Total Synthesis of Mycalamide A and 7-*epi*-Mycalamide A

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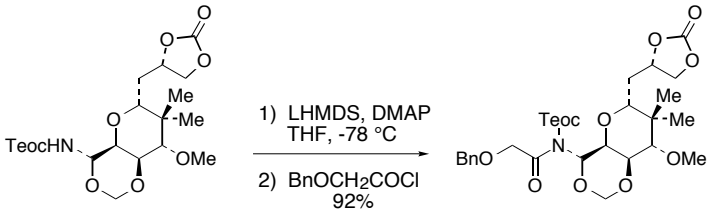
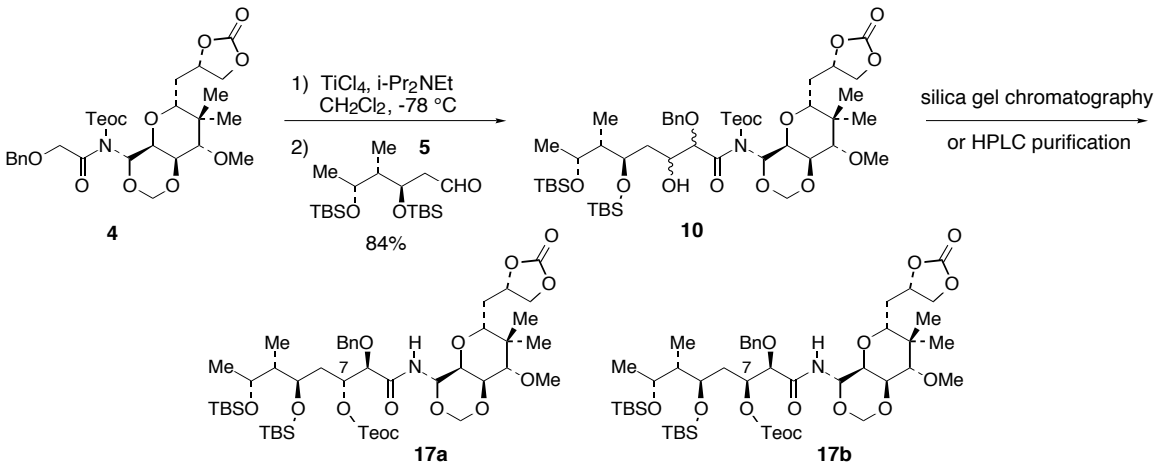
SUPPORTING INFORMATION

Experimental procedures for the synthesis of **4**-**19**, epi-mycalamide A, and mycalamide A, plus tabulated spectroscopic data (18 pages). This material is available free of charge via the Internet at http://pubs.acs.org. See any current masthead page for ordering information.



2 **4**

***N*-Benzyloxyacetyl-*N*-(2-trimethylsilylethoxycarbonyl)-mycalamine (4)**. To a -78°C solution of carbamate **2**[1] (0.217 g, 0.47 mmol) in THF (6 mL) was added DMAP (0.104 g, 0.85 mmol) followed by a solution of LHMDS in THF (0.59 mL, 1.0 M, 0.59 mmol). The resulting yellow solution was stirred for 30 min, at which time benzyloxyacetyl chloride (0.112 mL, 0.71 mmol) was added dropwise. This mixture was stirred for 30 min at -78 °C, warmed to 0 °C, stirred an additional 30 min, then poured into a mixture of EtOAc (20 mL) and saturated $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was further extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product by flash chromatography (40% EtOAc/hexanes) provided imide **4** (0.265 g, 92%) as a clear oil: $[\alpha]_D^{26}$ +76.4° (*c* 3.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.38 (m, 5 H), 6.23 (d, *J* = 10.4 Hz, 1 H), 5.09 (A of AB, J_{AB} = 6.8 Hz, 1 H), 4.96 (B of AB, J_{AB} = 6.8 Hz, 1 H), 4.75 (dd, *J* = 10.4, 7.6 Hz, 1 H), 4.64 (A of AB, J_{AB} = 9.6 Hz, 1 H), 4.56 (B of AB, J_{AB} = 9.6 Hz, 1 H), 4.53 (m, 4 H), 4.32 (m, 3 H), 3.97 (dd, *J* = 7.6, 5.8 Hz, 1 H), 3.58 (s, 3 H), 3.47 (d, *J* = 5.8 Hz, 1 H). 3.35 (br d, *J* = 5.6 Hz, 1 H), 1.85 (m, 1 H), 1.68 (dd, *J* = 14.0, 8.4 Hz, 1 H), 1.09 (m, 2 H), 0.99 (s, 3 H), 0.87 (s, 3 H), 0.06 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 154.9, 153.0, 136.9, 128.5, 128.1, 127.9, 87.4, 78.7, 77.1, 74.9, 74.6, 74.5, 73.5, 71.3, 69.3, 67.4, 66.9, 61.8, 41.3, 33.7, 22.9, 17.4, 12.9, -1.7; IR (thin film) 2956, 2899, 2884, 1800, 1742, 1703,1388, 1174, 1033; HRMS calcd for $C_{29}H_{47}N_2O_{11}Si$ ($M^+ + NH_4^+$) 627.2949, found 627.2980.



Aldol Reaction of 4 and 5. To a -78 °C solution of imide **4** (0.131 g, 0.215 mmol) and activated 4 Å mol. sieves (0.050 g) in CH_2Cl_2 (2.5 mL) was added a solution of $TiCl_4$ in CH_2Cl_2. (0.215 mL, 1.0 M, 0.215 mmol). The mixture was stirred for 2 min, then diisopropylethylamine (0.045 mL, 0.258 mmol) was added, immediately producing a dark purple solution.[2,3] After 50 min, a solution of aldehyde **5**[4] (0.105 g, 0.280 mmol) in CH_2Cl_2 (0.5 mL) was added and the resulting solution was stirred for 2.5 hours at -78 °C. MeOH (0.5 mL) was added to quench the reaction, and after the purple color had dissipated the reaction mixture was immediately poured into a biphasic solution containing EtOAc (15 mL) and pH 7 buffer (25 mL). The phases were separated and the aqueous phase was further extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with pH 7 buffer (15 mL), H_2O (10 mL), and brine (10 mL), then dried (Na_2SO_4) and concentrated. Purification of the crude product by flash chromatography (25% EtOAc/hexanes) using Davisil Grade 643, Type 150A, 200-425 mesh silica gel (Fisher) provided a mixture of aldol diastereomers **10a-d** (0.146 g, 69%) in a 5:4:1:1 ratio, in addition to recovered imide **4** (39 mg, 29%). Recycle of recovered **4** using the procedure described above to provide additional amounts of the aldol products **10a-d** (32 mg, 15%). Using this set of purification conditions, a mixture of aldols **10a,c,d** (ca. 5:1:1 ratio) was separated from aldol **10b** (ca. 90% purity). Attempts to separate the aldol products via silica gel chromatography resulted in substantial loss of material owing to the facile N → O migration of the Teoc protecting group. Attempted separation of the aldols via HPLC resulted in complete N → O migration of the Teoc group, giving **17a** and **17b** as the major products in a 5 : 4 ratio. Therefore, the mixture of aldols was used without purification in all subsequent experiments.

