Total Synthesis of (–)-Stemonine

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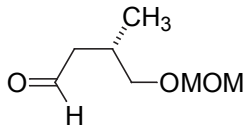
Supporting Information

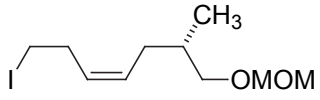
The experimental details for compound **16** and spectral data for characterizations of compounds **4**, **6**, **10**, **11**, **13**, **15**, **16**, **19**, **1** and the proton NMR spectrum of synthetic (–)-stemonine (**1**) are provided.



6

(3*S*)-4-(Methoxymethoxy)-3-methylbutanal (6).

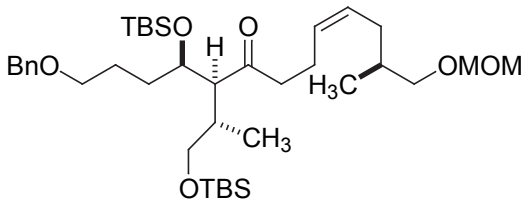
R_f 0.32 (33% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.7 Hz, 1H), 4.56 (m, 2H), 3.44 (dd, *J* = 9.3, 5.1 Hz, 1H), 3.31 (s, 3H), 3.29 (dd, *J* = 9.3, 7.8 Hz, 1H), 2.52 (ddd, *J* = 9.6, 6.0, 2.4 Hz, 1H), 2.36 (m, 1H), 2.26 (ddd, *J* = 16, 6.3, 2.1 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.0, 96.5, 72.2, 55.2, 48.3, 28.9, 17.0.



4

(2*S*)-7-Iodo-1-(Methoxymethoxy)-2-methyl-4-heptene (4).

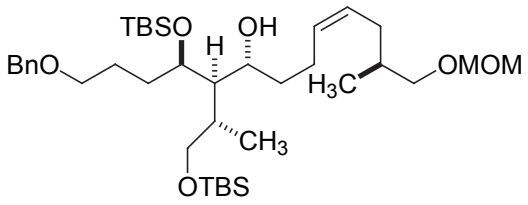
R_f 0.46 (20% EtOAc in hexanes); $[\alpha]_D^{21}$ –3.3 (c 4.4, $CHCl_3$); IR (neat) 2954, 2928, 1463, 1242, 1151, 1111, 1047, 920 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.51 (m, 1H), 5.44 – 5.36 (m, 1H), 4.62 (s, 2H), 3.41 – 3.33 (m, 5H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.64 (m, 2H), 2.21 – 2.12 (m, 1H), 1.98 – 1.75 (m, 2H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.5, 129.4, 96.8, 72.8, 55.4, 34.1, 31.7, 31.6, 17.1, 5.5; HRMS *m/e* calcd. for $C_{10}H_{19}O_2I - OCH_3$, 267.0430 found 267.0401.



10

(*Z*)-(4*R*,5*R*,12*S*)-1-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-5-[(*S*)-2-(*tert*-butyl-dimethylsilanyloxy)-1-methylethyl]-13-methoxymethoxy-12-methyltridec-9-en-6-one (10).

R_f 0.11 (15% EtOAc in hexanes); $[\alpha]_D^{21}$ +14 (c 2.0, CH_2Cl_2); IR (neat) 2940, 2860, 1710, 1460, 1360, 1250, 1100, 1040, 830, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 5.40 – 5.32 (m, 2H), 4.61 (s, 2H), 4.48 (s, 2H), 4.00 (m, 1H), 3.60 – 3.52 (m, 1H), 3.45 – 3.28 (m, 8H), 2.98 (dd, *J* = 6.9, 6.9 Hz, 1H), 2.68 (ddd, *J* = 7.2, 7.2, 18 Hz, 1H), 2.46 (ddd, *J* = 7.2, 7.2, 18 Hz, 1H), 2.35 – 1.85 (m, 5H), 1.85 – 1.15 (m, 5H), 0.90 (s, 9H), 0.93 – 0.80 (m, 24H), 0.04 – 0.01 (m, 12H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7, 138.7, 129.6, 128.3, 127.5, 127.4, 96.6, 72.9, 72.8, 71.4, 70.5, 65.9, 58.1, 55.1, 46.9, 34.9, 34.0, 31.1, 30.2, 26.0, 21.0, 18.4, 18.1, 16.9, 15.1; –4.0, –4.2, –5.4; HRMS *m/e* calcd. for $C_{38}H_{70}O_6Si_2 - C_4H_9$ 621.4008, found 621.4013.

