Supporting Information

Lobatamide C: Total Synthesis, Stereochemical Assignment, Preparation of Simplified Analogues, and V-ATPase Inhibition Studies

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General Information: ¹H NMR spectra were recorded on a 400 MHz spectrometer with CDCl₃ as the solvent unless otherwise stated. ¹³C NMR spectra were recorded on a 75.0 MHz spectrometer with CDCl₃ as the solvent unless otherwise stated. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as [α]_D (concentration in grams/100 mL, solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC (CHIRALCEL OD, Column No. OD00CE-AI015). X-ray crystal structure analysis was performed by Dr. Emil Lobkovsky (Department of Chemistry and Chemical Biology, Cornell University). Copper (I) thiophenecarboxylate (CuTC) was prepared from Cu₂O and thiophene-2-carboxylic acid according to the procedure of Allred and Liebeskind.¹ Cs₂CO₃ was obtained from Chemetall GmbH. *N,N*-dimethylacetamide (DMA) was distilled from BaO under vacuum and stored over 4Å molecular sieves prior to use. (*R,R*)-Salen-Co catalyst was obtained from Rhodia Chirex (Boston, MA). Sep-Pak® Vac 12cc C18 cartridges were obtained from Waters, Inc. 5.0 M HF-pyridine/pyridine solution was prepared by mixing HF-pyridine (70% HF, 1 mL), pyridine (2 mL) and distilled THF (5

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¹ Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

mL). Cp₂ZrHCl was freshly prepared according to the procedure of Buchwald *et. al.*² All other reagents were purchased from Sigma-Aldrich, Lancaster, and Strem Chemicals. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.

General Procedure for the preparation of enamides: Enamide **4**.

E,E-2,4-Hexadienamide (**3**) (83 mg, 0.75 mmol), copper (I) thiophenecarboxylate (CuTC) (28.6 mg, 0.15 mmol), and Cs₂CO₃ (245 mg, 0.75 mmol) were placed in an oven-dried 10 mL Schlenk flask equipped with a stir bar. Anhydrous NMP (2 mL) was added to the Schlenk flask using an oven-dried syringe. The suspension was degassed using high vacuum until gas evolution ceased. *E*-1-iodo-1-heptene (**1**) (112 mg, 0.5 mmol, 79 μ L) was added to the flask using a microliter syringe. The mixture was degassed again with high vacuum until no further gas evolution was observed and the suspension was stirred at 90 °C for 12 h under argon. The red slurry was cooled to room temperature, diluted with ether, and the ether extracts washed with pH 7 buffer. The aqueous layer was extracted twice further with ether. The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated. Pure enamide **4** (71 mg, 69 % yield) was obtained as a white solid after flash chromatography on silica gel (hexanes: EtOAc = 4:1, 1% Et₃N). M.p. 116~117 °C; IR (thin film): 3247, 2921, 1654, 1629, 1534, 1350 cm⁻¹; ¹H NMR (400MHz, CDCl₃): δ 7.23 (1H, dd, *J* = 14.8, 10 Hz), 7.16 (1H, d, *J* = 9.6 Hz), 6.82 (1H, dd, *J* = 14, 10.8 Hz), 6.12 (2H, m), 5.71 (1H, d, *J* = 14.8 Hz), 5.16 (1H, dt, *J* = 14, 7.2 Hz), 1.82 (3H, d, *J* = 5.6 Hz), 1.30 (6H, m), 2.01 (2H, m), 0.86 (3H, t, *J* = 6 Hz) ppm; ¹³C NMR (67.5 MHz, CDCl₃): δ 163.1, 142.4, 138.6, 129.7, 122.6, 120.7, 113.6, 31.3, 29.7, 29.5, 22.5, 18.6, 14.0 ppm; HRMS (EI): calcd. for C₁₃H₂₁NO 207.1623, found 207.1588.

² Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, 28, 3895.

Enamide 2: Prepared in 71% yield according to the general procedure. mp. 83~84 °C; IR (neat): 3272, 2961, 1635, 1529, 1319 cm^{-1} ; ^1H NMR: δ 7.77 (2H, d, $J = 7.2$ Hz), 7.50~7.39 (3H, m), 6.93 (1H, dd, $J = 14, 10$ Hz), 5.30 (1H, dt, $J = 14, 7.2$ Hz), 2.05 (2H, dt, $J = 7.2, 7.2$ Hz), 1.39~1.27 (6H, m), 0.87 (3H, t, $J = 6.8$ Hz) ppm; ^{13}C NMR (67.5 MHz) δ 164.3, 133.9, 131.7 (2C), 128.6 (2C), 127.1, 122.8, 114.4, 31.2, 29.7, 29.5, 22.5, 14.0 ppm; HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}$ 217.1467, found 217.1450.

Enamide 6: Prepared in 57% yield according to the general procedure. mp. 169~170°C; IR (neat): 3308, 1661, 1639, 1521 cm^{-1} ; ^1H NMR: δ 7.83 (2H, d, $J = 8$ Hz), 7.73 (1H, dd, $J = 14.4, 10.8$ Hz), 7.55~7.46 (3H, m), 7.37~7.19 (5H, m), 6.24 (1H, d, $J = 14.4$ Hz) ppm; ^{13}C NMR δ 165.5, 137.1, 134.6, 133.2, 129.9 (2C), 129.8 (2C), 128.1 (2C), 127.8, 126.7 (2C), 124.1, 114.7 ppm; HRMS (EI): calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}$ 223.0997, found 223.1007.

Enamide 7: Prepared in 58% yield according to the general procedure. IR (neat): 3279, 1646, 1627, 1528, 1345, 1255 cm^{-1} ; ^1H NMR: δ 7.64 (2H, m), 7.34~7.15 (6H, m), 6.15 (2H, m), 5.81 (1H, d, $J = 15.2$ Hz), 1.83 (3H, d, $J = 5.2$ Hz) ppm; ^{13}C NMR δ 164.5, 144.2, 104.3, 137.2, 130.7, 129.7 (2C), 127.6, 126.6 (2C), 124.1, 121.4, 113.9, 19.7 ppm; HRMS (EI): calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}$ 213.1154, found 213.1176.

Enamide 8: Prepared in 75% yield according to the general procedure. IR (neat): 2957, 1695, 1660, 1388, 1077 cm^{-1} ; ^1H NMR: δ 8.21 and 8.00 (each 1H, s, major and minor rotamers), 7.06 (1H, d, $J = 14$ Hz, minor rotamers), 6.40 (1H, d, $J = 14.0$ Hz, major rotamers), 5.04 (1H, dt, $J = 14, 7$ Hz), 2.95 and 2.99 (each 3H, s, major and minor rotamers), 2.02 (2H, dt, $J = 7.0, 7.0$ Hz), 1.38~1.23 (6H, m), 0.85 (3H, t, $J = 6.4$ Hz) ppm; ^{13}C NMR (major and minor rotamers): δ 163.0, 161.7, 129.2, 125.3, 114.3, 112.6, 34.0,

32.3, 31.2, 31.0, 30.8, 30.7, 28.5, 23.5, 15.0 ppm; HRMS (EI): calcd. for C₉H₁₇NO 155.1310, found 155.1325.

Enamide 9: Prepared in 70% yield according to the general procedure.

IR (neat): 3025, 1685, 1641, 1311, 1249, 1069 cm⁻¹, ¹H NMR: δ 8.41 and 8.14 (each 1H, s, major and minor rotamers), 7.86 (1H, d, *J* = 14.8 Hz, minor rotamers), 7.15 (1H, d, *J* = 14.0 Hz, major rotamers), 7.36~7.17 (5H, m), 6.04 (1H, d, *J* = 14.8 Hz), 3.13 and 3.16 (each 3H, s, major and minor rotamers) ppm; ¹³C NMR (major and minor rotamers): δ 162.5, 161.1, 135.9, 128.7, 126.6, 125.7, 125.3, 124.2, 112.4, 110.9, 33.0, 27.5 ppm; HRMS(EI): calcd. for C₉H₉NO 161.0841, found 161.0842.

Enamide 12: Prepared in 23% yield according to the general procedure.

Reaction was performed at 60 °C. M.p. 93~94 °C; IR (neat): 3027, 2921, 1635, 1524, 1304 cm⁻¹, ¹H NMR δ 7.58 (2H, d, *J* = 7.2 Hz), 7.50 (1H, dd, *J* = 7.2, 7.2 Hz) 7.40 (2H, dd, *J* = 7.2, 7.2 Hz) 7.28~7.21 (5H, m), 7.14 (1H, dd, *J* = 7.2, 6.8 Hz), 6.87 (1H, dd, *J* = 10.4, 8.8 Hz), 4.92 (1H, dt, *J* = 8.8, 7.6 Hz), 2.74 (2H, t, 7.2 Hz), 2.38 (2H, m); ¹³C NMR δ 164.5, 141.7, 133.8, 131.9, 128.68, 128.66, 128.59, 127.1, 126.3, 122.2, 110.9, 35.3, 28.3 ppm; HRMS(CI): calcd. for [M+1]⁺ C₁₇H₁₈NO 252.1388, found 252.1389.

Acid 18: 5-hydroxy-2 (5*H*)-furanone (1.5 g, 15 mmol), methoxylamine hydrochloride (1.378 g, 16.5 mmol) was dissolved in 36 mL of water. The solution was stirred at room temperature for 1h. To the solution was added

NaCl (5 g) and the mixture extracted with EtOAc (3 × 40 mL). The organic layers were combined, dried with anhydrous MgSO₄, and concentrated. The product was obtained as pale yellow crystals (1.78 g, 92% yield). IR (neat): 3000 (br s), 1700, 1617, 1444, 1257, 1041 cm⁻¹; ¹H NMR: δ 8.80 (1H, d, *J*=10.4 Hz), 6.17 (1H, dd, *J*=11.6, 10.4 Hz), 6.00 (1H, d, *J*=11.6 Hz), 3.96 (3H, s) ppm; ¹³C NMR δ 170.8, 147.2, 139.1, 122.0, 62.5 ppm. CIHRMS: calcd. for C₅H₇NO₃ 129.0426, found 129.0408.