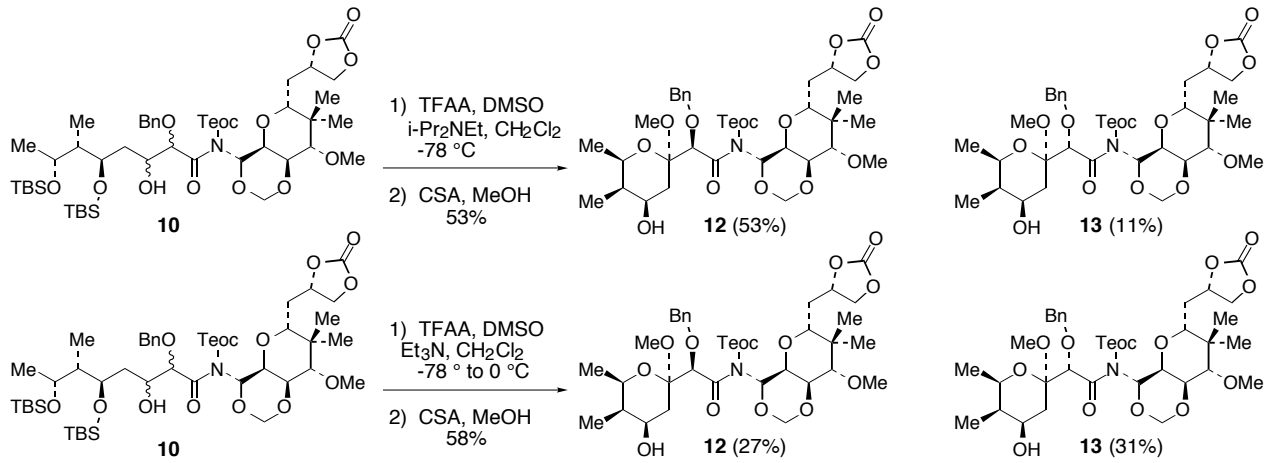
Partial data for **10a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 - 7.27 (m, 5 H), 6.10 (d, J = 10.3 Hz, 1 H), 5.06 (A of AB, J_{AB} = 6.8 Hz, 1 H), 4.92 (B of AB, J_{AB} = 6.6 Hz, 1 H), 4.66 - 4.60 (m, 4 H), 4.54 (t,

J = 7.9 Hz, 1 H), 4.48 (d, J = 11.7 Hz, 1 H), 4.31 - 4.17 (m, 4 H), 4.03 - 4.00 (m, 1 H), 3.97 (dd, J = 8.3, 5.4 Hz, 1 H), 3.58 (s, 3 H), 3.47 (d, J = 10.3 Hz, 1 H), 3.39 (d, J = 10.3 Hz, 1 H), 2.88 (d, J = 5.3 Hz, 1 H), 1.89 (m, 1 H), 1.71 - 1.62 (m, 3 H), 1.40 (t, J = 11.5 Hz, 1 H), 1.13 (d, J = 6.1 Hz, 3 H), 1.08 - 0.85 (m, 8 H), 1.00 (s, 3 H), 0.89 (s, 9 H), 0.88 (s, 9 H), 0.09 - 0.05 (m, 21 H).

Data for **17a** and **17b**, products of N → O Teoc isomerization of **10a** and **10b**. The stereochemistry at C(7) of **17a** and **17b** has not been assigned rigorously.

^{1}H NMR data for **17a**: (500 MHz, $CDCl_3$) δ 7.38 - 7.33 (m, 5 H), 7.17 (d, J = 9.8 Hz, 1 H), 5.66 (t, J = 10.0 Hz, 1 H), 5.39 (d, J = 9.8 Hz, 1 H), 5.09 (d, J = 6.8 Hz, 1 H), 4.84 (d, J = 7.0 Hz, 2 H), 4.77 (A of AB, J_{AB} = 11.0 Hz, 1 H), 4.61 (t, J = 8.1 Hz, 1 H), 4.53 (B of AB, J_{AB} = 11.0 Hz, 1 H), 4.23 - 4.18 (m, 3 H), 4.07 (d, J = 2.3 Hz, 1 H), 3.93 (dd, J = 8.2, 6.7 Hz, 1 H), 3.81 (dd, J = 10.0, 7.0 Hz, 2 H), 3.56 (s, 3 H), 3.46 (dd, J = 8.4, 6.3 Hz, 1 H), 3.42 (d, J = 10.5 Hz, 1 H), 3.19 (d, J = 10.9 Hz, 1 H), 2.02 - 1.96 (m, 1 H), 1.86 (dd, J = 14.4, 9.8 Hz, 1 H), 1.71 - 1.63 (m, 3 H), 1.14 (d, J = 6.0 Hz, 3 H), 1.08 - 1.00 (m, 2 H), 1.00 (s, 3 H), 0.93 - 0.86 (m, 6 H), 0.92 (s, 9 H), 0.88 (s, 9 H), 0.09 - 0.05 (m, 21 H).

^{1}H NMR data for **17b**: (500 MHz, $CDCl_3$) δ 7.39 - 7.33 (m, 5 H), 6.89 (d, J = 9.1 Hz, 1 H), 5.63 (t, J = 9.5 Hz, 1 H), 5.23 - 5.21 (m, 1 H), 5.11 (A of AB, J_{AB} = 6.8 Hz, 1 H), 4.89 (B of AB, J_{AB} = 6.8 Hz, 1 H), 4.71 (d, J = 5.6 Hz, 2 H), 4.65 (A of AB, J_{AB} = 10.9 Hz, 1 H), 4.50 (B of AB, J_{AB} = 10.9 Hz, 1 H), 4.24 - 4.19 (m, 3 H), 4.07 (d, J = 2.3 Hz, 1 H), 3.97 (dd, J = 13.0, 9.0 Hz, 1 H), 3.79 - 3.78 (m, 2 H), 3.61 - 3.57 (m, 1 H), 3.59 (s, 3 H), 3.44 (d, J = 10.5 Hz, 1 H), 3.31 (d, J = 10.2 Hz, 1 H), 1.91 - 1.83 (m, 3 H), 1.72 - 1.67 (m, 2 H), 1.09 (d, J = 6.1 Hz, 3 H), 1.06 - 1.02 (m, 2 H), 1.03 (s, 3 H), 0.93 - 0.84 (m, 6 H), 0.93 (s, 9 H), 0.89 (s, 9 H), 0.09 - 0.05 (m, 21 H).



Methyl Ketals 12 and 13.