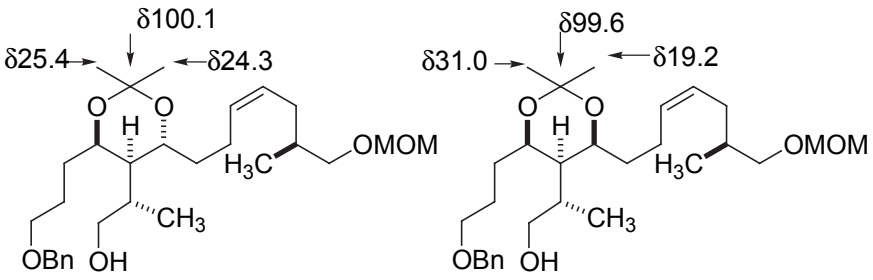


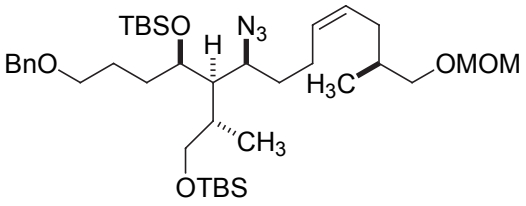
11

(*Z*)-(4*R*,5*R*,6*R*,12*S*)-1-Benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-5-[(*S*)-2-(*tert*-butyldimethylsilanyloxy)-1-methylethyl]-13-methoxymethoxy-12-methyltridec-9-en-6-ol (11).

R_f 0.18 (10% EtOAc in hexanes); $[\alpha]_D^{21}$ +1.9 (c 0.76, $CHCl_3$); IR (neat) 3505, 2927, 2857, 1466, 1462, 1388, 1357, 1257, 1047, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 5H), 5.49 – 5.34 (m, 2H), 4.60 (s, 2H), 4.49 (s, 2H), 4.09 – 4.15 (m, 1H), 3.90 – 3.83 (m, 2H), 3.47 – 3.29 (m, 9H), 2.29 – 2.19 (m, 1H), 2.17 – 2.07 (m, 2H), 1.99 – 1.92 (m 2H), 1.80 – 1.61 (m, 5H), 1.59 – 1.48 (m, 3H), 1.02 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 131.0, 128.3, 127.7, 127.6, 127.5, 96.5, 74.8, 72.9, 72.8, 70.7, 70.1, 66.6, 55.1, 46.6, 36.9, 34.7, 34.0, 31.1, 30.6, 26.7, 25.9, 25.8, 23.6, 18.3, 17.9, 16.9, 15.2, –4.0, –4.2, –5.4; MS (FAB/NBA/Na) *m/e* (relative intensity) 703 (10), 385 (5), 293 (18), 185 (80), 136 (100); HRMS *m/e* calcd. for $C_{38}H_{72}O_6Si_2Na$ $(M+Na)^+$ 703.4765, found 703.4784.

Assignment of stereochemistry of C_{9a} by ^{13}C NMR analysis of the 1,3-*syn* and 1,3-*anti* acetonides.



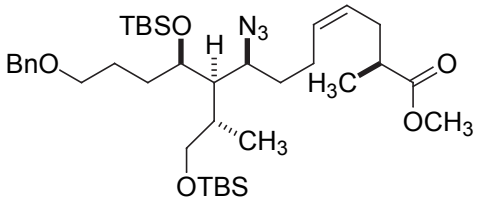


13

{(4*R*,5*R*,6*S*,12*S*)-(*Z*)-6-Azido-4-(*tert*-butyl-dimethyl-silanyloxy)-5-[(*S*)-2-(*tert*-butyl-dimethylsilanyloxy)-1-methylethyl]-13-methoxymethoxy-12-methyl-tridec-9-enyloxymethyl}-benzene (13).