2Z-butenamide 16: Oxime acid **18** (770 mg, 6.0 mmol) was dissolved in 20 mL anhydrous THF. To the solution was added ethyl chloroformate (716.2 mg, 6.6 mmol) and triethylamine (920 μ L, 6.6 mmol) sequentially at 0 °C. The mixture was stirred at 0 °C for 30 minutes. Ammonium hydroxide (28~30%) (1213 μ L, 9.0 mmol) was added to the flask dropwise and the mixture was stirred at room temperature for 1.5 h. The suspension was filtered using a fritted funnel, and the filtrate concentrated and redissolved in CH_2Cl_2 . The CH_2Cl_2 solution was washed with saturated Na_2CO_3 solution and dried with Na_2SO_4 . Concentration *in vacuo* provided pure amide **16** (729 mg, 95%) as a pale yellow solid. IR (neat): 3397, 1669, 1617, 1437, 1341, 1043 cm^{-1} ; ^1H NMR: δ 8.95 (1H, d, $J=10$ Hz), 6.49 (1H, dd, $J=11.6$, 10 Hz), 5.95 (1H, d, $J=11.6$ Hz), 5.56 (2H, br s), 3.92 (3H, s) ppm; ^{13}C NMR (67.5 MHz) δ 167.2, 147.5, 134.8, 124.6, 62.3 ppm; HRMS (EI): calcd. for $\text{C}_5\text{H}_8\text{N}_2\text{O}_2$ 128.0586, found 128.0608.

2E-butenamide 17: 2Z-butenamide **16** (150 mg, 1.17 mmol) was dissolved in 2.4 mL methanol. To the solution was added 1.2 mL concentrated hydrochloric acid (37%) and the mixture was stirred

at room temperature for 4 h. The reaction solution was neutralized and further basified to pH 12 with saturated Na_2CO_3 solution, and extracted with ethyl acetate (4×5 mL). The organic layers were combined, washed with saturated NaCl solution, dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2 /acetone= 2 : 1) afforde amide **17** (121 mg, 81%) as a white solid. IR (neat): 3147, 1669, 1616, 1405, 1037 cm^{-1} ; ^1H NMR (DMSO): δ 7.94 (1H, d, $J=10$ Hz), 7.64 (1H, br s), 7.20 (1H, br s), 6.85 (1H, dd, $J=16$, 10 Hz), 6.30 (1H, d, $J=16$ Hz), 3.80 (3H, s) ppm; ^{13}C NMR δ 168.0, 151.1, 135.1, 134.1, 64.1 ppm; HRMS (EI): calcd. for $\text{C}_5\text{H}_8\text{N}_2\text{O}_2$ 128.0586, found 128.0608.

Enamide 19: Prepared in 57% yield according to the general procedure using dimethylacetamide (DMA) as solvent. IR (neat): 3172, 2922, 1646,

1533, 1350, 1264 cm^{-1} ; ^1H NMR: δ 7.76 (1H, d, $J=10$ Hz), 7.26 (1H, dd, $J=15.2$, 10 Hz), 7.05 (1H, d, $J=10$ Hz), 6.81 (1H, dd, $J=14$, 10 Hz), 6.06 (1H, d, $J=15.6$ Hz), 5.21 (1H, dt, $J=14$, 7 Hz), 3.93 (3H, s), 2.02 (2H, dt, $J=7$, 7 Hz), 1.37~1.23 (6H, m), 0.86 (3H, t, $J=6.8$ Hz) ppm; ^{13}C NMR δ 162.7, 147.7, 134.7, 128.5, 122.2, 115.0, 62.4, 31.2, 29.7, 29.4, 22.4, 13.9 ppm; HRMS (EI): calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$ 224.1525, found 224.1571.

Enamide 20. Prepared in 52% yield according to the general procedure using dimethylacetamide (DMA) as solvent. IR (neat): 3240, 1642, 1617, 1521, 1050 cm^{-1} ; ^1H

NMR: δ 7.79 (1H, d, $J=10$ Hz), 7.60 (1H, dd, $J=14.4$, 10.8 Hz), 7.37~7.18 (6H, m), 6.16 (1H, d, $J=14.8$ Hz), 6.14 (1H, d, $J=14.8$ Hz), 3.95 (3H, s) ppm; ^{13}C NMR (DMSO) δ 162.7, 143.9, 137.3, 134.1, 131.1, 129.7 (2C), 127.4, 126.3 (2C), 124.4, 114.1, 63.0 ppm; HRMS (EI): calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$ 230.1055, found 230.1061.

Enamide 21: 2Z-butenamide **16** (49 mg, 0.38 mmol), CuTC (23 mg, 0.12 mmol), Rb_2CO_3 (65 mg, 0.28 mmol) and DMA (1.0 mL) were added to an oven-dried 10 mL

Schlenk flask. The suspension was degassed using high vacuum until gas evolution ceased and the Schlenk flask refilled with argon. To the flask was added *E*-1-iodo-1-heptene **1** (56 mg, 0.25 mmol, 41 μL) and *N,N'*-dimethylethylenediamine (**24**) (11 mg, 0.12 mmol). The mixture was degassed again with high vacuum for 1 min, refilled with argon, and stirred at 60 $^\circ\text{C}$ for 12 h. The reaction mixture was cooled to rt, diluted with EtOAc, filtered through silica gel, and concentrated *in vacuo*. Purification on silical gel (hexanes: EtOAc = 3:1, 1% Et_3N) provided pure enamide **21** as a white solid (29 mg, 52 %). IR (neat): 3255, 2928, 1635, 1521, 1054 cm^{-1} ; ^1H NMR (DMSO): δ 10.09 (1H, d, $J=10$ Hz), 8.93 (1H, d, $J=10.4$ Hz), 6.60 (1H, dd, $J=14.4$, 10 Hz), 6.46 (1H, dd, $J=10.8$, 10.8 Hz), 6.06 (1H, d, $J=11.6$ Hz), 5.21 (1H, dt, $J=14.4$, 7.2 Hz), 3.81 (3H, s), 1.94 (2H, dt, $J=7.2$, 7.2 Hz), 1.30~1.18 (6H, m), 0.81 (3H, s, 7.2 Hz) ppm; ^{13}C NMR δ 162.8, 148.9, 136.2, 125.8, 123.3, 116.2, 63.4, 32.3, 30.9, 30.3, 23.6, 15.0 ppm; HRMS (EI): calcd. for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$ 224.1525, found 224.1519.

Enamide 22: 2Z-butenamide **16** (23 mg, 0.18 mmol), CuTC (7 mg, 0.036 mmol), Cs₂CO₃ (42 mg, 0.13 mmol), and DMA (0.5 mL) were placed in an oven-dried 10 mL Schlenk flask. The suspension was degassed using high vacuum until gas evolution ceased and the flask refilled with argon. To the suspension was added Z-vinyl iodide **11** (31 mg, 0.12 mmol, 20 μ L) and *N,N'*-dimethylethylenediamine (**24**) (6.3 mg, 0.072 mmol). The mixture was degassed again with high vacuum for 1 min, refilled with argon, and stirred at 60 °C for 14.5 h. The reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through silica gel, and concentrated *in vacuo*. The pure enamide **22** (17 mg, 55 %) was obtained as a yellow solid after flash chromatography on silica gel (hexane: ethyl acetate= 3:1, 1% Et₃N). mp. 103~105 °C; IR (neat): 3025, 2944, 1643, 1518, 1222, 1048 cm⁻¹; ¹H NMR δ 8.95 (1H, d, *J* = 10.0 Hz), 7.31~7.18 (5H, m), 6.69 (1H, dd, *J* = 10.4, 8.8 Hz), 6.52 (1H, br s), 6.43 (1H, dd, *J* = 11.6, 10.0 Hz), 5.60 (1H, d, *J* = 11.6 Hz), 4.86 (1H, dd, *J* = 8.8, 8.0 Hz), 3.91 (3H, s), 2.70 (2H, t, *J* = 7.2 Hz), 2.30 (2H, m); ¹³C NMR δ 161.9, 147.7, 141.6, 135.3, 128.7, 128.6, 126.4, 124.3, 121.6, 111.3, 62.3, 35.2, 28.2; HRMS (CI): calcd. for [M+1]⁺ C₁₅H₁₉N₂O₂ 259.1447, found 259.1441.

***N,N*-Divinyl amide 23:** 2Z-butenamide **16** (33 mg, 0.26 mmol), CuTC (13 mg, 0.066 mmol), Cs₂CO₃ (85 mg, 0.26 mmol) and DMA (0.5 mL) were added to an oven-dried 10 mL Schlenk flask. The suspension was degassed using high vacuum until gas evolution ceased and the Schlenk flask refilled with argon. To the flask was added *E*-1-iodo-1-heptene **1** (50 mg, 0.22 mmol, 35 μ L) and 2,2,6,6-tetramethyl-3,5-heptanedione (**22**) (12 mg, 0.066 mmol). The mixture was degassed again with high vacuum for 1 min, refilled with argon, and stirred at 60 °C for 12 h. The reaction mixture was cooled to rt, diluted with EtOAc, filtered through silica gel, and concentrated *in vacuo*. Purification on silical gel (hexanes: EtOAc = 5:1, 1% Et₃N) provided enamide **21** (10 mg, 20%) and *N,N*-divinyl amide **23** (12 mg, 17 %) as a yellow

oil. **23**: IR (neat): 3446, 2928, 1652, 1421, 1247, 1045 cm^{-1} ; ^1H NMR δ 8.82 (1H, d, J = 8.0 Hz), 7.02 (1H, br s), 6.40 (2H, m), 5.90 (1H, br s), 5.53 (1H, s), 5.15 (1H, s), 3.91 (3H, s), 2.10 (4H, br s), 1.39 (4H, br s), 1.29 (8H, br s), 0.88 (6H, t, J = 6.4 Hz); ^{13}C NMR δ 163.3, 148.2, 134.6 (br s), 133.6, 126.2 (br s), 125.4, 125.3 (br s), 117.3 (br s), 62.2, 31.2, 29.9, 28.5, 22.3, 13.9; MS (CI): 321.3 $[\text{M}+1]^+$, 289.2, 208.3, 152.1, 112.1, 32.0; CIHRMS: calcd. for $[\text{M}+1]^+$ $\text{C}_{19}\text{H}_{33}\text{N}_2\text{O}_2$, 321.2542, found 321.2550.