Method A: Oxidation of 10a-10b without Epimerization of C(7). To a -78 °C solution of DMSO (0.085 mL, 1.20 mmol) in CH_2Cl_2 (0.5 mL) was added TFAA (0.112 mL, 0.80 mmol) dropwise over 1 min.[5] This mixture was stirred for 25 min, then a solution of aldol products **10** (39 mg, 0.040 mmol; a 5 : 4 : 1 : 1 mixture of the four diastereomers) in CH_2Cl_2 (0.4 mL) was added dropwise. This mixture was stirred for 4 h at -78 °C, then diisopropylethylamine (0.28 mL, 1.40 mmol) was added. The solution was stirred for 30 min at -78 °C, then warmed to 0 °C and immediately poured into a flask containing pH 7 buffer (30 mL) and EtOAc (15 mL). The organic phase was removed and the aqueous phase was further extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with pH 7 buffer (10 mL), H_2O (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated, providing the intermediate (crude) β-keto imides (27 mg) in a 4.5 : 1 ratio. Due to the instability of the β-keto imides, they were immediately used without further purification.

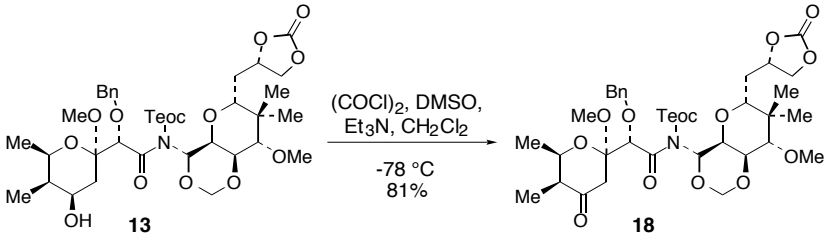
To a solution of the crude β-keto imides in MeOH (2 mL) was added a solution of CSA in MeOH (0.040 mL, 0.1 M, 0.0040 mmol). The solution was stirred for 8 h, then poured into a mixture of half-saturated $NaHCO_3$ (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous layer was further extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude product by flash chromatography (55% EtOAc/hexanes) provided **13** (4.5 mg, 11%) followed by the 7-*epi*- diastereomer **12** (2.3 mg, 53%) as clear oils.

Data for **12**: $[\alpha]_D^{26}$ +53° (*c* 0.83, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.36 (m, 5 H), 6.06 (d, *J* = 10.5 Hz, 1 H), 5.13 (s, 1 H), 5.06 (A of AB, J_{AB} = 6.5 Hz, 1 H), 4.96 (B of AB, J_{AB} = 6.5 Hz, 1 H), 4.78 (A of AB, J_{AB} = 11.0 Hz, 1 H), 4.68 (B of AB, J_{AB} = 11.0 Hz, 1 H), 4.55 (m, 1 H), 4.48-4.53 (m, 1 H), 4.28-4.38 (m, 4 H), 4.12 (m, 1 H), 3.89 (dd, *J* = 5.0, 4.0 Hz, 1 H), 3.82 (dq, *J* = 2.0, 7.0 Hz, 1 H), 3.57 (s, 3 H), 3.45 (d, *J* = 10.5 Hz, 1 H), 3.40 (d, *J* = 10.5 Hz, 1 H), 3.24 (s, 3 H), 1.92-2.05 (m, 2 H), 1.85 (m, 2 H), 1.64 (m, 1 H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.10 (m, 2 H), 0.98 (s, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.87 (s, 3 H), 0.08 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 154.9, 153.6, 137.4, 128.5, 128.1, 127.8, 102.2, 87.7, 80.2, 78.9, 77.8, 74.6, 74.4, 74.3, 74.1, 69.5, 68.7, 67.7, 67.2, 67.0, 61.8, 49.2, 41.2, 38.6, 33.9, 31.5, 23.1, 18.0, 17.5, 13.2, 3.8, -1.6; IR (thin film) 3200-3700 (br s), 2973, 2900, 1798, 1732, 1715, 1455, 1383, 1175, 1090, 1030; FAB HRMS calcd for $C_{37}H_{57}NO_{12}SiNa$ (M^+ + Na) 790.3446, found 790.3440.

Data for **13:** $[\alpha]_D^{26}$ +87° (*c* 0.81, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5 H), 6.02 (d, *J* = 10 Hz, 1 H), 5.31 (s, 1 H), 5.05 (A of AB, J_{AB} = 7 Hz, 1 H), 4.98 (B of AB, J_{AB} = 7 Hz, 1 H), 4.94 (dd, *J* = 8, 10 Hz, 1 H), 4.74 (m, 2 H), 4.72 (A of AB, J_{AB} = 12 Hz, 1 H), 4.41 (B of AB, J_{AB} = 12 Hz, 1 H), 4.31 (dd, *J* = 8, 10 Hz, 1 H), 4.21 (m, 2 H), 4.11 (m, 1 H), 4.03 (m, 1 H), 3.80 (dq, *J* = 2.5, 6.5 Hz, 1 H), 3.57 (s, 3 H), 3.37 (d, *J* = 10 Hz, 1 H), 3.34 (d, *J* = 9 Hz, 1 H), 2.94 (s, 3 H), 1.98 (m, 2 H), 1.77 (m, 2 H), 1.40 (m, 1 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.01 (s, 3 H), 0.90-1.02 (m, 2 H), 0.90 (s, 3 H), 0.80 (d, *J* = 7 Hz, 3 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 154.9, 154.2, 137.2, 128.5, 128.4, 128.0, 101.0, 86.7, 79.6, 79.3, 76.4, 74.7, 74.2, 73.8, 72.3, 69.8, 68.6, 68.5, 67.0, 66.6, 61.8, 47.7, 40.9, 38.7, 33.9, 32.3, 23.2, 17.7, 17.3, 13.4, 3.5, -1.7; IR (thin film) 3200-3700 (br s), 2972, 2899, 1803, 1743, 1697, 1455, 1382, 1308, 1177, 1091, 1064, 1033; FAB HRMS calcd for $C_{37}H_{57}NO_{14}SiNa$ (M^+ + Na) 790.3446, found 790.3446.

