Supporting Information I

Synthesis of Reblastatin, Autolytimycin, Non-Benzoquinone Analogs: Potent Inhibitors of Heat Shock Protein 90 (Hsp90)

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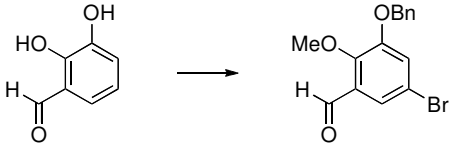
General Information: All reactions were carried out in oven or flame-dried glassware under argon atmosphere. Triethylamine, diisopropylethylamine, and 2,6-lutidine were distilled and stored over potassium hydroxide. *N,N*-Dimethylformamide and dimethylsulfoxide were distilled over calcium hydride and stored over 4 Å molecular sieves. *N*-Butyllithium standardized by titration with menthol/1,10-phenanthroline. Oxalyl chloride was freshly distilled immediately before use. Copper (I) iodide (99.999 % purity) and all other reagents were used as supplied. CH_2Cl_2, MeOH, PhMe, Et_2O, PhH, THF, CH_3CN were obtained from a dry solvent system (alumina) and used without further drying. Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography with 0.20 mm silica gel 60 Å plates. Flash chromatography was performed on 32-63 μm 60 Å silica gel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ (DMSO) at 400 MHz and 75 (100) MHz, respectively. Chemical shifts are reported in parts per million using the solvent internal standard (chloroform, 7.24 and 77.0 ppm, respectively). Data are reported as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, m = multiplet, br = broad, ovlp = overlapping), coupling constant, integration. Diastereomeric ratios were determined by ^{1}H NMR (400 MHz) analysis of crude mixtures, operating at signal/noise ratio of 200:1. Infrared spectra were recorded as thin films on NaCl plates on a Fourier transform spectrometer (FTIR). Optical rotations were measured using a sodium (589, D line) lamp and are reported as follows: concentration (*c* in g/100mL) and solvent. High resolution mass spectra (HRMS) were recorded with an electrospray ionization mass spectrometer.

Experimental Procedures



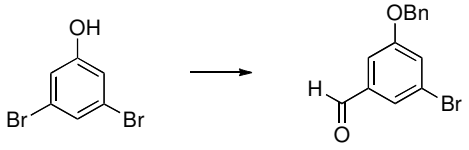
15a

3-(benzyloxy)-5-bromo-2-methoxybenzaldehyde (15a). To a suspension of dry sodium hydride (4.34 g, 181 mmol) in tetrahydrofuran (70.0 mL) at room temperature was added a solution of 2,3-dihydroxybenzaldehyde (10.0 g, 72.4 mmol) in tetrahydrofuran (35.0 mL). The reaction stirred for 1 hour and benzyl bromide (8.61 mL, 72.4 mmol) in tetrahydrofuran (17.5 mL) was added. Reaction mixture stirred for 24 hours and was poured into water. The aqueous layer was extracted with chloroform and acidified to pH 2 with 1 M HCl and extracted with more chloroform. The latter layers were washed with 1 M HCl, dried over magnesium sulfate and filtered over silica gel. Recrystallization of the residue from ethanol provided the desired product as yellow needles in 73 % yield (11.6 g, 50.9 mmol). Mp: 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.10 (s, 1H), 9.90 (s, 1H), 7.44-7.28 (m, 5H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 6.88 (t, *J* = 8.0 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.5, 152.3, 147.2, 136.5, 128.6, 128.1, 127.4, 125.3, 121.1, 121.0, 119.4, 71.5; IR (neat) ν_{max}: 3060, 2937, 2360, 1653, 1455, 1252, 733 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{14}H_{12}O_3$ $[M+]^+$ 228.0786, found 228.0789.

To a solution of 3-(benzyloxy)-2-hydroxybenzaldehyde (15.0 g, 65.7 mmol) in acetic acid (330 mL) was added sequentially sodium acetate (8.62 g, 105 mmol) and bromine (4.40 mL, 85.4 mmol). The reaction stirred for 30 minutes before acetic acid was concentrated *in vacuo*. The residue was diluted with water and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried with magnesium sulfate, filtered over silica gel, and concentrated under reduced pressure. The crude aromatic bromide was used in the next step without further purification (18.2 g, 59.3 mmol, 90 %). Mp: 109-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.95 (s, 1H), 9.84 (s, 1H), 7.43-7.30 (m, 6H), 7.21 (d, *J* = 2.0 Hz, 1H), 5.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 151.5, 148.3, 135.7, 128.7,

128.4, 127.5, 126.8, 123.4, 121.6, 110.8, 71.7; IR (neat) ν_{max}: 3100, 1654, 1456, 1246, 867, 766 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{14}H_{11}BrO_3$ $[M+]^+$ 305.9892, found 305.9900.

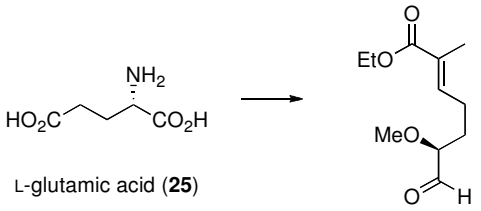
To a solution of 3-(benzyloxy)-5-bromo-2-hydroxybenzaldehyde (18.0 g, 58.6 mmol) in *N*,*N*-dimethylformamide (240 mL) at room temperature was added potassium carbonate (9.72 g, 70.3 mmol) and dimethyl sulfate (6.71 mL, 70.9 mmol). The reaction stirred for 24 hours and water (200 mL) was added. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The redish residue was recrystallized from ethanol and put in freezer overnight. Aldehyde **15a** was isolated as cream crystals (16.4 g, 51.1 mmol, 87 %). Mp: 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.44-7.36 (m, 5H), 7.29 (d, *J* = 2.4 Hz, 1H), 5.11 (s, 1H), 3.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 152.9, 152.3, 135.6, 130.6, 128.8, 128.5, 127.5, 122.6, 122.2, 116.7, 71.4, 62.3; IR (neat) ν_{max}: 1683, 1575, 1268, 1243, 861, 733 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{15}H_{13}BrO_3$ $[M+]^+$ 320.0048, found 320.0084.



15b

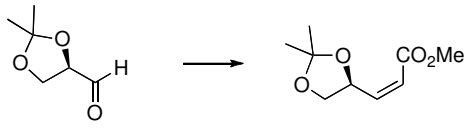
3-(benzyloxy)-5-bromobenzaldehyde (15b). To a solution of 3,5-dibromophenol (17.3 g, 68.7 mmol) in acetone (140 mL) at room temperature was added potassium carbonate (14.2 g, 103 mmol) followed by benzyl bromide (8.98 mL, 75.5 mmol). Reaction was allowed to run at room temperature for 16 hours. The heterogeneous mixture was filtered over Celite®, rinsed with ethyl acetate, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (silica, 10% EtOAc/hexanes) affords *bis*-bromo phenol as a colorless oil (23.0g, 67.2 mmol, 97.8%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57-7.50 (m, 5H), 7.43 (dt, *J* = 1.6, 3.4 Hz, 1H), 7.24 (d, *J* = 1.6, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 135.7, 128.7, 128.3, 127.5, 126.6, 123.1, 117.2, 70.5; IR (neat) ν_{max}: 3080, 3033, 2933, 2871, 1583, 1436, 1256, 1024, 830, 746, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{13}H_{10}Br_2O$ $[M+23]^+$ 362.8996, found 362.8986.

To a solution of *bis*-bromide (12.2 g, 35.7 mmol) in tetrahydrofuran (360 mL) at –78 °C was added *n*-BuLi in hexane (2.50 M, 15.7 mL) dropwise. Reaction stirred for 30 minutes and *N*,*N*-dimethylformamide (4.14 mL, 53.5 mmol) was added in one portion. Reaction was warmed to room temperature and stirred for additional 30 minutes. Reaction solution was poured into vigorously stirring solution of 10% *aq.* KH_2PO_4 and diethyl ether (310 mL:190 mL). The biphasic mixture stirred for additional 10 minutes. The organic layer was separated and the aqueous solution was extracted with diethyl ether (2x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 5% EtOAc/hexanes) gives aldehyde **15b** as a white solid (9.0 g, 30.9 mmol, 86.6%). Mp: 52 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.88 (s, 1H), 7.58 (t, *J* = 1.6, 1H), 7.42-7.33 (m, 7H), 5.09 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.5, 159.8, 138.6, 135.6, 128.7, 128.4, 127.5, 125.9, 124.6, 123.5, 113.0, 70.5; IR (neat) ν_{max}: 3068, 3033, 2837, 2727, 1702, 1570, 1270, 1028, 847, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{14}H_{11}BrO_2$ $[M+23]^+$ 312.9840, found 312.9851.



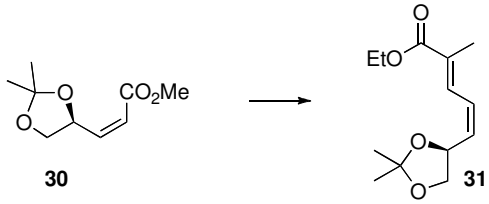
L-glutamic acid (**25**) **12a**

For preparation of (*S*,*E*)-ethyl 6-methoxy-2-methyl-7-oxohept-2-enoate (12a) see: Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026.



29 **30**

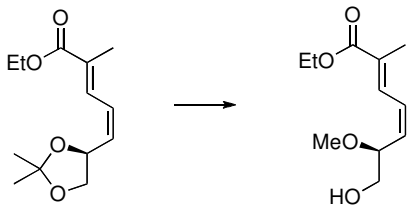
For preparation of (*S*,*Z*)-methyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (30) see: Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822.



30 **31**

(2*E*,4*Z*)-ethyl 5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpenta-2,4-dienoate (31). To a solution of ester **30** (4.00 g, 20.0 mmol) in methylene chloride (200 mL) at –78 °C was added diisobutylaluminum hydride (1.00 M in hexane, 21.0 mL) dropwise. Reaction stirred at –78 °C for 1 hour and was quenched by addition of methanol (0.850 mL) followed by water. The mixture was allowed to warm up to room temperature and magnesium sulfate was added and stirred for another 10 minutes. The white suspension was filtered over Celite® and washed with methylene chloride. Concentration of solvents provided crude aldehyde which was used in the next step without further purification.

To a solution of aldehyde in benzene (220 mL) was added (carbethoxyethylidine)triphenylphosphorane (9.47 g, 26.1 mmol). Reaction was heated at reflux for one hour, cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (silica, 10% EtOAc/hexanes) afforded conjugated ester **31** as a yellow oil (4.00g, 16.6 mmol, 83%, 2 steps). $[\alpha]_D^{20}$ –50.2° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42 (dt, *J* = 1.4, 12.0 Hz, 1H), 6.43 (dt, *J* = 1.2, 12.0 Hz, 1H), 5.75 (dd, *J* = 9.2, 10.0 Hz, 1H), 5.05 (dq, *J* = 1.2, 7.0, 15.4, 1H), 4.20 (q, *J* = 7.2, 14.0 Hz, 2H), 4.14 (dd, *J* = 6.4, 8.0 Hz, 1H), 3.57 (t, *J* = 7.8 Hz, 1H), 1.92 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 168.1, 134.8, 131.4, 130.0, 126.8, 109.7, 72.0, 71.97, 69.4, 60.8, 26.7, 25.8, 14.3, 12.4; IR (neat) ν_{max}: 2986, 2936, 2873, 1709, 1370, 1247, 1061, 859, 743 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{13}H_{20}O_4$ $[M+23]^+$ 263.1259, found 263.1257.



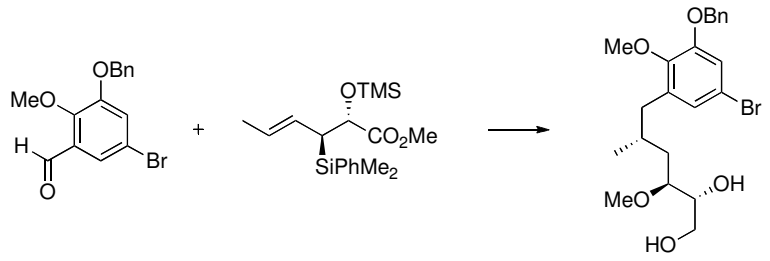
31 **32**

(*S*,2*E*,4*Z*)-ethyl 7-hydroxy-6-methoxy-2-methylhepta-2,4-dienoate (32). To a solution of acetonide **31** (2.27 g, 9.45 mmol) in ethanol (95.0 mL) at room temperature was added Amberlyst 15 (4.15 mmol/g loading; 228 mg). Reaction was heated to reflux for 3 hours, cooled to room temperature, filtered over Celite®, washed with ethyl acetate and concentrated under reduced pressure. The resulting diol was unstable to purification by flash chromatography and was used crude in the next step.

To a solution of diol (1.89 g, 9.44 mmol) in methylene chloride (94.0 mL) at 0 °C was added triethylamine (1.58 mL, 11.3 mmol) followed by 4-dimethylaminopyridine (80.7 mg, 0.661 mmol) and TBSCl (1.49 g, 9.91 mmol). Reaction mixture was allowed to warm up to room temperature overnight and was quenched by addition of pH 7 phosphate buffer. The aqueous layer was extracted with methylene chloride (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 10% EtOAc/hexanes) provided silyl ether as a colorless oil (2.30 g, 7.31 mmol, 77.4%, 2 steps). $[\alpha]_D^{20}$ +17.0° (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, *J* = 12.4 Hz, 1H), 6.40 (t, *J* = 11.6 Hz, 1H), 5.71 (dd, *J* = 11.2 Hz, 1H), 4.72 (quint. *J* = 4.6, 7.8 Hz, 1H), 4.21 (dq, *J* = 1.2, 7.0, 14.2 Hz, 2H), 3.63 (A of ABx, *J* = 3.6, 10.0 Hz, 1H), 3.46 (B of ABx, *J* = 9.2 Hz, 1H), 2.63 (br. d, *J* = 2.0 Hz, 1H), 1.93 (s, 3H), 1.29 (dt, *J* = 1.2, 7.0 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 168.2, 135.8, 131.8, 129.6, 126.2, 68.7, 66.6, 60.7, 25.9, 18.3, 14.3, 12.5, –5.3, –5.4; IR (neat) ν_{max}: 3470, 2930, 2858, 1709, 1472, 1367, 1256, 1108, 838, 779, 668 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{16}H_{30}O_4Si$ $[M+23]^+$ 337.1811, found 337.1815.

