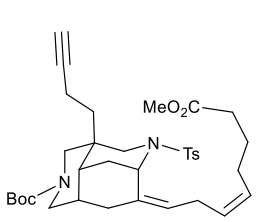




17

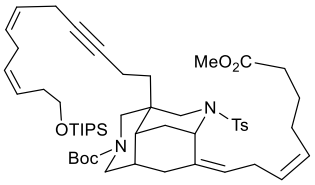
400 MHz; $CDCl_3$; Me_4S





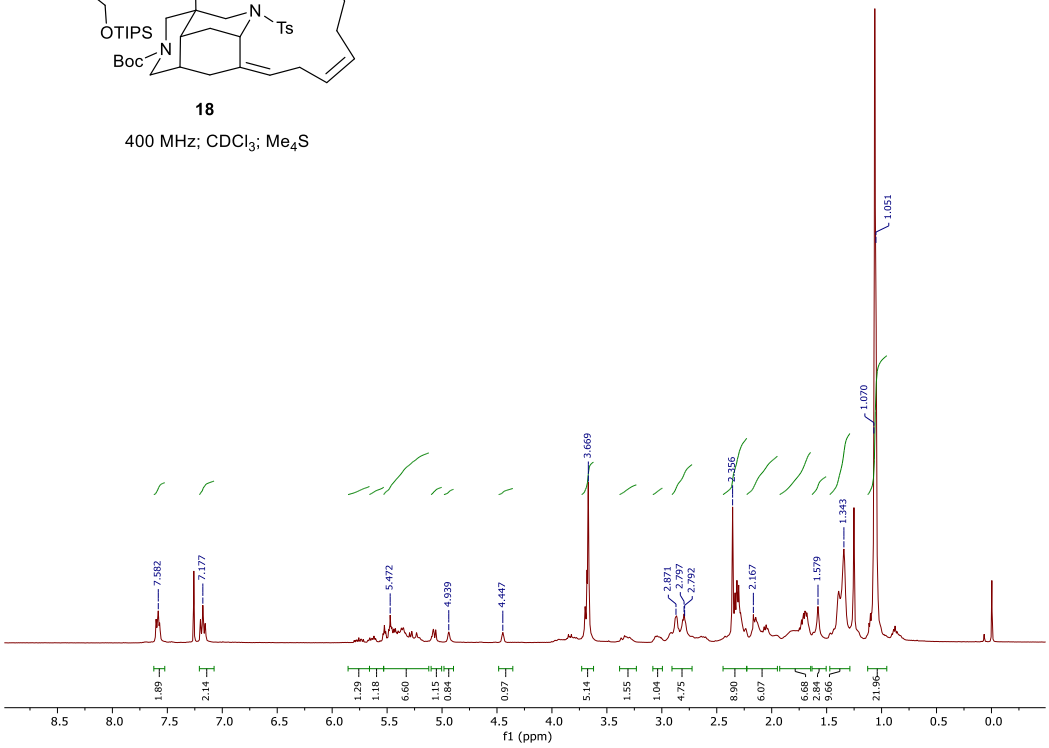
17

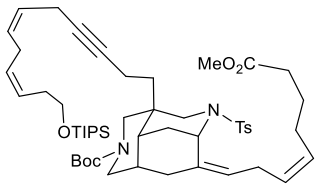
100.6 MHz; $CDCl_3$; Me_4Si



