Total Synthesis of (–)-Stemospironine

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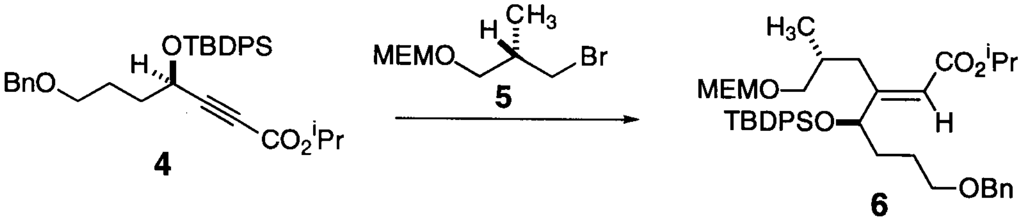
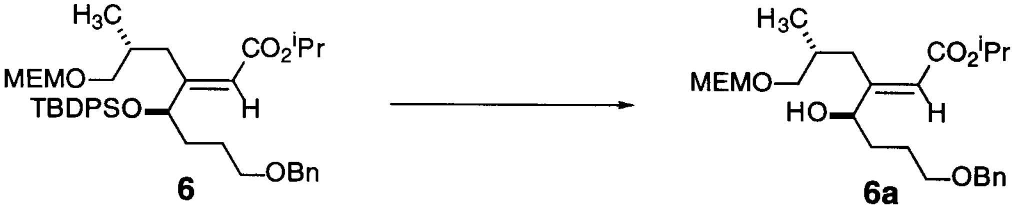
Supporting Information
for ol016336a

Experimental procedures and spectral data for eleven compounds of the synthesis pathway to (–)-stemospironine are provided. (24 pages)



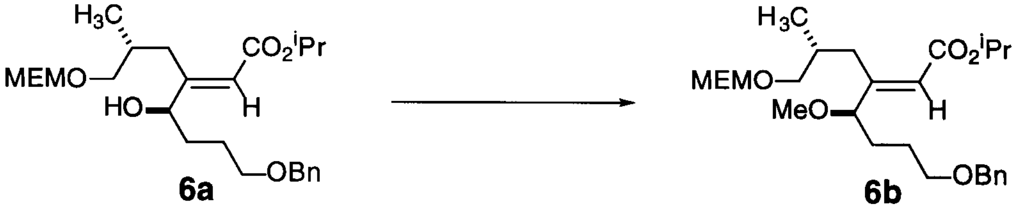
(2E, 4R)-(-)-Isopropyl-7-benzyloxy-4-*tert*-butyldiphenylsilyloxy-3-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-sept-2-en-1-oate ester (6).

To a 50 mL, 3-neck round bottom flask, equipped with a reflux condenser, containing flame-dried Mg° turnings (2.85 g, 117 mmol) under argon at room temperature, was added THF (6.5 mL) followed by 1,2-dibromoethane (100 µL, 1.16 mmol) resulting in gas evolution and refluxing of the THF. Once this reaction subsided, and the solution had returned to room temperature, a THF solution (6.0 mL) of **5** (2.74 g, 11.4 mmol) was added at a sufficient rate to maintain a gentle reflux. The Grignard solution was then allowed to cool to room temperature, and the grey solution was transferred dropwise, via syringe, to a 100 mL round bottom flask containing a THF solution (36.0 mL) of **4** (2.00 g, 3.79 mmol) and CuBr·DMS (468 mg, 2.28 mmol) at –78 °C. After stirring at –78 °C for 12 h, the lime-green heterogeneous reaction mixture was slowly warmed to room temperature over a period of 8–10 h. The reaction was diluted with Et_2O and quenched via addition of saturated aqueous NH_4Cl (50.0 mL). The biphasic mixture was vigorously stirred for 30 min prior to separation of the layers. The organic phase was washed with NH_4Cl (3 x 75 mL) followed by back-extraction of the combined aqueous extracts with Et_2O (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to yield a greenish-yellow oil. This oil was then purified via column chromatography (5% EtOAc/hexanes to 20% EtOAc/hexanes) to yield 1.8 g of **6** (70 %) as a light yellow oil: R_f = 0.72 in 50% EtOAc/hexanes; $[\alpha]_D^{28}$ –2.3° (c 3.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3059, 2934, 2862, 1706, 1650, 1469, 1387, 1240, 1109, 1048, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (d, J = 6.8 Hz, 3H), 1.09 (s, 9H), 1.27 (d, J = 7.2 Hz, 6H), 1.40–1.68 (m, 6H), 1.95 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.04 (dd, *J* = 12.8, 10.0 Hz, 1H), 3.23 (d, *J* = 2.4 Hz, 1H), 3.26–3.39 (m, 4H), 3.36 (s, 3H), 3.48–3.60 (m, 4H), 4.31 (m, 1H), 4.41 (s, 2H), 4.55 (s, 2H), 5.02 (septet, *J* = 6.4 Hz, 1H), 6.25 (s, 1H), 7.27–7.41 (m, 11H), 7.60–7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 19.3, 21.9, 22.0, 23.5, 27.1, 31.7, 32.2, 33.2, 58.9, 66.6, 66.8, 70.2, 71.7, 72.7, 72.6, 73.1, 73.9, 95.3, 117.8, 127.4, 127.5, 127.5, 127.6, 128.3, 129.7, 129.7, 133.2, 133.8, 135.9, 135.9, 138.6, 160.2, 166.4; MS (DCI, NH_3) *m/z* (relative intensity) 287 (5), 257 (22), 200 (9), 199 (49), 197 (17), 168 (5), 167 (6), 139 (9), 137 (6), 135 (9), 105 (6), 92 (16), 91 (100), 89 (59), 79 (7), 78 (19), 77 (16); HRMS *m/z* calcd. for $C_{37}H_{49}O_7Si$ (M^+ –^{t}Bu) 633.3247, found 633.3232; Anal. calcd. for C, H: C, 71.27; H, 8.46. Found: C, 71.14; H, 8.43.



(2E, 4R)-(-)-Isopropyl-7-benzyloxy-4-hydroxy-3-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-sept-2-en-1-oate ester (6a).

To a 500 mL round bottom flask containing **6** (4.40 g, 7.76 mmol) in THF (38.0 mL) at room temperature was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 39.0 mL, 39.0 mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with EtOAc (50 mL) and H_2O (100 mL). The aqueous phase was extracted with EtOAc (3 x 100 mL), then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to yield a brown oil. This oil was then purified via column chromatography (40% EtOAc/hexanes) to yield 2.65 g of alcohol **6a** (75%) as a pale yellow oil: R_f = 0.31 in 40% EtOAc/hexanes; $[\alpha]_D^{30}$ –25° (c 2.4 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3393, 3014, 2934, 2876, 1703, 1455, 1373, 1215, 1104, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 2.0 Hz, 3H), 1.26 (d, *J* = 2.4 Hz, 3H), 1.52–1.61 (m, 2H), 1.68–1.85 (m, 4H), 2.04–2.20 (m, 2H), 3.01 (dd, *J* = 12.2, 7.6 Hz, 1H), 3.39 (s, 3H), 3.40–3.55 (m, 5H), 3.65–3.67 (m, 2H), 4.16 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.52 (s, 2H), 4.68 (AB_q, J_{AB} = 6.4 Hz, Δv_{AB} = 7.1 Hz, 2H), 5.01 (septet, *J* = 6.0 Hz, 1H), 6.05 (s, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 21.9, 26.0, 33.4, 33.7, 59.0, 66.7, 66.8, 70.3, 71.8, 73.1, 74.2, 95.5, 116.3, 127.7, 128.4, 138.0, 163.2, 166.4; MS (DCI, NH_3) *m/z* (relative intensity) 453 (25), 377 (62), 347 (37), 317 (52), 269 (51), 227 (28), 197 (84), 185 (50), 155 (25), 91 (100), 89 (56); HRMS *m/z* calcd. for $C_{25}H_{41}O_7$ (M^+ + 1) 453.2853, found 453.2854; Anal. calcd. for C, H: C, 66.35; H, 8.91. Found: C, 66.26; H, 8.90.

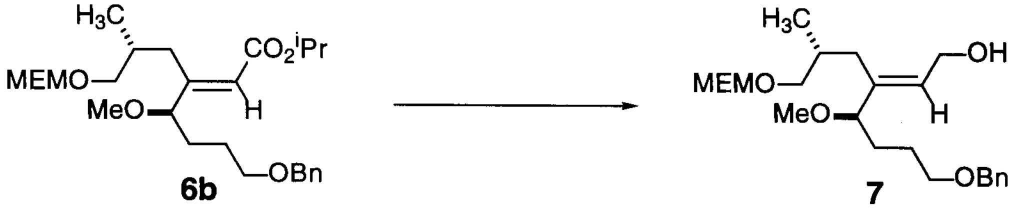


6a **6b**

(2E, 4R)-(-)-Isopropyl-7-benzyloxy-4-methoxy-3-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-sept-2-en-1-oate ester (6b).