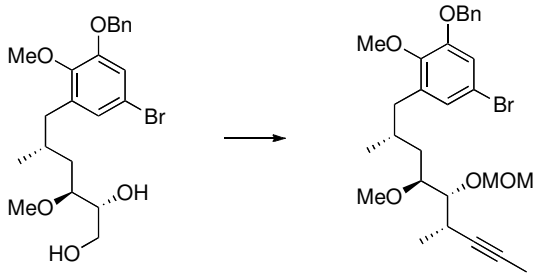
To a solution of secondary alcohol (2.30 g, 7.31 mmol) in methylene chloride (360 mL) at room temperature was added sequentially 4 Å molecular sieves (4.70 g), Proton Sponge™ (4.70 g, 21.9 mmol) and trimethyloxonium tetrafluoroborate (2.70 g, 18.3 mmol). The heterogeneous reaction was allowed to stir for 16 hours, filtered over Celite®, and washed with methylene chloride. The volatiles were concentrated under reduced pressure and the white residue was dissolved in ethyl acetate. The organic layer was washed with 1 M HCl solution (2x). The aqueous layers were extracted with ethyl acetate (2x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 15% EtOAc/hexanes) yields methyl ether as a yellow oil (2.00 g, 6.09 mmol, 83.3%). $[\alpha]_D^{20}$ +25.5° (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (dt, *J* = 1.4, 11.6 Hz, 1H), 6.51 (dt, *J* = 1.2, 11.6 Hz, 1H), 5.63 (t, *J* = 10.0 Hz, 1H), 4.26 (m, 1H), 4.21 (q, *J* = 7.2, 14.0 Hz, 2H), 4.71 (A of ABx, *J* = 6.2, 10.4 Hz, 1H), 3.55 (B of ABx, *J* = 5.4, 10.4 Hz, 1H), 3.32 (s, 3H), 1.94 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 136.3, 132.2, 129.2, 127.5, 78.0, 65.7, 60.7, 56.9, 25.8, 18.3, 14.3, 12.4, -5.3, -5.4; IR (neat) ν_{max}: 2930, 2858, 2822, 1711, 1464, 1248, 1106, 839, 778, 667 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{17}H_{32}O_4Si$ $[M+23]^+$ 351.1968, found 351.1958.

To a solution of TBS ether (2.00 g, 6.09 mmol) in a mixture of methylene chloride (61.0 mL) and methanol (61.0 mL) at 0 °C was added 10-camphorsulfonic acid (424 mg, 1.83 mmol) in one portion. Reaction was allowed to stir at 0 °C for 2 hours before it was quenched by addition of saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 30% EtOAc/hexanes) yields alcohol **32** as a yellow oil (1.20 g, 5.60 mmol, 92.0%). $[\alpha]_D^{20}$ –45.7° (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (dt, *J* = 1.4, 12.0 Hz, 1H), 6.55 (dt, *J* = 1.2, 12.0 Hz, 1H), 5.60 (dd, *J* = 10.4 Hz, 1H), 4.34 (m, 1H), 4.21 (q, *J* = 7.4, 14.2 Hz, 2H), 3.56 (t, *J* = 6.2 Hz, 3H), 3.33 (s, 3H), 2.13 (t, *J* = 6.4 Hz, 1H), 1.95 (s, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 134.5, 131.2, 130.2, 128.4, 77.6, 65.0, 60.9, 56.7, 14.3, 12.5; IR (neat) ν_{max}: 3463, 2982, 2933, 2823, 1708, 1249, 1103, 746 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{11}H_{18}O_4$ $[M+23]^+$ 237.1103, found 237.1101.



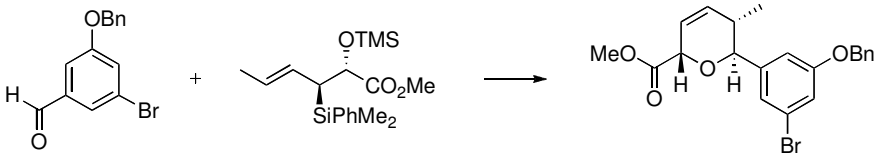
15a **18** **21a**

For preparation of (2*R*,3*S*,5*R*)-6-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-3-methoxy-5-methylhexane-1,2-diol (21a) see: Qin, H.-L.; Lowe, J. T.; Panek, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 38.



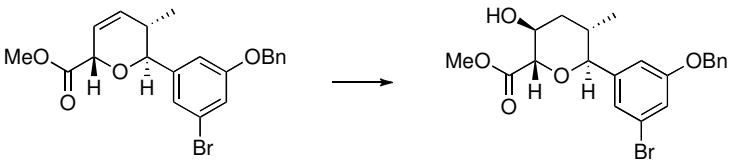
21a **11a**

For preparation of 1-(benzyloxy)-5-bromo-2-methoxy-3-((2*R*,4*S*,5*R*,6*S*)-4-methoxy-5-(methoxymethoxy)-2,6-dimethylnon-7-ynyl)benzene (11a) from (2*R*,3*S*,5*R*)-6-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-3-methoxy-5-methylhexane-1,2-diol (21a) see: Wrona, I. E.; Gabarda, A. E.; Evano, G.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 15026.



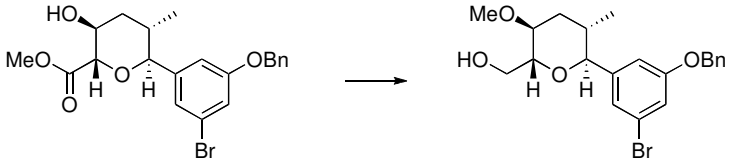
15b **18** **19b**

(2*S*,5*S*,6*S*)-methyl 6-(3-(benzyloxy)-5-bromophenyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-carboxylate (19b). To a solution of benzaldehyde **15b** (9.00 g, 30.9 mmol) and (*E*)-crotylsilane **18** (12.5 g, 35.5 mmol) in methylene chloride (600 mL) at –50 °C was added trifluoromethanesulfonic acid (2.74 mL, 30.9 mmol) dropwise. Reaction was allowed to stir for 12 hours at –50 °C before it was quenched by addition of saturated solution of sodium bicarbonate. The aqueous phase was extracted with methylene chloride (2x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 10% EtOAc/hexanes) yields dihydropyran **19b** as a clear oil (12.0 g, 28.8 mmol, 93.0%). $[\alpha]_D^{20}$ –71.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 7.16 (t, *J* = 1.6 Hz, 1H), 7.07 (t, *J* = 2.0 Hz, 1H), 6.95 (dt, *J* = 1.2, 2.4 Hz, 1H), 5.89 (m, 2H), 5.03 (s, 2H), 4.86 (q, *J* = 2.8, 6.0 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 3.75 (s, 3H), 2.39 (m, 1H), 0.81 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 159.4, 143.3, 136.3, 133.6, 128.6, 128.1, 127.5, 123.3, 122.7, 122.4, 117.7, 113.3, 79.3, 73.1, 70.3, 52.1, 34.7, 16.4; IR (neat) ν_{max}: 3037, 2955, 2875, 1753, 1570, 1443, 1272, 1148, 1109, 782 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{21}H_{21}BrO_4$ $[M+23]^+$ 439.0521, found 439.0535.



19b **17b**

(2*S*,3*S*,5*S*,6*S*)-methyl 6-(3-(benzyloxy)-5-bromophenyl)-3-hydroxy-5-methyltetrahydro-2*H*-pyran-2-carboxylate (17b). To a solution of dihydropyran **19b** (6.00 g, 14.4 mmol) in tetrahydrofuran (150 mL) at 0 °C was added BH_3•THF complex in tetrahydrofuran (1.11 M, 22.0 mL) dropwise. Reaction was allowed to warm up to room temperature on its own and stirred for an additional 1 hour at room temperature (about 3 hours). The reaction was cooled to 0 °C and quenched by sequential addition of sodium hydroxide in water (2.00 M, 35.9 mL) and 30% H_2O_2 (14.7 mL). The quenched reaction was stirred for 1/2 hour at 0 °C and for 1/2 hour at room temperature. The mixture was diluted with water and the aqueous layer was extracted with diethyl ether (5x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 30% EtOAc/hexanes) provides alcohol **17b** as a white foam (3.00 g, 28.8 mmol, 47.0%). $[\alpha]_D^{20}$ –7.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 7.14 (t, *J* = 1.4 Hz, 1H), 7.06 (t, *J* = 2.2 Hz, 1H), 6.92 (dd, *J* = 1.4, 2.2 Hz, 1H), 5.03 (s, 2H), 4.49 (t, *J* = 1.8 Hz, 1H), 4.33 (m, 2H), 3.79 (s, 3H), 2.20 (d, *J* = 7.2 Hz, 1H), 2.10 (m, 1H), 1.94 (ddt, *J* = 1.6, 3.6, 14.4, 1H), 1.50 (ddd, *J* = 2.8, 3.6, 12.2, 14.4 Hz, 1H) 0.70 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 159.3, 143.2, 136.2, 128.5, 128.1, 127.5, 123.1, 122.6, 117.4, 113.4, 81.5, 78.3, 70.2, 65.8, 52.2, 35.8, 29.6, 17.5; IR (neat) ν_{max}: 3412, 2953, 2928, 2872, 1747, 1570, 1441, 1270, 1136, 1057, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{21}H_{23}BrO_5$ $[M+23]^+$ 457.0627, found 457.0672.

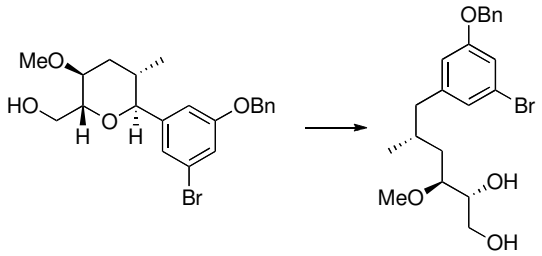


17b **20b**

((2*R*,3*S*,5*S*,6*S*)-6-(3-(benzyloxy)-5-bromophenyl)-3-methoxy-5-methyltetrahydro-2*H*-pyran-2-yl)methanol (20b). To a solution of alcohol **17b** (5.70 g, 13.1 mmol) in methylene chloride (6.50 mL) at room temperature was added sequentially 4 Å molecular sieves (8.50 g), *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine (8.42 g, 39.3 mmol), and trimethyloxonium tetrafluoroborate (4.84 g, 32.7 mmol). Reaction was allowed to stir for 16 hours at room temperature and was filtered over Celite® and washed with methylene chloride. The volatiles were concentrated under reduced pressure and the white residue was redissolved in ethyl acetate. The organic layer was washed with 1 M HCl solution (2x). The aqueous layers were extracted with ethyl acetate (2x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 15% EtOAc/hexanes) affords product as a white foam (5.30 g, 11.8 mmol, 90.1%). $[\alpha]_D^{20}$ –12.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.31 (m, 5H), 7.15 (t, *J* = 1.4 Hz, 1H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.93 (dd, *J* = 1.4, 2.0 Hz, 1H); 5.02 (s, 2H), 4.66 (br. s, 1H), 4.32 (d, *J* = 10.4 Hz, 1H), 3.79 (obs. m, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 2.10-2.01 (m, 2H), 1.35 (dt, *J* = 2.6, 12.6, 15.2 Hz, 1H), 0.63 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.1, 159.3, 143.6, 136.3, 128.6, 128.1, 127.5, 123.3, 122.6, 117.5, 113.4, 81.7, 75.0, 74.8, 70.2, 56.6, 52.1, 33.3, 29.9, 17.6; IR (neat) ν_{max}: 2952, 2928, 2873, 2826, 1748, 1570, 1441, 1141, 1095, 995, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{22}H_{25}BrO_5$ $[M+23]^+$ 471.0783, found 471.0774.

To a solution ester (6.00 g, 13.0 mmol) in diethyl ether (260 mL) at 0° C was added lithium tetrahydroborate (582 mg, 26.7 mmol). Reaction was stirred for 1/2 hour at 0 °C and 1 hour at room

temperature. Water was carefully added and the reaction mixture was extracted with diethyl ether (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 30% EtOAc/hexanes) gives alcohol **20b** as a yellow foam (4.90 g, 11.6 mmol, 89%). $[\alpha]_D^{20}$ +16.4° (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.31 (m, 5H), 7.12 (t, *J* = 1.4 Hz, 1H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.92 (t, *J* = 1.6 Hz, 1H), 5.02 (s, 2H), 4.15 (d, *J* = 8.4 Hz, 1H), 3.94-3.84 (m, 2H), 3.60 (m, 1H), 3.37 (s, 3H), 3.31 (q, *J* = 3.6, 8.0 Hz, 1H), 2.18 (m, 1H), 1.90 (m, 2H), 1.53 (ddd, *J* = 3.6, 10.4, 14.0 Hz, 1H), 0.79 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 159.4, 143.8, 136.2, 128.6, 128.1, 127.5, 122.9, 122.7, 117.2, 113.1, 78.8, 75.4, 73.7, 70.2, 60.7, 56.3, 32.2, 30.4, 18.0; IR (neat) ν_{max}: 3433, 2929, 2873, 2825, 1570, 1440, 1270, 1046, 833, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{21}H_{25}BrO_4$ $[M+23]^+$ 443.0834, found 443.0838.