18

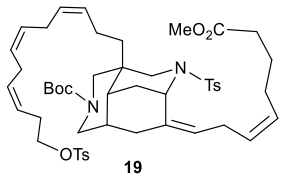
400 MHz; $CDCl_3$; Me_4S





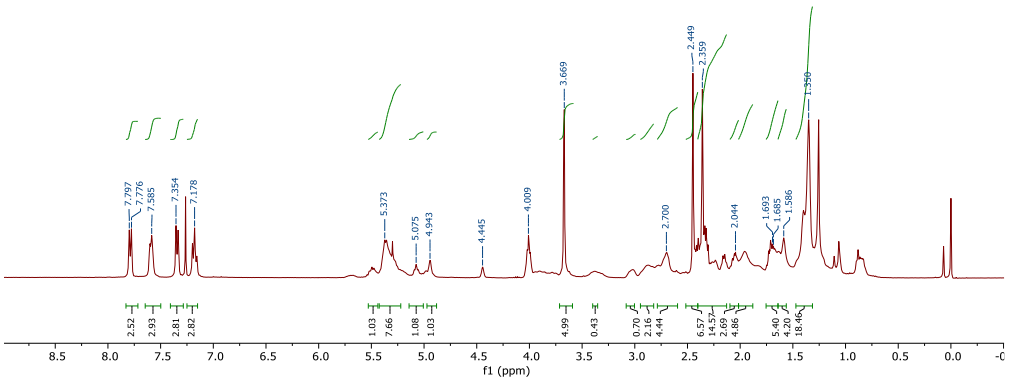
18

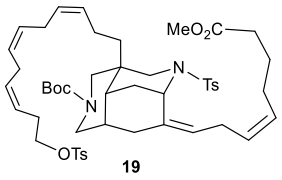
100.6 MHz; $CDCl_3$; Me_4Si



19

400 MHz; $CDCl_3$; Me_4S