R_f 0.60 (20% EtOAc in hexanes); $[\alpha]_D^{21}$ +5.7 (c 0.77, $CHCl_3$); IR (neat) 2955, 2930, 2883, 2856, 2098, 1258, 1090, 1048, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.33 (m, 5H), 5.43 (t, J = 4.8 Hz, 2H), 4.62 (s, 2H), 4.50 (s, 2H), 3.87 – 3.86 (m, 1H), 3.72 – 3.68 (m, 1H), 3.57 (A of ABX, J_{AB} = 9.9, J_{AX} = 5.2 Hz, 1H), 3.53 (B of ABX, J_{AB} = 9.9 Hz, J_{BX} = 5.7 Hz, 1H), 3.46 (t, J = 6.2 Hz, 2H), 3.41 (A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 6.1 Hz, 1H), 3.37 (s, 3H), 3.34 (B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 6.6 Hz, 1H), 2.25 – 2.13 (m, 3H), 2.01 – 1.94 (m, 2H), 1.84 – 1.76 (m, 1H), 1.71 – 1.58 (m, 5H), 1.51 – 1.44 (m, 2H), 1.00 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 129.5, 128.6, 128.3, 127.6, 127.4, 96.5, 72.8, 72.7, 72.2, 70.2, 67.2, 62.1, 55.1, 47.3, 34.8, 33.9,

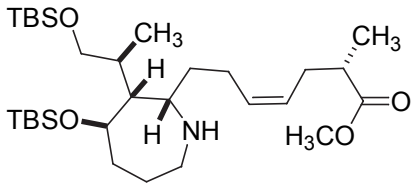
33.9, 31.0, 30.7, 26.6, 26.0, 25.8, 24.7, 18.4, 18.0, 16.8, 16.1, –4.8,–4.2, –5.3; MS (FAB/NBA/Na) *m/e* (relative intensity) 678 (7), 620 (5), 546 (10), 281 (40), 221 (35), 185 (72), 147 (100); HRMS *m/e* calcd. for $C_{38}H_{72}O_5Si_2N$ $(M\text{-}N_2+H)^+$ 678.4949, found 678.4931.



15

(*Z*)-(2*S*,8*S*,9*R*,10*R*)-8-Azido-13-benzyloxy-10-(*tert*-butyldimethylsilanyloxy)-9-[(*S*)-2-(*tert*-butyldimethylsilanyloxy)-1-methylethyl]-2-methyltridec-4-enoic acid methyl ester (15).

R_f 0.44 (20% EtOAc in hexanes); $[\alpha]_D^{21}$ +7.5 (c 0.81, $CHCl_3$); IR (neat) 2955, 2930, 2884, 2857, 2098, 1741, 1462, 1361, 1257, 1166, 1090, 836, 811, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.30 (m, 5H), 5.45 – 5.40 (m, 1H), 5.36 – 5.30 (m, 1H), 4.47 (s, 2H), 3.83 (m, 1H), 3.69 – 3.65 (m, 4H), 3.54 (A of ABX, J_{AB} = 9.9 Hz, J_{AX} = 5.41 Hz, 1H), 3.50 (B of ABX, J_{AB} = 9.9 Hz, J_{BX} = 5.6 Hz, 1H), 3.43 (t, J = 6.1 Hz, 2H), 2.50 – 2.42 (m, 1H), 2.40 – 2.33 (m, 1H), 2.26 – 2.18 (m, 2H), 2.15 – 2.05 (m, 1H), 1.95 – 1.90 (m, 1H), 1.68 – 1.55 (m, 6H), 1.47 – 1.43 (m, 1H), 1.13 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03 (s, 6H), 0.01(s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 139.4, 130.5, 128.3, 127.6, 127.4, 127.2, 72.8, 72.2, 70.2, 67.2, 62.1, 51.5, 47.4, 39.5, 34.7, 34.0, 31.1, 30.8, 26.6, 26.0, 25.9, 24.6, 18.4, 17.9, 16.5, 16.1, –4.1, –4.2, –5.3, –5.4; MS (FAB/NBA/Na) *m/e* (relative intensity) 663 (5), 604 (3), 530 (7), 293 (10), 185 (65), 147 (100); HRMS *m/e* calcd. for $C_{37}H_{67}O_5N_3Si_2Na$ $(M+Na)^+$ 712.4517, found 712.4505.