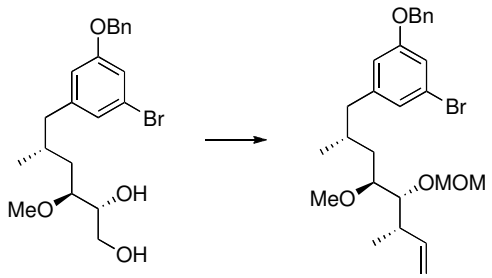
20b **21b**

(2*R*,3*S*,5*R*)-6-(3-(benzyloxy)-5-bromophenyl)-3-methoxy-5-methylhexane-1,2-diol (21b). To a suspension of aluminum trichloride (7.75 g, 58.1 mmol) in methylene chloride (500 mL) at –78 °C was added anisole (58.0 mL, 534 mmol) dropwise. The light yellow solution was stirred for an additional 5 minutes before alcohol **20b** (4.90 g, 11.6 mmol) in methylene chloride (80.0 mL) was added dropwise. The reaction mixture was allowed to warm up to 0 °C over 3 hours (on its own) and stirred for an additional 1 hour at that temperature. Reaction was quenched by slow addition of 0.5 M HCl (80.0 ml). The biphasic mixture was diluted with ammonium chloride and extracted with ethyl acetate (2x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 50% EtOAc/hexanes) yields phenol as a colorless oil (3.60 g, 10.9 mmol, 94.0%).

To a solution of the above phenol (1.35 g, 4.08 mmol) in methylene chloride (24.0 mL) at room temperature was added triethylsilane (5.21 mL, 32.6 mmol) followed by scandium(III) triflate (3.01 g, 6.11 mmol). The sealed tube was closed and the reaction was allowed to run at 42 °C for 48 hours. Upon completion, the mixture was cooled to room temperature and \was quenched by addition of water. The aqueous layer was extracted with methylene chloride (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 80% EtOAc/hexanes) affords diol as a colorless oil (1.20 g, 3.60 mmol, 88.2%).

To a solution of the above diol (2.90 g, 8.70 mmol) in acetone (50.0 mL) was added potassium carbonate (1.80 g, 13.0 mmol) followed by benzyl bromide (1.14 mL, 9.57 mmol). The heterogenous mixture stirred at room temperature for 48 hours before it was filtered over Celite® and washed with ethyl acetate. The solvent was concentrated under reduced pressure and the resulting residue was purified by flash chromatography (silica, 60% EtOAc/hexanes) to afford diol **21b** as a yellow oil (3.40 g, 8.00 mmol, 92.0%). $[\alpha]_D^{20}$ –2.2° (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.28 (m, 5H), 6.96 (t, *J* = 2.2 Hz, 1H), 6.90 (t, *J* = 1.4 Hz, 1H), 6.69 (t, *J* = 2.2 Hz, 1H), 5.00 (s, 2H), 3.73-3.62 (m, 3H), 3.40 (s, 3H), 3.38 (t, *J* = 3.6 Hz, 1H) 2.58 (A of ABq, *J* = 5.8, 13.2 Hz, 1H), 2.41 (d, *J* = 5.2 Hz, 1H), 2.31 (B of ABq, *J* = 8.8, 13.2 Hz, 1H), 2.11 (dd, *J* = 3.4, 8.0 Hz, 1H), 1.91 (m, 1H), 1.62 (dtd, *J* = 4.2, 9.6, 14.0 Hz, 1H), 1.16 (dtd, *J* = 3.6, 9.6, 14.0 Hz, 1H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 159.2, 144.1, 136.4, 128.5, 128.0, 127.4, 124.8, 122.4, 115.3, 114.9, 80.7, 72.7, 70.1,

63.3, 58.4, 43.9, 37.4, 31.1, 19.0; IR (neat) ν_{max}: 3405, 2930, 1603, 1566, 1447, 1269, 1156, 1096, 1028, 851, 736, 697 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{21}H_{27}BrO_4$ $[M+23]^+$ 445.0990, found 445.0980.



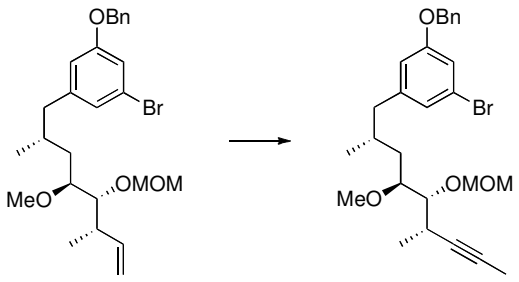
21b **22b**

1-(benzyloxy)-3-bromo-5-((2*R*,4*S*,5*R*,6*S*)-4-methoxy-5-(methoxymethoxy)-2,6-dimethyloct-7-enyl)benzene (22b). To a solution of diol **21b** (0.270 g, 0.596 mmol) in acetone (6.00 mL) and water (6.00 mL) mixture was added sodium bicarbonate (0.150 g, 1.79 mmol) and sodium metaperiodate (0.191 g, 0.893 mmol). The resulting suspension was stirred at room temperature for 2 hours. The solution was diluted with water followed and ethyl acetate. The aqueous phase was saturated with solid sodium chloride and extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude aldehyde **14b** was used in the next step without further purification.

To a flame dried round bottom flask was added 4 Å powdered molecular sieves (600 mesh, 0.330 g), toluene (4.00 mL) and 1.00 M of (4*S*,5*S*,*Z*)-diisopropyl 2-(but-2-enyl)-1,3,2-dioxaborolane-4,5-dicarboxylate **13** in toluene (1.66 mL) under an atmosphere of nitrogen. The reaction mixture was allowed to stir for 20 minutes at room temperature before it was cooled to –78 °C. A solution of aldehyde **14b** (0.200 g, 0.475 mmol) in toluene (1.00 mL) was added dropwise *via* a cannula. The reaction mixture stirred at –78 °C for 16 hours before it was quenched with 1 N NaOH solution (5 mL). The two-phase mixture was allowed to warm up to room temperature and stirred for 1 hour. The solution mixture was filtered over a pad of Celite® and the aqueous phase was extracted with diethyl ether (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/hexanes) to yield homoallylic alcohol as a viscous clear oil, dr 20:1. $[\alpha]_D^{20}$ –18.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 6.95 (t, *J* = 2.0 Hz, 1H), 6.91 (t, *J* = 2.0 Hz, 1H), 6.70 (t, *J* = 2.0 Hz, 1H), 5.60 (m, 1H), 5.02 (m, 4H), 3.61 (dt, *J* = 2.4, 9.2 Hz, 1H), 3.33 (s, 3H), 3.25 (dt, *J* = 2.4, 10.8 Hz, 1H), 2.58 (A of ABx, *J* = 5.8, 13.2 Hz, 1H), 2.29 (B of ABx, *J* = 9.0, 13.2 Hz, 1H), 2.22 (obs. m, 1H), 2.05 (d, *J* = 2.4 Hz, 1H), 1.93 (m, 1H), 1.63 (ddd, *J* = 3.2, 10.6, 14.0 Hz, 1H), 1.18 (ddd, *J* = 2.4, 10.4, 14.4 Hz, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 159.2, 144.5, 139.8, 136.4, 128.6, 128.0, 127.5, 124.8, 122.4, 115.3, 115.2, 114.9, 80.0, 73.1, 70.1, 57.0, 44.4, 40.4, 34.4, 30.8, 18.5, 17.5; IR (neat) ν_{max}: 3451, 3067, 2928, 1603, 1567, 1448, 1269, 1087, 916, 697 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{24}H_{31}BrO_3$ $[M+23]^+$ 469.1354, found 469.1335.

To a solution of alcohol (1.80 g, 4.02 mmol) in methylene chloride (20.0 mL) and *N*,*N*-diisopropylethylamine (4.20 mL, 24.1 mmol) at 0 °C was added DMAP (147 mg, 1.21 mmol) and chloromethyl methyl ether (1.22 mL, 16.1 mmol) dropwise. The reaction was allowed to warm up to room temperature overnight and was quenched by addition of saturated solution of sodium bicarbonate. The aqueous layer was extracted with methylene chloride (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 5% EtOAc/hexanes) to yield MOM-ether **22b** as a yellow oil (64%, three steps). $[\alpha]_D^{20}$ +17.2° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 6.94 (t, *J* = 2.0 Hz, 1H), 6.92 (t, *J* = 1.6 Hz, 1H), 6.71 (dd, *J* = 1.6, 2.0 Hz, 1H), 5.67 (m, 1H), 5.00 (m, 4H),

4.81 (A of ABq, J = 6.4 Hz, 1H), 4.62 (B of ABq, J = 6.8 Hz, 1H), 3.61 (dd, J = 2.0, 8.8 Hz, 1H), 3.39 (s, 3H), 3.32 (m, 1H), 3.31 (s, 3H), 2.64 (A of ABx, J = 5.2, 13.6 Hz, 1H), 2.27 (obs. q, J = 8.8, 15.6 Hz, 1H), 2.24 (B of ABx, J = 9.2, 13.6 Hz, 1H), 1.93 (m, 1H), 1.68 (ddd, J = 3.2, 10.6, 14.0 Hz, 1H), 1.21 (ddd, J = 2.0, 10.2, 14.0 Hz, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.75 (d, J = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 159.2, 144.6, 140.9, 136.5, 128.6, 128.0, 127.5, 124.9, 122.2, 115.2, 114.9, 114.8, 97.4, 80.7, 79.0, 70.0, 57.0, 56.0, 44.3, 40.6, 36.4, 31.0. 18.5, 17.6; IR (neat) ν_{max}: 2957, 2926, 1604, 1448, 1154, 1097, 1032, 918, 696 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{26}H_{35}BrO_4$ $[M+23]^+$ 513.1616, found 513.1606.



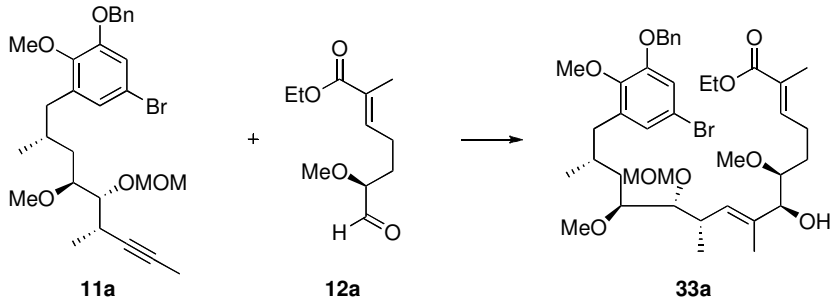
22b **11b**

1-(benzyloxy)-3-bromo-5-((2*R*,4*S*,5*R*,6*S*)-4-methoxy-5-(methoxymethoxy)-2,6-dimethylnon-7-ynyl)benzene (11b). To a solution of alkene **22b** (0.420 g, 0.710 mmol) in a 4:1 mixture of acetone (6.40 mL) and water (1.60 mL) was added *N*-methylmorpholine-*N*-oxide (0.166 g, 1.42 mmol). Osmium tetraoxide (0.20 M in toluene, 530 μL) was added dropwise and the reaction flask was stoppered. The reaction mixture stirred at room temperature for 4 hours before it was quenched with saturated solution of sodium thiosulfate. The aqueous layer was saturated with solid NaCl and extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude diol was used without further purification in the next step.

To solution of diol (0.440 g, 0.703 mmol) in dry benzene (14.0 mL) was added potassium carbonate (0.292 g, 2.11 mmol) followed by lead tetraacetate (0.468 g, 1.05 mmol). The reaction stirred for 30 minutes before it was quenched with saturated solution of sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Used directly in the next step.

To a suspension of potassium *tert*-butoxide (0.108 g, 0.967 mmol) in tetrahydrofuran (1.00 mL) under an atmosphere of Nitrogen at –78 °C was added dimethyl diazomethylphosphonate (0.166 g, 1.10 mmol) in tetrahydrofuran (1.00 mL) dropwise. The reaction mixture stirred for 15 minutes before a –78 °C solution of aldehyde **23b** (0.164 g, 0.276 mmol) in tetrahydrofuran (1.00 mL) was added dropwise. The reaction mixture stirred for 15 minutes at –78 °C and was diluted with ethyl acetate and washed with brine. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 2-5% EtOAc/hexanes) yielded terminal alkyne as a yellow oil (80%). $[\alpha]_D^{20}$ +8.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.31 (m, 5H), 6.94 (m, 2H), 6.72 (t, J = 1.8 Hz, 1H), 5.00 (s, 2H), 4.81 (A of ABq, J = 6.8 Hz, 1H), 4.65 (B of ABq, J = 6.8 Hz, 1H), 3.72 (dd, J = 2.0, 8.8 Hz, 1H), 3.67 (dt, J = 2.2, 8.0 Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.64 (A of ABx, J = 5.4, 13.2 Hz, 1H), 2.51 (m, 1H), 2.28 (B of ABx, J = 9.2, 13.6 Hz, 1H), 2.11 (d, J = 2.4 Hz, 1H), 1.97 (m, 1H), 1.69 (ddd, J = 3.6, 10.2, 14.0 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H), 1.25 (m, 1H), 0.82 (d, J = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 159.3, 144.6, 136.5, 128.6, 128.1, 127.5, 124.9, 122.3, 115.2, 114.9, 97.4, 85.8, 80.7, 78.7, 70.7, 70.1, 57.1, 56.2, 44.2, 36.5, 31.1, 28.2, 18.6, 18.1; IR (neat) ν_{max}: 3297, 2931, 2823, 1567, 1448, 1157, 1097, 1030 920, 697 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{26}H_{33}BrO_4$ $[M+23]^+$ 511.1460, found 511.1450.