Alkyne 36. Trimethylsilyl acetylene (3025 mg, 30.8 mmol) was dissolved in 30 mL dry toluene and cooled to $-35\text{ }^{\circ}\text{C}$. To the solution was added 16 mL of $n\text{-BuLi}$ (1.93 M solution in hexanes). The mixture was stirred at $-35\text{ }^{\circ}\text{C}$ for 15 min, then warmed to $0\text{ }^{\circ}\text{C}$. To the white suspension was added dropwise at $0\text{ }^{\circ}\text{C}$ 31 mL of Et_2AlCl (1.0 M solution in hexanes). The white heterogeneous mixture was vigorously stirred at $0\text{ }^{\circ}\text{C}$ for 1 h and (*R*)-ethyl-3,4-epoxybutyrate (**35**) (2000 mg, 15.4 mmol) in 15 mL toluene was added dropwise *via* syringe. The reaction mixture was vigorously stirred at $0\text{ }^{\circ}\text{C}$ for 2 h. The reaction was slowly quenched with saturated ammonia chloride solution (0.25 mL per mmol Al) followed by 1.0 M HCl solution (0.33 mL per mmol Al). The resulting mixture was stirred at room temperature for 30 min, filtered through a pad of Celite, and the filter pad washed with EtOAc. The organic layers were combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 4 : 1) provided 2.54 g (72 %) of alkyne **36** as a colorless oil. $[\alpha]_D^{23} +23.4^{\circ}$ (c 1.32, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 4.16 (3H, m), 2.66 (1H, dd, J = 16.4, 3.6 Hz), 2.54~2.41 (3H, m), 1.27 (3H, t, J = 6.8 Hz), 0.14 (9H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 173.3, 103.3, 88.7, 67.6, 61.5, 41.2, 28.9, 15.1, 0.99; IR (neat) 3460 (br), 2961, 2904, 2176, 1734, 1408, 1250, 1160, 1028 cm^{-1} ; MS (EI) m/z 229 (M^++1), 189, 139, 117, 73; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{21}\text{O}_3\text{Si}$ 229.1260, found 229.1278.

Alkyne 37: Alkyne **36** (1000 mg, 4.39 mmol) was dissolved in 6 mL of anhydrous DMF. To the solution was added imidazole (597 mg, 8.78 mmol) and chlorodiethylisopropylsilane (795 mg,

4.82 mmol). The reaction mixture was stirred at room temperature for 12 h, then quenched with pH 7 buffer and extracted with EtOAc (3 ×). The organic layers were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) provided 1.51 g (97 %) of **37** as a colorless oil. $[\alpha]_D^{23} +15.4^\circ$ (*c* 1.47, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.27 (1H, m), 4.09 (2H, m), 2.62 (1H, m), 2.48~2.40 (3H, m), 1.22 (3H, t, *J* = 7.2 Hz), 0.93 (13H, m), 0.60 (4H, m), 0.10 (9H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 172.3, 104.3, 88.0, 69.3, 61.3, 43.3, 30.1, 18.2, 15.1, 14.0, 7.9, 4.8, 1.0; IR (neat) 2958, 2178, 1739, 1416, 1250, 1159, 1107, 1018, 969 cm⁻¹; CIHRMS calculated for C₁₈H₃₆O₃Si₂ 356.2203, found 356.2198.

Bromoalkyne 38: Alkyne **37** (1000 mg, 2.81 mmol) was dissolved in 5 mL of distilled acetone. To the resulting solution was added NBS (550 mg, 3.10 mmol), AgNO₃ (50 mg, 0.28 mmol) and H₂O (100 mg, 5.6 mmol). The mixture was stirred at rt for 3 h, at which time the acetone was removed *in vacuo* and the residue re-dissolved in hexane. The suspension was filtered through a pad of silica gel and the pad washed further with hexanes. The filtrate was combined and concentrated *in vacuo* to afford 1.0 g (98 %) of bromoalkyne **38** as a colorless oil. $[\alpha]_D^{23} +17.5^\circ$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 4.27 (1H, m), 4.10 (2H, q, *J* = 5.4 Hz), 2.60 (1H, dd, *J* = 15.2, 4.8 Hz), 2.48 (1H, dd, *J* = 15.2, 7.2 Hz), 2.41 (2H, d, *J* = 6.8 Hz), 1.24 (3H, t, *J* = 5.4 Hz), 0.96~0.91 (13H, m), 0.64~0.59 (4H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 171.3, 76.9, 68.1, 60.6, 42.5, 40.6, 29.0, 17.4, 14.4, 13.2, 7.1, 4.0, 3.9; IR (neat) 2956, 2877, 1160, 1107, 1015 cm⁻¹; CIHRMS $[M+H]^+$ calculated for C₁₅H₂₈BrO₃Si 363.0991, found 363.1032.

Vinyl Stannane 39: Bromoalkyne **38** (1000 mg, 2.75 mmol) was dissolved in 55 mL of distilled THF in a flame-dried flask. Pd(PPh₃)₄ (158 mg, 0.14 mmol) was added to the solution and the flask was cooled to -78 °C. To the yellow solution was added Bu₃SnH (2401 mg, 8.25 mmol) dropwise *via* syringe. The solution was stirred for 1 h at -78 °C and 1 h at rt. The reaction mixture was concentrated and purified on neutral alumina (hexane : EtOAc = 10 : 1)

to afford 1.37 g (86%) of stannyl alkene **39** as a colorless oil. $[\alpha]_D^{23} + 8.7^\circ$ (*c* 1.73, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.94 (2H, m), 4.23 (1H, m), 4.09 (2H, q, *J* = 7.2 Hz), 2.42 (2H, m), 2.35 (2H, br s), 1.46 (6H, m), 1.31~1.22 (9H, m), 0.95 (13H, m), 0.86~0.82 (15H, m), 0.61 (4H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 172.0, 144.8, 132.1, 69.4, 60.4, 46.6, 42.6, 29.3, 28.5, 27.5, 26.9, 17.5, 14.4, 13.8, 13.7, 13.3, 9.7, 7.2, 4.2, 4.1; IR (neat) 2956, 1738, 1461, 1094, 1013 cm⁻¹; CIHRMS calculated for C₂₇H₅₆O₃SiSn 576.3026, found 576.3042.

Vinyl iodide 34: Vinyl Stannane **39** (1365 mg, 2.37 mmol) was dissolved in 2 mL of distilled THF. To the solution was added dropwise a solution of I₂ (663 mg, 2.61 mmol in 3 mL of distilled THF) at 0 °C. The solution was stirred at 0 °C for 30 min, quenched with 2 mL of 0.1 N Na₂S₂O₃ solution, and extracted with EtOAc (3 ×). The organic layers were combined, dried over MgSO₄, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1 ~ 10 : 1) provided 910 mg (93%) of vinyl iodide **34** as a colorless oil. $[\alpha]_D^{23} + 12.5^\circ$ (*c* 1.71, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 6.51 (1H, dt, *J* = 14.8, 7.6 Hz), 6.07 (1H, d, *J* = 14.8 Hz), 4.20 (1H, m), 4.10 (2H, q, *J* = 7.2 Hz), 2.42 (2H, m), 2.29~2.24 (2H, m), 1.24 (3H, t, *J* = 7.2 Hz), 0.95 (13H, m), 0.61 (4H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 172.1, 143.1, 78.5, 69.1, 61.4, 44.9, 43.3, 18.2, 15.2, 14.0, 8.0, 4.8; IR (neat) 2955, 1736, 1376, 1239, 1096, 951 cm⁻¹; MS (EI) *m/z* 413 (*M*⁺+1), 368, 325, 245, 129, 103; CIHRMS [*M*+H]⁺ calculated for C₁₅H₃₀IO₃Si 413.1009, found 413.0968.

Enamide 40: To a flame-dried Schlenk flask was added amide **17** (559 mg, 4.37 mmol), CuTC (348 mg, 1.82 mmol), Cs₂CO₃ (1425 mg, 4.37 mmol), 1,10-phenanthroline (328 mg, 1.82 mmol), 1,5-diphenyl-1,4-pentadien-3-one (170 mg, 0.73 mmol), and 10 mL distilled DMA. The flask was degassed under high vacuum with vigorous stirring for 5 min and refilled with argon. To the suspension was added vinyl iodide **34** (1500 mg, 3.64 mmol) under argon. The suspension was degassed again under high vacuum for 2 min, refilled with argon, and sealed. The

mixture was stirred at 65 °C for 17 h. The black suspension was diluted with EtOAc, filtered through a pad of Celite, and the filtrate concentrated *in vacuo*. Purification on silica gel (hexane: EtOAc = 3 : 1, 0.5% Et₃N) provided 780 mg (52%) of enamide **40** as a pale yellow solid. M.p. 76-77 °C; $[\alpha]_D^{23} +24.7^\circ$ (*c* 1.11, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.75 (1H, d, *J* = 10.0 Hz), 7.27 (1H, dd, *J* = 15.2, 10.0 Hz), 7.13 (1H, d, *J* = 10.8 Hz), 6.85 (1H, dd, *J* = 14.4, 10.8 Hz), 6.07 (1H, d, *J* = 15.2 Hz), 5.21 (1H, dt, *J* = 14.4, 7.2 Hz), 4.20 (1H, m), 4.09 (2H, q, *J* = 7.2 Hz), 3.93 (3H, s), 2.40 (2H, d, *J* = 6.4 Hz), 2.27 (2H, m), 1.23 (3H, t, *J* = 7.2 Hz), 0.95 (13H, m), 0.61 (4H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 171.6, 161.7, 147.7, 134.8, 128.6, 124.9, 109.4, 69.2, 62.4, 60.3, 42.1, 38.1, 17.2, 14.1, 12.9, 6.9, 3.8; IR (thin film) 3175, 1736, 1649, 1534, 1357, 1086, 1043, 960 cm⁻¹; CIHRMS calculated for [M+H]⁺ C₂₀H₃₇N₂O₅Si 413.2472, found 413.2475.