To a pre-mixed solution of 60% NaH dispersion in oil (499 mg, 12.5 mmol) and MeI (1.94 mL, 31.2 mmol) in DMF (25 mL) at 0 °C was added alcohol **6a** (2.80g, 6.23 mmol) as a solution in DMF (5.0 mL). The reaction mixture was slowly warmed to room temperature, and stirred for a total of 5 h, at which time the reaction was complete by tlc. The reaction mixture was then diluted with Et_2O (30 mL) and aqueous NH_4Cl (30 mL), followed by separation of the layers, and extraction of the aqueous phase with Et_2O (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a yellow oil which was purified via column chromatography (20% EtOAc/hexanes) to yield 2.2 g (76%) of desired methyl ether **6b** as a light yellow oil: R_f = 0.45 in 40% EtOAc/hexanes; $[\alpha]_D^{23}$ –3.6° (c 5.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3031, 2854, 1711, 1646, 1456, 1373, 1272, 1244, 1200, 1081, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.26 (d, *J* = 6.4 Hz, 6H), 1.43–1.52 (m, 2H), 1.60–1.82 (m, 4H), 1.94–2.10 (m, 2H), 3.07 (dd, *J* =

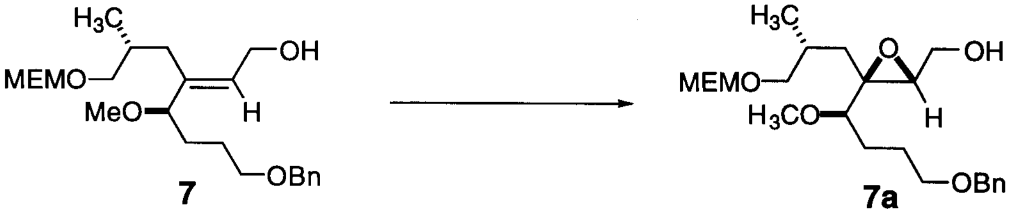
12.2, 9.2 Hz, 1H), 3.25 (s, 3H), 3.39 (s, 3H), 3.42 (d, *J* = 6.0 Hz, 2H), 3.44–3.50 (m, 2H), 3.53–3.55 (m, 2H), 3.56 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.66–3.69 (m, 2H), 4.48 (s, 2H), 4.70 (s, 2H), 5.02 (septet, *J* = 6.0 Hz, 1H), 5.96 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 21.8, 21.9, 25.9, 31.8, 32.7, 33.5, 57.0, 58.9, 66.7, 66.9, 70.0, 71.7, 72.8, 73.2, 83.5, 95.6, 116.7, 127.4, 127.5, 128.3, 138.5, 159.7, 166.2; MS (DCI, NH_3) *m/z* (relative intesity) 391 (31), 273 (28), 269 (34), 227 (25), 197 (78), 155 (30), 91 (100), 89 (86), 71 (30); HRMS *m/z* calcd. for $C_{26}H_{43}O_7$ (M^+ + 1) 467.3010, found 467.3012; Anal. calcd. for C, H: C, 66.93; H, 9.07. Found: C, 66.71; H, 9.00.



(2E, 4R)-(+)-7-Benzyloxy-4-methoxy-3-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-sept-2-en-1-ol (7).

Diisobutylaluminum hydride (1.0 M in hexanes, 10.7 mL, 10.7 mmol) was added to a solution of ester **6b** (1.98 g, 4.28 mmol) in CH_2Cl_2 (20 mL) at –78 °C. After 2 h, aqueous 20% Rochelle's salt (40 mL) was then added, and the solution allowed to warm to room temperature and vigorously stirred for 3 h. The layers were separated, and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated into a yellow oil, which was purified by column chromatography (50% EtOAc/hexanes) to yield 1.6 g (91%) of **7** as a clear colorless oil: R_f = 0.20 in 50% EtOAc/hexanes; $[\alpha]_D^{24}$ +16.2° (c 8.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3457, 2929, 2871, 1456, 1364, 1108, 1047, 849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J* = 6.8 Hz, 3H), 1.54–1.80 (m, 6H), 1.85–1.97 (m, 2H), 2.06–2.13 (m, 1H), 3.22 (s, 3H), 3.39 (s, 3H), 3.40 (d, *J* = 5.2 Hz, 2H), 3.44–3.51 (m, 3H), 3.54–3.56 (m, 2H), 3.67–3.69 (m, 2H), 4.20 (AB of ABX, J_{AB} = 12.4 Hz, J_{AX} = 6.4 Hz, J_{BX} = 7.6 Hz, $\Delta\upsilon_{AB}$ = 44.5 Hz, 2H), 4.49 (s, 2H), 4.70 (ABq, J_{AB} = 6.4 Hz, $\Delta\upsilon_{AB}$

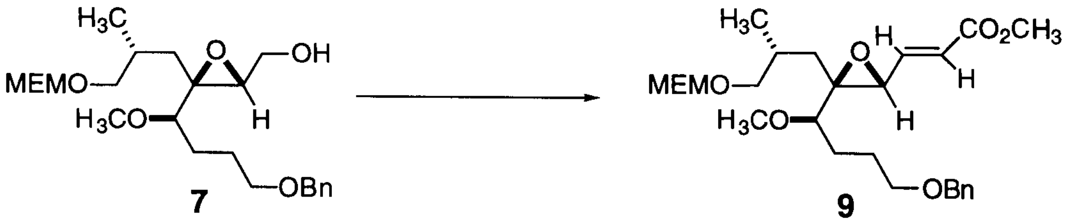
= 6.7 Hz, 2H), 5.71 (t, *J* = 6.8 Hz, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 26.2, 31.5, 31.6, 32.9, 56.4, 58.9, 66.8, 70.2, 71.8, 72.8, 72.9, 84.9, 95.7, 127.4, 127.6, 128.3, 138.6, 139.7; MS (DCI, NH_3) *m/z* (relative intensity) 273 (39), 195 (36), 153 (42), 141 (64), 125 (43), 123 (41), 111 (46), 95 (51), 91 (100), 89 (88), 71 (72); HMRS *m/z* calcd. for $C_{23}H_{37}O_5$ (M^+ –OH) 393.2642, found 393.2625; Anal. calcd for C, H: C, 67.26; H, 9.33. Found: C, 67.14; H, 9.31.



(2R, 3S, 4R)-(+)-7-Benzyloxy-4-methoxy-3-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-sept-2,3-epoxy-1-ol (7a).

To a flame dried 100 mL pear-shaped flask under argon containing SiO_2 (88 mg, 1.5 mmol) and CaH_2 (31 mg, 0.70 mmol) in CH_2Cl_2 (30 mL) was added neat $Ti(O^iPr)_4$ (2.2 mL, 7.3 mmol) at room temperature. Following cooling of the solution to –20 °C via cryocool™, neat (–)-DIPT (1.40 mL, 8.04 mmol) was added, producing a pale yellow solution. This mixture was allowed to stir for 20 min at –20 °C prior to the addition of 7 (3.0 g, 7.3 mmol) as a solution in CH_2Cl_2 (15 mL). Stirring was continued for an additional 20 min, followed by the addition of ^tBuOOH (3.8 M in toluene, 4.8 mL, 18 mmol). After stirring at –20 °C for 72 h, the reaction was quenched at –20 °C via addition of 10% aqueous tartaric acid (50 mL) followed by warming to room temperature with vigorous stirring for 30 min. The organic phase was washed with brine (1 x 10 mL) with back-extraction of the combined aqueous phases with Et_2O (4 x 50 mL) and EtOAc (2 x 50 mL). The combined organic extracts were then concentrated to approximately 50 mL, treated with aqueous NaOH (1.0 M, 30 mL) and the biphasic mixture stirred for 30 min. The layers were separated, and the aqueous phase was extracted with EtOAc (4 x 50 mL).

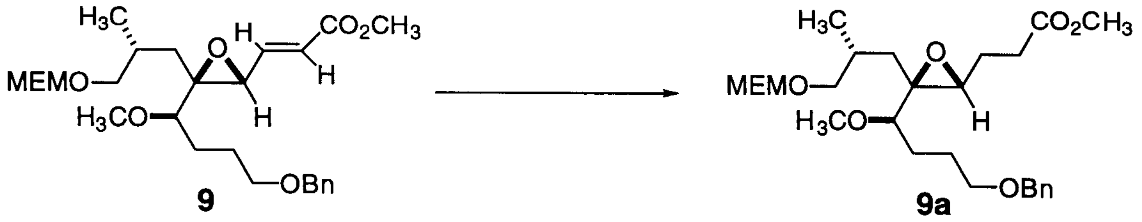
The organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to a yellowish oil which was purified via column chromatography (20%–40%–50% EtOAc/hexanes) to yield 3.0 g (95%) of epoxides as a 4 : 1 (β/α) mixture, which were separable only by careful column chromatography: R_f = 0.20 in 50% EtOAc/hexanes; $[\alpha]_D^{23}$ +5.8° (c 10.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3451, 2930, 2874, 1748, 1454, 1363, 1099, 1046, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.8 Hz, 3H), 1.37 (dd, *J* = 14.8, 8.0 Hz, 1H), 1.46–1.55 (m, 1H), 1.63–1.85 (m, 6H), 2.03–2.11 (m, 1H), 2.40–2.43 (m, 1H), 3.07 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.14 (apparent triplet, *J* = 6.0 Hz, 1H), 3.36 (s, 3H), 3.38 (s, 3H), 3.40–3.50 (m, 4H), 3.52–3.55 (m, 2H), 3.65–3.67 (m, 2H), 3.72–3.76 (m, 2H), 4.50 (s, 2H), 4.68 (AB_q, J_{AB} = 6.8 Hz, Δv_{AB} = 11.3 Hz, 2H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 25.9, 28.4, 30.3, 31.6, 59.0, 59.1, 60.6, 62.7, 66.9, 70.1, 71.7, 72.8, 73.0, 82.0, 95.6, 127.5, 127.6, 128.3, 138.5; HRMS (FAB, Na) *m/z* calcd. for $C_{23}H_{38}O_7Na$ (M^+ + Na) 449.2515, found 449.2525; Anal. calcd. for C, H: C, 64.76; H, 8.98. Found: C, 64.66; H, 9.08.