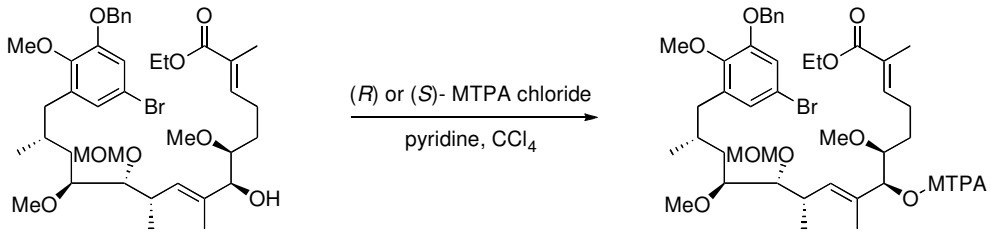
To a solution of terminal alkyne (0.355 g, 0.602 mmol) in tetrahydrofuran (6.00 mL) at –78 °C under an atmosphere of Nitrogen was added lithium hexamethyldisilazide (1.0 M in THF, 1.3 mL) dropwise. The reaction mixture was allowed to stir for 30 minutes at –78 °C before methyl iodide (375 μL, 6.02 mmol) was added dropwise. The reaction mixture was stirred for one hour at –78 °C and one hour at room temperature. The mixture was quenched by addition of water. The aqueous phase was extracted with ethyl ether (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 4% EtOAc/hexanes) provides methyl alkyne **11b** as a clear oil (334 mg, 0.554 mmol, 92%). $[\alpha]_D^{20}$ +7.9° (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 6.94 (m, 2H), 6.73 (br. s, 1H), 5.00 (s, 2H), 4.81 (A of ABq, *J* = 6.4 Hz, 1H), 4.64 (B of ABq, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 8.8 Hz, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 2.66 (A of ABx, *J* = 5.2, 13.6 Hz, 1H), 2.43 (m, 1H), 2.26 (B of ABx, *J* = 9.6, 13.6 Hz, 1H), 1.96 (m, 1H), 1.76 (d, *J* = 2.4 Hz, 3H), 1.67 (ddd, *J* = 3.6, 10.4, 14.4 Hz, 1H), 1.27 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 144.7, 136.5, 128.6, 128.0, 127.5, 124.9, 122.3, 115.2, 114.9, 97.3, 80.9, 80.5, 79.2, 78.0, 70.1, 57.0, 56.1, 44.2, 36.5, 31.1, 28.5, 18.6, 18.5, 3.4; IR (neat) ν_{max}: 3065, 3033, 2920, 2822, 1604, 1567, 1448, 1269, 1154, 1033, 920, 697 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{27}H_{35}BrO_4$ $[M+23]^+$ 525.1616, found 525.1654.



11a **12a** **33a**

(2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-ethyl 15-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-7,11-dihydroxy-6,12-dimethoxy-2,8,10,14-tetramethylpentadeca-2,8-dienoate (33a): To a sealed tube containing **11a** (13.0 mg, 0.0244 mmol) was added toluene (300 μL). Bis(cyclopentadienyl)zirconium chloride hydride (13.2 mg, 0.0512 mmol) was added and the reaction mixture was heated to 50 °C. After 6 hours, the reaction tube was allowed to cool to room temperature and then it was cooled to –65 °C. 2.00 M of dimethylzinc in toluene (13.4 μL) was added dropwise and the solution mixture was warmed to 0 °C. (*S*,*E*)-ethyl 6-methoxy-2-methyl-7-oxohept-2-enoate **12a** (7.83 mg, 0.0366 mmol) was added dropwise to the reaction mixture dropwise. After 1 hour at 0 °C, the reaction mixture was quenched with saturated solution of ammonium chloride. The aqueous layer was extracted with diethyl ether (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (25% EtOAc/hexanes) to yield a yellow glass **33a** (9.50 mg, 0.0135 mmol, 55%). $[\alpha]_D^{20}$ +10.0° (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.43-7.32 (m, 5H), 6.92 (q, *J* = 2.2, 5.4 Hz, 2H), 6.66 (dt, *J* = 6.0, 1.2 Hz, 1H), 5.30 (d, *J* = 9.2 Hz, 1H), 5.04 (s, 2H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.13 (q, *J* = 7.0, 14.2 Hz, 2H), 3.83 (m, 1H), 3.78 (s, 3H), 3.58 (d, *J* = 8.8 Hz, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.27 (s, 3H), 3.19 (m, 1H), 2.59 (m, 3H), 2.40 (dd *J* = 9.4, 13.4 Hz, 1H), 2.23 (m, 2H), 1.95 (m, 1H), 1.80 (s, 3H), 1.70 (m, 1H), 1.61 (s, 3H), 1.53 (m, 2H), 1.24 (m, 4H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 152.4, 147.0, 141.1, 136.9, 136.4, 133.8, 131.6, 128.6, 128.2, 128.0, 127.3, 125.6, 115.7, 115.0, 97.4, 81.3, 81.2, 79.7, 78.5, 70.8, 60.5, 60.4, 58.4, 56.9, 56.1, 37.7, 36.7, 34.5, 30.5, 29.3, 23.9, 19.0, 17.7, 14.2, 12.5, 12.4; IR (neat) ν_{max}: 3481, 2928, 2825, 1709, 1478, 1274, 1096, 1031 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{39}H_{57}BrO_9$ $[M+1]^+$ 749.3264, found 749.3218.

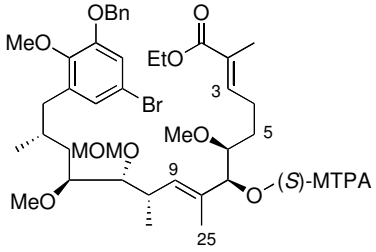
Determination of configuration at C7 alcohol:



33a

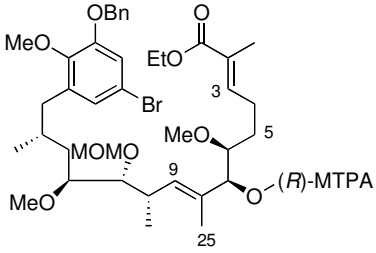
To solution of alcohol (2.0 mg, 0.0027mmol) in carbon tetrachloride (200 μL) was added pyridine (10 μl, 0.12 mmol) and (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (2 μL, 0.011 mmol). The reaction was stoppered and stirred for 24 hours at room temperature. Concentration of the solvent under reduced pressure was followed by column chromatography. The pure (*R*)- and (*S*)- Mosher esters were analyzed by NMR:

From (*R*)-MTPA-Cl:



δ C(9) = 5.32 ppm
δ C(25) = 1.44 ppm
δ C(5) = 2.25 ppm
δ C(3) = 6.61 ppm

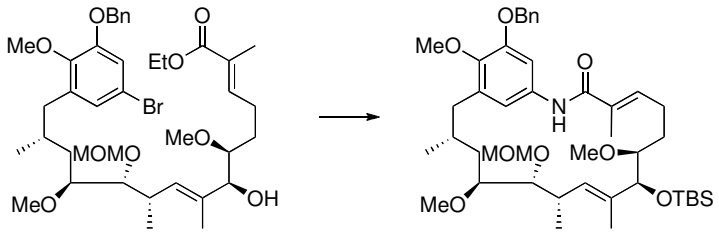
From (*S*)-MTPA- Cl:



δ C(9) = 5.38 ppm
δ C(25) = 1.61 ppm
δ C(5) = 2.22 ppm
δ C(3) = 6.59 ppm

Difference in chemical shifts:

$\Delta\delta_{SR}$ C(9) = – 0.06
$\Delta\delta_{SR}$ C(25) = – 0.17
$\Delta\delta_{SR}$ C(5) = + 0.03
$\Delta\delta_{SR}$ C(3) = + 0.02



33a **34a**

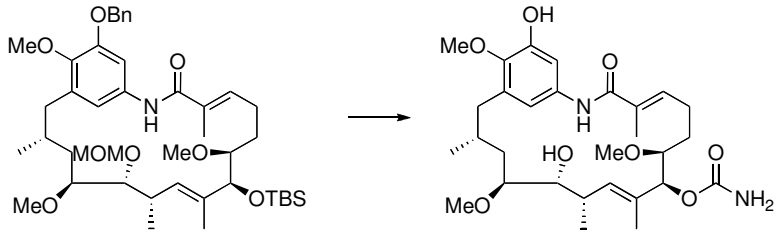
(4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-20-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-13-(methoxymethoxy)-4,10,12,16-tetramethyl-8,14,19-trimethoxy-2-aza-bicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-3-one (34a): To a solution of alcohol **33a** (13.0 mg, 0.0173 mmol) in methylene chloride (200 μL) at 0 °C was added 2,6-lutidine (8.03 μL, 0.0694 mmol) and *tert*-

butyldimethylsilyl trifluoromethanesulfonate (7.96 μL, 0.0347 mmol). Reaction was allowed to stir for 2 hours at 0 °C and was quenched by addition of saturated solution of sodium bicarbonate. The aqueous layer was extracted with methylene chloride (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 10% EtOAc/hexanes) to yield TBS ether as a yellow glass (13.0 mg, 0.0173 mmol, 87%). $[\alpha]_D^{20}$ +21.9° (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.24 (m, 5H), 6.92 (s, 2H), 6.41 (t, *J* = 7.4 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 1H). 5.04 (s, 2H), 4.83 (d, *J* = 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.11 (q, *J* = 7.2, 14.4 Hz, 2H), 3.93 (d, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 3.57 (d, *J* = 9.6 Hz, 1H), 3.44 (s, 3H), 3.38 (s, 3H), 3.25 (s, 3H), 3.18 (d, *J* = 10.4 Hz, 1H), 3.06 (m, 1H), 2.57 (dd, *J* = 5.8, 13.4 Hz, 1H), 2.44 (m, 2H), 2.23 (m, 2H), 1.95 (m, 1H), 1.79 (s, 3H), 1.75 (m, 1H), 1.58 (s, 3H), 1.45 (m, 1H) 1.31- 1.12 (m, 5H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.73 (d, *J* = 6.4 Hz, 3H), 0.05 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 152.4, 147.1, 141.6, 137.0, 136.5, 135.0, 130.7, 128.6, 128.0, 127.9, 127.3, 125.6, 115.7, 115.0, 97.4, 83.5, 81.1, 80.7, 79.4, 70.8, 60.5, 60.3, 59.8, 56.8, 56.1, 37.7, 36.6, 34.4, 30.3, 30.2, 25.8, 24.9, 19.0, 18.1, 17.7, 14.2, 12.5, 12.4, –4.6, –4.9; IR (neat) ν_{max}: 2955, 2929, 1710, 1473, 1277, 1111, 1031, 837 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{45}H_{71}BrO_9Si$ $[M]^+$ 862.4051, found 862.4046.

Into a 10mL round bottom flask containing ester (12.0 mg, 0.0139 mmol) was added a mixture of tetrahydrofuran (400 μL), methanol (400 μL), and water (200 μL). Lithium hydroxide, monohydrate (11.6 mg, 0.278 mmol) was added and reaction mixture was allowed to stir for 48 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with pH 4.5 NaH_2PO4 (10 mL) and extracted with methylene chloride (5x) with aqueous phase saturated with solid NaCl each time. The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude acid was used in the next step without further purification.

To a solution of acid (17.0 mg, 0.0203 mmol) in methylene chloride (1.00 mL) at –20 °C, was added sequentially triethylamine (85.4 μL, 0.50 M solution in methylene chloride) and ethyl chloroformate (46.8 μL, 0.50 M solution in methylene chloride). The reaction mixture was allowed to stir for 30 minutes at –20 °C (checked by TLC) before anhydrous ammonia (*l*) was bubbled into the solution (until the disappearance of the mixed anhydride by TLC). The reaction was quenched with water and warmed to room temperature. The aqueous layer was extracted with methylene chloride (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (silica, 30-80% EtOAc/hexanes) to yield amide as a yellow glass (10.0 mg, 0.0120 mmol, 59%) and recovered acid as a clear glass (6.0 mg, 0.0072 mmol). $[\alpha]_D^{20}$ +14.0° (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43-7.30 (m, 5H), 6.92 (q, *J* = 2.2, 6.2 Hz, 2H), 6.28 (t, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 5.04 (s, 2H), 4.82 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 3.59 (d, *J* = 8.4 Hz, 1H), 3.44 (s, 3H), 3.38 (s, 3H), 3.33 (d, *J* = 4.8 Hz, 1H), 3.26 (s, 3H), 3.18 (d, *J* = 10.4 Hz, 1H), 3.06 (m, 1H), 2.59 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.47 (m, 1H), 2.40 (dd, *J* = 9.4, 13.2 Hz, 1H), 2.20 (m, 2H), 1.93 (m, 1H), 1.79 (s, 3H), 1.70 (m, 1H), 1.57 (s, 3H), 1.43 (m, 1H), 1.31-1.13 (m, 2H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 152.4, 147.0, 137.1, 137.0, 136.3, 134.9, 130.7, 130.2, 128.6, 128.1, 127.4, 125.6, 115.7, 114.9, 97.4, 83.6, 81.2, 80.8, 79.5, 70.8, 60.5, 59.8, 56.8, 56.1, 37.7, 36.7, 34.3, 30.5, 30.3, 25.8, 24.9, 19.0, 18.1, 17.6, 12.7, 12.5, –4.6, –4.9; IR (neat) ν_{max}: 3348, 3189, 2929, 2856, 1676, 1473, 1108, 1031, 838 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{43}H_{68}BrNO_8Si$ $[M]^+$ 833.3898, found 833.3405. HRMS does not fall within the (+/- 3 mDa) limit to assign a unique molecular formula to this substance and insufficient quantity of sample for re-analysis.

To a solution of amide (10.0 mg, 0.0120 mmol) in toluene (0.800 mL) in a sealed tube was added potassium carbonate (4.96 mg, 0.0359 mmol). Copper(I) iodide (1.1 mg, 0.0060 mmol) and *N*,*N*'-dimethyl-1,2-ethanediamine (1.28 μL, 0.0120 mmol) were added sequentially and sealed tube was closed. The green suspension was heated to 100 °C for 36 hours. Contents were filtered over plug of silica and washed with ethyl acetate. Concentration of the solvent followed by flash chromatography (silica, 20-100% EtOAc/hexanes) yields product **34a** as a clear glass (8.0 mg, 0.0106 mmol, 83 %). $[\alpha]_D^{20}$ +79.3° (*c* 0.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.31 (m, 6H), 6.89 (bs, 1H), 6.40 (d, *J* = 2.0 Hz,1H), 5.99 (t, *J* = 5.8 Hz, 1H), 5.07 (d, 1H), 5.07 (s, 2H), 4.79 (d, *J* = 6.8 Hz , 1H), 4.64 (d, *J* = 6.4 Hz, 1H), 3.80 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.49 (d, *J* = 8.4 Hz, 1H), 3.47 (s, 3H), 3.41 (s, 3H), 3.33 (s, 3H), 3.23 (m, 1H), 3.01 (t, *J* = 8.0 Hz, 1H), 2.66-2.50 (m, 3H), 2.23 (m, 1H), 2.14 (m, 1H), 1.78 (m, 1H), 1.62 (br s, 4H), 1.46 (s, 3H), 1.23 (m, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.79 (br d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 152.1, 145.3, 137.1, 136.7, 135.2, 134.6, 133.5, 132.1, 128.6, 128.0, 127.3, 119.7, 117.6, 105.6, 97.5, 83.4, 82.5, 80.8, 77.2, 70.6, 60.9, 60.8, 57.5, 56.1, 35.6, 35.3, 34.1, 33.0, 31.3, 25.8, 24.5, 20.0, 18.1, 16.9, 13.4, 11.2, –4.7, –4.8; IR (neat) ν_{max}: 3261, 2953, 2929, 1652, 1108, 1032, 837 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{43}H_{67}NO_8Si$ $[M]^+$ 753.4636, found 753.4647.