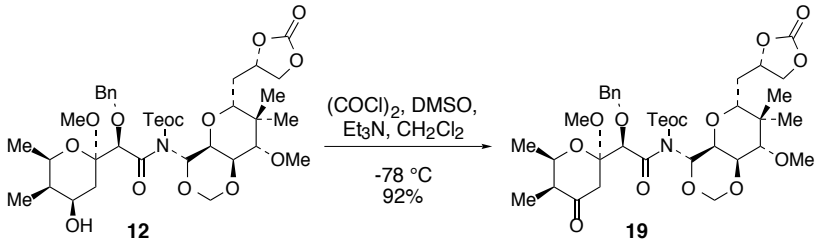
Method B. Oxidation of 10a-10b with Epimerization of C(7). To a -78 °C solution of DMSO (0.058 mL, 0.822 mmol) in CH_2Cl_2 (0.9 mL) was added TFAA (0.078 mL, 0.549 mmol) dropwise over 1 min.[10] After 25 min, a solution of aldols **10a-d** (27 mg, 0.027 mmol, a 5 : 4 : 1 : 1 mixture of the four isomers) in CH_2Cl_2 (0.4 mL) was added dropwise. The mixture was stirred for 4 h at -78 °C, then triethylamine (0.19 mL, 1.08 mmol) was added. The solution was stirred for 30 min at -78 °C, then warmed to 0 °C and stirred for an additional 30 min at 0 °C. The solution was then poured into a flask containing pH

7 buffer (30 mL) and EtOAc (15 mL). The organic phase was removed and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with pH 7 buffer (10 mL), H_2O (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated, affording a 1.1 : 1 mixture of intermediate β-keto imides which were converted to the methyl ketals **12** (5.7 mg, 27%) and **13** (6.3 mg, 31%) using the procedure described in Method A.

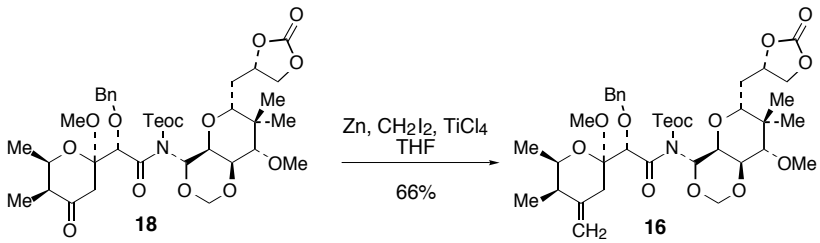


4-Oxo-7-benzyloxy-N(9)-2-trimethylsilylethoxycarbonyl-O(17)-O(18)-carbonyl-mycalamide A (18). To a -78 °C solution of DMSO (0.022 mL, 0.31 mmol) in CH_2Cl_2 (0.8 mL) was added oxalyl chloride (0.018 mL, 0.21 mmol). Fifteen minutes later, a solution of alcohol **13** (8 mg, 0.010 mmol) in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred for an additional 20 min, then Et_3N (0.059 mL, 0.42 mmol) was added dropwise.[5] The solution was stirred at -78 °C for 1 h, slowly warmed to 0 °C over 10 min, and then stirred for 30 min at 0 °C. The reaction was poured into a mixture of pH 7 buffer (20 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with pH 7 buffer (10 mL), H_2O (10 mL), and brine (10 mL), dried (Na_2SO_4), and concentrated to afford a crude yellow oil. Purification of the crude product by flash chromatography (75% Et_2O/hexanes) provided ketone **18** (6.5 mg, 81%) as a clear oil: $[\alpha]_D^{26}$ +85° (*c* 0.53, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5 H), 5.98 (d, *J* = 10.0 Hz, 1 H), 5.34 (s, 1 H), 5.03 (A of AB, J_{AB} = 6.8 Hz, 1 H), 5.00 (m, 1 H), 4.99 (B of AB, J_{AB} = 6.8 Hz, 1 H), 4.75 (A of AB, J_{AB} = 12.0 Hz, 1 H), 4.63 (m, 2 H), 4.47 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.33 (dd, *J* = 7.6, 10.0 Hz, 1 H), 4.22 (m, 2 H), 4.12 (dq, *J* = 3.2, 6.4 Hz, 1 H), 4.03 (dd, *J* = 6.0, 8.4 Hz, 1 H), 3.58 (s, 3 H), 3.35 (d, *J* = 10.0 Hz, 1 H), 3.31 (d, *J* = 9.2 Hz, 1 H), 3.00 (s, 3 H), 2.75 (A of AB, J_{AB} = 11.0 Hz, 1 H), 2.56 (B of AB, J_{AB} = 11.0 Hz, 1 H), 2.28 (dq, *J* = 3.2, 7.2 Hz, 1 H), 1.99 (m, 1 H), 1.76 (m, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.07 (d, *J* = 7.2 Hz, 3 H), 1.01 (s, 3 H), 0.86-1.00 (m, 2 H), 0.90 (s, 3 H), 0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 172.3, 154.7, 154.4, 136.9, 128.5, 128.4, 128.1, 102.3, 87.1,

79.8, 76.0, 74.9, 74.4, 73.9, 72.4, 69.5, 68.3, 68.2, 66.8, 61.8, 48.7, 48.2, 41.7, 40.9, 33.7, 30.3, 23.2, 17.5, 16.8, 13.5, 9.8, -1.7; IR (thin film) 2954, 2905, 1809, 1745, 1716, 1695, 1466, 1455, 1384, 1310, 1169, 1090, 1034; FAB HRMS calcd for $C_{37}H_{55}NO_{14}SiNa$ (M^+ + Na) 788.3289, found 788.3318.

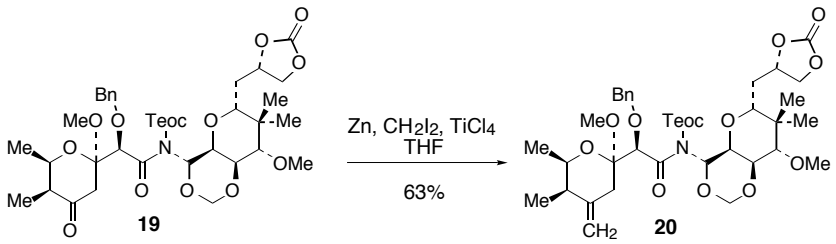


4-Oxo-7-benzyloxy-N(9)-2-trimethylsilylethoxycarbonyl-O(17)-O(18)-carbonyl-7-*epi*-mycalamide A (19). Oxidation of **12** (12 mg, 0.016 mmol) using the procedure described for the synthesis of **18** provided ketone **19** (11 mg, 92%) as a clear oil: $[\alpha]_D^{26}$ +61° (*c* 1.00, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.38 (m, 5 H), 6.01 (d, *J* = 10.5 Hz, 1 H), 5.31 (s, 1 H), 5.06 (A of AB, J_{AB} = 7.0 Hz, 1 H), 4.94 (B of AB, J_{AB} = 7.0 Hz, 1 H), 4.86 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.75 (B of AB, J_{AB} = 11.3 Hz, 1 H), 4.57 (dd, *J* = 7.5, 6.0 Hz, 1 H), 4.48 (m, 1 H), 4.28-4.38 (m, 4 H), 4.13 (m, 1 H), 3.89 (dd, *J* = 5.0, 9.0 Hz, 1 H), 3.58 (s, 3 H), 3.46 (d, *J* = 10.5 Hz, 1 H), 3.41 (d, *J* = 10.5 Hz, 1 H), 3.27 (s, 3 H), 3.23 (A of AB, J_{AB} = 15.5 Hz, 1 H), 2.53 (B of AB, J_{AB} = 15.5 Hz, 1 H), 2.33 (dq, *J* = 2.8, 7.0 Hz, 1 H), 1.85 (m, 1 H), 1.28 (d, *J* = 6.5 Hz, 3 H), 1.16 (d, *J* = 7.0 Hz, 3 H), 1.13 (m, 2 H), 0.99 (s, 3 H), 0.87 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.9, 173.8, 154.9, 153.6, 137.1, 128.6, 128.2, 127.7, 103.6, 87.7, 79.6, 78.6, 77.8, 74.6, 74.4, 74.3, 74.1, 69.5, 68.1, 67.3, 67.2, 61.9, 49.7, 48.5, 41.4, 41.3, 34.0, 23.0, 17.5, 17.1, 13.0, 10.0, -1.6; IR (thin film) 2954, 1809, 1716, 1384, 1309, 1250, 1175, 1091, 1034, 860, 839, 734; FAB HRMS calcd for $C_{37}H_{55}NO_{14}SiNa$ (M^+ + Na) 788.3289, found 788.3285.