Enamide acid 28: Enamide **40** (80 mg, 0.19 mmol) was dissolved in 1.0 mL of MeOH. To the solution was added 0.8 mL of 5.0 M LiOH solution. The yellow mixture was stirred at room temperature for 2

h. The reaction solution was carefully acidified to pH 4 with 5% HCl solution, and extracted with EtOAc (3 ×). The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo* to afford 22 mg (77%) of the somewhat labile enamide acid **28** as a white solid. IR (neat): 3280, 2940, 1650, 1622, 1534, 1046 cm⁻¹; ¹H NMR: δ 7.75 (1H, d, *J* = 10.0 Hz), 7.65 (1H, d, *J* = 10.4 Hz), 7.26 (1H, dd, *J* = 15.6, 10.0 Hz), 6.86 (1H, dd, *J* = 14.4, 10.4 Hz), 6.11 (1H, d, *J* = 15.6 Hz), 5.21 (1H, dt, *J* = 14.4, 7.2 Hz), 4.16 (1H, m), 3.93 (3H, s), 2.48 (2H, m), 2.30 (2H, m), 0.95 (13H, m), 0.63 (4H, m); ¹³C NMR δ 177.0, 164.3, 149.7, 135.7, 130.6, 126.3, 112.3, 71.3, 63.0, 44.6, 39.5, 17.9, 14.2, 7.6, 4.8, 4.7; HRMS (CI): calcd. for [M+1]⁺ C₁₈H₃₃N₂O₅Si 385.2159, found 385.2169.

1,3-benzodioxan-4-one 42: To a flame-dried flask was added CuI (5.86 g, 30.7 mmol) and 60 mL of distilled ether. To the suspension was added 38.3 mL of MeLi (1.6 M in ether) dropwise at 0 °C. The yellow solution was stirred at 0 °C for 0.5 h and cooled to -78 °C. Aryl triflate **41** (5 g, 15.3 mmol) dissolved in 60 mL of distilled THF was added to the above

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cuprate solution dropwise at $-78\text{ }^{\circ}\text{C}$. The resulting mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then warmed to $0\text{ }^{\circ}\text{C}$. MeI (13 g, 91.9 mmol) was added and the solution was stirred at $0\text{ }^{\circ}\text{C}$ for 10 min. The mixture was warmed to rt and quenched with sat. NH_4Cl solution. The mixture was extracted with EtOAc (3 $\times$), and the organic layers were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 10 : 1) provided 2.5 g (85%) of **42** as a white solid. M.p. $79\text{--}80\text{ }^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 7.36 (1H, dd, J = 8.0, 7.6 Hz), 6.89 (1H, d, J = 7.6 Hz), 6.78 (1H, d, J = 8.0 Hz), 2.66 (3H, s), 1.69 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 161.6, 158.0, 144.6, 136.0, 126.7, 116.0, 113.6, 106.1, 77.6, 26.7, 22.9; IR (thin film) max 1724, 1605, 1477, 1311, 1269, 1209, 1052 cm^{-1} ; MS (EI) m/z 192, 134, 106, 78; CIHRMS calculated for $\text{C}_{11}\text{H}_{12}\text{O}_3$: 192.0786, found: 192.0776.

Benzyl bromide 31: Acetonide **42** (78 mg, 0.41 mmol) was dissolved in 4 mL of CCl_4 .

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To the solution was added NBS (80 mg, 0.45 mmol) and AIBN (6.6 mg, 0.04 mmol). The solution was refluxed for 2 h and concentrated *in vacuo*. The residue was purified on silica gel (hexane: EtOAc = 10 : 1) to afford 90 mg (78 %) of product **31** as a white solid. Mp. $74\text{--}75\text{ }^{\circ}\text{C}$; IR (neat): 3019, 1732, 1606, 1481, 1216 cm^{-1} ; ^1H NMR: δ 7.46 (1H, dd, J = 8.4, 7.6 Hz), 7.14 (1H, dd, J = 7.6, 0.8 Hz), 6.92 (1H, dd, J = 8.4, 0.8 Hz), 5.03 (2H, s), 1.71 (6H, s); ^{13}C NMR δ 159.7, 157.2, 141.6, 135.6, 125.7, 118.0, 111.3, 105.6, 30.7, 25.3; HRMS (CI): calcd. for $\text{C}_{11}\text{H}_{11}\text{BrO}_3$ 269.9892, found 269.9849.

Acetonide 43: $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (229 mg, 0.22 mmol) and AsPh_3 (407 mg, 1.33 mmol)

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were added to a flame-dried Schlenk tube, degassed with high vacuum, refilled with argon, and suspended in 5 mL of distilled THF. After 15 min of stirring at rt, the suspension became yellow. To the suspension was added a mixture of vinyl stannane **32** (1854 mg, 5.32 mmol) and benzylic bromide **31** (1200 mg, 4.43 mmol) in 10 mL of distilled THF. The resulting solution was refluxed for 3.5 h, cooled to room temperature, diluted with EtOAc, and filtered through a pad of silica gel. The filtrate was concentrated

in vacuo. Purification on silica gel (hexane : EtOAc = 20 : 1) afforded 1539 mg (92 %) of product **43** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.39 (1H, dd, J = 8.0, 7.6 Hz), 6.95 (1H, d, J = 7.6 Hz), 6.79 (1H, d, J = 8.0 Hz), 5.36 (1H, t, J = 7.6 Hz), 4.24 (2H, s), 3.86 (2H, d, J = 7.6 Hz), 1.77 (3H, s), 1.68 (6H, s), 0.88 (9H, s), 0.05 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 160.4, 157.1, 146.3, 136.6, 135.3, 124.5, 123.6, 115.3, 111.9, 105.0, 61.8, 31.8, 25.8, 25.4, 21.1, 18.1, -5.5; IR (neat) 2954, 2856, 1739, 1476, 1312, 1270, 1046 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{21}\text{H}_{33}\text{O}_4\text{Si}$ 377.2148, found 377.2140.

Acetonide 44: Compound **43** (50 mg, 0.13 mmol) was dissolved in 0.5 mL of distilled THF. To the solution was added 1.5 mL of 5.0 M HF-pyridine/pyridine solution. The mixture was stirred at 0 °C for 1 h, quenched with pH 7 buffer, and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexane:EtOAc=1:1) provided 29 mg (86%) of **44** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.42 (1H, dd, J = 8.0, 7.6 Hz), 6.95 (1H, d, J = 7.6 Hz), 6.82 (1H, d, J = 8.0 Hz), 5.27 (1H, t, J = 6.8 Hz), 4.20 (2H, s), 3.85 (2H, d, J = 6.8 Hz), 1.80 (3H, s), 1.68 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 160.6, 157.3, 146.2, 136.2, 135.6, 125.2, 125.1, 115.6, 120.0, 105.3, 61.4, 32.7, 25.4, 21.3; IR (neat) 3427, 2942, 1734, 1582, 1477, 1315, 1047 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{15}\text{H}_{19}\text{O}_4$ 263.1283, found 263.1300.

Alkyne 33: (*R*)-(+)-3-butyne-2-ol (2000 mg, 28.6 mmol) was dissolved in 20 mL of anhydrous DMF. To the solution was added imidazole (2910 mg, 42.8 mmol) and chlorodiethylisopropylsilane (7052 mg, 42.8 mmol). The reaction mixture was stirred at room temperature for 26 h, then quenched with pH 7 buffer and extracted with EtOAc (3 $\times$). The organic layers were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) provided 5.2 g (91%) of **33** as colorless oil. $[\alpha]_D^{23} +40.3^\circ$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 4.51 (1H, dq, J = 6.4, 1.5 Hz), 2.35 (1H, d, J = 1.5 Hz), 1.42 (3H, d, J = 6.4 Hz), 1.00~0.96 (13H, m), 0.69~0.63 (4H, m); ^{13}C NMR (75.0 MHz, CDCl_3) δ 86.7,

71.2, 58.8, 25.7, 17.4, 13.2, 7.1, 3.8; IR (thin film) 3311, 2956, 2877, 1463, 1243, 1103, 1059, 975 cm^{-1} ; MS (EI) m/z 199 ($M^+ + 1$), 169, 155, 127, 111; CIHRMS $[M+H]^+$ calculated for $\text{C}_{11}\text{H}_{23}\text{OSi}$ 199.1518, found 199.1544.

Divinylcarbinol 49a: Activated MnO_2 (4954 mg, 52.8 mmol) was added to an oven-dried flask and suspended in 10 mL of distilled CH_2Cl_2 . To the suspension was added (Z)-3-iodo-2-methyl-2-propen-1-ol (523 mg, 2.64 mmol) and the resulting mixture was stirred at rt for 20 min. The black suspension was filtered through a pad of Celite. Concentration of the filtrate *in vacuo* provided aldehyde **48** (466 mg, 2.38 mmol, 90%) as a yellow solid, which was quickly advanced to the next step due to its instability.