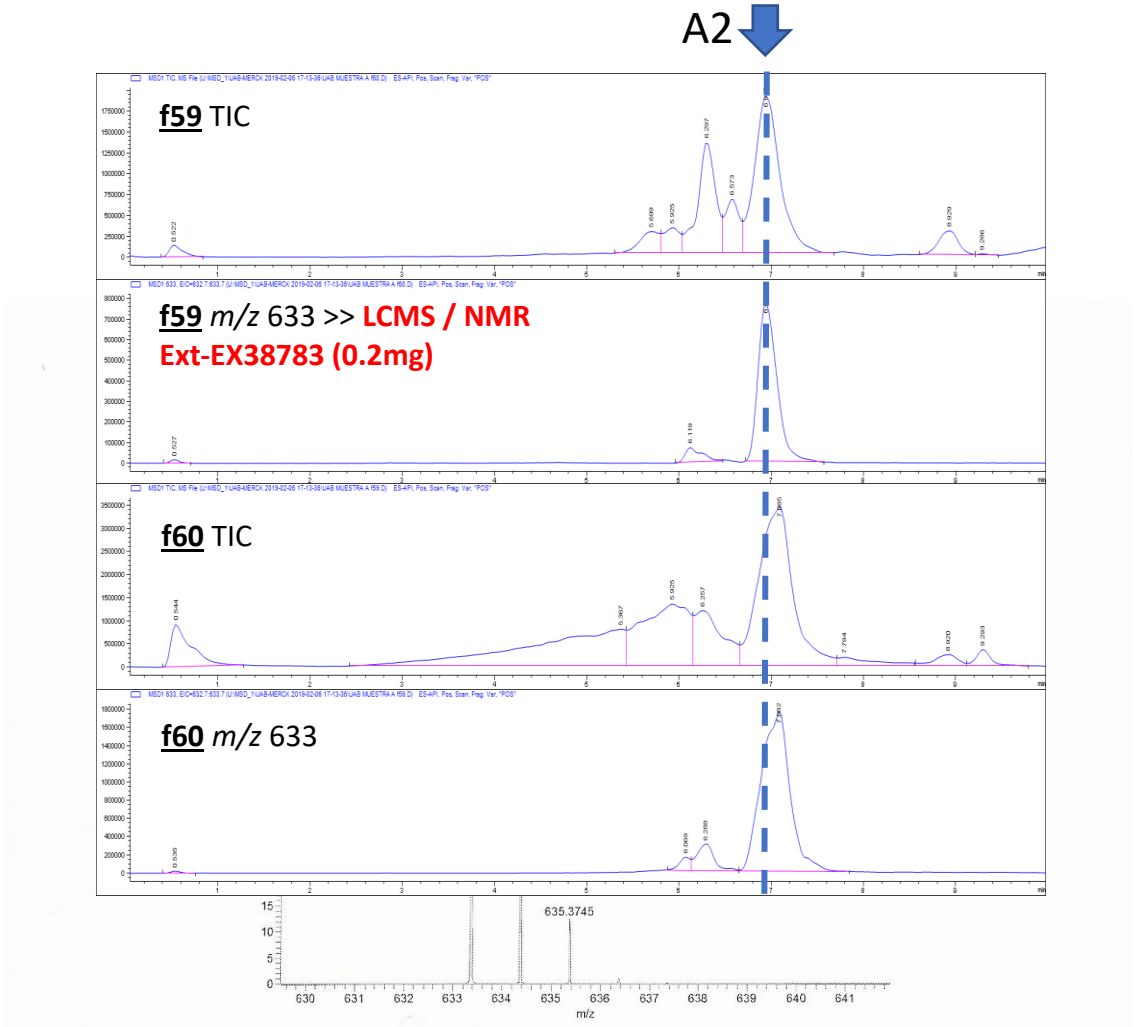


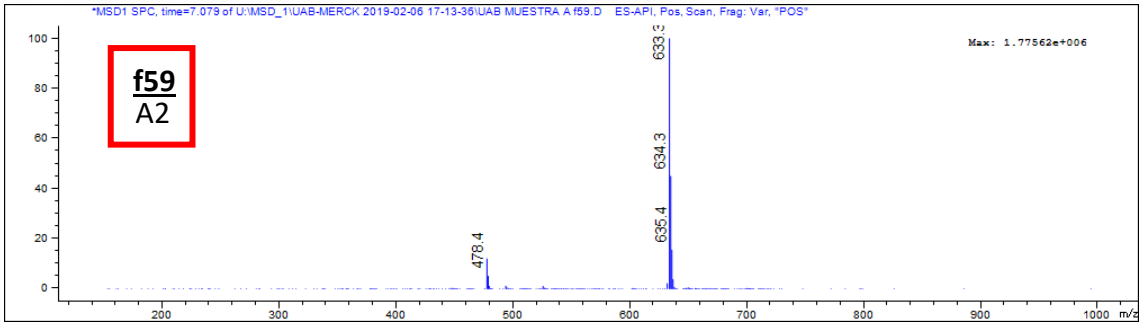


19

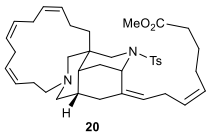
100.6 MHz; $CDCl_3$; Me_4Si

LCMS compound **20** (5-100 ACN/AQ TFA+NH4COOH 10min, *m/z* 633)