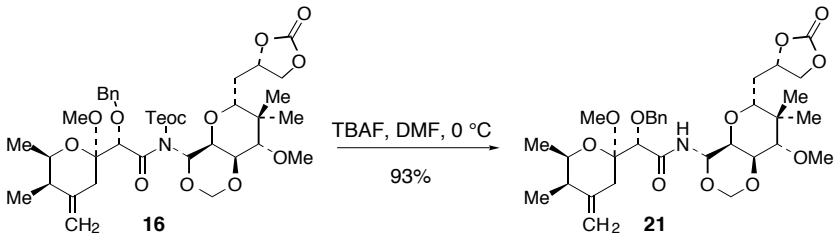


7-Benzyloxy-N(9)-2-trimethylsilylethoxycarbonyl-O(17)-O(18)-carbonyl mycalamide A (16). To a rapidly stirred heterogeneous solution of Zn (23 mg, 0.35 mmol) in rigorously

deoxygenated THF (0.6 mL) was added CH_2I_2 (0.015 mL, 0.19 mmol) dropwise.[6] The resulting solution was stirred for 45 min, then cooled to 0 °C. A solution of $TiCl_4$ in CH_2Cl_2 (0.035 mL, 1.0 M, 0.035 mmol) was added via syringe with the needle tip placed in the THF solution of the zinc carbenoid. After 5 min, the resulting dark purple solution was warmed to 23 °C and stirred for 30 min. A solution of ketone **18** (5.3 mg, 0.007 mmol) in deoxygenated THF (0.2 mL) was added dropwise, with the solution maintaining a dark purple color. After 10 min, the reaction was added via syringe to a mixture of half saturated $NaHCO_3$ (10 mL) and EtOAc (10 mL). The aqueous phase was separated and further extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to afford a crude brown oil. Purification of the crude product by flash chromatography (30% EtOAc/hexanes) provided alkene **16** (3.5 mg, 66%) as a clear oil; $[\alpha]_D^{26}$ +76° (*c* 0.25, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.43 (m, 5 H), 6.01 (d, *J* = 10.0 Hz, 1 H), 5.33 (s, 1 H), 5.04 (A of AB, J_{AB} = 7.0 Hz, 1 H), 4.99 (B of AB, J_{AB} = 7.0 Hz, 1 H), 4.97-5.01 (m, 1 H), 4.80 (br s, 1 H), 4.76 (A of AB, J_{AB} = 12.0 Hz, 1 H), 4.72 (br s, 1 H), 4.70 (m, 1 H), 4.64-4.69 (m, 1 H), 4.43 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.32 (dd, *J* = 8.0, 10.0 Hz, 1 H), 4.21 (m, 2 H), 4.03 (dd, *J* = 6.0, 8.0 Hz, 1 H), 3.84 (dq, *J* = 3.0, 6.5 Hz, 1 H), 3.58 (s, 3 H), 3.36 (d, *J* = 10.0 Hz, 1 H), 3.32 (d, *J* = 10 Hz, 1 H), 2.96 (s, 3 H), 2.38 (A of AB, J_{AB} = 15 Hz, 1 H), 2.34 (B of AB, J_{AB} = 15 Hz, 1 H), 2.17 (dq, *J* = 3.0, 7.0 Hz, 1 H), 1.96 (m, 1 H), 1.75 (dd, *J* = 10.0, 13.0 Hz, 1 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 1.01 (s, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 3 H), 0.88-1.00 (m, 2 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 154.9, 154.4, 145.9, 137.2, 128.6, 128.4, 128.0, 110.4, 100.6, 86.7, 79.7, 79.5, 76.5, 74.8, 74.1, 73.9, 72.2, 69.7, 69.3, 68.6, 66.5, 61.8, 48.0, 41.2, 40.9, 33.9, 33.4, 23.2, 17.6, 17.3, 13.3, 11.9, -1.7; IR (thin film) 3477, 3415, 3069, 2956, 1809, 1743, 1694, 1455, 1382, 1310, 1094, 1043, 860, 839, 735; FAB HRMS calcd for $C_{38}H_{57}NO_{13}SiNa$ (M^+ + Na) 786.3497, found 786.3535.

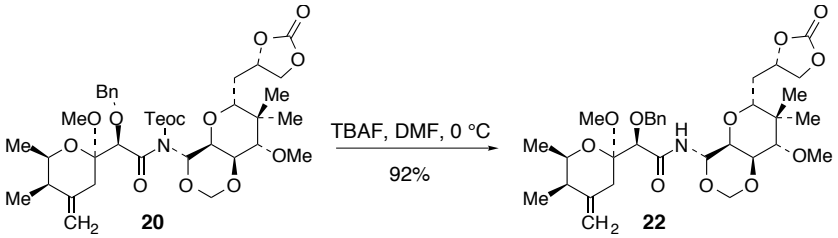


7-Benzyloxy-N(9)-2-trimethylsilylethoxycarbonyl-O(17)-O(18)-carbonyl *epi*-mycalamide A (20). Methylenation of **19** (9 mg, 0.012 mmol) using the procedure described for the synthesis of **16** provided **20** (5.7 mg, 63%) as a clear oil; $[\alpha]_D^{26}$ +61° (*c* 0.37, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.36 (m, 5 H), 6.08 (d, *J* = 10.5 Hz, 1 H), 5.17 (s, 1 H), 5.05 (A of AB, J_{AB} = 6.7 Hz, 1 H), 4.94 (B of AB, J_{AB} = 6.7 Hz, 1 H), 4.85 (br s, 1 H), 4.84 (A of AB, J_{AB} = 10.0 Hz, 1 H), 4.72 (br s, 1 H), 4.71 (B of AB, J_{AB} = 10.0 Hz, 1 H), 4.48-4.57 (m, 2 H), 4.28-4.39 (m, 4 H), 3.89 (m, 2 H), 3.57 (s, 3 H), 3.46 (d, *J* = 10.5 Hz, 1 H), 3.40 (d, *J* = 10.5 Hz, 1 H), 3.26 (s, 3 H), 2.93 (br d, *J* = 14.5 Hz, 1 H), 2.35 (m, 1 H), 2.22 (dq, *J* = 2.5, 7.0 Hz, 1 H), 1.86 (m, 1 H), 1.64 (m, 1 H), 1.17 (d, *J* = 7.0 Hz, 3 H), 1.11 (m, 2 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 0.98 (s, 3 H), 0.87 (s, 3 H), 0.08 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 154.9, 153.6, 147.0, 137.5, 128.5, 128.1, 127.8, 109.9, 102.0, 87.7, 80.5, 78.8, 77.6, 74.6, 74.33, 74.29, 74.0, 69.7, 69.4, 67.3, 67.0, 61.8, 49.6, 41.3, 33.9, 32.9, 29.7, 23.0, 17.9, 17.5, 13.1, 11.9, -1.6; IR (thin film) 2964, 1811, 1733 (br), 1654, 1454, 1382, 1260, 1091, 1033, 798; FAB HRMS calcd for $C_{38}H_{57}NO_{13}SiNa$ (M^+ + Na) 786.3497, found 786.3535.