To an oven-dried flask was added Cp_2ZrHCl (500 mg, 1.94 mmol) and 5 mL of distilled CH_2Cl_2 . To the white suspension was added alkyne **33** (349 mg, 1.76 mmol) dropwise. The resulting mixture was stirred at rt for 30 min. The white suspension became a pale yellow solution. The solution was cooled to -78°C and 2.1 mL of 1.0 M Et_2Zn solution in hexane was added. After 10 min of stirring at the same temperature, amino thiol **74** (34 mg, 0.176 mmol) in 0.1 mL of CH_2Cl_2 was added. The mixture was warmed gradually to -30°C over 1 h. Freshly prepared aldehyde **48** (dissolved in 4 mL of distilled CH_2Cl_2) was added dropwise. The reaction was stirred at -30°C for 21 h, warmed to rt, and finally quenched with a small amount of saturated NaHCO_3 solution. The white reaction mixture was filtered through a pad of silica gel, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexanes : EtOAc = 10 : 1) provided 477 mg (68 %) of **49a** as colorless oil.³ Chiral HPLC analysis shows dr = 2:1 (Chiralcel OD, 2% *i*PrOH/hexane, 0.5 mL/min, $R_{t\text{major}}$ =11.2 min, $R_{t\text{minor}}$ =12.3 min). The stereochemistry of the major product was confirmed to be *S* by Mosher ester analysis. ^1H NMR (400 Hz, CDCl_3) δ 5.95 (1H, d, J = 1.2 Hz), 5.85 (1H, dd, J = 15.6, 5.2 Hz), 5.61 (1H, dd, J = 15.6, 5.6 Hz), 5.13 (1H, m), 4.33 (1H, m), 1.83 (3H, d, J = 1.2 Hz), 1.22 (3H, d, J = 6.0 Hz), 0.96 (13H, m), 0.61 (4H, m); ^{13}C NMR (75.0 MHz, CDCl_3) δ 148.2, 137.5, 127.6, 77.2,

³ Divinylcarbinol **49** (dr=1:1) was obtained using a similar procedure without adding the chiral ligand **74**. (Me_2Zn was used instead of Et_2Zn and aldehyde **48** was added at 0°C , 3 h, 87% yield).

75.5, 69.4, 25.6, 19.7, 18.3, 14.1, 8.0, 4.8; *NOED* (400 MHz, CDCl₃) irradi. δ 5.95 (H-1): 5.3 % enhancement at Me; IR (neat) 3398, 2955, 2875, 1462, 1150, 1088, 1011, 970 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₁₅H₃₀IO₂Si 397.1060, found 397.1046.

Mosher Ester Analysis of Divinylcarbinol **49a**

(dr=2:1): Alcohol **49a** (12 mg, 0.03 mmol), (*R*) or (*S*)-MTPA acid (7 mg, 0.03 mmol), DMAP (0.4 mg, 0.003 mmol) was dissolved in 0.5 mL of CH₂Cl₂

followed by adding DCC (6.8 mg, 0.033 mmol) at rt. The mixture was stirred at rt for 30 min, filtered through a pad of silica gel, washed with CH₂Cl₂, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 50 : 1) afforded (*R*) or (*S*)-MTPA ester of **49a**. The absolute configuration was determined by analysis of the ¹H chemical shift differences. The above figure shows the $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) for the Mosher esters of the major diastereomer of **49a**.

Vinyl iodide 50. Divinylcarbinol **49** (477 mg, 1.20 mmol) was dissolved in 2.4 mL of DMF. To the solution was added TBSCl (362 mg, 2.40 mmol) and imidazole (163 mg, 2.40 mmol). The reaction mixture was stirred at room temperature

for 24 h, quenched with water, and extracted with EtOAc (3 ×). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) provided 571 mg (93%) of **50** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.82 (1H, dd, *J* = 15.2, 5.6 Hz), 5.81 (1H, s), 5.48 (1H, dd, *J* = 15.2, 3.2 Hz), 5.06 (1H, m), 4.30 (1H, m), 1.75 (3H, s), 1.20 (3H, d, *J* = 6.4 Hz), 0.96 (13H, m), 0.88 (9H, s), 0.58 (4H, m), 0.06 (3H, s), 0.03 (3H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 148.5, 135.3, 127.7, 76.8, 72.7, 68.8, 26.0, 24.9, 18.7, 18.4, 17.5, 13.3, 7.2, 4.0, -4.6; IR (neat) 2955, 2861, 1463, 1253, 1090, 836 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₂₁H₄₄IO₂Si₂ 511.1925, found 511.1883.

Vinyl stannane 51: Vinyl iodide **50** (571 mg, 1.12 mmol) was dissolved in 6 mL of

distilled ether. To the solution was added 0.84 mL of *n*-BuLi solution (2.79 M in hexane) dropwise at -78°C and the reaction was stirred at the same temperature for 2 h. 2.2 mL of 1.0 M Me_3SnCl solution in THF was added dropwise to the reaction mixture at -78°C followed by stirring at the same temperature for another 1 h. The reaction solution was warmed to room temperature, quenched with water, and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo* to provide 601 mg (98%) of **51** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.69 (1H, dd, $J = 15.6, 5.6$ Hz), 5.53 (1H, dd, $J = 15.6, 4.4$ Hz), 5.49 (1H, m), 4.57 (1H, m), 4.30 (1H, m), 1.75 (3H, d, $J = 0.9$ Hz), 1.19 (3H, d, $J = 6.4$ Hz), 0.96 (13H, m), 0.88 (9H, s), 0.60 (4H, m), 0.14 (9H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 156.8, 134.6, 130.6, 123.9, 110.2, 77.9, 26.1, 24.9, 20.6, 18.5, 17.6, 13.4, 7.3, 4.0, -4.4, -8.0; IR (neat) 2956, 2862, 1463, 1252, 1090 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{53}\text{O}_2\text{Si}_2\text{Sn}$: 549.2606, found: 549.2589.

Fragment 52: $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (47 mg, 0.045 mmol) and AsPh_3 (83 mg, 0.27 mmol) were added to a flame-dried Schlenk tube, degassed with high vacuum, refilled with argon, and suspended in 2 mL of distilled THF. After 15 min of stirring at rt, to the suspension was added a mixture of vinyl stannane **51** (493 mg, 0.90 mmol, dr=1:1) and benzylic bromide **31** (269 mg, 0.99 mmol) in 3 mL of distilled THF. The resulting solution was refluxed for 3 h, cooled to room temperature, diluted with EtOAc, and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) afforded 287 mg (56 %) of product **52** (dr=1:1) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (1H, dd, $J = 7.6, 7.6$ Hz), 6.93 (1H, d, $J = 7.6$ Hz), 6.79 (1H, d, $J = 7.6$ Hz), 5.66 (1H, dd, $J = 15.2, 8.8$ Hz), 5.51 (1H, dd, $J = 15.2, 4.8$ Hz), 5.32 (1H, m), 5.11 (1H, d, $J = 8.8$ Hz), 4.28 (1H, m), 3.90 (2H, m), 1.69 (6H, s), 1.65 (3H, s), 1.17 (3H, d, $J = 6.4$ Hz), 0.94 (13H, m), 0.87 (9H, s), 0.58 (4H, m), 0.02 (3H, s), -0.01 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 160.5, 157.2, 146.4, 139.0, 135.3, 134.2, 129.7, 124.5,

122.5, 115.4, 112.0, 105.1, 70.3, 68.7, 31.6, 25.7, 25.5, 24.7, 18.1, 17.7, 17.2, 12.9, 6.9, 3.5, -4.9, -5.1; IR (neat) 2955, 2861, 1740, 1584, 1476, 1313, 1079, 1046 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{32}\text{H}_{55}\text{O}_5\text{Si}_2$ 575.3588, found 575.3611.

Fragment 29: Compound **52** (187 mg, 0.33 mmol) was dissolved in 1.0 mL of distilled THF. To the solution was added 2.6 mL of 5.0 M HF-pyridine/pyridine solution. The mixture was stirred at 0 °C for 1 h, quenched with pH 7 buffer, and extracted with EtOAc (3 ×). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*.

Purification on silica gel (hexane:EtOAc = 4:1) provided 100 mg (69%) of **29** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.39 (1H, dd, J = 8.4, 7.6 Hz), 6.93 (1H, d, J = 7.6 Hz), 6.80 (1H, d, J = 8.4 Hz), 5.73 (1H, dd, J = 15.2, 4.8 Hz), 5.58 (1H, dd, J = 15.2, 4.0 Hz), 5.32 (1H, m), 5.13 (1H, d, J = 4.8 Hz), 4.14 (1H, br s), 3.75 (2H, m), 1.68 (6H, s), 1.65 (3H, s), 0.87 (9H, s), 0.03 (3H, s), -0.002 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 160.5, 157.2, 146.2, 138.5, 135.3, 133.6, 133.5, 131.0, 124.5, 122.9, 115.4, 105.1, 70.2, 68.2, 31.6, 25.7, 25.5, 23.2, 18.1, 17.7, -5.0, -5.1; IR (neat) 3428, 2928, 2856, 1738, 1583, 1477, 1314, 1270, 1046 cm^{-1} ; CIHRMS calculated for $\text{C}_{25}\text{H}_{38}\text{O}_5\text{Si}$ 446.2489, found 446.2512.