(2E, 4R, 5R, 6R)-(+)-Methyl-9-benzyloxy-6-methoxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4,5-epoxy-non-2-enoate ester (9).

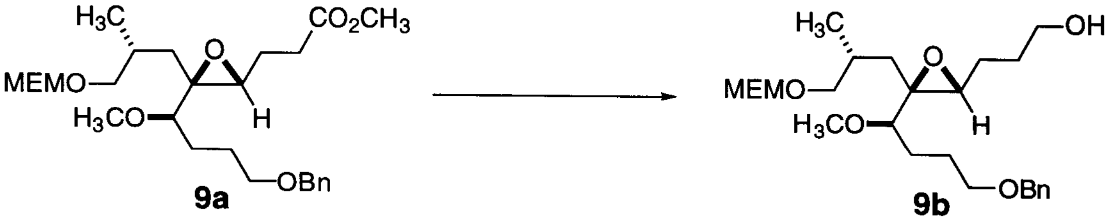
To a flame dried 25 mL round-bottom flask under argon containing a CH_2Cl_2 solution (6.0 mL) of **7** (500 mg, 1.17 mmol) was added pyridine (1.90 mL, 23.5 mmol). The solution was then cooled to 0 °C followed by addition of solid Dess–Martin Periodinane (1.00 g, 2.35 mmol) and slow warming to room temperature. After stirring at room temperature for 2 h the reaction was complete by tlc. The solution was recooled to 0 °C and the ylide, (carbomethoxymethylene)triphenylphosphorane

(985 mg, 2.93 mmol), was added. The solution was allowed to slowly warm to room temperature with stirring for 1h, followed by quenching via addition of 10% HOAc (5.0 mL). The biphasic mixture was diluted with Et_2O (10 mL) followed by separation of the layers. The organic layer was washed with 10% HOAc (2 x 10 mL) and saturated $NaHCO_{3(aq)}$ (2 x 20 mL), then dried ($MgSO_4$), filtered and concentrated to yield a yellowish-brown oil. Purification of this oil via column chromatography (20% EtOAc/hexanes) allowed for the isolation of 339 mg (60%) of **9** as a single alkene diastereomer: $R_f = 0.45$ in 50% EtOAc/hexanes; $[\alpha]_D^{33}$ +12.5° (c 10.8 mg/mL, $CHCl_3$); IR ($CHCl_3$) 2949, 2876, 1655, 1440, 1364, 1307, 1264, 1196, 1120, 1048, 979, 920, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.03 (d, J = 5.6 Hz, 3H), 1.16 (dd, J = 11.6, 7.6 Hz, 1H), 1.41–1.50 (m, 1H), 1.62–1.80 (m, 4H), 1.87(dd, J = 11.6, 3.6 Hz, 1H), 2.00–2.08 (m, 1H), 3.28–3.32 (m, 2H), 3.37 (s, 3H), 3.38 (s, 3H), 3.45–3.50 (m, 2H), 3.52–3.57 (m, 4H), 3.63–3.65 (m, 2H), 3.75 (s, 3H), 4.49 (s, 2H), 4.66 (s, 2H), 6.09 (d, J = 12.4 Hz, 1H), 6.84 (dd, J = 12.6, 5.2 Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 25.7, 28.8, 30.4, 31.7, 51.7, 56.5, 59.0, 59.8, 66.7, 70.0, 71.7, 72.8, 73.0, 79.8, 95.5, 124.5, 127.5, 127.6, 128.3, 138.5, 143.0, 166.0; HRMS (FAB, Na) m/z calcd. for $C_{26}H_{40}O_8Na$ (M^+ + Na) 503.2622, found 503.2620; Anal. calcd. for C, H: C, 64.98; H, 8.39. Found: C, 64.80; H, 8.41.



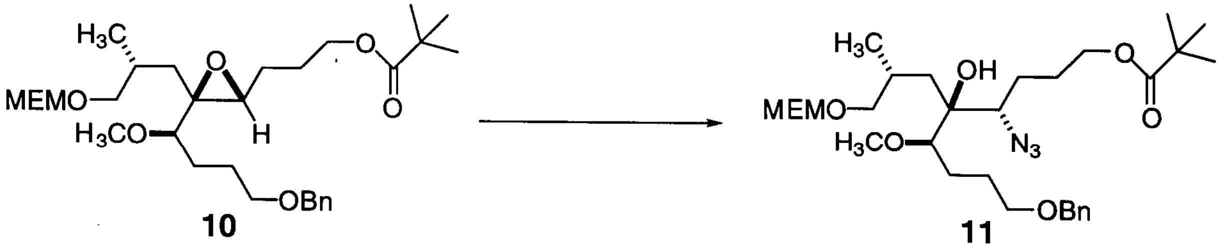
(4R, 5R, 6R)-(+)-Methyl-9-benzyloxy-6-methoxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4,5-epoxynonanoate ester (9a).

To a 100 mL round-bottom flask containing a THF solution (30.0 mL) of **9** (1.40 g, 2.94 mmol) under argon at room temperature was added 5% Rh/Al_2O_3 (285 mg, 20% by weight). The flask was then purged with $H_{2(g)}$ and left under 1 atm of $H_{2(g)}$ for 1 h at which time the reaction was complete by tlc. Dilution of the reaction mixture with EtOAc (20 mL) followed by filtration and removal of solvent *in vacuo* resulted in the isolation of a light yellow oil. Purification of this oil via column chromatography (20%–40% EtOAc/hexanes) resulted in the isolation of 1.28 g (90%) of the saturated ester **9a** as a clear colorless oil: R_f = 0.35 in 40% EtOAc/hexanes; $[\alpha]_D^{24}$ +13.4° (c 4.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 2930, 2875, 1740, 1453, 1365, 1273, 1201, 1173, 1119, 1044, 982, 921, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 6.8 Hz, 3H), 1.21 (dd, J = 14.8, 8.8 Hz, 1H), 1.37–1.49 (m, 1H), 1.54–2.06 (m, 6H), 2.41–2.55 (m, 2H), 2.93 (dd, J = 7.6, 5.6 Hz, 1H), 3.11 (dd, J = 8.8, 2.8 Hz, 1H), 3.34 (s, 3H), 3.36 (d, J = 6.0 Hz, 2H), 3.39 (d, J = 4.8 Hz, 2H), 3.45–3.51 (m, 2H), 3.53–3.56 (m, 2H), 3.65–3.67 (m, 2H), 3.68 (s, 3H), 4.50 (s, 2H), 4.69 (s, 2H), 7.26–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 23.6, 26.0, 28.7, 30.5, 31.0, 51.6, 58.1, 59.0, 59.4, 63.0, 66.8, 70.2, 71.8, 72.8, 73.3, 81.4, 95.6, 127.5, 127.6, 128.3, 138.6, 173.2; HRMS (FAB, Na) *m/z* calcd. for $C_{26}H_{42}O_8Na$ (M^+ + Na) 505.2779, found 505.2798; Anal. calcd. for C, H: C, 64.71; H, 8.77. Found: C, 64.62; H, 8.77.



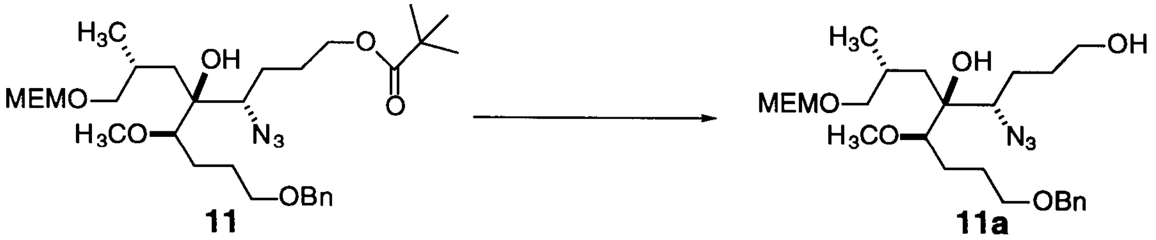
(4R, 5R, 6R)-(+)-9-Benzyloxy-6-methoxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4,5-epoxynona-1-ol (9b).

To a 250 mL round-bottom flask under argon containing an Et_2O solution (25 mL) of **9a** (1.24 g, 2.56 mmol) at room temperature was added solid $LiBH_4$ (57.0 mg, 2.56 mmol). Methanol (105 µL, 2.56 mmol) was slowly added to the cloudy mixture with gas evolution resulting in a clear, colorless solution. The solution was stirred for 3 h then quenched via slow addition of aqueous NH_4Cl (5.0 mL). The reaction mixture was then diluted with Et_2O (50 mL) and aqueous NH_4Cl (50 mL) followed by vigorous stirring of the biphasic mixture for 1 h. The aqueous phase was extracted with EtOAc (3 x 50 mL)and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to yield a cloudy oil which was purified via column chromatography (50% to 100% EtOAc/hexanes) to yield 1.05 g (90%) of primary alcohol **9b** as a colorless oil: $R_f = 0.06$ in 50% EtOAc/hexanes; $[\alpha]_D^{24}$ +8.9° (c 5.5 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3476, 3087, 3031, 2958, 2922, 2855, 1455, 1363, 1107, 1047, 932, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 5.2 Hz, 3H), 1.23 (dd, J = 11.8, 7.2 Hz, 1H), 1.40–1.57 (m, 2H), 1.62–1.79 (m, 6H), 1.84 (dd, J = 11.8, 4.4 Hz, 1H), 1.93–2.04 (m, 2H), 2.92 (dd, J = 5.8, 4.0 Hz, 1H), 3.10 (dd, J = 7.0, 1.6 Hz, 1H), 3.34 (s, 3H), 3.36 (d, J = 6.8 Hz, 2H), 3.37 (s, 3H), 3.45–3.49 (m, 2H), 3.52–3.54 (m, 2H), 3.65–3.69 (m, 4H), 4.49 (s, 2H), 4.68 (s, 2H), 7.26–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 24.5, 26.0, 28.5, 29.7, 30.5, 31.3, 58.9, 59.2, 59.3, 62.3, 63.0, 66.7, 70.2, 71.8, 72.8, 73.3, 81.6, 95.6, 127.4, 127.5, 128.3, 138.6; HRMS (FAB, Na) *m/z* calcd. for $C_{25}H_{42}O_7Na$ (M^+ + Na) 477.2830, found 477.2839.