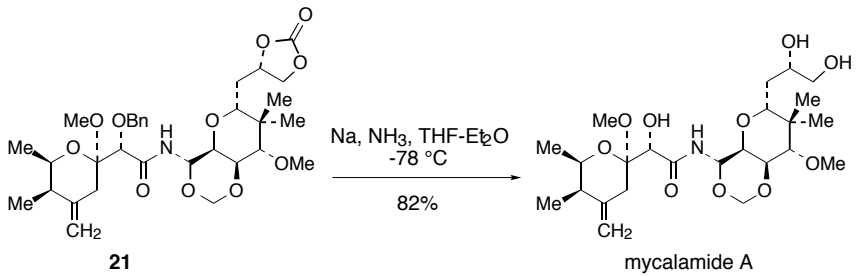


7-Benzyloxy-O(17)-O(18)-carbonyl-mycalamide A (21). To a 0 °C solution of imide **16** (2.2 mg, 0.0029 mmol) in DMF (0.8 mL) was added TBAF (0.0115 mL, 1.0 M in THF, 0.0115 mmol), immediately producing a yellow solution and small amounts of gaseous evolution. The mixture was stirred for 30 min, then the reaction mixture was poured into a mixture of EtOAc (10 mL), saturated $NaHCO_3$ (3 mL), and brine (10 mL). The layers were separated and the aqueous layer was further extracted with EtOAc (4 x 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated to give a yellow oil. Purification of the crude product by flash chromatography (47% EtOAc/hexanes) provided amide **22** (1.7 mg, 93%) as a clear oil: $[\alpha]_D^{26}$ +53° (*c* 0.17, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32-7.40 (m, 5 H), 7.21 (d, *J* = 10.0 Hz, 1 H), 5.76 (dd, *J* = 10.0, 10.0 Hz, 1 H), 5.10 (A of AB, J_{AB} = 7.0 Hz, 1 H), 4.86 (B of AB, J_{AB} = 7 Hz, 1 H), 4.85 (br s, 1 H), 4.77 (A of AB, J_{AB}

= 12.0 Hz, 1 H), 4.74 (br s, 1 H), 4.71 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.59 (m, 1 H), 4.53 (m, 1 H), 4.22 (dd, *J* = 7.5, 10.0 Hz, 1 H), 4.04 (s, 1 H), 4.00 (dd, *J* = 7.5, 9.0 Hz, 1 H), 3.92 (dq, *J* = 2.5, 6.5 Hz, 1 H), 3.74 (dd, *J* = 7.5, 10.0 Hz, 1 H), 3.56 (s, 3 H), 3.44 (d, *J* = 10.0 Hz, 1 H), 3.40 (d, *J* = 10.0 Hz, 1 H), 3.21 (s, 3 H), 2.43 (s, 2 H), 2.22 (dq, *J* = 2.5, 7.0 Hz, 1 H), 1.96 (ddd, *J* = 4.5, 6.5, 9.0 Hz), 1.69 (dd, *J* = 10.0, 14.0 Hz, 1 H), 1.88 (d, *J* = 6.5 Hz, 3 H), 1.00 (s, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 155.0, 146.0, 136.8, 128.6, 128.3, 128.2, 110.3, 100.1, 86.7, 80.1, 78.8, 75.0, 74.8, 74.3, 74.1, 73.9,69.6, 69.4, 61.8, 49.3, 41.33, 41.27, 34.4, 33.7, 23.2, 17.8, 11.8; IR (thin film) 3479, 3412, 3069, 2974, 2938, 1799, 1694, 1520, 1455, 1374, 1092, 1035, 734; FAB HRMS calcd for $C_{32}H_{45}NO_{11}Na$ (M^+ + Na) 642.2890, found 642.2910.

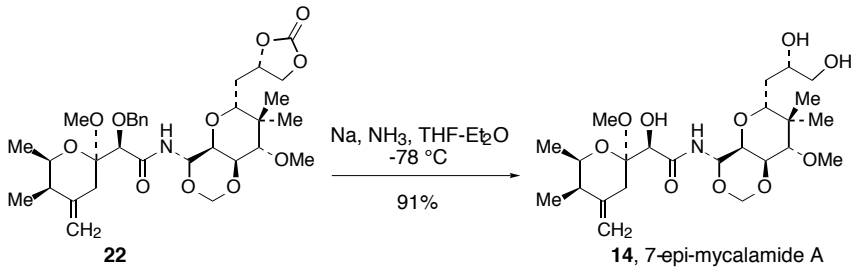


7-*epi*-Benzyloxy-O(17)-O(18)-carbonyl-mycalamide A (22). Treatment of **20** (3.5 mg, 0.0046 mmol) with TBAF (0.018 mL, 1.0 M in THF, 0.018 mmol) using the procedure described for the synthesis of **21** provided amide **22** (2.6 g, 92%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.38 (m, 5 H), 6.92 (d, *J* = 9.5 Hz, 1 H), 5.68 (dd, *J* = 9.5, 9.5 Hz, 1 H), 5.10 (A of AB, J_{AB} = 7.0 Hz, 1 H), 4.87 (B of AB, J_{AB} = 7.0 Hz, 1 H), 4.79-4.86 (m, 2 H), 4.83 (br s, 1 H), 4.76 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.68 (B of AB, J_{AB} = 11.3 Hz, 1 H), 4.60 (br s, 1 H), 4.23 (dd, *J* = 7.5, 10.5 Hz, 1 H), 4.11 (s, 1 H), 3.88-3.94 (m, 2 H), 3.75 (dd, *J* = 7.0, 10.0 Hz, 1 H), 3.58 (s, 3 H), 3.44 (d, *J* = 11.0 Hz, 1 H), 3.31 (s, 3 H), 3.24 (d, *J* = 10.5 Hz, 1 H), 2.78 (A of AB, J_{AB} = 13.5 Hz, 1 H), 2.20 (dq, *J* = 2.2, 7.2 Hz, 1 H), 1.97 (m, 1 H), 1.93 (B of AB, J_{AB} = 13.5 Hz, 1 H), 1.69 (m, 1 H), 1.18 (d, *J* = 6.5 Hz, 3 H), 1.03 (d, *J* = 6.5 Hz, 3 H), 1.01 (s, 3 H), 0.89 (s, 3 H). Due to the instability of **22**, it was used immediately in the next step without further characterization.