Compound 30: PPh_3 (22 mg, 0.084 mmol), enamide acid **28** (22 mg, 0.056 mmol), alcohol **29** (25 mg, 0.056 mmol) were added to an oven-dried flask and dissolved in 0.5 mL distilled THF. To the reaction solution was added DIAD (17 mg, 0.084 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 40 min, quenched with pH 7 buffer,

extracted with EtOAc (3 ×), and concentrated *in vacuo*. Purification on a Waters Sep-Pak C18 cartridge (MeCN/ H_2O , 60-100%) afforded 26 mg (58%) of **30** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.75 (1H, d, J = 10.4 Hz), 7.52 (1H, d, J = 11.6 Hz), 7.41

(1H, dd, $J = 8.0, 7.2$ Hz), 7.27 (1H, dd, $J = 15.2, 10.4$ Hz), 6.95 (1H, d, $J = 7.2$ Hz), 6.88 (1H, m), 6.82 (1H, d, $J = 8.0$ Hz), 6.13 (1H, d, $J = 15.2$ Hz), 5.69 (1H, dd, $J = 15.2, 6.0$ Hz), 5.57 (1H, dd, $J = 15.2, 4.0$ Hz), 5.33 (2H, m), 5.23 (1H, dt, $J = 14.4, 6.4$ Hz), 5.14 (1H, br s), 4.17 (1H, br s), 3.93 (3H, s), 3.91~3.83 (2H, m), 2.42 (2H, m), 2.25 (2H, m), 1.69 (6H, s), 1.62 (3H, s), 1.26 (3H, d, $J = 6.4$ Hz), 0.93 (13H, m), 0.87 (9H, s), 0.59 (4H, m), 0.02 (3H, s), -0.009 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 170.7, 161.6, 160.9, 157.3, 147.9, 146.2, 138.5, 135.6, 134.9, 134.6, 132.6, 128.9, 128.7, 124.9, 124.7, 122.9, 115.5, 109.4, 105.3, 70.3, 70.0, 69.0, 62.5, 42.5, 37.8, 31.6, 25.7, 25.6, 20.4, 18.1, 17.6, 17.2, 12.8, 6.9, 3.6, -5.1; IR (neat) 2934, 1737, 1653, 1314, 1254, 1044 cm^{-1} ; CIHRMS calculated for $\text{C}_{43}\text{H}_{68}\text{N}_2\text{O}_9\text{Si}_2$ 812.4463, found 812.4413.

Lactone 56: Compound 30

(18 mg, 0.022 mmol) was dissolved in 0.5 mL distilled THF. To the solution was

added 0.266 mL 5.0 M HF/pyridine-pyridine solution. The reaction mixture was stirred at rt for 16 h, quenched with pH 7 buffer, extracted with EtOAc (3 $\times$), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2 :EtOAc=2:1~0:1) afforded 4 mg (32 %) labile compound **55** as a colorless oil. Compound **55** (3 mg, 0.005 mmol) was dissolved in 0.25 mL THF. To the solution was added 0.6 mg NaH at 0 $^\circ\text{C}$. After stirring at the same temperature for 2 h, the reaction was quenched with pH 4 buffer, extracted with EtOAc (3 $\times$), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on Waters Sep-Pak cartridge (MeOH/ H_2O 60-80%) provided 0.8 mg (30%) lactone **56** (dr=1:1) as a white solid. M.p. 150~152 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 10.93 (1H, s) 7.76 (1H, d, $J = 10.0$ Hz), 7.40 (1H, dd, $J = 8.4, 7.2$ Hz), 7.41 (1H, br s), 7.26 (1H, dd, $J = 15.6, 10.4$ Hz), 6.89 (2H, m), 6.68 (1H, d, $J = 7.2$ Hz), 6.47 (1H, m), 6.14 (1H, d, $J = 10.4$ Hz), 6.09 (1H, d, $J = 15.6$ Hz), 5.72 (1H, dd, $J = 15.2, 6.4$ Hz), 5.45 (1H, m), 5.26 (1H, dt, $J = 14.4, 7.2$ Hz), 4.96 (1H, d, $J = 12.0$ Hz), 4.03 (1H, br s), 3.93 (3H, s), 3.15 (1H, m), 2.87 (1H, d, $J = 16.0$ Hz), 2.45 (2H, m), 2.24 (2H, m), 1.88 (3H, s), 1.34 (3H, d, $J = 6.8$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 172.2, 170.0, 162.3, 161.8, 147.9, 139.4, 136.4,

135.2, 134.7, 134.3, 128.6, 127.2, 126.9, 125.1, 118.1, 116.4, 109.3, 108.3, 83.6, 71.3, 68.0, 62.5, 40.9, 36.9, 31.8, 20.2, 12.8; IR (neat) 3499, 3268, 3020, 1720, 1662, 1648, 1619, 1215, 1049 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_8$ 513.2237, found 513.2212.

Enamide 59. Prepared in 50% yield according to the procedure for enamide **40**. M.p. 143-145 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.76 (1H, d, J =10.4 Hz), 7.26 (1H, dd, J = 15.6, 10.4 Hz), 7.08 (1H, d, J =10.4 Hz), 6.87 (1H, dd, J =14.0, 10.4 Hz), 6.07 (1H, d, J =15.6 Hz), 5.28 (1H, dt, J =14.0, 7.2 Hz), 3.93 (3H, s), 3.68 (2H, t, J =6.4 Hz), 2.27 (2H, m), 1.03 (21H, m); ^{13}C NMR (75.0 MHz, CDCl_3) δ 161.7, 147.9, 135.1, 128.8, 123.9, 111.4, 63.7, 62.7, 33.8, 18.2, 12.2; IR (thin film) 3174, 3027, 2939, 2865, 1647, 1535, 1045 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{35}\text{N}_2\text{O}_3\text{Si}$ 355.2417, found 355.2379.

Enamide alcohol 60. Enamide **59** (100 mg, 0.28 mmol) was dissolved in 3 mL of distilled THF. To the solution was added 0.364 mL (0.364 mmol, 1.3 equiv) of tetrabutylammonium fluoride (TBAF) solution (1.0 M in THF) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and at rt for 20 min. The solution was quenched with pH 7 buffer solution and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel with EtOAc provided 45 mg (80 %) of enamide alcohol **60** as a white solid. M.p. 188-189 °C; ^1H NMR (400 MHz, CD_3OD) δ 7.83 (1H, d, J =10.4 Hz), 7.12 (1H, dd, J = 15.6, 10.4 Hz), 6.79 (1H, d, J =14.4 Hz), 6.26 (1H, d, J =15.6 Hz), 5.35 (1H, dt, J =14.4, 7.2 Hz), 3.88 (3H, s), 3.53 (2H, t, J =6.4 Hz), 2.23 (2H, m); ^{13}C NMR (75.0 MHz, CD_3OD) δ 164.4, 149.7, 135.7, 130.5, 125.6, 113.2, 63.2, 63.0, 34.6; IR (thin film) 2366, 1650, 1615, 1436, 1045 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_3$ 198.1004, found 198.0992.

Salicylate enamide 57. To an oven-dried Schlenk tube was added enamide alcohol **60** (24

mg, 0.12 mmol), cyanomethyl ester **61** (23.5 mg, 0.13 mmol), K₂CO₃ (0.7 mg, 0.005 mmol), and 1.5 mL of DMA. The resulting solution was heated at 90 °C for 1 h and

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quenched with pH 7 buffer. The mixture was extracted with EtOAc (3 ×). The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. Purification on silica gel (hexane: EtOAc = 2 : 1) provided 35 mg (90%) of salicylate enamide **57** as a white solid. M.p. 153-155 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.73 (1H, s), 7.81 (1H, dd, *J* = 8.0, 1.6 Hz), 7.76 (1H, d, *J* = 10.4 Hz), 7.44 (1H, ddd, *J* = 8.0, 8.0, 1.6 Hz), 7.28 (1H, dd, *J* = 15.6, 10.4 Hz), 7.06 (1H, d, *J* = 10.0 Hz), 6.99 (1H, d, *J* = 14.0 Hz), 6.95 (1H, d, *J* = 8.0 Hz), 6.86 (1H, dd, *J* = 8.0, 8.0 Hz), 6.06 (1H, d, *J* = 15.6 Hz), 5.24 (1H, dt, *J* = 14.0, 7.2 Hz), 4.35 (2H, t, *J* = 6.4 Hz), 3.94 (3H, s), 2.53 (2H, m); ¹³C NMR (75.0 MHz, CD₃OD) δ 172.3, 165.3, 163.8, 150.4, 137.9, 136.7, 132.0, 131.1, 127.3, 121.3, 119.4, 114.6, 112.4, 67.0, 63.8, 31.6; IR (thin film) 3264, 1653, 1622, 1484, 1245, 1210, 1039 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₁₆H₁₉N₂O₅ 319.1294, found 319.1306.

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Cyanomethyl ester 64. *O*-Anisic acid (500 mg, 3.29 mmol) was dissolved in 4 mL of distilled acetone. To the solution was added ClCH₂CN (348 mg, 4.61 mmol) and Et₃N (0.64 mL, 4.61 mmol). The reaction solution was refluxed for 3 h, filtered through silica gel, and concentrated *in vacuo*. Purification on silica gel (hexane/EtOAc=2:1) afforded 625 mg (99.5%) **64** as a white solid. M.p. 28-30 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.85 (1H, dd, *J* = 8.0, 1.2 Hz), 7.55 (1H, dd, *J* = 8.4, 8.4 Hz), 7.00 (2H, m), 4.91 (2H, s), 3.91 (3H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 164.1, 160.1, 135.1, 132.3, 120.3, 117.1, 114.7, 112.2, 55.9, 48.4; IR (thin film) 3009, 2950, 2841, 1734, 1600, 1491, 1237, 1073 cm⁻¹; CIHRMS [M]⁺ calculated for C₁₀H₉NO₃ 191.0582, found 191.0576.

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Analogue 65. Prepared in 28% yield according to procedure for compound **57**. White solid. M.p. 107-109 °C; ¹H NMR (400

MHz, CDCl₃) δ 7.75 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 10.0 Hz), 7.54 (1H, d, J = 10.0 Hz), 7.44 (1H, dd, J = 8.0, 7.2 Hz), 7.25 (1H, dd, J = 15.6, 10.0 Hz), 6.95 (3H, m), 6.07 (1H, d, J = 15.6 Hz), 5.23 (1H, dt, J = 14.4, 7.2 Hz), 4.27 (2H, t, J = 6.4 Hz), 3.92 (3H, s), 3.85 (3H, s), 2.47 (2H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 166.5, 162.1, 159.4, 148.0, 135.1, 133.9, 131.8, 129.0, 125.1, 120.4, 120.3, 112.3, 109.8, 64.6, 62.7, 56.1, 29.9; IR (thin film) 3281, 2939, 1654, 1252, 1042 cm⁻¹; CIHRMS [M⁺] calculated for C₁₇H₂₀N₂O₅ 332.1372, found 332.1354.