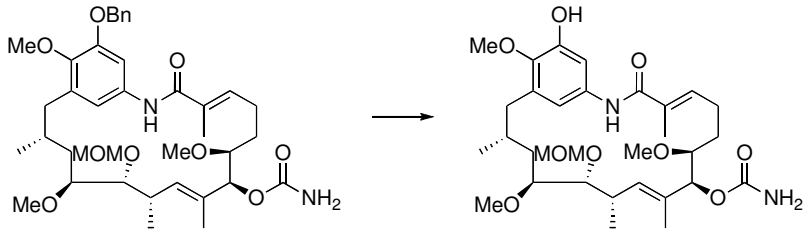


34a **1**

Reblastatin (1). To a solution of TBS ether **34a** (13.0 mg, 0.0172 mmol) in tetrahydrofuran (1.30 mL) in a nalgene vial, was added premixed solution of [pyridine hydrofluoride:pyridine:THF (1:1:2.5) by volume] (600 μL) dropwise. The reaction was allowed to run at room temperature for 24 hours before another 600 μL of HF mixture was added. The reaction stirred for another 12 hours and was quenched by addition of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica, 50-100% EtOAc/hexanes) to yield secondary alcohol as a clear glass (10.0 mg, 0.0156 mmol, 89%). *This material was used immediately in the next step with out further purification.*

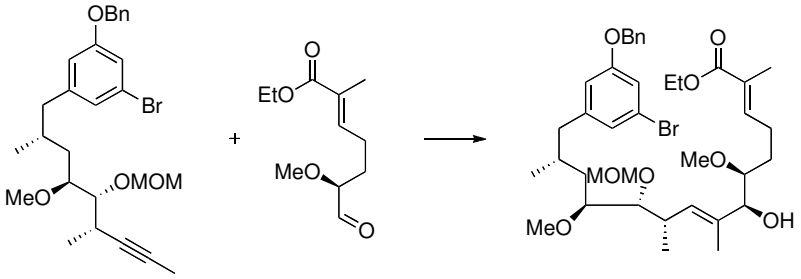
To a solution of secondary alcohol (4.0 mg, 0.0063 mmol) in CH_2Cl_2 (800 μL) was added trichloroacetyl isocyanate (1.5 μL, 0.0126 mmol). The reaction was stirred for 15 minutes and methanol (1.0 mL) was added followed by potassium carbonate (4.0 mg). The reaction stirred for ½ hour (monitor by TLC) before solvent was evaporated *in vacuo.* The crude product was purified by quick plug to yield carbamate as a clear glass and immediately used in the next step (3.5 mg, 0.0051 mmol, 80%). $[\alpha]_D^{20}$ +80.0° (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (bs, 1H), 7.46-7.27 (m, 5H), 6.39 (d, *J* = 2.8 Hz, 1H), 6.07 (t, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 9.6 Hz, 1H), 5.22 (s, 1H), 5.10 (q, *J* = 7.6, 12.0 Hz, 2H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.4 Hz, 1H), 3.76 (s, 3H), 3.58 (d, *J* = 9.2 Hz, 1H), 3.41 (s, 3H), 3.39 (m, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.23 (d, *J* = 5.6 Hz, 1H), 2.63-2.44 (m, 4H), 2.24 (m, 1H), 1.83 (s, 3H), 1.57 (s, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 156.6, 152.1, 144.5, 137.2, 136.1, 134.7, 130.0, 128.6, 128.0, 127.6, 114.9, 104.3, 97.3, 84.3, 80.5, 80.0, 77.4, 70.6, 61.1, 59.0, 56.8, 56.2, 37.0, 34.7, 34.4, 29.9, 29.3, 26.0, 20.9, 17.8, 13.8, 13.3; IR (neat) ν_{max}: 3342, 2927, 1718, 1664, 1033, 754 cm^{-1}; HRMS (CI, FAB) *m/z* calc'd for $C_{38}H_{54}N_2O_9$ $[M+1]^+$ 683.3908, found 683.3877.

To a suspension of aluminum trichloride (11.7 mg, 0.0879 mmol) in methylene chloride (2.20 mL) at –78 °C was added anisole (2.90 mL) dropwise. The light yellow solution was stirred for an additional 5 minutes before carbamate (6.0 mg, 0.00879 mmol) in methylene chloride (0.700 mL) was added dropwise. The reaction mixture was allowed to warm up to 0 °C over 3 hours (on its own) and stirred for an additional 1 h at room temperature. Reaction was quenched by slow addition of 0.5 M HCl. The biphasic mixture was diluted with ammonium chloride and extracted with ethyl acetate (3x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 1-5% MeOH/CH_2Cl_2) yields reblastatin (**1**) as a white solid (3.60 mg, 3.28 mmol, 75%). $[\alpha]_D^{20}$ +58° (*c* 0.1, MeOH); Mp: 228 °C; ^{1}H NMR (300 MHz, DMSO): δ 9.23 (s, 1H), 6.86 (br. s, 1H), 6.50 (br. s, 2H), 6.29 (br. s, 1H), 5.86 (br. t), 5.29 (d, *J* = 9.9 Hz, 1H), 4.86 (d, *J* = 7.2 Hz, 1H), 4.35 (br. d, *J* = 5.1 Hz, 1H), 3.62 (s, 3H), 3.32 (s, 3H), 3.32 (m, 1H), 3.27 (m, 1H), 3.21 (s, 3H), 3.02 (m, 1H), 2.56 (dd, *J* = 6.6, 13.5 Hz, 1H), 2.36 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 2.10 (m, 1H), 1.74 (m, 1H), 1.67 (s, 3H), 1.54 (m, 1H), 1.42 (s, 3H), 1.35 (m, 1H), 1.27 (m, 1H), 1.15 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO): δ 170.3, 156.1, 149.7, 142.5, 134.5, 133.4, 132.2, 129.7, 114.7, 107.2, 81.1, 80.7, 79.5, 73.6, 59.8, 58.3, 56.4, 35.8, 34.3, 33.7, 31.2, 29.8, 23.6, 19.8, 16.1, 13.1, 11.7; IR (neat) ν_{max}: 3351, 2926, 1717, 1653, 1608, 1457, 1381, 1289, 1092, 1029, 862 cm^{-1}; HRMS (CI, FAB) *m/z* calc'd for $C_{29}H_{44}N_2O_8$ $[M]^+$ 548.3098, found 548.3139.



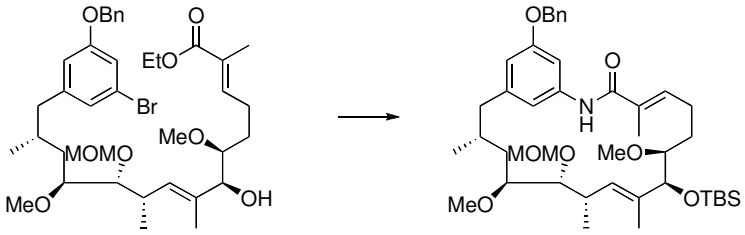
6

(4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*) Carbamic acid 20-hydroxy-13-(methoxymethoxy)-4,10,12,16-tetramethyl-8,14,19-trimethoxy-3-oxo-2-aza-bicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-9-yl ester (6). To a solution of carbamate (5.00 mg, 0.0073 mmol) in methylene chloride (0.800 μL) at –78 °C was added BCl_3 (1.0 M in hexane, 77.0 μL, 0.077 mmol). The reaction mixture was allowed to stir for 16 hours before MeOH (1.0 mL) was added followed by saturated solution of sodium bicarbonate. The mixture was allowed to reach room temperature and stirred for another ½ hour. The aqueous phase was extracted with ethyl acetate (3x). The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and concentrated. The crude product was purified with flash chromatography (silica, 10% MeOH/CH_2Cl_2) to yield reblastatin (**1**) (2.00 mg, 0.00365 mmol, 53%) and MOM-protected reblastatin **6** as a clear glass (0.60 mg, 0.00101 mmol, 14.0%). $[\alpha]_D^{20}$ +99.5° (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (bs, 1H), 7.30 (bs, 1H), 6.33 (d, *J* = 2.4 Hz, 1H), 6.03 (t, *J* = 7.2 Hz, 1H), 5.69 (s, 1H), 5.36 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = Hz, 1H), 4.84 (A of ABq, *J* = 6.8 Hz, 1H), 4.76 (ovp bs, 2H), 4.63 (B of ABq, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 3.59 (d, *J* = 8.8 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.37 (ovp m, 1H), 3.29 (s, 3H), 3.21 (m, 1H), 2.50 (bm, 4H), 2.20 (m, 1H), 1.81 (s, 3H), 1.68 (m, 1H), 1.55 (s, 3H), 1.45 (m, 2H), 1.29 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 156.5, 149.5, 142.7, 135.3, 134.6, 133.7, 130.1, 106.4, 97.5, 84.3, 80.5, 80.2, 77.4, 70.5, 61.8, 59.1, 56.8, 56.3, 36.7, 35.0, 34.7, 31.2, 29.9, 29.4, 25.8, 20.7, 18.0, 13.5; IR (neat) ν_{max}: 3359, 2923, 1701, 1653, 1559, 1457, 1096 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{31}H_{48}N_2O_9$ $[M]^+$ 592.3360, found 592.3350.



11b **12a** **33b**

(2*E*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*)-ethyl 15-(3-(benzyloxy)-5-bromophenyl)-7-hydroxy-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10-trimethylpentadeca-2,8-dienoate (33b). Prepared as per **33a** (Cp_2ZrHCl, $ZnMe_2$, toluene). Purification by flash chromatography (silica, 30% EtOAc/hexanes) provided 40-89% of the secondary alcohol as a yellow oil. $[\alpha]_D^{20}$ +12.2° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.28 (m, 5H), 6.94 (s, 1H), 6.91 (s, 1H), 6.71 (s, 1H), 6.66 (t, *J* = 7.4 Hz, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.99 (s, 2H), 4.81 (A of ABq, *J* = 6.4 Hz, 1H), 4.60 (B of ABq, *J* = 6.4 Hz, 1H), 4.13 (q, *J* = 7.4, 14.6 Hz, 1H), 3.84 (dd, *J* = 3.2, 6.4 Hz, 1H), 3.60 (d, *J* = 9.2 Hz, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 3.28 (s, 3H), 3.20 (m, 2H), 2.64 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.54 (d, *J* = 2.8 Hz, 1H), 2.51 (m, 1H), 2.24 (m, 3H), 1.94 (m, 1H), 1.81 (s, 3H)1.72 (m, 1H), 1.61 (s, 3H), 1.54 (m, 1H), 1.28 (m, 1H), 1.23 (t, *J* = 6.4 Hz, 1H), 1.14 (m, 1H), 1.06 (d, *J* = 6.4 Hz, 1H), 0.72 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 167.8, 159.2, 144.3, 140.9, 136.4, 133.8, 131.4, 128.5, 128.2, 128.0, 127.4, 124.8, 122.3, 115.1, 114.9, 97.3, 81.2, 81.0, 79.4, 78.6, 70.0, 60.3, 58.4, 56.8, 56.0, 44.1, 36.4, 34.4, 30.8, 29.3, 23.9, 18.6, 17.7, 14.2, 12.3; IR (neat) ν_{max}: 3457, 2928, 1708, 1448, 1269, 1097, 1030, 697 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{38}H_{55}BrO_8$ $[M+23]^+$ 741.2978, found 741.3000.



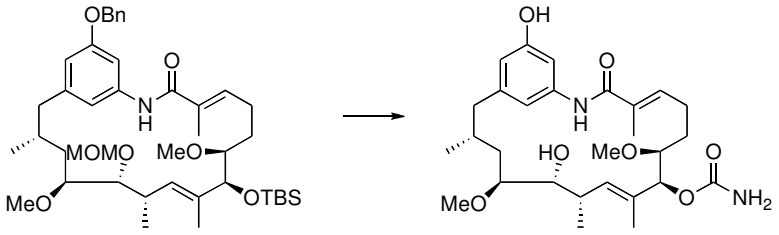
33b **34b**

(4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-20-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-8,14-dimethoxy-13-(methoxymethoxy)-4,10,12,16-tetramethyl-2-aza-bicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-3-one (34b): Prepared as per route to **34a.**

(TBSOTf, 2,6-lutidine, CH_2Cl_2). Purification by flash chromatography (silica, 20% EtOAc/hexanes) provided 95% of TBS-ether as a yellow oil. $[\alpha]_D^{20}$ +16.9° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.29 (m, 5H), 6.93 (s, 1H), 6.91 (s, 1H), 6.71 (s, 1H), 6.64 (dt, *J* = 1.6, 7.4 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 4.99 (s, 1H), 4.83 (A of ABq, *J* = 6.4 Hz, 1H), 4.60 (B of ABq, *J* = 6.4 Hz, 1H), 4.11 (q, *J* = 7.0, 14.2 Hz, 1H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 3.44 (s, 3H), 3.38 (s, 3H), 3.26 (s, 3H), 3.18 (d, *J* = 10.8 Hz, 1H), 3.06 (ddd, *J* = 2.8, 7.0, 10.0 Hz, 1H), 2.64 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.46 (m, 1H), 2.23 (m, 3H), 1.93 (m, 1H), 1.79 (s, 3H), 1.73 (m, 1H), 1.56 (s, 3H), 1.46 (m, 1H), 1.30 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.12 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.71 (d, *J* = 6.4 Hz, 1H), 0.05 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 168.0, 159.3, 144.5, 141.5, 136.5, 135.0, 130.5, 128.6, 128.0, 127.5, 124.9, 122.3, 115.2, 114.9, 97.4, 83.4, 81.0, 80.6, 79.2, 70.1, 60.3, 59.8, 56.8, 56.1, 44.2, 36.4, 30.8, 30.1, 25.8, 24.9, 18.7, 18.1, 17.8, 14.2, 12.5, 12.4, -4.7, -4.9; IR (neat) ν_{max}: 2955, 2928, 2856, 2823, 1710, 1448, 1258, 1111, 1031, 837, 776 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{44}H_{69}BrO_8Si$ $[M+23]^+$ 855.3843, found 855.3819.