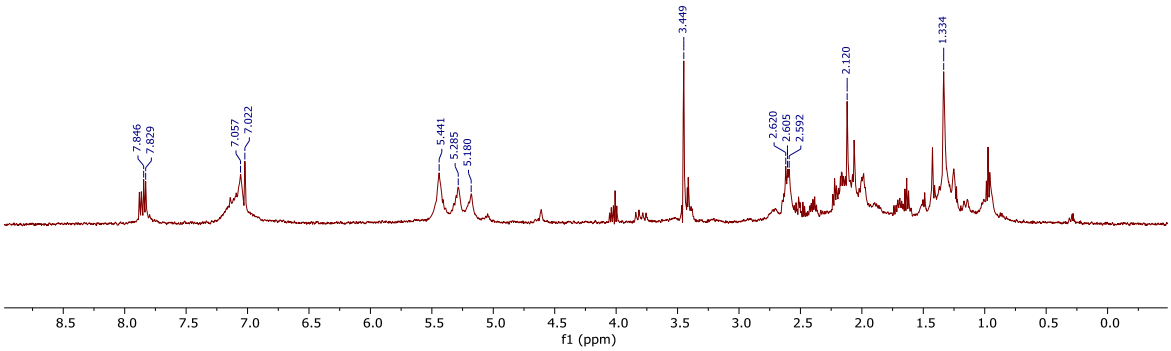


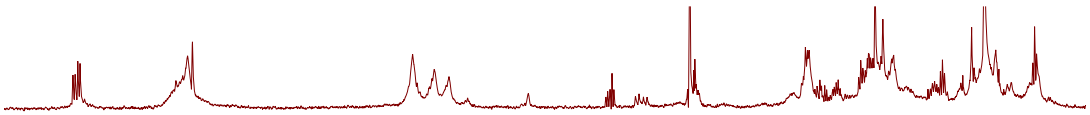
f59 *m/z* 633
Ext-EX38783_Toluene-d_24C_RT_190219
(H9 rack1, 172)