(4S, 5R, 6R)-(+)-*tert*-Butyl-9-benzyloxy-6-methoxy-5-hydroxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4-azidononanoate ester (11).

To a 10 mL round bottom flask under argon containing a DMPU solution (2.0 mL) of epoxide **10** (100 mg, 0.186 mmol) at room temperature was added solid NH_4Cl (50 mg, 0.929 mmol) followed by LiN_3 (91.0 mg, 1.86 mmol). The slurry was placed in a pre-heated oil bath at 130 °C producing a clear yellow solution. The reaction was fitted with a glass stopper, sealed with teflon tape, and immersed in the oil bath for a total of 16 h. After cooling to room temperature, the reaction was diluted with Et_2O (5.0 mL) and H_2O (3.0 mL). The layers were separated from the biphasic mixture, and the aqueous phase extracted with Et_2O (3 x 20 mL), followed by drying of the organic extracts over $MgSO_4$. Following filtration and removal of solvent *in vacuo*, the resulting crude yellow oil was purified via column chromatography (20% Et_2O/CH_2Cl_2) to yield 90 mg (83%) of azide **11** as a light yellow oil: R_f = 0.60 in 20% EtOAc/hexanes; $[\alpha]_D^{28}$ +1.7° (c 4.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3410, 2960, 2934, 2876, 2104, 1719, 1455, 1285, 1162, 1096, 1043, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 3H), 1.20 (s, 9H), 1.46–1.80 (m, 11H), 1.84–1.95 (m, 2H), 1.98–2.06 (m, 1H), 3.25 (t, J = 9.2 Hz, 1H), 3.30–3.33 (m, 2H), 3.37 (s, 3H), 3.40 (s, 3H), 3.47–3.54 (m, 6H), 3.65–3.68 (m, 2H), 3.96 (s, 1H), 4.09 (t, J = 5.6 Hz, 2H), 4.51 (s, 2H), 4.71 (AB_q, J_{AB} = 7.2 Hz, Δv_{AB} = 8.9 Hz, 2H), 7.26–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.2, 27.1, 27.2, 27.3, 27.9, 28.6, 38.7, 59.0, 59.8, 64.0, 67.2, 69.4, 70.5, 71.6, 72.9, 74.5, 78.3, 84.8, 95.5, 127.5, 127.8, 128.3, 138.5, 178.5; HRMS (FAB, Na) *m/z* calcd. for $C_{30}H_{51}N_3O_8Na$ (M^+ + Na) 582.3757, found 582.3761.

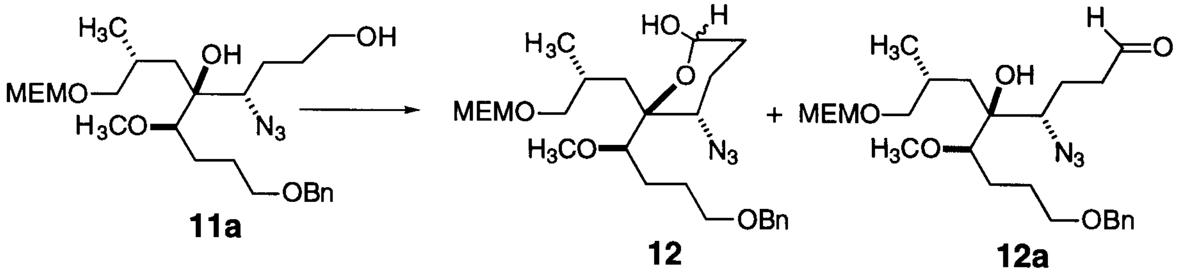


11

11a

(4S, 5R, 6R)-(-)-9-Benzyloxy-6-methoxy-5-hydroxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4-azidononan-1-ol (11a).

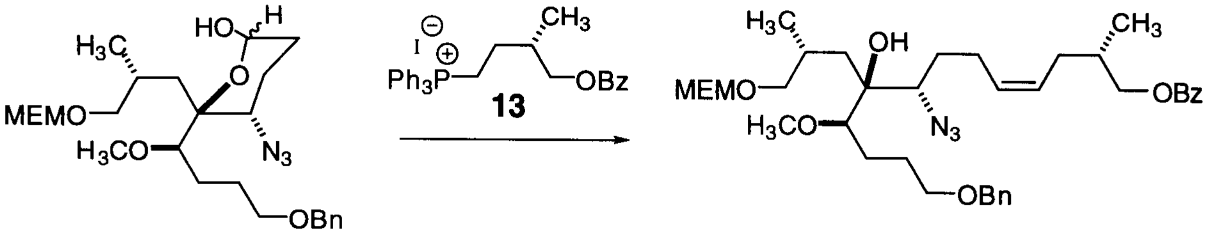
To a THF-MeOH-H_2O solution (7 : 2 : 1, 2.0 mL) of **11** (91 mg, 0.16 mmol) at room temperature was added lithium hydroxide monohydrate (16 mg, 0.38 mmol). The reaction was allowed to stir at room temperature for a total of 24 h, then diluted with Et_2O (5.0 mL) and aqueous NH_4Cl (3.0 mL). The layers were separated, and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated into an oil which was purified by preparative thin layer chromatography (2 x 0.5 mm, 100% EtOAc) to yield 70 mg (90%) of the desired diol **11a** as a clear colorless oil: $R_f = 0.14$ in 50% EtOAc/hexanes; $[\alpha]_D^{28}$ −1.6° (c 3.8 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3426, 2928, 2869, 2098, 1731, 1454, 1364, 1274, 1084, 1043, 921, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.8 Hz, 3H), 1.24 (s, 1H), 1.49–1.94 (m, 12H), 2.02–2.10 (m, 1H), 3.25 (t, J = 9.2 Hz, 1H), 3.31 (dd, J = 8.2, 2.8 Hz, 1H), 3.35 (m, 1H), 3.38 (s, 3H), 3.42 (s, 3H), 3.48–3.54 (m, 5H), 3.66–3.71 (m, 4H), 4.51 (s, 2H), 4.71 (AB_q, J_{AB} = 6.4 Hz, $\Delta\upsilon_{AB}$ = 9.7 Hz, 2H), 7.26–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 25.8, 27.3, 27.8, 28.5, 30.7, 38.6, 58.9, 59.9, 62.2, 67.1, 69.1, 70.5, 71.6, 72.8, 74.5, 78.2, 84.8, 95.4, 127.5, 127.6, 128.3, 138.4; HRMS (FAB, Na) m/z calcd. for $C_{25}H_{43}N_3O_7Na$ (M^+ + Na) 520.3001, found 520.2980; Anal. calcd. for C, H: C, 60.34; H, 8.71. Found: C, 60.10; H, 8.69.



11a **12** **12a**

(4S, 5R, 6R)-(+)-9-Benzyloxy-6-methoxy-5-hydroxy-5-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-4-azidononan-1-al (12a and its lactol 12).

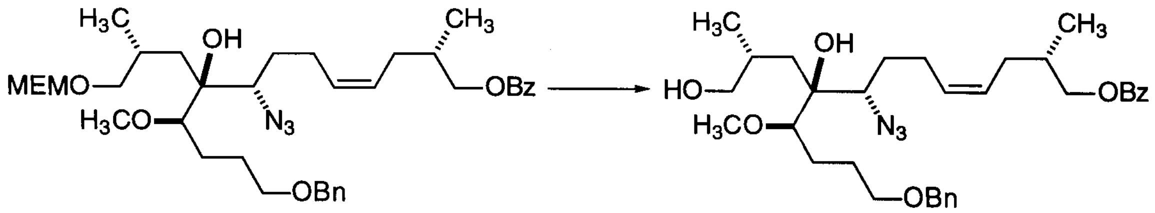
To a 5 mL round bottom flask under argon containing CH_2Cl_2 (1.0 mL) at −78 °C was added neat oxalyl chloride (24 µL, 0.28 mmol) followed by neat DMSO (35 µL, 0.49 mmol) with the rapid evolution of gas. This solution was allowed to stir at −78° C for 10 min followed by the addition of **11a** (60 mg, 0.12 mmol) as a solution in CH_2Cl_2 (1.5 mL). The solution was stirred for an additional 15 min, followed by the addition of Et_3N (100 µL, 0.72 mmol) and slow warming of the reaction mixture to room temperature. After stirring at room temperature for 30 min, the mixture was poured into Et_2O (10 mL) and diluted with aqueous NH_4Cl (5 mL). The layers were separated and the organic phase washed with aqueous $NaHCO_3$ (5 mL), followed by extraction of the combined aqueous extracts with Et_2O (1 x 20 mL). The combined organic extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a light yellow oil which was purified via preparative thin layer (silica gel) chromatography (1 x 0.5 mm, 50% EtOAc/hexanes) to yield 58 mg (97%) of **12** and **12a** as a mixture of diastereomeric lactols and free aldehyde: $R_f = 0.33$ in 50% EtOAc/hexanes; $[\alpha]_D^{24}$ +14.0 (c 3.5 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3413, 3007, 2935, 2878, 2103, 1724, 1602, 1456, 1243, 1197, 1102, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 7.2$ Hz, 3H), 1.07 (d, $J = 7.2$ Hz, 3H), 1.40–2.12 (m, 12H), 2.54–2.70 (m, 1H), 2.91 (d, $J = 6.0$ Hz, 1H), 3.14–3.72 (m, 16H), 3.99 (dd, $J = 11.2, 4.8$ Hz, 1H), 4.14 (s, 1H), 4.49 (s, 3H), 4.50 (s, 3H), 4.64 (AB_q, $J_{AB} = 6.8$ Hz, $\Delta v_{AB} = 7.3$ Hz, 2H), 4.70 (AB_q, $J_{AB} = 6.4$ Hz, $\Delta v_{AB} = 10.7$ Hz, 2H), 4.95 (m, 1H), 5.04 (m, 1H), 7.26–7.33 (m, 5H), 9.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 19.3, 22.2, 23.4, 27.2, 27.8, 27.9, 28.4, 28.7, 29.4, 31.2, 38.7, 41.7, 57.2, 58.9, 59.7, 62.1, 66.6, 67.2, 68.9, 70.2, 70.5, 71.6, 71.7, 72.8, 74.1, 74.4, 78.4, 83.2, 84.6, 85.9, 90.4, 95.4, 127.4, 127.6, 128.3, 138.5, 201.4; HRMS (FAB, Na) *m/z* calcd. for $C_{25}H_{41}N_3O_7Na$ (M^+ + Na) 518.2844, found 518.2820; Anal. calcd. for C, H: C, 60.59; H, 8.34. Found: C, 60.55; H, 8.36.