((i) LiOH; (ii) EtOCOCl, NEt_3, CH_2Cl_2; NH_3). Purification by flash chromatography (silica, 50% EtOAc/hexanes) provided 60% (2 steps) of amide as a yellow oil and recovered acid in 40%. $[\alpha]_D^{20}$ +10.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.29 (m, 5H), 6.94 (s, 1H), 6.91 (s, 1H), 6.71 (s, 1H), 6.32 (t, *J* = 6.6 Hz, 1H), 5.41 (br. s, 2H), 5.13 (d, *J* = 9.6 Hz, 1H), 4.99 (s, 2H), 4.82 (A of ABq, *J* = 6.8 Hz, 1H), 4.60 (B of ABq, *J* = 6.4 Hz, 1H), 3.94 (d, *J* = 6.8 Hz, 1H), 3.59 (d, *J* = 9.6 Hz, 1H), 3.43 (s, 3H), 3.38 (s, 3H), 3.27 (s, 3H), 3.18 (d, *J* = 10.8 Hz, 1H), 3.07 (ddd, *J* = 2.4, 6.8, 9.6 Hz, 1H), 2.65 (dd, *J* = 5.2, 13.6 Hz, 1H), 2.46 (m, 1H), 2.21 (m, 3H), 1.92 (m, 1H), 1.80 (s, 3H), 1.71 (ddd, *J* = 3.6, 10.8, 14.4 Hz, 1H), 1.56 (s, 3H), 1.46 (m, 1H), 1.27 (m, 1H), 1.13 (m, 1H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H), 0.71 (d, *J* = 6.4 Hz, 1H), 0.05 (s, 3H), –0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 159.2, 144.5, 137.3, 136.4, 134.9, 130.5, 130.0, 128.6, 128.1, 127.5, 124.9, 122.3, 115.2, 115.0, 97.4, 83.6, 81.1, 80.3, 79.4, 70.1, 59.7, 56.8, 56.1, 44.2, 36.4, 34.3, 30.9, 30.2, 25.8, 24.8, 18.8, 18.1, 17.6, 12.64, 12.56, –4.7, –4.9; IR (neat) ν_{max}: 3342, 2954, 2927, 1684, 1457, 1376, 1250, 1110, 1030, 837 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{42}H_{66}BrNO_7Si$ $[M+23]^+$ 826.3690, found 826.3662.

(CuI, K_2CO_3, diamine ligand, toluene). Purification by flash chromatography (silica, 50% EtOAc/hexanes) provided 82% of macrolactam as a clear oil. $[\alpha]_D^{20}$ +49.6° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.30 (m, 5H), 7.13 (br. s, 1H), 6.69 (br. s, 1H), 6.55 (s, 1H), 6.36 (s, 1H), 5.85 (t, *J* = 6.0 Hz, 1H), 5.00 (s, 2H), 4.98 (d, 1H), 4.81 (A of ABq, *J* = 6.4 Hz, 1H), 4.65 (B of ABq, *J* = 6.8 Hz, 1H), 3.77 (d, *J* = 7.6 Hz, 1H), 3.54 (d, *J* = 8.8 Hz, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 3.31 (s, 3H), 3.12 (d, *J* = 10.0 Hz, 1H), 2.98 (dt, *J* = 3.0 Hz, 7.8 Hz, 1H), 2.78 (dd, *J* = 4.0, 13.2 Hz, 1H), 2.43 (m, 1H), 2.36 (dd, *J* = 6.4, 13.6 Hz, 1H), 2.20 (m, 1H), 2.11 (m, 1H), 1.91 (m, 1H), 1.74 (s, 3H), 1.62 (m, 1H), 1.53 (s, 1H), 1.25 (m, 1H), 1.17-1.08 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 1H), 0.86 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 1H), 0.04 (s, 3H), -0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 173.0, 159.1, 142.1, 139.1, 136.6, 136.1, 134.6, 131.1, 131.0, 128.6, 128.0, 127.5, 118.0, 113.8, 105.7, 97.6, 83.3, 82.4, 82.0, 79.6, 70.0, 60.8, 57.0, 56.2, 42.9, 34.4, 33.5, 31.3, 30.7, 25.8, 23.7, 18.4, 18.1, 17.6, 13.7, 11.0, -4.7, -4.9; IR (neat) ν_{max}: 3300, 2927, 2856, 1664, 1594, 1461, 1111, 1032, 837 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{42}H_{65}NO_7Si$ $[M+23]^+$ 746.4428, found 746.4434.

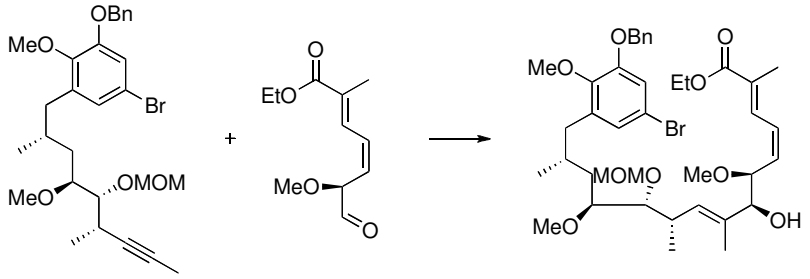


34b **2**

Autolytimycin (2). Prepared as per route to reblastatin (**1**).

((i) HF•pyr, THF; (ii) $Cl_3CCONCO$, CH_2Cl_2; MeOH, K_2CO_3). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provided 80% (2 steps) of carbamate as a clear glass. $[\alpha]_D^{20}$ +49.3° (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (br. s, 1H), 7.43-7.28 (m, 6H), 6.53 (s, 1H), 6.39 (s, 1H), 5.98 (t, *J* = 6.4 Hz, 1H), 5.35 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 4.0 Hz, 1H), 5.02 (s, 2H), 4.83 (A of ABq, *J* = 6.4 Hz, 1H), 4.78 (br. s, 2H), 4.63 (B of ABq, *J* = 6.4 Hz, 1H), 3.59 (d, *J* = 9.2 Hz, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 3.34 (m, 1H), 3.29 (s, 3H), 3.20 (m, 1H), 2.74 (d, *J* = 10.0 Hz, 1H), 2.52-2.38 (m, 2H), 2.18 (m, 2H), 1.83 (s, 3H), 1.61 (m, 2H), 1.52 (s, 3H), 1.44 (m, 2H), 1.28 (m,1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 171.2, 159.1, 156.5, 143.4, 139.5, 136.8, 133.9, 131.1, 129.7, 128.5, 127.9, 127.6, 115.4, 113.1, 104.4, 97.3, 83.5, 80.6, 80.1, 79.9, 77.2, 70.0, 59.0, 56.6, 56.1, 42.9, 42.2, 35.5, 34.5, 29.4, 25.0, 19.7, 17.8, 13.3, 13.0; IR (neat) ν_{max}: 3345, 2927, 1733, 1653, 1457, 1375, 1154, 1106, 1032, 837, 740 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{37}H_{52}N_2O_8$ $[M+23]^+$ 675.3621, found 675.3606.

($AlCl_3$, anisole). Purification by flash chromatography (silica, 1-5% MeOH/CH_2Cl_2) provided 76% of autolytimycin (**2**) as a white solid. $[\alpha]_D^{20}$ +32.5° (*c* 0.4, MeOH); Mp: 246 °C; ^{1}H NMR (d_6-DMSO, 50 °C, 300 MHz): δ 9.20 (s, 1H), 9.13 (s, 1H), 6.65 (s, 1H), 6.34 (br. s, 2H), 6.25 (s, 2H), 5.75 (br t, *J* = 6.2, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 4.86 (d, *J*= 7.2 Hz, 1H), 4.18 (d, *J* = 4.8 Hz, 1H), 3.38 (m, 1H), 3.32 (s, 3H), 3.24 (m, 1H), 3.23 (s, 3H), 3.01 (m, 1H), 2.54 (dd, *J* = 5.1, 13.2 Hz, 1H), 2.35 (m, 1H), 2.28 (dd, *J* = 6.0, 12.9, Hz, 1H), 2.17 (m, 1H), 2.07 (m, 1H), 1.78 (m, 1H), 1.71 (s, 3H), 1.51 (m, 1H), 1.41 (s, 3H), 1.29 (m, 1H), 1.25 (m, 1H), 1.17 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (d_6-DMSO, 50 °C, 75 MHz): δ 170.8, 157.4, 156.1, 141.2, 140.1, 134.2, 133.1, 131.8, 129.9, 115.0, 112.6, 105.8, 80.7, 80.65, 79.5, 73.4, 58.2, 56.3, 42.7, 34.0, 33.5, 30.5, 29.6, 23.3, 18.7, 16.6, 13.2, 11.7; IR (neat) ν_{max}: 3332, 3272, 3197, 2913, 2877, 2824, 1711, 1653, 1617, 1593, 1399, 1383, 1109, 1039, 872 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{28}H_{42}N_2O_7$ $[M+23]^+$ 541.2890, found 541.2900.

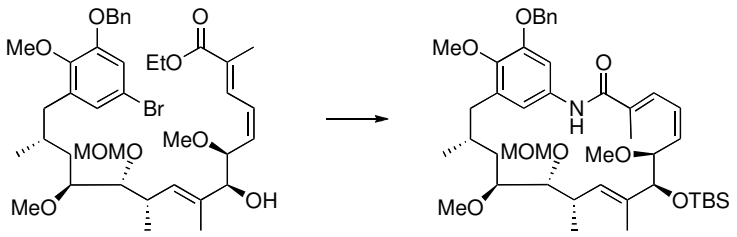


11a **12b** **35**

(2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*R*)-ethyl 15-(3-(benzyloxy)-5-bromo-2-methoxyphenyl)-7-hydroxy-6,12-dimethoxy-11-(methoxymethoxy)-2,8,10,14-tetramethylpentadeca-2,4,8-trienoate (35).

To a solution of alcohol **32** (65.0 mg, 0.303 mmol) in methylene chloride (3.00 mL) at room temperature was added sequentially 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (4.74 mg, 0.0303 mmol) and iodobenzene diacetate (107 mg, 0.334 mmol). Reaction stirred for 24 hours (monitored by TLC). The mixture was concentrated under reduced pressure and crude aldehyde **12b** was used directly in the next step (60.0 mg, 0.283 mmol, 93.4%).

Using **11a** and **12b** as per **33a** ($ZrCp_2HCl$, $ZnMe_2$, toluene). Purification by flash chromatography (silica, 30% EtOAc/hexanes) provided 51-62% of secondary alcohol as a yellow oil. $[\alpha]_D^{20}$ + 64.4° (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (m, 6H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.53 (t, *J* = 11.6 Hz, 1H), 5.47 (t, *J* = 10.4 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 5.04 (s, 2H), 4.77 (A of ABx, *J* = 6.8 Hz, 1H), 4.58 (B of ABx, *J* = 6.8 Hz, 1H), 4.18 (dq, *J* = 1.4, 7.2, 14.4 Hz, 2H), 4.12 (d, *J* = 10.0 Hz, 1H), 3.89 (dd, *J* = 1.8, 8.0 Hz, 1H), 3.77 (s, 3H), 3.51 (dd, *J* = 2.0 Hz, 8.4 Hz, 1H), 3.37 (s, 3H), 3.29 (s, 3H), 3.28 (s, 3H), 3.16 (d, *J* = 9.2 Hz, 1H), 2.83 (d, *J* = 2.0 Hz, 1H), 2.2.57 (A of ABq, *J* = 5.6, 13.2 Hz, 1H), 2.46 (m, 1H), 2.37 (B of ABq, *J* = 9.0, 13.2 Hz, 1H), 1.88 (s, 3H), 1.88 (m, 1H), 1.65 (m, 1H), 1.58 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.14 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 1H), 0.70 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 168.0, 152.4, 147.1, 137.0, 136.5, 133.3, 133.2, 132.6, 131.2, 130.5, 128.9, 128.6, 128.1, 127.3, 125.7, 115.6, 115.1, 97.3, 81.1, 80.0, 79.9, 78.7, 70.8, 60.8, 60.5, 56.9, 56.5, 56.0, 37.8, 37.0, 34.3, 30.6, 19.2, 17.3, 14.3, 12.8, 12.4; IR (neat) ν_{max}: 3462, 2929, 2823, 1707, 1477, 1248, 1096, 1030, 746 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{39}H_{55}BrO_9$ $[M+23]^+$ 769.2927, found 769.2930.



35 36

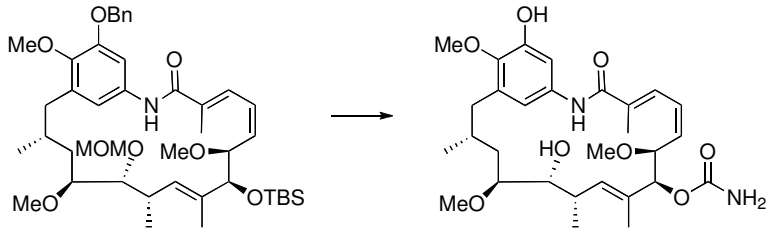
(4*E*,6Z,8S,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-20-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)-13-(methoxymethoxy)-8,14,19-trimethoxy-4,10,12,16-tetramethyl-2-aza-bicyclo[16.3.1]docosa-1(21),4,6,10,18(22),19-hexaen-3-one (36). Prepared as per route to **34a**.