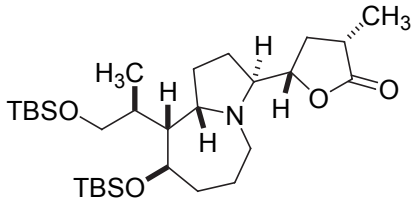
16

***Z*)-(*S*)-7-{(2*S*,3*R*,4*R*)-4-(*tert*-butyl-dimethyl-silanyloxy)-3-[(*S*)-2-(*tert*-butyl-dimethylsilanyloxy)-1-methylethyl]azepan-2-yl}-2-methylhept-4-enoic acid methyl ester (16).**

A benzene solution (3.09 mL) of azido aldehyde **2** (37 mg, 61 μmol) was treated with ethyldiphenylphosphine (19 μL, 93 μmol). Reaction was then stirred at 22 °C for 18 h. Benzene was then removed at reduced pressure, and anhydrous THF was added followed by solid $NaBH_4$ (1.5 eq.) and MeOH (1.5 eq.). The reduction was complete within 5 min at room temperature. Workup with 1M HCl was necessary to hydrolyze the nitrogen-boron complex. Basification with solid K_2CO_3 followed by the addition of aqueous Na_2CO_3 allowed for the isolation of crude amine upon extraction with EtOAc. The amine was purified via flash chromatography with deactivated silica gel (3% Et_3N in hexanes) utilizing a gradient solvent system beginning with EtOAc:Hexanes:Et_3N (15:84:1 by volume) and increasing solvent polarity to EtOAc:Hexanes:Et_3N:MeOH (15:84:1:1 by volume) to afford 22 mg (70%) of amine **16** as a colorless oil.

The imine could be isolated following rapid purification via flash silica gel chromatography. Pure imine decomposed within 2 h at room temperature. Imine was characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.43 (m, 1H), 5.33 – 5.26 (m, 1H), 4.20 (s, 1H), 3.66 (s, 3H), 3.56 (A of ABX, J_{AB} = 10.1 Hz, J_{AX} = 4.04 Hz, 1H), 3.46 (B of ABX, J_{AB} = 10.1 Hz, J_{BX} = 3.5 Hz, 1H), 2.80 (m, 1H), 2.46 (qt, J = 6.9, 6.9 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.25 – 2.18 (m, 2H), 1.82 – 1.57 (m, 8H), 1.43 – 1.31 (m, 2H), 1.14 (d, J = 6.8 Hz, 3H). 1.02 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (m, 12 H).

Spectral data for amine 16: R_f 0.51 (80% EtOAc : 18% Hexanes : 1% MeOH : 1% NH_4OH); $[\alpha]_D^{21}$ +17.8 (c 1.11, $CHCl_3$); IR (neat) 2954, 2930, 2857, 1742, 1472, 1462, 1360, 1255, 1165, 1079, 836, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.49 – 5.43 (m, 1H), 5.33 – 5.26 (m, 1H), 4.01 (m, 1H), 3.66 (s, 3H), 3.61 (A of ABX, J_{AB} = 10.0 Hz, J_{AX} = 5.0 Hz, 1H), 3.52 (B of ABX, J_{AB} = 10.0 Hz, J_{BX} = 5.4 Hz, 1H), 3.14 (ddd, *J* = 5.9, 5.1, 1.2 Hz, 1H), 2.95 (td, *J* = 12.7, 4.7 Hz, 1H), 2.78 (ddd, *J* = 15.1, 10.2, 4.7 Hz, 1H), 2.46 (qt, *J* = 6.9, 6.9 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.25 – 2.18 (m, 1H), 2.12 – 1.94 (m, 3H), 1.82 – 1.60 (m, 5H), 1.57 – 1.48 (m, 1H), 1.43 – 1.31 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 132.0, 126.2, 77.2, 69.6, 66.9, 53.2, 52.5, 51.5, 47.2, 39.6, 36.9, 34.7, 33.3, 31.2, 26.0, 25.8, 22.0, 18.3, 18.1, 18.0, 16.5, –4.5, –4.6, –5.4; MS (FAB/NBA/Na) *m/e* (relative intensity) 556 (61), 557 (20), 442 (15), 336 (10), 292 (15), 268 (25), 196 (18), 176 (38), 136 (98); HRMS *m/e* calcd. for $C_{30}H_{62}O_4NSi_2$ $(M+H)^+$ 556.4217, found 556.4217.