12 **14**

(4Z, 2S, 8S, 9R, 10R)-(+)-8-Azido-13 -benzyloxy-10-methoxy-9-[(2R)-3-methoxyethoxymethoxy-2-methylpropyl]-2-methyl-9-hydroxytridec-4-en-1-benzoate ester (14).

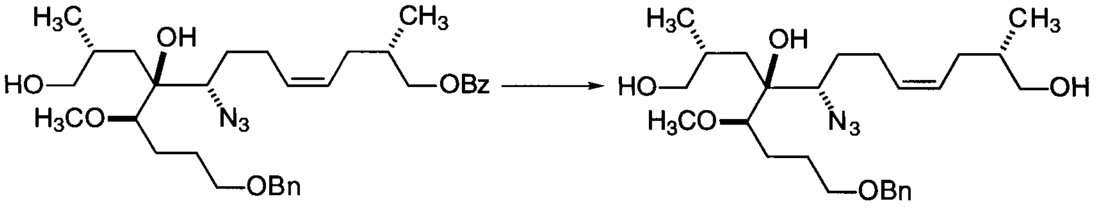
To a 25 mL pear-shaped flask containing a THF solution (6.0 mL) of 95% potassium *t*-butoxide (42.0 mg, 0.351 mmol) at –10 °C was added **13** (204 mg, 0.351 mmol) in one portion, immediately producing an orange heterogeneous solution. This solution was allowed to stir at –10 °C for 1 min, followed by addition of **12** (51 mg, 0.103 mmol) as a solution in THF (1.0 mL). After 5 min, the reaction was diluted with Et_2O (5 mL) and aqueous NH_4Cl (5 mL), discharging the orange color. The layers were separated, and the organic phase washed with H_2O (1 x 10 mL) and brine (1 x 10 mL), followed by back-extraction of the combined aqueous extracts with Et_2O (1 x 25 mL). The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a light yellow oil which as purified via preparative thin layer (silica gel) chromatography (2 x 0.5 mm, 30% EtOAc/hexanes) to give 53 mg (77%) of a single alkene isomer **14** as a colorless oil: R_f = 0.22 in 20% EtOAc/hexanes; $[\alpha]_D^{27}$ +4.5° (c 5.3 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3394, 3009, 2958, 2933, 2876, 2105, 1713, 1601, 1454, 1365, 1315, 1277, 1177, 1112, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 6.4 Hz, 3H), 1.20 (t, J = 6.8 Hz, 1H), 1.46–1.80 (m, 8H), 1.83–1.93 (m, 1H), 1.98–2.32 (m, 7H), 3.23 (t, J = 9.2 Hz, 1H), 3.29–3.32 (m, 1H), 3.37 (s, 3H), 3.39 (s, 3H), 3.46–3.53 (m, 6H), 3.64–3.67 (m, 2H), 3.96 (s, 1H), 4.18 (AB of ABX, J_{AB} = 10.7 Hz, J_{AX} = 6.0 Hz, J_{BX} = 6.0 Hz, Δv_{AB} = 23.3 Hz, 2H), 4.50 (s, 2H), 4.70 (AB_q, J_{AB} = 6.8 Hz, Δv_{AB} = 8.5 Hz, 2H), 5.48 (m, 2H), 7.26–7.57 (m, 7H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 16.7, 19.3, 25.2, 27.3, 27.9, 28.4, 29.2, 30.9, 33.2, 38.6, 59.0, 59.8, 65.8, 67.1, 69.0, 69.2, 70.6, 71.6, 72.8, 74.5, 78.3, 84.7, 95.5, 127.5, 127.6, 128.2, 128.3, 129.5, 130.1, 130.4, 132.8, 138.5, 166.5; HRMS (FAB, Na) *m/z* calcd. for $C_{37}H_{55}N_3O_8Na$ (M^+ + Na) 692.3890, found 692.3900.



14 **14a**

(4Z, 2S, 8S, 9R, 10R)-(+)-8-Azido-13 -benzyloxy-10-methoxy-9-[(2R)-3-hydroxy-2-methylpropyl]-2-methyl-9-hydroxytridec-4-en-1-benzoate ester (14a).

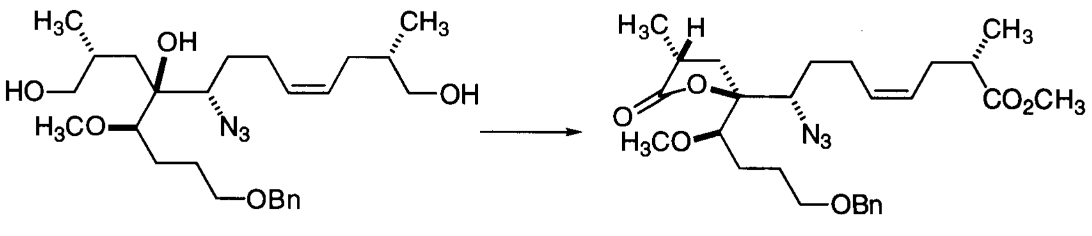
To a 100 mL round bottom flask containing a THF solution (15 mL) of **14** (270 mg, 0.40 mmol) at room temperature was slowly added 37% aqueous HCl (5.0 mL) dropwise over a period of 3 h. The mixture was cooled to 0 °C and diluted with EtOAc (20 mL) and H_2O (10 mL), followed by slow addition of solid $NaHCO_3$ until gas evolution ceased. The layers were then separated, the aqueous phase extracted with EtOAc (2 x 25 mL) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated. The yellow-orange residue was purified via column chromatography (20% Et_2O/CH_2Cl_2) to yield 170 mg (72%) of diol **14a** as a colorless oil: $R_f = 0.37$ in 40% Et_2O/CH_2Cl_2; $[\alpha]_D^{24}$ +5.4° (c 8.4 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3384, 3008, 2959, 2875, 2104, 1713, 1602, 1453, 1388, 1277, 1214, 1111, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 1.55–2.29 (m, 12H), 3.25 (t, $J = 9.2$ Hz, 2H), 3.34 (dd, $J = 7.4, 3.6$ Hz, 2H), 3.40 (s, 3H), 3.43 (dd, $J = 10.8$, 2.8 Hz, 1H), 3.48–3.53 (m, 2H), 3.58–3.62 (m, 1H), 4.18 (AB of ABX, $J_{AB} = 10.9$ Hz, $J_{AX} = 7.3$ Hz, $J_{BX} = 5.9$ Hz, $\Delta v_{AB} = 45.0$ Hz, 2H), 4.52 (s, 2H), 5.42–5.53 (m, 2H), 7.26–7.59 (m, 6H), 8.04–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 19.2, 25.4, 27.3, 27.8, 29.5, 30.4, 30.9, 31.1, 33.3, 39.1, 59.3, 69.0, 69.3, 70.6, 73.0, 78.4, 84.9, 127.6, 127.7, 128.4, 129.5, 130.1, 130.5, 132.8, 138.4, 166.7; HRMS (FAB, Na) *m/z* calcd. for $C_{33}H_{47}N_3O_6Na$ (M^+ + Na) 604.3365, found 604.3352.



14a **15**

(4Z, 2S, 8S, 9R, 10R)-(+)-8-Azido-13 -benzyloxy-10-methoxy-9-[(2R)-3-hydroxy-2-methylpropyl]-2-methyl-9-hydroxytridec-4-en-1-ol (15).