Cyanomethyl ester 69. Compound **42** (2.85 g, 14.8 mmol) was dissolved in 15 mL of THF and KOH (4.2 g, 74.2 mmol) solution in 15 mL of water was added. The mixture was refluxed overnight, cooled to room temperature, acidified to pH 1, and extracted with EtOAc (3 $\times$). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford 2.3 g (99%) of 6-methyl salicylic acid as a white solid.

6-methyl salicylic acid (1000 mg, 6.58 mmol) was dissolved in 7 mL of distilled acetone. To the solution was added Et₃N (1.33 mL, 9.54 mmol), chloroacetonitrile (720 mg, 9.54 mmol) and the mixture was refluxed for 3 h. The solvent was removed *in vacuo* and pH 4 buffer was added. The aqueous layer was extracted with EtOAc (3 $\times$). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 4 : 1) provided 1 g (80%) of **69** as a white solid. M.p. 106-107 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.67 (1H, s), 7.33 (1H, dd, J = 8.0, 7.6 Hz), 6.86 (1H, d, J = 8.0 Hz), 6.74 (1H, d, J = 7.6 Hz), 4.99 (2H, s), 2.55 (3H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 170.3, 163.6, 141.7, 135.8, 123.6, 116.2, 114.0, 110.9, 48.9, 24.2; IR (thin film) 3061, 1668, 1608, 1438, 1376, 1252, 1209, 1118, 800 cm⁻¹; MS (EI) m/z 191, 134, 106, 78; CIHRMS calculated for C₁₀H₉NO₃: 191.0582, found: 191.0586.

Analogue 66. Prepared in 70% yield by the procedure reported for compound **57**. White solid. M.p. 155-157 °C; ¹H NMR (400 MHz,

CDCl₃) δ 11.3 (1H, s), 7.75 (1H, d, J = 10.4 Hz), 7.25 (3H, m), 6.97 (1H, dd, J = 14.0, 10.8

(Hz), 6.81 (1H, d, $J = 8.0$ Hz), 6.68 (1H, d, $J = 7.2$ Hz), 6.06 (1H, d, $J = 15.6$ Hz), 5.24 (1H, dt, $J = 14.0, 7.2$ Hz), 4.38 (2H, t, $J = 6.4$ Hz), 3.93 (3H, s), 2.53 (2H, m), 2.52 (3H, s); ^{13}C NMR (75.0 MHz, CD_3OD) δ 172.4, 164.4, 161.7, 149.6, 141.3, 135.8, 134.3, 130.3, 126.4, 123.5, 116.5, 115.9, 111.9, 66.5, 63.0, 30.8, 23.2; IR (thin film) 3267, 1653, 1623, 1209, 1042 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$ 332.1372, found 332.1352.

Enamide alcohol 70: Enamide **40** (600 mg, 1.45 mmol) was dissolved in 3 mL of distilled THF. To the solution was added 2.90 mL of tetrabutylammonium fluoride solution (1.0 M in THF). The reaction mixture was stirred at room temperature for 40 min. The solution was quenched with pH 7 buffer solution and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , concentrated *in vacuo*. Purification on silica gel (CH_2Cl_2 : MeOH = 10 : 1) provided 410 mg (99 %) of enamide alcohol **70** as a white solid. M.p. 153-155 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{23}$ -9.6 $^\circ$ (c 0.79, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 7.77 (1H, d, $J = 10.4$ Hz), 7.25 (1H, dd, $J = 15.2, 10.4$ Hz), 6.88 (1H, dd, $J = 14.0, 10.8$ Hz), 6.18 (1H, d, $J = 15.2$ Hz), 5.35 (1H, dt, $J = 14.0, 7.2$ Hz), 4.14 (2H, q, $J = 7.2$ Hz), 4.01 (1H, m), 3.93 (3H, s), 3.20 (1H, br s), 2.51~2.38 (2H, m), 2.23 (2H, m), 1.25 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75.0 MHz, acetone- d_6) δ 173.2, 163.1, 150.1, 135.2, 131.9, 127.0, 110.9, 69.9, 63.5, 61.5, 43.3, 39.4, 15.5; IR (thin film) 3437, 3308, 2940, 1717, 1646, 1619, 1531, 1048 cm^{-1} ; CIHRMS calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}_5$ 285.1450, found 285.1460.

Analogue 67. Prepared in 25% yield by the procedure reported for compound **57**. White

solid. $[\alpha]_{\text{D}}^{23}$ +16.7 $^\circ$ (c 0.12, MeOH); ^1H NMR (400 MHz, CDCl_3) δ 10.67 (1H, s), 7.77 (1H, dd, $J = 8.0, 1.6$ Hz), 7.75 (1H, d, $J = 10.4$ Hz), 7.44 (1H, ddd, $J = 8.0, 8.0, 1.6$ Hz), 7.26 (1H, dd, $J = 15.6, 10.4$ Hz), 7.17 (1H, d, $J = 10.4$ Hz), 6.95 (1H, d, $J = 14.0$ Hz), 6.95 (1H, d, $J = 8.0$ Hz), 6.85 (1H, ddd, $J = 8.0, 8.0, 0.8$ Hz), 6.04 (1H, d, $J = 15.6$ Hz), 5.50 (1H, m), 5.18 (1H, dt, $J = 14.0, 7.2$ Hz), 4.10 (2H, q, $J = 7.2$ Hz), 3.93 (1H, s), 2.74

(1H, dd, $J = 16.0, 7.6$ Hz), 2.66 (1H, dd, 15.6, 5.2 Hz), 2.51 (2H, m), 1.18 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 170.2, 169.5, 163.5, 162.1, 147.9, 136.1, 135.7, 130.1, 128.4, 126.0, 119.5, 117.9, 112.5, 107.6, 71.5, 62.8, 61.2, 38.9, 34.9, 14.3; IR (thin film) 3280, 2937, 1728, 1649, 1622, 1204, 1042 cm^{-1} ; EIMS 404.1, 266.1, 227.0, 155.1, 112.0; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_7$ 405.1662, found 405.1682.

Enamide acid 71: Enamide alcohol **70** (34 mg, 0.12 mmol) was dissolved in 0.5 mL of THF and 0.5 mL of MeOH. To the solution was added 0.48 mL of 5.0 M LiOH solution. The yellow mixture was stirred at room

temperature for 1 h. The reaction solution was carefully acidified to pH 4 with 5% HCl solution, and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , concentrated *in vacuo*, and purified using a Waters Sep-pak C18 cartridge (10–20% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$) to afford 22 mg (77%) of product **71** as a white solid. M.p 168–170 $^\circ\text{C}$; $[\alpha]_D^{23} -2.2^\circ$ (c 0.79, MeOH); ^1H NMR (400 MHz, acetone- d_6) δ 9.27 (1H, d, $J = 10.0$ Hz), 7.87 (1H, d, $J = 10.4$ Hz), 7.13 (1H, dd, $J = 15.2, 10.4$ Hz), 6.87 (1H, dd, $J = 14.4, 10.0$ Hz), 6.39 (1H, d, $J = 15.2$ Hz), 5.35 (1H, dt, $J = 14.4, 7.2$ Hz), 4.01 (1H, m), 3.87 (3H, s), 2.50–2.33 (2H, m), 2.25 (2H, m); ^{13}C NMR (75.0 MHz, CD_3OD) δ 175.7, 164.3, 149.6, 135.5, 130.4, 126.2, 112.3, 69.6, 62.9, 42.7, 38.8; IR (thin film) 3560, 3255, 1649, 1623, 1206, 1045, 971 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_5$ 257.1137, found 257.1137.

Analogue 68. Enamide acid **71** (40 mg, 0.156 mmol) was added to an oven-dried Schlenk flask and dissolved in 1.0 mL of distilled MeOH. To the solution was added 156 μL of 1.0 M Bu_4NOH solution in MeOH. The solution was stirred at rt for

20 min. The solvent was removed under vacuum and the residue was azeotroped with toluene. Cyanomethyl ester **69** (30 mg, 0.156 mmol) was added to the flask and the mixture was azeotroped with toluene again under high vacuum. Na_2CO_3 (17 mg, 0.156 mmol) and 1.2 mL of DMF was added to the flask. The resulting mixture was degassed under high

vacuum for 3 min and refilled with argon. To the solution was added 0.4 mL of distilled 2-butanone and the mixture was stirred at 80 °C for 1 h. The reaction was quenched with water, extracted with EtOAc. The aqueous layer was acidified to pH 4 and extracted with EtOAc (2 ×). The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. The crude was dissolved in 2 mL of THF. To the solution was added 0.16 mL of TMSCHN₂ solution (2.0 M in hexanes) at rt, followed by stirring at the same temperature for 1 h. The reaction was quenched with MeOH and concentrated *in vacuo*. Purification on silica gel (hexane: EtOAc= 3 : 1) afforded 21.4 mg (34%) of compound **68** as a white solid. M.p. 130–132 °C; $[\alpha]_D^{23} +34.1^\circ$ (*c* 0.22, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 11.14 (1H, s), 7.75 (1H, d, *J* = 10.0 Hz), 7.27 (1H, dd, *J* = 8.4, 7.6 Hz), 7.26 (1H, dd, *J* = 15.2, 10.0 Hz), 7.12 (1H, d, *J* = 10.0 Hz), 6.93 (1H, dd, *J* = 14.0, 10.4 Hz), 6.81 (1H, d, *J* = 8.4 Hz), 6.68 (1H, d, *J* = 7.6 Hz), 6.04 (1H, d, *J* = 15.2 Hz), 5.55 (1H, m), 5.18 (1H, dt, *J* = 14.0, 7.2 Hz), 3.94 (3H, s), 3.66 (3H, s), 2.73 (2H, m), 2.54 (2H, m), 2.48 (3H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 172.0, 171.6, 164.0, 162.6, 148.7, 142.3, 136.6, 135.5, 129.1, 126.8, 124.1, 116.8, 113.2, 108.5, 72.8, 63.7, 53.1, 39.3, 35.7, 25.3; IR (thin film) 3272, 1736, 1650, 1623, 1438, 1253, 1206, 1042 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₂₀H₂₅N₂O₇ 405.1662, found 405.1623.