Synthetic Mycalamide A. Liquid NH_3 (3 mL) was distilled from Na(s) via cannula to a -78 °C flask without a stir bar containing a small piece of sodium (approximately 3 mg, washed with hexanes). A solution of benzyl ether **21** (1.6 mg, 0.0024 mmol) in a THF (0.4 mL)/Et_2O (0.8 mL) mixture, was added dropwise over 1 min. The solution was periodically agitated for 30 min, then a 1 : 1 mixture of NH_4Cl (s) and $NaHCO_3$ (s) was added until the blue color disappeared. The solution was allowed to warm to 23 °C and then filtered. The filter cake was washed several times with EtOAc, and the combined filtrate and washings were concentrated to afford a crude yellow oil. Purification of the crude product by flash chromatography (30% EtOAc/hexanes -->80% EtOAc/hexanes --> 4% MeOH/4%*i*-PrOH/EtOAc) provided mycalamide A (0.0010 g, 82%) as a clear oil; $[\alpha]_D^{26}$ +74° (*c* 0.05, $CHCl_3$), literature (Kishi)[7] $[\alpha]_D^{26}$ +82.4° (*c* 0.37, $CHCl_3$); literature (Munro)[8] $[\alpha]_{365}^{26}$ +110°(c 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 9.7 Hz, 1 H), 5.88 (dd, *J* = 9.7, 9.7 Hz, 1 H), 5.15 (A of AB, J_{AB} = 7.0 Hz, 1 H), 4.89 (B of AB, J_{AB} = 7.0 Hz, 1 H), 4.86 (br s, 1 H), 4.75 (br s, 1 H), 4.31 (d, *J* = 1.7 Hz, 1 H), 4.24 (dd, *J* = 6.6, 10.0 Hz, 1 H), 4.01 (dq, *J* = 2.8, 6.6 Hz, 1 H), 3.86 (dd, *J* = 6.7, 9.7 Hz, 1 H), 3.75 (m, 1 H), 3.74 (ROH, br s, 1 H), 3.65 (dd, *J* = 4.4, 8.1 Hz, 1 H), 3.59 (dd, *J* = 3.6, 11.4 Hz, 1 H), 3.57 (s, 3 H), 3.47 (d, *J* = 10.3 Hz, 1 H), 3.40 (dd, *J* = 6.0, 11.1 Hz, 1 H), 3.31 (s, 3 H), 3.14 (ROH, br s, 1 H), 2.40 (A of AB, J_{AB} = 15.0 Hz, 1 H), 2.37 (B of AB, J_{AB} = 15.0 Hz, 1 H), 2.26 (dq, *J* = 2.7, 7.1 Hz, 1 H), 2.21 (ROH, br s, 1 H), 1.56 (m, 2 H), 1.21 (d, *J* = 6.6 Hz, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.00 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.68, 145.56, 110.62, 99.77, 86.83, 79.13, 79.06, 74.39, 73.77, 72.92, 71.54, 71.29, 69.80, 66.52, 61.82, 48.97, 41.63, 41.33, 33.76, 32.01, 23.13, 17.89, 13.51, 12.04; IR (thin film) 3100-3700 (br s), 2971, 2918, 1679, 1526, 1469, 1383, 1264, 1193, 1172, 1094, 1074, 1033, 938, 878, 790; FAB HRMS calcd for $C_{24}H_{41}NO_{10}Na$ (M^+ + Na) 526.2628, found 526.2633. Synthetic

mycalamide A was identical to a sample generously provided by Prof. Kishi. Among other comparisons, a 1 : 1 mixture of Kishi's sample and our synthetic sample existed as one compound by ^{1}H NMR analysis.



7-*epi*-Mycalamide A . Benzyl ether **22** (1.4 g, 0.0020 mmol) was converted to 7-epi-mycalamide A using the procedure described above for synthesis of mycalamide A from benzyl ether **21**. Purification of the crude product by flash chromatography (30% EtOAc/hexanes →80% EtOAc/hexanes → 1% MeOH/EtOAc) provided C(7)-*epi*-mycalamide A **14** (1.0 mg, 91%) as a clear oil; $[\alpha]_D^{26}$ +90° (*c* 0.09, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 9.8 Hz, 1 H), 5.86 (dd, *J* = 9.8, 9.8 Hz, 1 H), 5.14 (A of AB, J_{AB} = 6.8 Hz, 1 H), 4.88 (B of AB, J_{AB} = 6.8 Hz, 1 H), 4.87 (br s, 1 H), 4.77 (br s, 1 H), 4.27 (s, 1 H), 4.25 (dd, *J* = 7.1, 10.7 Hz, 1 H), 3.98 (dq, *J* = 2.6, 6.5 Hz, 1 H), 3.86 (dd, *J* = 7.0, 9.8 Hz, 1 H), 3.73 (m, 1 H), 3.64 (ddd, *J* = 3.0, 5.5, 10.0 Hz, 1 H), 3.58 (s, 3 H), 3.55 (dd, *J* = 2.3, 9.6 Hz, 1 H), 3.46 (d, *J* = 10.5 Hz, 1 H), 3.41 (ROH, d, *J* = 2.2 Hz, 1 H), 3.33 (dd, *J* = 6.6, 12.2 Hz, 1 H), 3.33 (s, 3 H), 3.19 (ROH, br s, 1 H), 2.63 (A of AB, J_{AB} = 14.4 Hz, 1 H), 2.32 (ROH, d, *J* = 6.1 Hz, 1 H), 2.29 (B of AB, J_{AB} = 14.4 Hz, 1 H), 2.24 (dq, *J* = 2.3, 6.9 Hz, 1 H), 1.55-1.61 (m, 2 H), 1.20 (d, *J* = 6.5 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 0.99 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$ containing 0.05% pyridine) δ 171.35, 145.62, 110.72, 100.41, 86.67, 78.97, 78.61, 74.46, 73.51, 72.23, 71.40, 69.64, 66.53, 61.90, 49.52, 41.77, 41.09, 33.17, 31.98, 22.98, 17.79, 13.18, 11.74; DEPT NMR (125 MHz, $CDCl_3$) δ 110.72 (-), 86.66 (-), 78.95 (+), 78.60 (+), 77.19 (+), 74.45 (+), 73.50 (+), 72.20 (+), 71.39 (+), 69.63 (+), 66.51 (-), 61.90 (+), 49.50 (+), 41.07 (+), 33.16 (-), 31.97 (-), 22.97 (+), 17.79 (+), 13.17 (+), 11.73 (+); IR (thin film) 3150-3700 (br), 2969, 2935, 1686, 1523, 1383, 1262, 1192, 1100, 1074, 1032; FAB HRMS calcd for $C_{24}H_{41}NO_{10}Na$ (M^+ + Na) 526.2628, found 526.2640. Our ^{1}H NMR and ^{13}C NMR data are consistent with the analogous spectra provided by Prof. Nakata.[9]