To a 50 mL round bottom flask containing diol **14a** (172 mg, 0.295 mmol) in a solution of THF-MeOH-H_2O (7 : 2 : 1, 17 mL) was added lithium hydroxide monohydrate (124 mg, 2.95 mmol). After stirring at room temperature for 24 h, the reaction was diluted with EtOAc (10 mL) and aqueous NH_4Cl (10 mL). The layers were separated from the biphasic mixture, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated, resulting in a light yellow oil which was purified by column chromatography (40% EtOAc/hexanes) to yield 118 mg (84%) of triol **15** as a clear colorless oil: $R_f = 0.31$ in 50% EtOAc/hexanes; $[\alpha]_D^{23}$ +5.1° (c 5.2 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3376, 2958, 2933, 2874, 2104, 1730, 1456, 1363, 1260, 1197, 1095, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 1.54–2.24 (m, 12H), 3.23 (t, J = 10.0 Hz, 2H), 3.35 (dd, J = 7.2, 2.8 Hz, 1H), 3.40 (s, 3H), 3.45–3.53 (m, 5H), 3.59 (dd, J = 10.4, 3.6 Hz, 1H), 4.52 (s, 2H), 5.02 (s, 1H), 5.40–5.52 (m, 2H), 6.98 (s, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 19.2, 25.3, 27.3, 27.7, 29.4, 30.8, 30.9, 36.1, 39.3, 59.4, 67.7, 68.9, 69.3, 70.5, 72.1, 78.4, 84.7, 127.6, 127.7, 128.4, 129.3, 129.5, 138.2; HRMS (FAB, Na) m/z calcd. for $C_{26}H_{43}N_3O_5Na$ (M^+ + Na) 500.3103, found 500.3118.

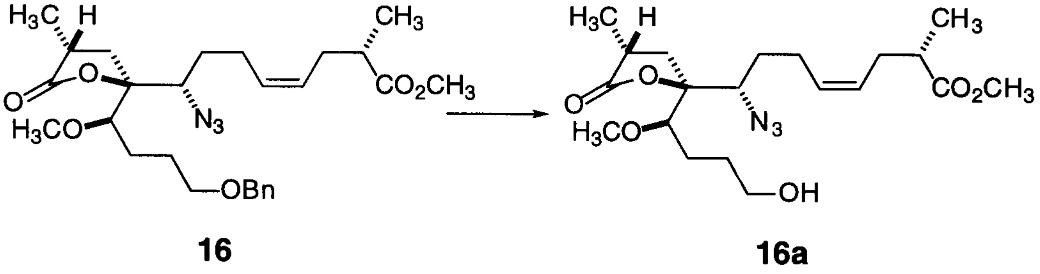


15 **16**

(3R, 5S)-(+)-5-[(1'R)-4'-Benzyloxy-1'-methoxybutyl]-5-[(4"Z, 1"S, 7"S)-methyl-1"-azido-7"-methyloct-4"-en-8"-oate]-3-methyl-(3H)-furan-2-one (16).

To a 15 mL round bottom flask containing a THF solution (3.5 mL) of **15** (25 mg, 0.050 mmol) at 0 °C was added a small scoup of celite followed by Jones' reagent (3.0 M, 10 drops, excess). The reaction was then allowed to stir at 0 °C for 1.5 h at which point an additional 5 drops of Jones' reagent was added. Stirring was continued for 30 min, followed by quenching of the excess Jones' reagent via addition of neat ^{i}PrOH (800 μL, excess) and dilution with Et$_2$O (5 mL). The solution was allowed to stir and warm to room temperature. Once all chromium salts had precipitated from solution, the reaction mixture was filtered through a plug of celite with the aid of EtOAc yielding a bright yellow filtrate. Solvent was removed from the filtrate under reduced pressure and the resultant yellow oil dissolved in Et$_2$O (10 mL). The ethereal solution was cooled to 0 °C and freshly prepared CH$_2$N$_2$ (solution prepared from the reaction between N-nitroso-N-methylurea and 40% KOH in Et$_2$O) was added dropwise until the yellow color of the CH$_2$N$_2$ persisted. Excess CH$_2$N$_2$ was quenched via addition of solid MgSO$_4$, followed by filtration of the reaction mixture and removal of solvent *in vacuo* to yield a yellow oil. Purification of this oil was accomplished via silica gel chromatography (50% EtOAc/hexanes) to yield 16.8 mg (65%) of **16** as a light yellow oil: R_f = 0.69 in 50% EtOAc/hexanes; $[\alpha]_D^{22}$ +4.5° (c 2.2 mg/mL, CHCl$_3$); IR (CHCl$_3$) 2935, 2855, 2105, 1770, 1729, 1602, 1455, 1362, 1279, 1199, 1098, 1006, 909 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.16 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 7.2 Hz, 3H), 1.56–1.88 (m, 4H), 2.19–2.54 (m, 7H), 2.83 (m, 1H), 3.35 (dd, J =

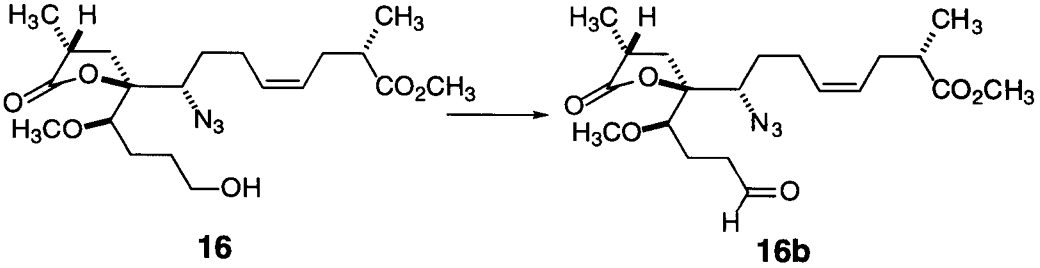
7.4, 4.4 Hz, 1H), 3.44 (s, 3H), 3.47–3.54 (m, 4H), 3.66 (s, 3H), 4.50 (s, 2H), 5.41 (m, 2H), 7.26–7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.7, 24.3, 26.8, 26.9, 28.7, 31.2, 34.3, 34.4, 39.4, 51.5, 59.8, 70.0, 72.9, 83.4, 88.1, 127.5, 127.6, 128.1, 128.3, 129.7, 138.4, 176.5, 179.0; HRMS (FAB, Na) *m/z* calcd. for $C_{27}H_{39}N_3O_6Na$ (M^+ + Na) 524.2739, found 524.2747.



(3R, 5S)-(+)-5-[(1'R)-4'-Hydroxy-1'-methoxybutyl]-5-[(4"Z, 1"S, 7"S)-methyl-1"-azido-7"-methyloct-4"-en-8"-oate]-3-methyl-(3H)-furan-2-one (16a).

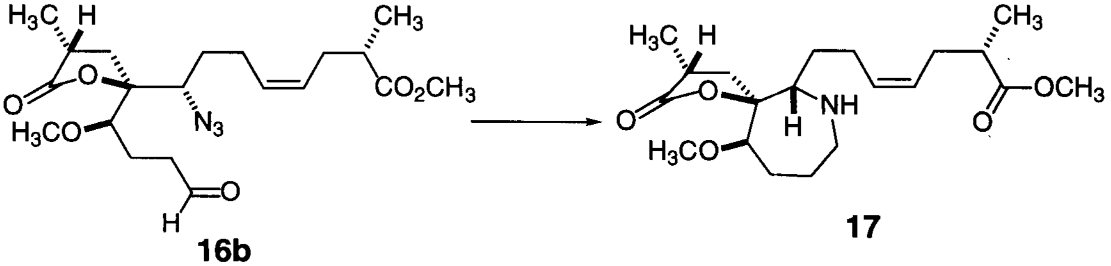
To a 10 mL round bottom flask containing a CH_2Cl_2 solution (1.0 mL) of **16** (40 mg, 0.08 mmol) at –78 °C was slowly added (dropwise over 15 min) a clear colorless solution of BCl_3 (1.0 M in CH_2Cl_2, 240 μL, 0.24 mmol). Dry ice was then removed from the cooling bath, and the solution allowed to slowly warm to –10° C. Temperature was maintained at –10° C for 2.5 h, followed by cooling of the reaction mixture to –78° C and quenching via dropwise addition of neat MeOH (500 μL). Following warming to room temperature, the reaction was partitioned between Et_2O (2 mL) and aqueous NH_4Cl (1 mL) and vigorously stirred for 1 h. The layers were separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic extracts were then dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a yellow oil which was purified via silica gel chromatography (100% EtOAc) to yield 20mg (61%) of alcohol **16a** as a light yellow oil: R_f = 0.36 in 100% EtOAc; $[\alpha]_D^{22}$ +8.7° (c 1.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3510, 2955, 2934, 2105, 1770, 1728, 1458, 1378, 1261, 1216, 1172, 1098, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.54–1.86 (m, 7H), 2.19–2.54 (m, 5H), 2.78–

2.88 (m, 1H), 3.36 (dd, J = 7.0, 4.0 Hz, 1 H), 3.46 (s, 3H), 3.54 (dd, J = 10.8, 2.8 Hz, 1H), 3.65–3.71 (m, 2H), 3.67 (s, 3H), 5.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.7, 24.3, 26.3, 28.8, 29.8, 31.2, 34.4, 39.5, 51.6, 59.7, 62.5, 65.8, 83.6, 88.1, 128.2, 129.7, 176.6, 179.1; HRMS (FAB, Na) *m/z* calcd. for $C_{20}H_{33}N_3O_6Na$ (M^+ + Na) 434.2269, found 434.2277.



(3R, 5S)-(+)-5-[(1'R)-Methoxy-butyr-4'-al]-5-[(4"Z, 1"S, 7"S)-methyl-1"-azido-7"-methyloct-4"-en-8"-oate]-3-methyl-(3H)-furan-2-one (16b).