(TBSOTf, 2,6-lutidine, CH_2Cl_2). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provided 95% of TBS-ether as a yellow oil. $[\alpha]_D^{20}$ + 66.1° (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J* = 12.0 Hz, 1H), 7.37 (m, 5H), 6.92 (d, *J* = 2.4 Hz, 2H), 6.45 (t, *J* = 11.6 Hz, 1H), 5.45 (t, *J* = 10.6 Hz, 1H), 5.15 (d, *J* = 9.6 Hz, 1H), 5.04 (s, 2H), 4.81 (A of ABx, *J* = 6.4 Hz, 1H), 4.59 (B of ABx, *J* = 6.4 Hz, 1H), 4.19 (q, *J* = 7.0, 14.2 Hz, 2H), 4.094 (dd, *J* = 6.8, 9.8 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 3.56 (d, *J* = 9.2 Hz, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.2.4 (s, 3H), 3.19 (d, *J* = 10.4 Hz, 1H), 2.59 (A of ABx, *J* = 5.6, 13.2 Hz, 1H), 2.43 (obs. m, 1H), 2.39 (B of ABx, *J* = 9.2, 13.2 Hz, 1H), 1.91 (m, 1H), 1.86 (s, 3H), 1.70 (m, 1H), 1.56 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 2H), 1.14 (m, 1H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.85 (s, 9H), 0.71 (d, *J* = 6.4 Hz, 3H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.2, 152.4, 147.1, 137.1, 136.5, 134.7, 134.6, 132.0, 131.5, 129.5, 128.6, 128.0, 127.5, 127.3, 125.6, 115.7. 115.1, 97.4, 81.2, 81.1, 80.0, 79.5, 70.8, 60.7, 60.5, 56.8, 56.7, 56.1, 37.8, 36.7, 34.3, 30.5, 25.8, 19.2, 18.2, 17.5, 14.3, 12.7. 12.4, –4.7, –4.9; IR (neat) ν_{max}: 2955, 2928, 2856, 2821, 1708, 1472, 1248, 1101, 1030, 838 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{45}H_{69}BrO_9Si$ $[M+23]^+$ 883.3792, found 883.3769.

((i) LiOH; (ii) $(CH_3)_2CHCH_2OCOCl$, NEt_3; NH_3). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provided 75% of amide as a yellow oil and recovered acid in 25%. $[\alpha]_D^{20}$ + 64.9° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.30 (m, 6H), 6.92 (d, *J* = 4.4 Hz, 1H), 6.40 (t, *J* = 11.6 Hz, 1H), 5.41 (t, *J* = 10.6 Hz, 1H), 5.40 (br. s, 2H), 5.13 (d, *J* = 9.6 Hz, 1H), 5.04 (s, 2H), 4.81 (A of ABx, *J* = 6.4 Hz, 1H), 4.59 (B of ABx, *J* = 6.8 Hz, 1H), 4.10 (dd, *J* = 6.8, 10.0 Hz, 1H), 3.96 (d, *J* = 6.8 Hz, 1H), 3.77 (s, 3H), 3.55 (d, *J* = 9.6 Hz, 1H), 3.38 (s, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 3.18 (d, *J* = 10.0 Hz, 1H), 2.60 (A of ABx, *J* = 5.6, 13.2 Hz, 1H), 2.41 (m, 1H), 2.37 (B of ABx, *J* = 9.4, 13.2 Hz, 1H), 1.90 (m, 1H), 1.85 (s, 3H), 1.69 (m, 1H), 1.51 (s, 3H), 1.14 (m, 1H), 1.00 (d, *J* = 6.4 Hz, 1H), 0.85 (s, 9H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 170.5, 152.4, 147.1, 137.1, 136.4, 134.8, 133.9, 131.5, 131.0, 129.0, 128.6, 128.1, 127.4, 127.1, 125.7, 115.6, 115.0, 97.3, 81.5, 81.3, 79.9, 79.5, 70.8, 60.5, 56.8, 56.7, 56.1, 37.8, 36.8, 34.3, 30.6, 25.8, 19.2, 18.2, 17.4, 12.8, 12.4, –4.7, –4.8; IR (neat) ν_{max}: 3350, 3188, 2955, 2928, 2856, 2822, 1666, 1590, 1469, 1379, 1191, 1030, 838, 778 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{43}H_{66}BrNO_8Si$ $[M+23]^+$ 854.3639, found 854.3671.

(CuI, K_2CO_3, diamine ligand, toluene). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provided 80% of macrolactam as a yellow oil. $[\alpha]_D^{20}$ –8.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44-7.30 (m, 6H), 6.64 (br. s, 1H), 6.32 (m, 2H), 5.25 (br. s, 1H), 5.06 (s, 2H), 5.02 (br. s, 1H), 4.75 (br. s, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 3.91 (br. s, 1H), 3.80 (br. s, 1H), 3.78 (s, 3H), 3.40 (br. s, 1H), 3.38 (s, 3H), 3.28 (br. s, 3H), 3.20 (s, 3H), 3.00 (br. s, 1H), 2.76 (dd, *J* = 6.2, 14.0 Hz, 1H), 2.40 (m, 2H), 2.04 (m, 1H), 1.89 (s, 3H), 1.52 (m, 1H), 1.27 (br. s, 3H), 1.18 (dd, *J* = 7.2, 15.2 Hz, 1H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.83 (s, 12H), 0.02 (s, 3H), -0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ

173.0, 152.3, 145.4, 136.6, 134.5, 134.4, 134.3, 133.2, 131.6, 128.6, 128.0. 127.4, 127.0, 126.6, 117.6, 105.2, 97.7, 83.1, 82.2, 77.2, 80.0, 79.1, 70.6, 60.5, 56.7, 56.1, 36.1, 34.4, 30.9, 29.6, 25.7, 19.8, 18.2, 17.7, 14.0, 11.3, –4.7, –4.9; IR (neat) ν_{max}: 3268, 2954, 2929, 2856, 2822, 1654, 1596, 1104, 1030, 838, 778 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{43}H_{65}NO_8Si$ $[M+23]^+$ 774.4377, found 774.4356.

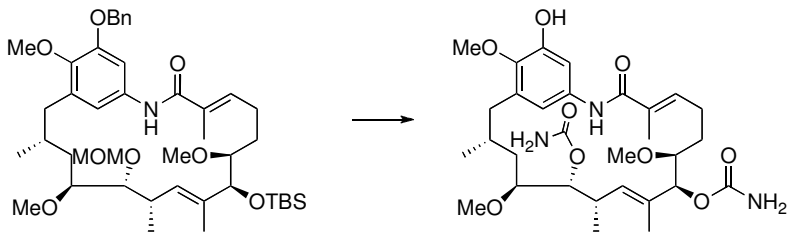


36 **7**

(4*E*,6*Z*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-Carbamic acid 13,20-dihydroxy-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3-oxo-2-aza-bicyclo[16.3.1]docosa-1(21),4,6,10,18(22),19-hexaen-9-yl ester (7). Prepared as per route to **1**.

((i) HF•pyr, THF; (ii) $Cl_3CCONCO$, CH_2Cl_2; MeOH, K_2CO_3). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provided 88% (2 steps) of carbamate as a yellow oil. $[\alpha]_D^{20}$ +69.5° (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.0 (br. s, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 2H), 6.71 (br. d, *J* = 11.2 Hz, 1H), 6.41 (ovlp t and s, *J* = 10.8 Hz, 2H), 5.54 (br. s, 2H), 5.34 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 2H), 4.80 (A of ABq, *J* = 6.8 Hz, 1H), 4.69 (br. s, 2H), 4.50 (B of ABq, *J* = 6.8 Hz, 1H), 4.38 (br. s, 1H), 3.78 (s, 3H), 3.51 (d, *J* = 8.8 Hz, 1H), 3.39 (s, 3H), 3.30 (br. s, 6H), 3.14 (br. s, 2H), 2.61 (br. s, 1H), 2.55 (br. s, 1H), 2.46 (br. d, *J* = 12.4 Hz, 1H), 1.96 s, 3H), 1.58 (br. s, 3H), 1.46 (br.s, 3H), 1.06 (d, *J* = 6.4 Hz, 1H), 0.88 (br d, *J* = 6.8 Hz, 1H)s; ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 173.0, 156.1, 152.1, 144.5, 136.9, 135.9, 134.4, 129.9, 128.5, 127.9, 127.4, 126.4, 114.4, 113.2, 103.0, 97.4, 84.1, 80.2, 77.2, 70.4, 60.8, 57.4, 56.9, 56.1, 37.0, 34.7, 29.7, 22.8, 20.6, 17.8, 14.8, 13.2.

($AlCl_3$, anisole, CH_2Cl_2). Purification by flash chromatography (silica, 80% EtOAc/hexanes) provides 75% of analog (**7**) as a clear glass. $[\alpha]_D^{20}$ +23.0° (*c* 0.3, MeOH); ^{1}H NMR (d_6-DMSO, 50 °C, 300 MHz): δ 10.3 (s, 1H), 10.1 (br. s, 1H), 7.97 (br. s, 1H), 7.50 (bs, 1H), 7.27 (t, *J* = 11.4 Hz, 1H), 7.13 (br. s, 3H), 6.28 (br. s, 1H), 6.15 (d, *J* = 8.7 Hz, 1H), 5.68 (d, *J* = 4.5 Hz, 1H), 5.11 (br. s, 1H), 4.65 (br. s, 1H), 4.45 (s, 3H), 4.10 (obs. m, 1H), 4.04 (br. s, 3H), 3.96 (s, 3H), 3.74 (br. s, 1H), 3.30 (m, 1H), 3.21 (m, 2H), 2.80 (br. s, 1H), 2.71 (s, 3H), 2.25 (br. s, 4H), 2.04 (m, 1H), 1.73 (d, *J* = 6.3 Hz, 3H), 1.64 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (d_6-DMSO, 50 °C, 75.0 MHz): δ 170.1, 166.9, 156.8, 151.1, 150.6, 143.3, 135.3. 135.1, 134.4, 133.9, 131.4, 127.6, 126.6, 107.8, 99.3, 82.5, 81.3, 74.0, 60.3, 57.7, 56.5, 36.9, 34.6, 29.8, 21.7, 16.7, 13.8, 12.8; IR (neat) ν_{max}: 3350, 2928, 1733, 1716, 1653, 1597, 1375, 1092 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{29}H_{42}N_2O_8$ $[M+23]^+$ 569.2839, found 569.2820.



34a **8**

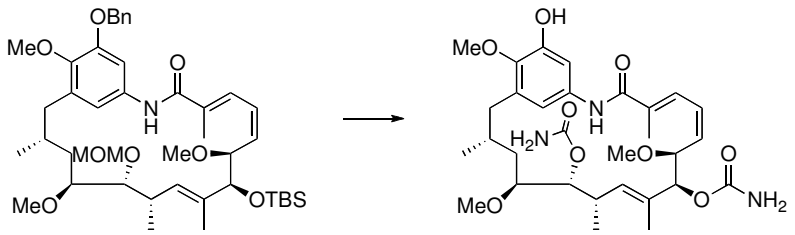
(4*E*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-*Bis*-Carbamic acid 20-(hydroxy)-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3-oxo-2-aza-bicyclo[16.3.1]docosa-1(21),4,10,18(22),19-pentaen-9,13-yl ester (8). To a solution of MOM ether **34a** (13.0 mg, 0.0172 mmol) in diethyl ether (0.500 mL) at room temperature was added magnesium dibromide (15.9 mg, 0.0862 mmol) followed by ethanethiol (3.20 uL, 0.0431

mmol). Reaction was allowed stir at room temperature for 48 hours. The mixture was quenched with saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (5x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 60% EtOAc/hexanes) to yield a colorless oil (12.0 mg, 0.0169 mmol, 98%).

To a solution of alcohol (12.0 mg, 0.0169 mmol) in THF (1.60 mL) in a nalgene vial was added HF•pyr stock solution (2.78:1:1.11, THF:HF•pyr:pyridine, 0.800 mL) at 0 °C. The reaction was allowed to run at room temperature for 48 hours before it was quenched by addition of saturated solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (5x). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 80% EtOAc/hexanes) to yield *bis*-alcohol a colorless glass (9.00 mg, 0.0151 mmol, 89%).

To a solution of diol (6.50 mg, 0.0109 mmol) in methylene chloride (1.10 mL) at room temperature was added trichloroacetyl isocyanate (3.12 μL, 0.0262 mmol). The reaction stirred for 15 minutes (monitor by TLC) before methanol (1.40 mL) followed by potassium carbonate (6.03 mg, 0.0436 mmol) were added. The reaction stirred for an additional 60 minutes (monitor by TLC) at room temperature before it was concentrated *in vacuo*. The residue was purified by flash chromatography (silica, 5% MeOH/CH_2Cl_2) to yield *bis*-carbamate a colorless glass (7.00 mg, 0.0103 mmol, 94%). $[\alpha]_D^{20}$ +5.7° (*c* 0.7, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H), 7.92 (br. s, 1H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 2H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.07 (t, *J* = 6.4 Hz, 1H), 5.34 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H), 4.99 (d, *J* = 7.6 Hz, 1H), 4.65 (br s, 5H), 3.79 (s, 3H), 3.56 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 3.14 (dt, *J* = 2.8, 7.8 Hz, 1H), 2.87 (dd, *J* = 4.4, 12.8 Hz, 1H), 2.70 (m, 1H), 2.36-2.19 (m, 3H), 1.88 (s, 3H), 1.82 (m, 1H), 1.63 (m, 1H), 1.51 (m, 1H), 1.48 (s, 3H), 1.28 (m, 2H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.0 MHz): δ 169.0, 156.6, 156.1, 151.9, 143.5, 137.1, 136.0, 134.8, 134.4, 134.1, 133.7, 130.8, 128.4, 127.8, 127.4, 113.8, 103.0, 82.1, 79.9, 79.8, 77.2, 70.3, 60.9, 59.9, 58.4, 35.5, 35.2, 32.9, 32.1, 30.8, 24.8, 21.1, 15.3, 12.8, 12.1; IR (neat) ν_{max}: 3347, 2928, 1716, 1610, 1382, 1324, 1111, 1037, 753 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{37}H_{51}N_3O_9$ $[M+23]^+$ 704.3523, found 704.3525.