Mycalamide A - ^{1}H NMR Comparisons

		Blunt[8,10]		Kishi[7]		Roush	
Proton #	mult	δ	*J* (Hz)	δ	*J* (Hz)	δ	*J* (Hz)
NH9	d	7.50	9.8	7.49	9.7	7.48	9.7
H10	dd	5.88	9.8, 9.8	5.88	9.7	5.88	9.7, 9.7
10-O-CH_2	AB	5.14	6.9	5.15	7.0	5.15	7.0
10-O-CH_2	AB	4.88	6.9	4.89	7.0	4.89	7.0
4=CH_2	s	4.85	--	4.86	--	4.86	--
4=CH_2	s	4.74	--	4.75	--	4.75	--
H7	d	4.31	--(s)--	4.31	--(s)--	4.31	1.7
H12	dd	4.23	6.7, 10.3	4.24	6.7, 10.2	4.24	6.6, 10.0
H2	dq	3.99	2.7, 6.6	4.00	2.7, 6.4	4.01	2.8, 6.6
H11	dd	3.87	6.7, 9.8	3.87	6.7, 9.6	3.86	6.7, 9.7
H17	m	3.75	--	3.75	--	3.75	--
R-OH	br s					3.74	--
H15	dd	3.65	5.1, 7.5	3.65	4.5, 7.	3.65	4.4, 8.1
13-O-Me	s	3.56	s	3.57	--	3.57	--
H18	dd	3.56	--(m)--	3.58	3.3, 11.2	3.59	3.6, 11.4
H13	d	3.47	10.3	3.47	10.2	3.47	10.3
H18	dd	3.39	6.2, 11.2	3.39	6.1, 11.2	3.40	6.0, 11.1
6-O-Me	s	3.30	--	3.31	--	3.31	--
R-OH	br s					3.14	--
H5	AB	2.37	--(m)--	2.38	--(m)--	2.40	15.0
H5	AB	2.37	--(m)--	2.38	--(m)--	2.37	15.0
H3	dq	2.25	2.7, 7.0	2.26	2.4, 7.0	2.26	2.7, 7.1
R-OH	br s					2.21	--
H16x2	m	1.55	--	1.56	--	1.56	--
2-Me	d	1.20	6.6	1.21	6.4	1.21	6.6
3-Me	d	1.00	7.0	1.01	7.0	1.01	7.1
14-Me(eq)	s	0.99	--	0.99	--	1.00	--
14-Me(ax)	s	0.88	--	0.88	--	0.89	--

Mycalamide A - ^{13}C NMR Comparisons

Carbon #	δ Kishi[7]	δ Roush	δ Munro[8,10]
8	171.79	171.68	171.52
4	145.56	145.56	145.40
4=CH_2	110.61	110.62	110.41
6	99.82	99.77	99.66
10-OCH_2	86.82	86.83	86.71
13	79.11	79.13	79.01
15	78.97	79.07	78.91
12	74.38	74.40	74.30
10	73.75	73.77	73.62
7	72.82	72.92	72.77
17	71.57	71.55	71.51
11	71.25	71.30	71.16
2	69.82	69.80	69.70
18	66.48	66.53	66.41
13-OMe	61.81	61.83	61.75
6-OMe	48.92	48.98	48.88
14	41.62	41.64	41.61
3	41.33	41.34	41.31
5	33.69	33.77	33.70
16	31.99	32.01	31.95
14-Me	23.11	23.13	23.10
2-Me (1)	17.89	17.90	17.89
14-Me	13.51	13.52	13.51
3-Me	12.02	12.04	12.03

7-*epi*-Mycalamide A - ^{1}H NMR Comparisons

		Nakata[9]		Roush	
Proton #	mult	δ	*J* (Hz)	δ	*J* (Hz)
NH9	d	7.40	9.8	7.39	9.8
H10	dd	5.85	9.8, 9.8	5.86	9.8, 9.8
10-O-CH_2	AB	5.14	7.0	5.14	6.8
10-O-CH_2	AB	4.87	7.0	4.88	6.8
4=CH_2	dd	4.87	2.1, 2.1	4.87	--(s)--
4=CH_2	dd	4.76	2.1, 2.1	4.77	--(s)--
H7	s	4.27	--	4.27	--
H12	dd	4.25	6.7, 10.7	4.25	7.1, 10.7
H2	dq	3.97	2.4, 6.4	3.98	2.6, 6.5
H11	dd	3.86	6.7, 9.8	3.86	7.0, 9.8
H17	m	3.72	--	3.73	--
H18	dd	3.64	3.4, 11.3	3.64	3.0, 5.5, 10.0 (ddd)
13-OMe	s	3.57	--	3.58	--
H15	dd	3.54	2.8, 9.2	3.55	2.3, 9.6
H13	d	3.46	10.7	3.46	10.5
R-OH	d			3.41	2.2
H18	dd	3.33	6.4, 11.3	3.33	6.6, 12.2
6-OMe	s	3.33	--	3.33	--
R-OH	br s	3.23	--	3.19	--
H5	ddd	2.63	2.1, 2.1, 14.3	2.63	14.4 (AB)
H5	d	2.28	14.3	2.29	14.4 (AB)
H3	dq	2.23	2.4, 7.0	2.24	2.3, 6.9
R-OH	d	2.17	--(s)--	2.32	6.1
H16	m	1.57	--	1.55-1.61	--
2-Me	d	1.19	6.4	1.20	6.5
3-Me	d	1.03	7.0	1.04	6.9
14-Me(eq)	s	0.98	--	0.99	--
14-Me(ax)	s	0.89	--	0.89	--

C(7)-*epi*-Mycalamide A - ^{13}C comparisons

Carbon #	δ Nakata[9]	δ Roush
8	171.37	171.35
4	145.61	145.62
4=CH_2	110.72	110.72
6	100.40	100.41
O(CH_2)O	86.66	86.67
13	78.98	78.97
15	78.56	78.61
11	77.20	77.19
12	74.45	74.46
10	73.51	73.51
7	72.23	72.23
17	71.42	71.40
2	69.65	69.64
18	66.50	66.53
13-OMe	61.90	61.90
6-OMe	49.52	49.52
14	41.76	41.77
3	41.08	41.09
5	33.15	33.17
16	31.98	31.98
14-β-Me	22.98	22.98
1	17.78	17.79
14-α-Me	13.17	13.18
3-Me	11.73	11.74

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