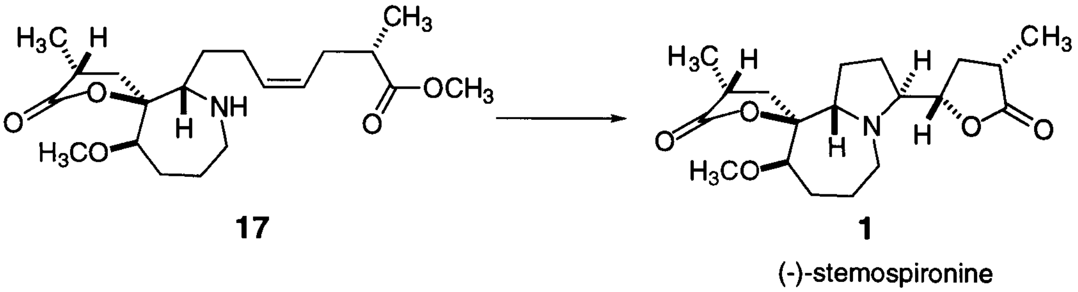
To a CH_2Cl_2 solution (2.5 mL) of alcohol **16a** (12 mg, 0.030 mmol) under argon at 0 °C was added Dess–Martin periodinane (26 mg, 0.060 mmol) followed by slow warming of the reaction mixture to 22 °C. After stirring at room temperature for 2 h, the reaction was complete by tlc. The reaction was quenched via addition of saturated aqueous $Na_2S_2O_3$ (5.0 mL), and diluted with Et_2O (15 mL). This biphasic mixture was vigorously stirred at room temperature for 1 h, the organic phase washed with saturated aqueous $NaHCO_3$ (10 mL). Aqueous extracts were then back extracted with Et_2O (1 x 20 mL), followed by drying of combined organic extracts over Na_2SO_4. Filtration of the drying agent, and removal of solvent *in vacuo* resulted in the isolation of a light yellow oil which was purified via silica gel chromatography (50% EtOAc/hexanes) to yield 7.1 mg (60%) of azido-aldehyde **16b** as a yellowish oil: R_f = 0.37 in 50% EtOAc/hexanes; $[\alpha]_D^{22}$ +10.9° (c 3.5 mg/mL, $CHCl_3$); IR ($CHCl_3$) 2996, 2934, 2876, 2604, 2459, 2105, 1950, 1774, 1729, 1489, 1448, 1383, 1352, 1241, 1125, 933, 841 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J = 6.8 Hz, 2H), 1.30 (d, J = 7.6 Hz, 3H), 1.59–1.68 (m, 2H), 1.73–1.94 (m, 5H), 2.18–2.54 (m, 7H), 2.64 (t, J = 7.2 Hz, 2H), 2.76–2.86 (m, 1H), 3.34 (dd, J = 7.2, 4.4 Hz, 1H), 3.42 (s, 3H), 3.54 (dd, J = 10.8, 2.4 Hz, 1H), 3.66 (s, 3H), 5.42 (m, 2H), 9.78 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 16.7, 21.9, 24.3, 28.8, 31.2, 34.1, 34.3, 39.4, 40.2, 51.6, 59.7, 65.3, 82.7, 88.1, 128.3, 129.6, 129.7, 176.5, 178.8; HRMS (FAB, Na) *m/z* calcd. for $C_{20}H_{31}N_3O_6Na$ (M^+ + Na) 432.2112, found 432.2119.



(3R, 5S, 6S, 11R)-(-)-1-Oxa-2-oxo-3-methyl-6-[(6'S)-methyl-6'-methylhepta-3'-en-7'-oate]-11-methoxy-7-azaspiro[4.6]undecane (17).

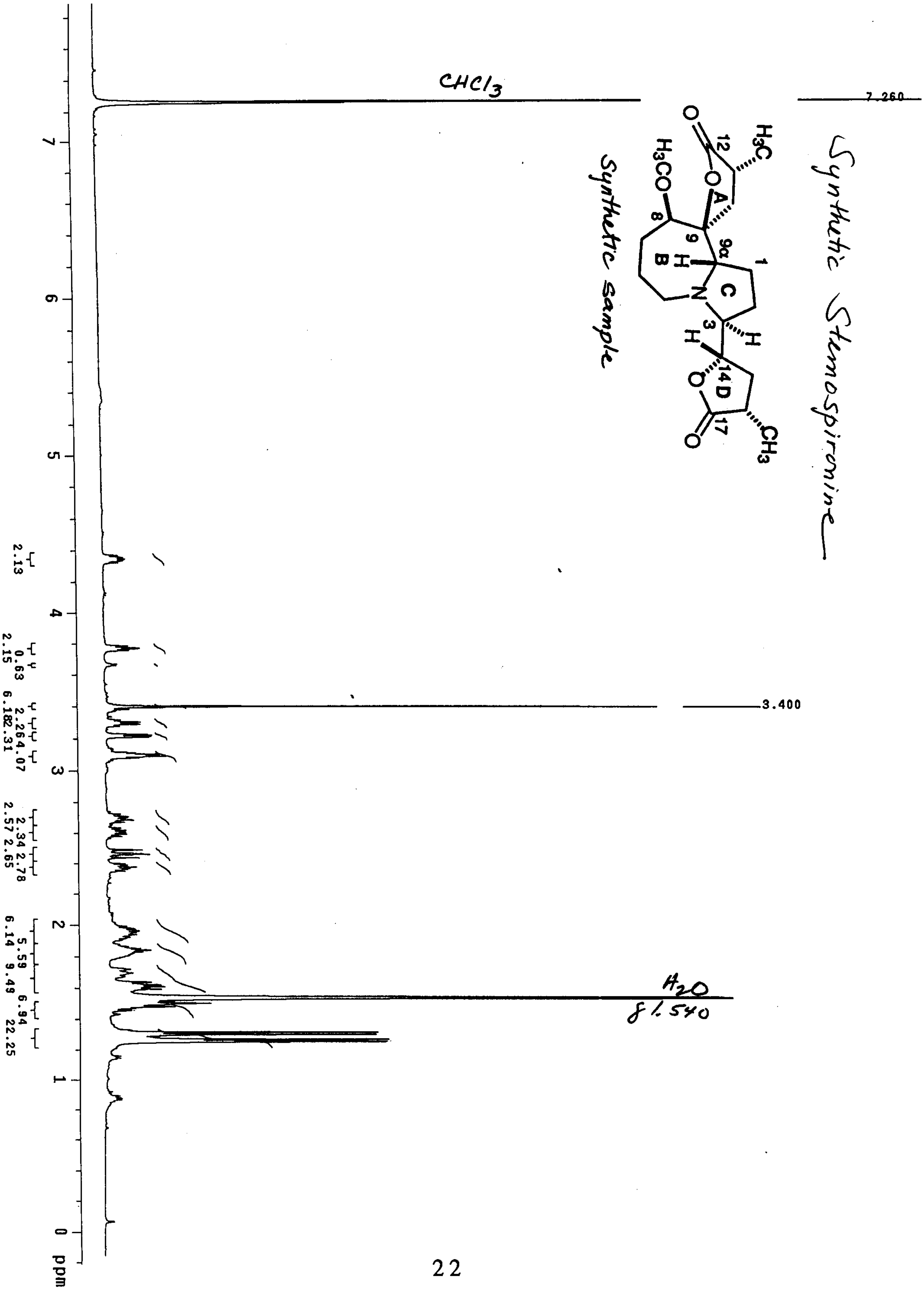
To a 50 mL pear-shaped flask under argon at room temperature containing azide **16b** (11 mg, 0.030 mmol) in THF (2.5 mL) was added solid PPh_3 (33 mg, 0.13 mmol). The reaction was sealed under argon with a glass stopper and allowed to stir at room temperature for 16 h at which point all of starting aldehyde **16b** had been consumed. $NaBH_4$ (3.0 mg, 0.080 mmol) and MeOH (3 μL, 0.08 mmol) were added. The resultant yellow solution was stirred at room temperature for 10 min. The entire reaction mixture was applied to a preparative thin layer chromatography plate (1/2 x 0.5 mm, 30% THF/EtOAc) to yield 6.0 mg (60%) of azepine **17** as a yellowish oil: R_f = 0.48 in 30% THF/CH_2Cl_2; $[\alpha]_D^{25}$ –7.7° (c 1.0 mg/mL, $CHCl_3$); IR ($CHCl_3$) 2960, 2929, 2855, 1760, 1727, 1602, 1461, 1261, 1198, 1101, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.42–1.63 (m, 4H), 1.81–1.92 (m, 4H), 2.10–2.28 (m, 3H), 2.34–2.87 (m, 6H), 3.10–3.15 (m, 1H), 3.24 (d, J = 8.4 Hz, 1H), 3.40 (s, 3H), 3.66 (s, 3H), 5.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 17.0, 24.4, 24.6, 27.0, 29.4, 31.2, 34.3, 35.7, 39.5, 49.2, 51.6, 57.9, 63.2, 87.1, 89.3, 127.4, 130.6, 176.6, 179.7; MS (DCI, NH_3) *m/z* (relative intensity) 336 (89), 248 (49), 236 (48), 167

(54), 149 (100), 135 (42), 111 (62), 109 (51), 97 (86), 95 (57), 85 (58), 83 (73), 82 (70), 71 (78); HRMS *m/z* calcd. for $C_{20}H_{34}NO_5$ (M^+ + 1) 368.2438, found 368.2443.



(–)-Stemospironine (1).