Prepared as per last step to reblastatin (**1**). ($AlCl_3$, anisole, CH_2Cl_2). Purification by flash chromatography (silica, 5% MeOH/CH_2Cl_2) provided 66% of analog (**8**) as a clear glass. $[\alpha]_D^{20}$ +13.5° (*c* 0.2, MeOH); ^{1}H NMR (*d*$_6$-DMSO, 50 °C, 300 MHz): δ 9.95 (s, 1H), 9.75 (s, 1H), 7.88 (s, 1H), 7.26 (s, 2H), 7.19 (s, 2H), 7.12 (s, 1H), 6.75 (t, *J* = 6.0 Hz, 1H), 6.03 (d, *J* = 9.3 Hz, 1H), 5.64 (d, *J* = 7.5 Hz, 1H), 5.43 (m, 1H), 4.46 (s, 3H), 4.14 (s, 3H), 4.09 (s, 3H), 3.96 (m, 2H), 3.41 (dt, *J* = 6.0, 13.4 Hz, 2H), 3.10 (dd, *J* = 6.8, 13.4 Hz, 1H), 2.97 (m, 2H), 2.57 (m, 1H), 2.50 (s, 3H), 2.32 (m, 1H), 2.23 (s, 3H), 2.16 (m, 2H), 1.97 (dd, *J* = 5.1, 13.9 Hz, 1H), 1.77 (d, *J* = 6.6 Hz, 3H), 1.65 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (*d*$_6$-DMSO, 50 °C, 75.0 MHz): δ 170.2, 157.7, 156.8, 150.6, 143.0, 135.7, 135.2, 134.2, 133.3, 133.0, 131.6, 115.2, 107.6, 81.2, 80.6, 80.1, 76.9, 60.6, 59.3, 58.0, 36.1, 35.5, 33.1, 32.7, 30.7, 24.7, 20.5, 16.8, 13.6, 12.3; IR (neat) ν_{max}: 3347, 2928, 1733, 1717, 1701, 1652, 1395, 1111, 1039 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{30}H_{45}N_3O_9$ $[M+23]^+$ 614.3054, found 614.3052.



36 **9**

(4*E*,6*Z*,8*S*,9*S*,10*E*,12*S*,13*R*,14*S*,16*R*)-*Bis*-Carbamic acid 20-(hydroxy)-8,14,19-trimethoxy-4,10,12,16-tetramethyl-3-oxo-2-aza-bicyclo[16.3.1]docosa-1(21),4,6,10,18(22),19-hexaen-9,13-yl ester (9). Prepared as per **8** ((i) $MgBr_2$, EtSH, Et_2O; (ii) HF•pyr, THF; (iii) $Cl_3CCONCO$, CH_2Cl_2; MeOH, K_2CO_3). Purification by flash chromatography (silica, 5% MeOH/CH_2Cl_2) provides 46% (3 steps) of *bis*-carbamate as a clear glass. $[\alpha]_D^{20}$ +58.5° (*c* 0.35, MeOH); IR (neat) ν_{max}: 3348, 2929, 1734, 1717, 1701, 1653, 1374, 1100, 1058, 778 cm^{-1}.

($AlCl_3$, anisole, CH_2Cl_2). Purification by flash chromatography (silica, 5% MeOH/CH_2Cl_2) provides 77% of analog (**9**) as a clear colorless glass. ^1H NMR (*d*$_6$-DMSO, 50 °C, 400 MHz): δ 10.25 (s, 1H), 9.91 (s, 1H), 7.64 (br. s, 1H), 7.33 (br. s, 1H), 7.24 (t, *J* = 10.8 Hz, 1H), 7.08 (m, 4H), 6.15 (br. t, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 5.71 (d, *J* = 6.9 Hz, 1H), 5.43 (m, 1H), 4.95 (br. s, 1H), 4.45 (s, 3H), 4.04 (s, 3H), 3.91 (s, 3H), 3.82 (br. s, 2H), 3.44 (A of ABx, *J* = 5.0, 14.0 Hz, 1H), 3.12 (B of ABx, *J* = 6.3, 14.0 Hz, 1H), 2.78 (m, 1H), 2.70 (s, 3H), 2.24 (m, 2H), 2.12 (br. s, 3H), 1.85 (m, 1H), 1.63 (m, 6H); ^{13}C NMR (*d*$_6$-DMSO, 50 °C, 75 MHz): δ 161.7, 157.5, 156.7, 150.7, 143.6, 135.6, 135.0, 133.7, 132.8, 131.6, 128.1, 126.1, 108.2, 115.7, 108.2, 81.1, 80.8, 77.5, 75.4, 60.4, 57.9, 56.4, 36.5, 34.2, 30.3, 20.2, 17.8, 14.2, 12.5; IR (neat) ν_{max}: 3347, 2928, 1733, 1717, 1701, 1652, 1395, 1111, 1039 cm^{-1}; HRMS (CI, NH_3) *m/z* calc'd for $C_{30}H_{43}N_3O_9$ $[M+23]^+$ 612.2897, found 612.2924.

^{1}H NMR (Synthetic at 300 MHz; Natural at 360 MHz)

Position	Synthetic	Natural	(Δ)δ
1-NH_2	9.23 (s)	9.26 (s)	0.03
3	5.86 (br. t)	5.87 (br. t)	0.01
4	2.10 (m) ,2.19 (m)	2.12 (m), 2.20 (m)	0.02, 0.01
5	1.27 (m), 1.35 (m)	1.29 (m), 1.35 (m)	0.02, 0.0
6	3.27 (m)	3.28 (m)	0.01
7	4.86 (d, 7.2)	4.87 (d, 7.5)	0.01
9	5.29 (d, 9.9)	5.31 (d, 9.8)	0.02
10	2.36 (m)	2.38 (m)	0.02
11	3.32 (m)	3.33 (m)	0.01
11-OH	4.35 (br. d, 5.1)	4.37 (br. d, 4.9)	0.02
12	3.02 (m)	3.03 (m)	0.01
13	1.15 (m), 1.54 (m)	1.17 (m), 1.55 (m)	0.02, 0.01
14	1.74 (m)	1.73 (m)	–0.01
15	2.34 (m), 2.56 (dd, 6.6, 13.5)	2.35 (m), 2.58 (dd, 6.3, 13.4)	0.01, 0.02
18-OH		9.40 (br. s)	
19	6.86 (br. s)	6.88 (br. s)	0.02
21	6.29 (br. s)	6.30 (br. s)	0.01
22	1.67 (s)	1.68 (s)	0.01
23	3.32 (s)	3.33 (s)	0.01
24-NH_2	6.50 (br. s)	6.51 (br. s)	0.01
25	1.42 (s)	1.44 (s)	0.02
26	0.90 (d, 6.6)	0.91 (d, 6.5)	0.01
27	3.21 (s)	3.23 (s)	0.02
28	0.80 (d, 6.3)	0.81 (d, 6.5)	0.01
29	3.62 (s)	3.63 (s)	0.01

^{13}C NMR (Synthetic at 75 MHz; Natural at 90 MHz)

Position	Synthetic	Natural	(Δ)δ
1	170.3	170.3	0
2	132.2	132.2	0
3	134.6	134.5	–0.1
4	23.6	23.6	0
5	29.8	29.8	0
6	79.5	79.5	0
7	80.7	80.7	0
8	129.7	129.7	0
9	133.5	133.4	–0.1
10	33.7	33.7	0
11	73.7	73.6	–0.1
12	81.1	81.1	0
13	34.4	34.3	–0.1
14	31.2	31.2	0
15	35.8	35.8	0
16	133.5	133.4	–0.1
17	142.5	142.5	0
18	149.9	149.7	–0.2
19	107.2	107.2	0
20	134.6	134.5	–0.1
21	114.9	114.7	–0.2
22	13.1	13.1	0
23	58.3	58.3	0
24	156.2	156.1	–0.1
25	11.7	11.7	0
26	16.1	16.1	0
27	56.5	56.4	–0.1
28	19.8	19.8	0
29	59.8	59.8	0

Autolytimycin Spectral Data Compared to Isolated Data

^{1}H NMR (Synthetic at 300 MHz, 50 °C; Natural at 500 MHz, 25 °C)

Position	Synthetic	Natural	(Δ)δ
1-NH_2	9.20 (s)	9.36 (s)	0.16
3	5.75 (br. s)	5.66 (br. s)	–0.09
4	2.07 (m), 2.17 (m)	2.03 (m), 2.16 (m)	–0.04, –0.01
5	1.25 (m), 1.29 (m)	1.17 (m), 1.23 (m)	–0.08, –0.06
6	3.26 (m)	3.19 (m) 3.26	–0.07
7	4.86 (d, 7.2)	4.83 (d, 7.5)	–0.03
9	5.25 (d, 9.6)	5.20 (d, 9.6)	–0.05
10	2.35 (m)	2.30 (m)	–0.05
11	3.38 (m)	3.39 (m)	0.01
11-OH	4.18 (d, 4.6)	*Signal not observed*	0.02
12	3.01 (m)	2.95 (d, 9.5)	–0.06
13	1.17 (m), 1.51 (m)	1.17 (m), 1.51 (m)	0.00, 0.00
14	1.78 (m)	1.80 (m)	0.02
15	2.28 (m), 2.54 (dd, 6.6, 13.5)	2.31 (m), 2.55 (m)	0.03, 0.01
17	6.25 (s)	6.26 (s)	0.01
18-OH	9.13 (s)	*Signal not observed*	0.00
19	6.65 (br. s)	6.58 (s)	–0.07
21	6.25 (br. s)	6.18 (s)	–0.07
22	1.71 (s)	1.71 (s)	0.00
23	3.32 (s)	3.31 (s)	–0.01
24-NH_2	6.34 (br. s)	Signal not observed	0.00
25	1.41 (s)	1.35 (s)	–0.06
26	0.92 (d, 6.6)	0.91 (d, 6.5)	–0.01
27	3.23 (s)	3.21 (s)	–0.02
28	0.75 (d, 6.9)	0.71 (d, 6.4)	–0.04

^{13}C NMR (Synthetic at 75 MHz, 50 °C; Natural at 125 MHz, 25 °C)

Position	Synthetic	Natural	(Δ)δ
1	170.8	171.1	0.3
2	131.8	131.7	–0.1
3	134.2	134.1	–0.1
4	23.3	23.2	–0.1
5	29.6	29.6	0
6	79.5	79.3	–0.2
7	80.7	80.8	0.1
8	129.9	129.8	–0.1
9	133.1	133.1	0
10	34.0	34.1	0.1
11	73.4	73.2	–0.2
12	80.7	80.5	–0.2
13	33.5	33.2	–0.2
14	30.5	30.4	–0.1
15	42.7	42.6	–0.1
16	141.2	141.1	–0.1
17	112.6	112.8	0
18	156.1	156.2	0.1
19	105.8	105.7	–0.1
20	140.1	140.0	–0.1
21	115.0	115.2	0.2
22	13.2	13.2	0
23	58.2	58.3	0.1
24	157.4	157.3	–0.1
25	11.7	11.6	0
26	16.6	11.6	0
27	56.3	56.3	0
28	18.7	18.5	0

Representative Procedures for SAR of Reblastatin and Structural Derivatives.

Competition assays.
For the competition studies, fluorescence polarization (FP) assays were performed as previously reported.[i] Briefly, FP measurements were performed on an Analyst GT instrument (Molecular Devices, Sunnyvale, CA). Measurements were taken in black 96-well microtiter plates (Corning # 3650) where both the excitation and the emission occurred from the top of the well. A stock of 10 μM GM-cy3B was prepared in DMSO and diluted with HFB buffer (20 mM Hepes (K), pH 7.3, 50 mM KCl, 2 mM DTT, 5 mM $MgCl_2$, 20 mM Na_2MoO_4, and 0.01% NP40 with 0.1 mg/mL BGG). To each 96-well were added 6 nM fluorescent GM (GM-cy3B), 10 nM Hsp90α protein (Stressgen # SPP776), and tested inhibitor (initial stock in DMSO) in a final volume of 100 μL HFB buffer. Drugs were added in triplicate wells. For each assay, background wells (buffer only), tracer controls (free, fluorescent GM only) and bound GM controls (fluorescent GM in the presence of Hsp90α) were included on each assay plate. GM and 17-AAG were used as positive control. The assay plate was incubated on a shaker at 4°C for 24 h and the FP values in mP were measured. The fraction of tracer bound to Hsp90 was correlated to the mP value and plotted against values of competitor concentrations. The inhibitor concentration at which 50% of bound GM was displaced was obtained by fitting the data. All experimental data were analyzed using SOFTmax Pro 4.3.1 and plotted using Prism 4.0 (Graphpad Software Inc., San Diego, CA).

Growth Assays. Growth inhibition studies were performed using the alamar blue assay as previously described[ii]. In summary, experimental cultures were plated at 20,000 cells/well for Kasumi-1 and MOLM-13 in microtiter plates (Corning # 3603). One column of wells was left without cells to serve as the blank control. Cells were allowed to grow overnight. The following day, growth medium having either drug or DMSO at four times the desired concentration was added to another microtiter plate (Nunc 167008) in triplicate and was serially diluted at a 1:1 ratio in the plate. The diluted drug or DMSO was then added to the plated cells in a 1:1 ratio. After 72 h, the cell growth in treated versus control wells was estimated by adding alamar blue (10% v/v of 440 μM solution of resazurin (Sigma #R7017)) and measuring fluorescence intensity after six hours. The IC_{50} was calculated as the drug concentration that inhibits cell growth by 50% compared with control growth.

[i] *Bioorganic and Med. Chem. Lett.* **2006**, *16*, 4515-4518.
[ii] *Eur. J. Biochem*. **2000**, *267*, 5421.