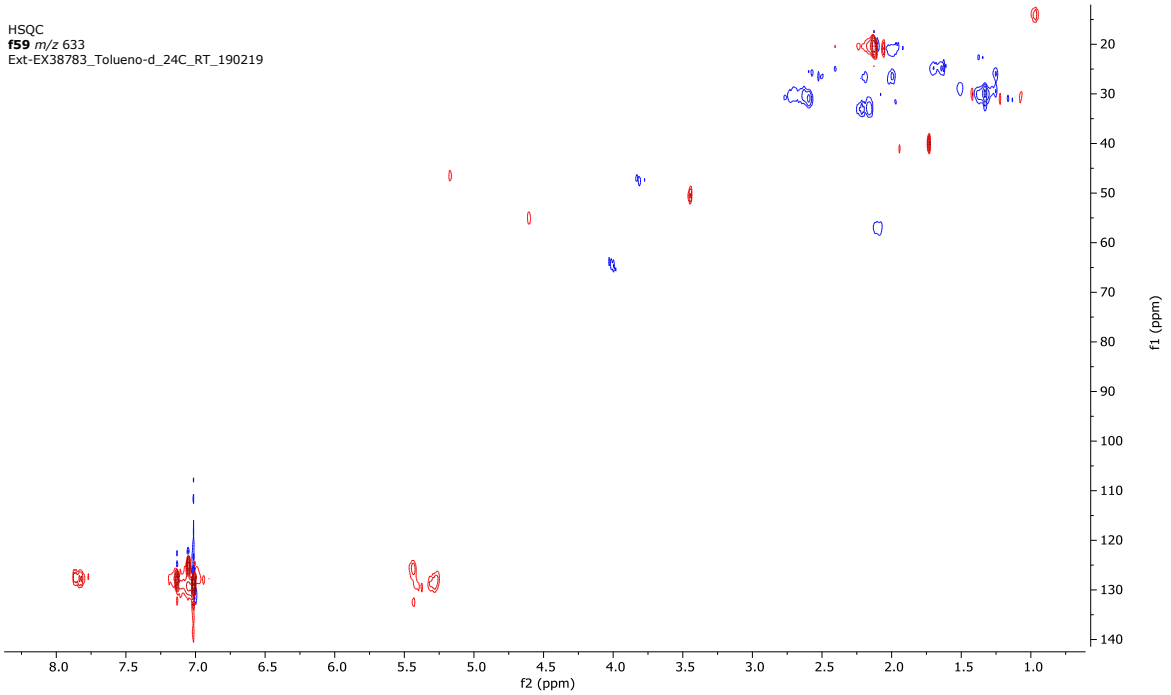
20

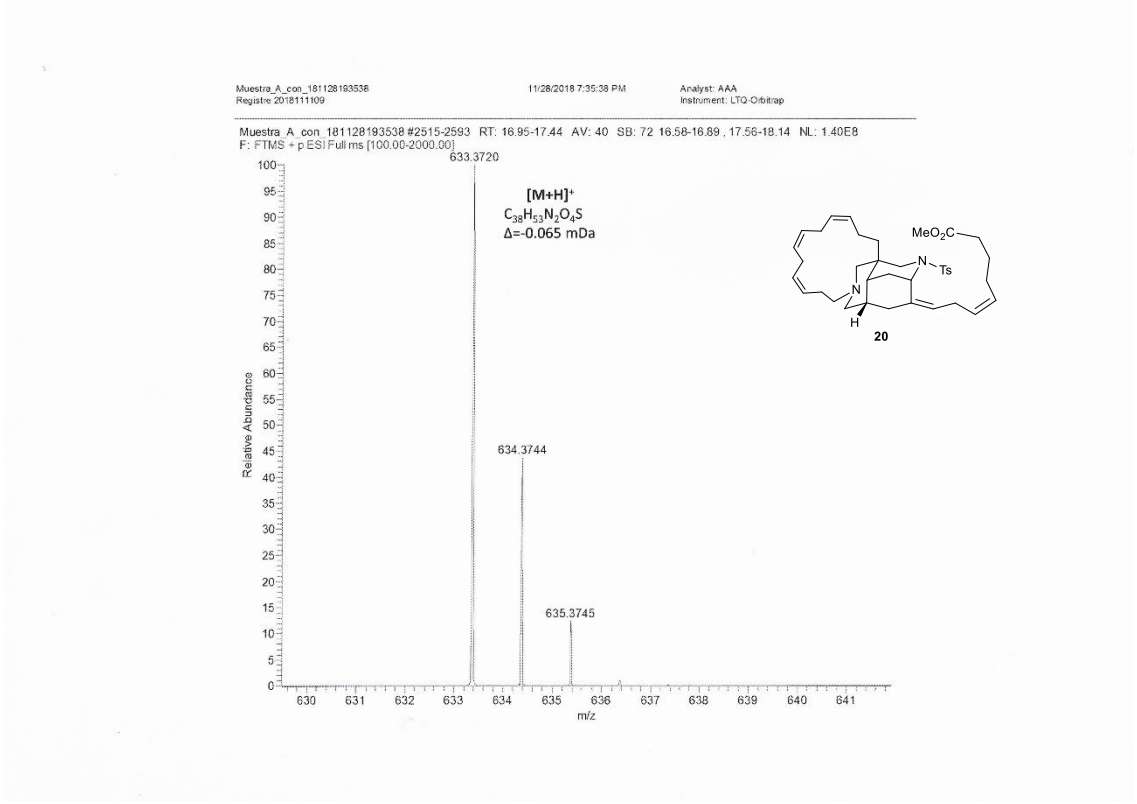
500 MHz; 1.7 mm microcryoprobe;
toluene-d8