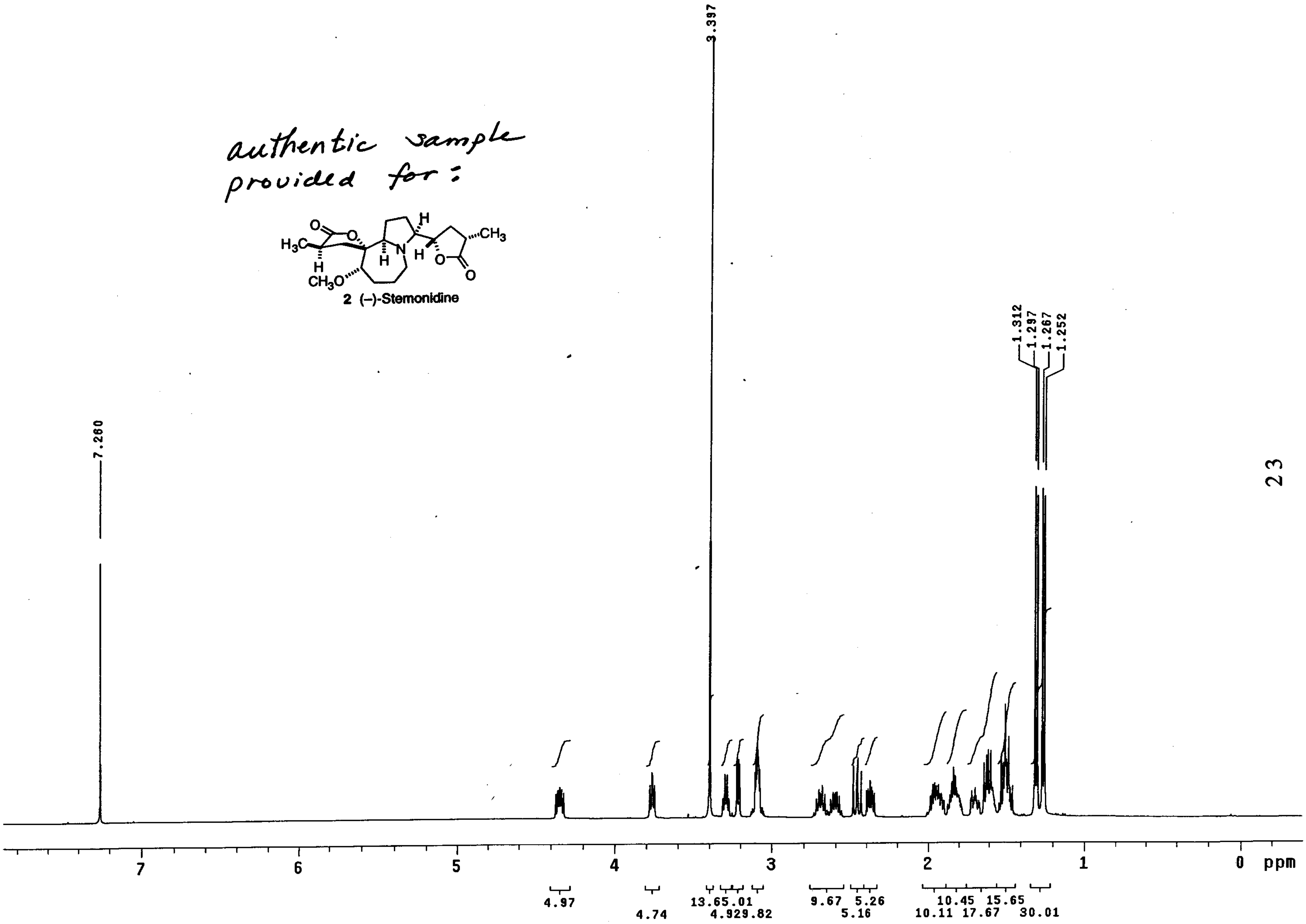
To an ethereal CH_2Cl_2 solution (1 : 2, 300 μL) containing azepine **17** (3.5 mg, 0.009 mmol) under argon at room temperature was added iodine (2.9 mg, 0.014 mmol). The mixture was sealed under argon with a glass stopper and covered with foil to exclude light. After stirring at room temperature for 72 h, the reaction was quenched via addition of 10% aqueous $NaHSO_3$ (1.0 mL) with vigorous stirring. The layers were separated, and the organic phase was applied directly to a silica gel thin layer chromatography plate (1/2 x 0.25 mm, 10% THF/CH_2Cl_2) to yield 1 mg (30%) of **1** as a light yellow oil: R_f = 0.67 in 30% THF/CH_2Cl_2; $[\alpha]_D^{25}$ –7.5° (c 0.8 mg/mL, $CHCl_3$); IR ($CHCl_3$) 3023, 2929, 2854, 1764, 1523, 1425, 1230, 1201, 1017, 928 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, *J* = 7.0 Hz, 3H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.45–1.52 (m, 3H), 1.58–1.64 (m, 2H), 1.68–1.73 (m, 1H), 1.77–1.87 (m, 2H), 1.89–1.99 (m, 2H), 2.38 (ddd, *J* = 12.2, 7.7, 5.0 Hz, 1H), 2.46 (dd, *J* = 14.0, 11.0 Hz, 1H), 2.56–2.65 (m, 1H), 2.65–2.74 (m, 1H), 3.05–3.11 (m, 2H), 3.21 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.30 (dd, *J* = 13.5, 6.5 Hz, 1H), 3.77 (m, 1H), 4.35 (ddd, *J* = 12.0, 6.5, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 90.5, 85.3, 80.0, 67.7, 63.1, 58.0, 48.9, 35.7, 35.0, 34.6, 27.0, 26.5, 25.7, 22.4, 17.5, 14.8; MS (DCI, NH_3) *m/z* (relative intensity) 320 (34), 252 (100), 182 (29), 149 (57), 97 (42), 95 (32), 83 (36), 71 (34); HRMS *m/z* calcd. for $C_{19}H_{30}NO_5$ (M^+ +1) 352.2125, found 352.2118.



Synthetic Stemospironine

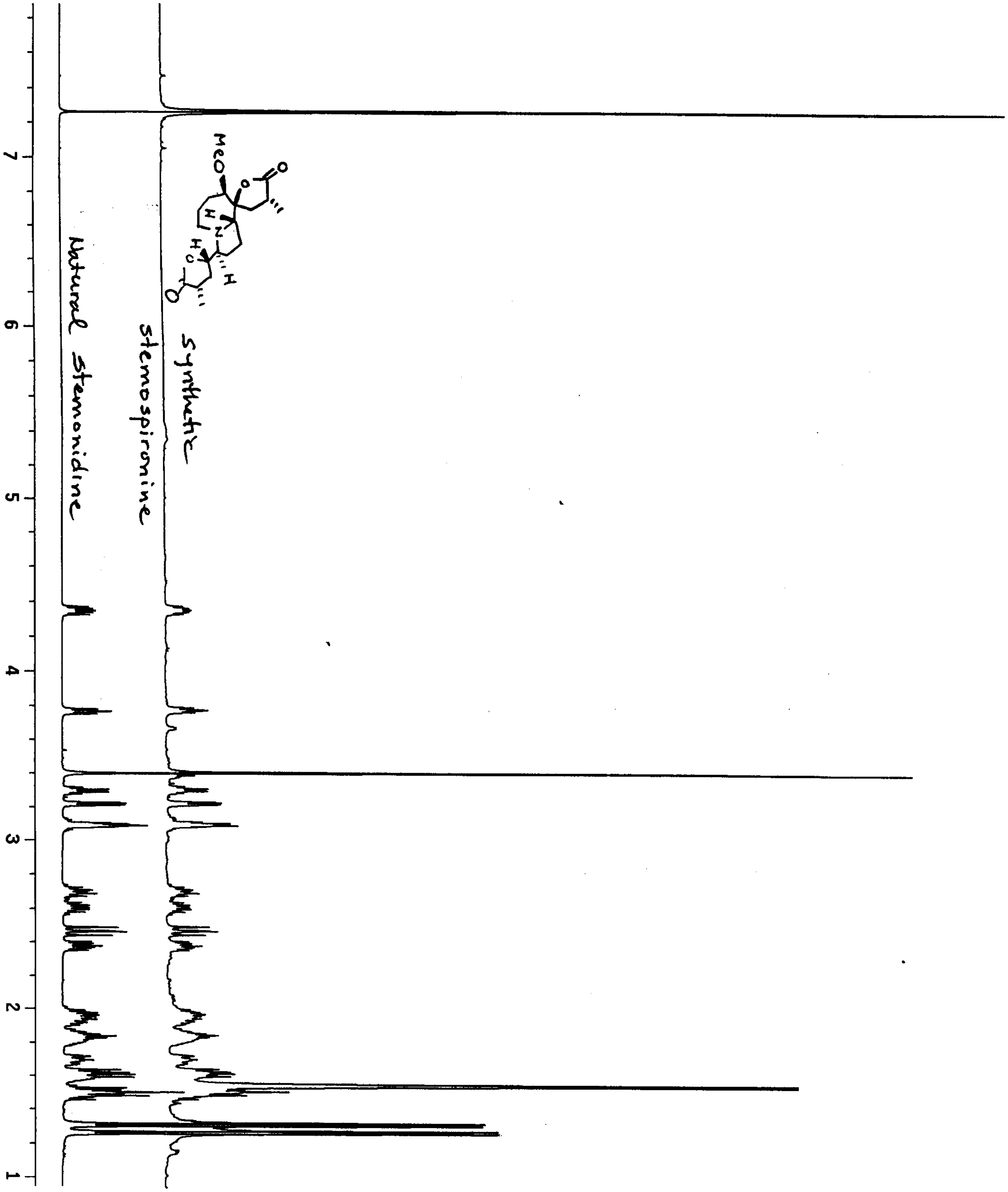
Synthetic sample

Stemonidine ?



authentic sample
provided for:

2 (–)-Stemonidine


synthetic
stemospironine
Natural stemonidine
MeO
O
H
N
7
6
5
4
3
2
1