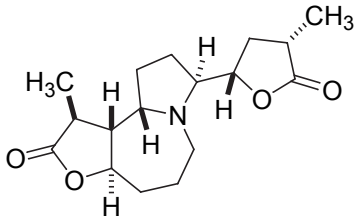


19

(3*S*,5*S*)-5-{(3*S*,8*R*,9*R*,9a*S*)-8-(*tert*-butyl-dimethyl-silanyloxy)-9-[(*S*)-2-(*tert*-butyl-dimethylsilanyloxy)-1-methylethyl]octahydropyrrolo[1,2-α]azepin-3-yl}-3-methyl-dihydrofuran-2-one (19).

R_f 0.87 (80% EtOAc : 18% Hexanes : 1% MeOH : 1% NH_4OH); $[\alpha]_D^{21}$ –14 (c 0.67, $CHCl_3$); IR (neat) 2955, 2927, 2856, 1778, 1463, 1261, 1072, 835, 773 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.21 (ddd, *J* = 11.0, 7.3, 5.8 Hz, 1H), 3.9 (m, 1H), 3.65 – 3.60 (m, 2H), 3.44 (dd, *J* = 9.8, 6.7 Hz, 1H), 3.16 (dt, *J* = 7.2, 7.2 Hz, 1H), 3.07 (t, *J* = 5.3 Hz,

2H), 2.61 – 2.54 (m, 1H), 2.33 (ddd, J = 12.8, 8.3, 5.2 Hz, 1H), 2.02 – 1.97 (m, 2H), 1.91 – 1.83 (m, 3H), 1.74 – 1.71 (m, 2H), 1.55 – 1.37 (m, 4H), 1.23 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H), 0.001 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.7, 82.6, 69.9, 67.4, 65.8, 58.6, 47.9, 36.2, 35.1, 34.8, 34.5, 29.6, 29.0, 27.0, 25.9, 25.8, 20.7, 18.3, 18.0, 16.0, 14.9, –4.1, –4.7, –5.3; MS (EI) *m/e* (relative intensity) 540 (10), 482 (12), 441 (59), 440 (71), 308 (20), 208 (30), 182 (57), 149 (34), 110 (47), 96 (58), 73 (100); HRMS *m/e* calcd. for $C_{29}H_{58}O_4NSi_2$ $(M+H)^+$ 540.3904, found 540.3903.



1

(1*S*,3a*R*,7*S*,9a*S*,9b*R*)-1-Methyl-7-((2*S*,4*S*)-4-methyl-5-oxotetrahydrofuran-2-yl)-decahydro-3-oxa-6a-azacyclopenta[*e*]azulen-2-one (1).

R_f 0.40 (4% MeOH in EtOAc); $[\alpha]_D^{21}$ –81.1 (c 0.2, acetone); IR (neat) 2926, 2850, 1769, 1457, 1187, 1126, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 4.12 (m, 2H), 3.67 (dt, J = 10.1, 5.0, 5.0 Hz, 1H), 3.53 (dd, J = 15.9, 4.8 Hz, 1H), 3.33 – 3.27 (m, 1H), 2.88 (dd, J = 15.8, 11.1 Hz, 1H), 2.61(ddq, J = 12.3, 8.4, 6.9 Hz, 1H), 2.46 – 2.22 (m, 4H), 1.96 – 1.90 (m, 1H), 1.88 – 1.81 (m, 1H), 1.69 – 1.30 (m, 6H), 1.26 (d, J = 7.1 Hz, 3H), 1.23 (d, J = 7.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 178.4, 83.4, 78.9, 75.9, 64.1, 58.5, 53.1, 46.3, 39.2, 34.9, 34.3, 27.2, 26.6, 20.7, 14.9, 13.9; MS (EI) *m/e* (relative intensity) 267 (5), 208 (100), 180 (20), 111 (70), 67 (42); HRMS *m/e* calcd. for $C_{17}H_{26}O_4N$ $(M+H)^+$ 308.1861, found 308.1846.