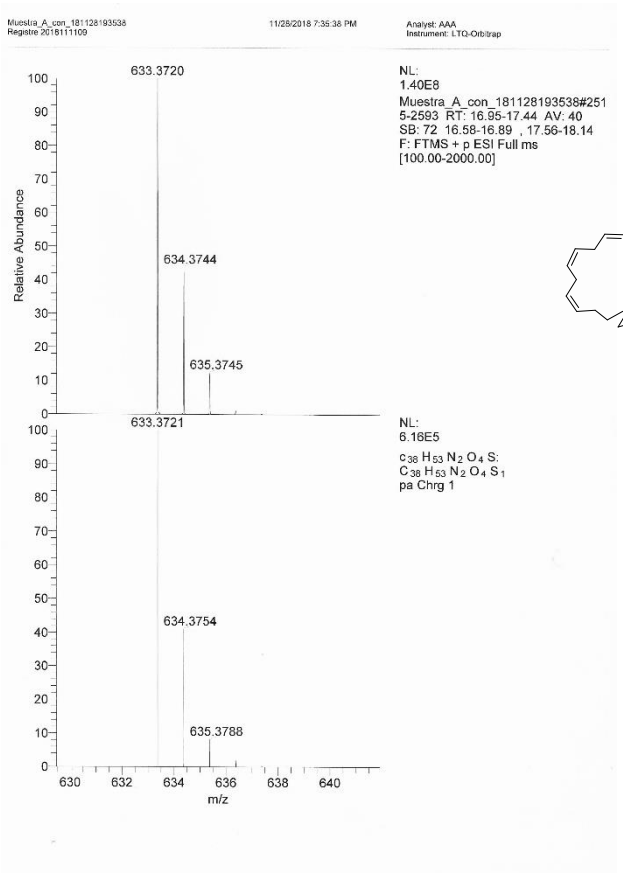


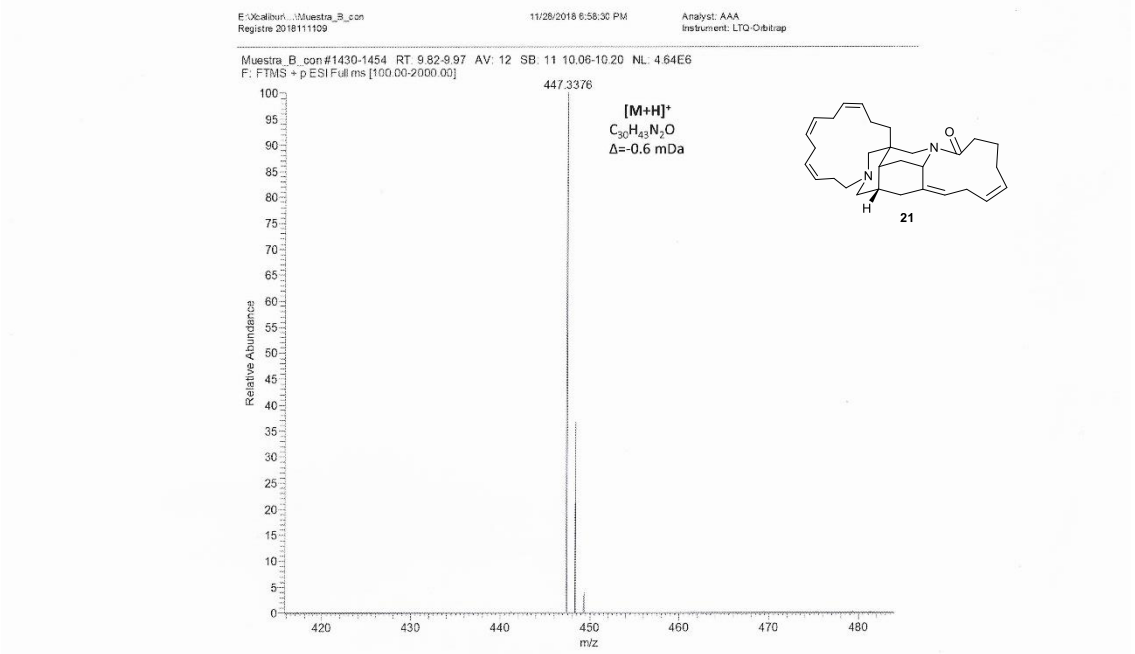


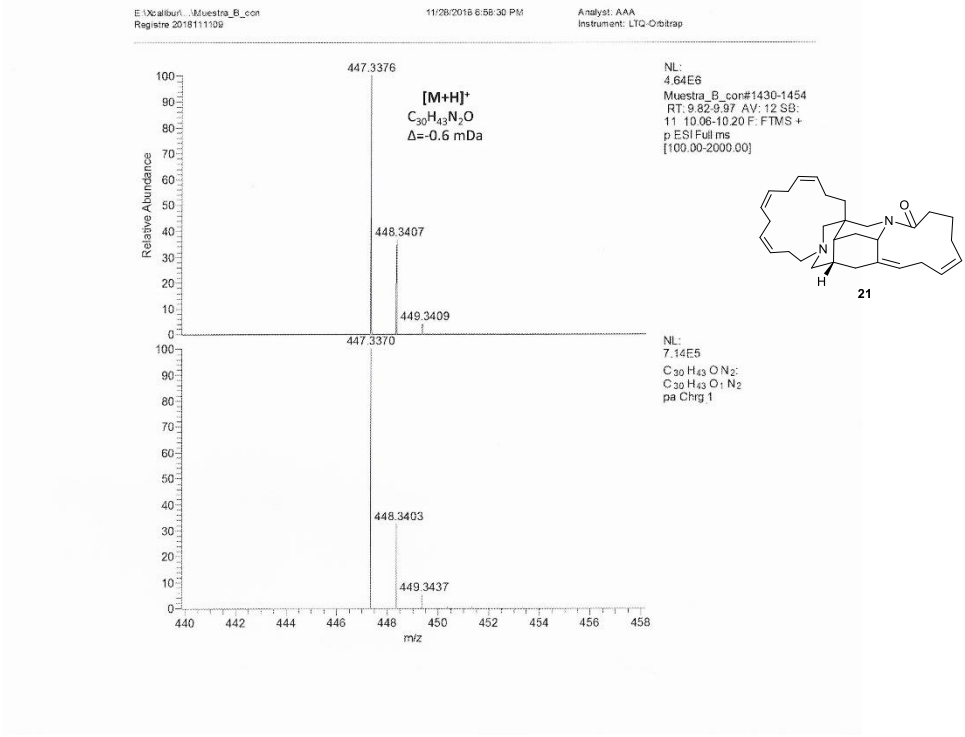
HSQC
f59 *m/z* 633
Ext-EX38783_Toluene-d_24C_RT_190219




Muestra_A_con_181128193538
Registre 2018111109
11/28/2018 7:35:38 PM
Analyst: AAA
Instrument: LTQ-Orbitrap
Muestra_A_con_181128193538 #2515-2593 RT: 16.95-17.44 AV: 40 SB: 72 16.58-16.89 , 17.56-18.14 NL: 1.40E8
F: FTMS + p ESI Full ms [100.00-2000.00]
633.3720
[M+H]+
C38H53N2O4S
Δ=-0.065 mDa
634.3744
635.3745
Relative Abundance
m/z
MeO2C
N
Ts
H
20


Muestra_A_con_181128193538
Registre 2018111109
11/28/2018 7:35:38 PM
Analyst: AAA
Instrument: LTQ-Orbitrap
633.3720
NL:
1.40E8
Muestra_A_con_181128193538#2515-2593 RT: 16.95-17.44 AV: 40
SB: 72 16.58-16.89 , 17.56-18.14
F: FTMS + p ESI Full ms
[100.00-2000.00]
634.3744
635.3745
Relative Abundance
633.3721
NL:
6.16E5
C38 H53 N2 O4 S:
C38 H53 N2 O4 S1
pa Chrg 1
634.3754
635.3788
m/z
MeO2C
N
Ts
H
20


E:\Xcalibur\...\Muestra_B_con
Registre 2018111109
11/28/2018 6:58:30 PM
Analyst: AAA
Instrument: LTQ-Orbitrap
Muestra_B_con #1430-1454 RT: 9.82-9.97 AV: 12 SB: 11 10.06-10.20 NL: 4.64E6
F: FTMS + p ESI Full ms [100.00-2000.00]
447.3376
[M+H]+
C30H43N2O
Δ=-0.6 mDa
Relative Abundance
m/z
21


E:\Xcalibur\...\Muestra_B_con
Registre 2018111109
11/28/2018 6:58:30 PM
Analyst: AAA
Instrument: LTQ-Orbitrap
447.3376
[M+H]+
C30H43N2O
Δ=-0.6 mDa
448.3407
449.3409
NL:
4.64E6
Muestra_B_con#1430-1454
RT: 9.82-9.97 AV: 12 SB:
11 10.06-10.20 F: FTMS +
p ESI Full ms
[100.00-2000.00]
447.3370
448.3403
449.3437
NL:
7.14E5
C30 H43 O N2:
C30 H43 O1 N2
pa Chrg 1
Relative Abundance
m/z
21