Cyanomethyl ester 75: Cyanomethyl ester **69** (2 g, 10.5 mmol) was dissolved in 11 mL of DMF. To the solution was added TBSCl (2.37 g, 15.7 mmol) and imidazole (1.07 g, 15.7 mmol). The solution was stirred at rt overnight, quenched with pH 7 buffer, and extracted with EtOAc (3 ×). The organic layers were combined, dried over Na₂SO₄, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 10 : 1) provided 3.18 g (99%) of product **75** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.18 (1H, dd, *J* = 8.0, 7.6 Hz), 6.79 (1H, d, *J* = 7.6 Hz), 6.67 (1H, d, *J* = 8.0 Hz), 4.87 (2H, s), 2.28 (3H, s), 0.94 (9H, s), 0.21 (6H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 167.0, 153.2, 137.6, 131.2, 124.2, 123.1, 116.7, 114.4, 48.7, 25.8, 19.6, 18.4, -4.0; IR (neat) 2956, 2932, 2859, 1750, 1469, 1294, 1257, 1075, 839 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₁₆H₂₄NO₃Si: 306.1525, found: 306.1507.

Benzylic bromide 76: Cyanomethyl ester **75** (800 mg, 2.62 mmol) was dissolved in 5 mL of CCl_4 . To the solution was added NBS (514 mg, 2.88 mmol) and AIBN (215 mg, 0.13 mmol). The solution was refluxed for 3 h and concentrated *in vacuo*. The residue was purified on silica gel (hexane:

EtOAc = 15 : 1) to afford 723 mg (72%) of product **76** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.27 (1H, dd, J = 8.0, 7.6 Hz), 6.98 (1H, d, J = 7.6 Hz), 6.81 (1H, d, J = 8.0 Hz), 4.91 (2H, s), 4.49 (2H, s), 0.95 (9H, s), 0.23 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 165.9, 154.1, 137.8, 132.0, 123.5, 123.0, 119.9, 114.2, 49.1, 30.1, 25.8, 18.4, -4.0; IR (neat) 2955, 2933, 2859, 1744, 1591, 1466, 1299, 1102, 1064, 841 cm^{-1} ; CIHRMS calculated for $\text{C}_{16}\text{H}_{22}\text{BrNO}_3\text{Si}$: 383.0552, found: 383.0580.

Cyanomethyl ester 77: $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (57 mg, 0.055 mmol) and AsPh_3 (101 mg, 0.33 mmol) were added to a flame-dried Schlenk tube, degassed with high vacuum, refilled with argon, and suspended in 2 mL of distilled THF. After 15 min of stirring at rt, the suspension became yellow. To the suspension was

added a mixture of vinyl stannane **51a** (601 mg, 1.10 mmol, $S:R=2:1$) and benzylic bromide **76** (422 mg, 1.10 mmol) in 3.5 mL of distilled THF. The resulting solution was refluxed for 3 h, cooled to room temperature, diluted with EtOAc, and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) afforded 499 mg (66%) of product **77** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.19 (1H, dd, J = 8.0, 8.0 Hz), 6.78 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz), 5.65 (1H, m), 5.53 (1H, m), 5.22 (1H, m), 5.01 (1H, m), 4.84 (2H, s), 4.29 (1H, m), 3.34 (2H, m), 1.64 (3H, s), 1.18 (3H, d, J = 6.4 Hz), 0.95 (22H, m), 0.87 (9H, s), 0.59 (4H, m), 0.22 (6H, s), 0.02 (3H, s), 0.003 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 166.8, 153.0, 140.7, 139.6, 134.6, 131.1, 129.3, 123.7, 121.9, 121.8, 116.7, 114.1, 70.6, 68.6, 48.6, 31.1, 25.8, 25.6, 24.7, 18.2, 18.1, 17.9, 17.3, 13.1, 7.0, 3.8, -4.2, -4.6, -4.9; IR (neat) 2955, 2860, 1751, 1583, 1466, 1256, 1096, 1063, 838 cm^{-1} ; CIHRMS calculated for

C₃₇H₆₅NO₅Si₃ 687.4171, found 687.4172.

Fragment 73: Compound **77** (499 mg, 0.73 mmol, *S*:*R*=2:1) was dissolved in 10 mL of distilled THF. The solution was cooled to 0 °C and 0.8 mL of 1.0 M TBAF solution in THF was added dropwise. The reaction mixture was stirred at 0 °C for 10 min, quenched with water, and extracted with EtOAc (3 ×). The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) provided 275 mg (67 %) of **73** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 10.52 (1H, s), 7.34 (1H, dd, *J* = 8.4, 7.6 Hz), 6.87 (1H, d, *J* = 8.4 Hz), 6.76 (1H, d, *J* = 7.6 Hz), 5.66 (1H, m), 5.52 (1H, m), 5.20 (1H, br s), 5.02 (1H, m), 4.98 (2H, s), 4.30 (1H, m), 3.67 (2H, m), 1.66 (3H, s), 1.18 (3H, d, *J* = 6.4 Hz), 0.96 (13H, m), 0.88 (9H, s), 0.59 (4H, m), 0.04 (3H, s), 0.02 (3H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 169.9, 163.4, 144.5, 139.4, 135.7, 134.8, 129.4, 122.9, 122.5, 116.6, 113.8, 110.7, 71.8, 69.5, 49.7, 35.1, 26.8, 25.7, 19.3, 19.0, 18.3, 14.1, 8.0, 4.8, -3.6, -3.8.; IR (neat) max 3192, 2955, 2861, 1675, 1609, 1450, 1250, 1112, 1007; CIHRMS calculated for C₃₁H₅₁NO₅Si₂ 573.3306, found 573.3289.

Acid 78: Enamide acid **71** (16 mg, 0.0625 mmol) was added to an oven-dried Schlenk flask and dissolved in 1.0 mL of distilled MeOH. To the solution was added 63 μL of 1.0 M NBu₄OH solution in MeOH. The solution was stirred at rt for 20 min. The solvent was removed under vacuum and the residue was azeotroped with toluene. Cyanomethyl ester **73** (36 mg, 0.0625 mmol, *S*:*R*=2:1) dissolved in 0.13 mL of toluene was added and the mixture was azeotroped again under high vacuum. Na₂CO₃ (6.6 mg, 0.0625 mmol) and 0.6 mL of DMF was added to the flask. The resulting mixture was degassed under high vacuum for 3 min and refilled with argon. To the solution was added 0.1 mL of distilled 2-

butanone and the mixture was stirred at 80 °C for 2 h. The reaction was quenched with water, extracted with EtOAc. The aqueous layer was acidified to pH 4 and extracted with EtOAc (2 ×). The organic layers were combined, concentrated *in vacuo*, and purified using a Waters Sep-Pak® C18 cartridge (50-80% CH₃CN/H₂O) to afford 34 mg of crude compound **78**. ¹H NMR (400 MHz, acetone-d₆) δ 7.86 (1H, d, *J* = 10.4 Hz), 7.31 (1H, dd, *J* = 8.0, 8.0 Hz), 7.12 (1H, dd, *J* = 15.6, 10.4 Hz), 6.95 (1H, dd, *J* = 14.0, 10.0 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d, *J* = 8.0 Hz), 6.36 (1H, d, *J* = 15.6 Hz), 5.76 (1H, m), 5.66 (1H, m), 5.61 (1H, m), 5.33 (2H, m), 5.24 (1H, m), 4.39 (1H, m), 3.86 (3H, s), 3.70 (2H, m), 2.82 (2H, m), 2.60 (2H, m), 1.68 (3H, s), 1.18 (3H, d, *J* = 6.0 Hz), 0.99 (13H, m), 0.91 (9H, m), 0.62 (4H, m), 0.10 (3H, s), 0.08 (3H, s); IR (neat) max 2954, 1653, 1578, 1456, 1362, 1251, 1047 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₄₀H₆₅N₂O₉Si₂ : 773.4229, found: 773.4204.

Hydroxy acid 72: Compound **78** (34 mg, 0.044 mmol, *S*:*R*=2:1) was dissolved in 0.5 mL of distilled THF. To the solution was added 0.026 mL of 5.0 M HF-pyridine/pyridine solution. The mixture was stirred at rt for 1 h, quenched with water, and extracted with EtOAc (3 ×). The organic layers were combined, concentrated *in vacuo*. Purification using a Waters Sep-Pak C18 cartridge (40-60% CH₃CN/H₂O) provided 17 mg (43%, 2 steps) of unstable compound **72** as colorless oil. The product was quickly advanced to the next step due to its instability. ¹H NMR (400 MHz, CD₃OD) δ 7.83 (1H, d, *J* = 10.4 Hz), 7.19 (1H, dd, *J* = 8.4, 7.6 Hz), 7.11 (1H, m), 6.85 (1H, d, *J* = 14.0 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 7.6 Hz), 6.26 (1H, d, *J* = 15.6 Hz), 5.73 (1H, dd, *J* = 14.8, 5.6 Hz), 5.58 (1H, dd, *J* = 14.8, 5.2 Hz), 5.54 (1H, m), 5.37 (1H, dt, *J* = 14.0, 6.8 Hz), 5.27 (1H, br s), 5.14 (1H, br s), 4.23 (1H, m), 3.89 (3H, s), 3.53 (2H, d, *J* = 7.2 Hz), 2.70 (2H, d, *J* = 6.0 Hz), 2.53 (2H, m), 1.65 (3H, s), 1.19 (3H, d, *J* = 6.4 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.03 (3H, s); IR (thin film) 3314, 2954, 2857, 1654, 1043 cm⁻¹; CIHRMS calculated for C₃₃H₄₈N₂O₉Si 644.3129, found 644.3190.

8-membered ring lactone 79 (dr=1:1): Obtained by HF-pyridine deprotection of **78** at rt for 4 h or storage of **72** at 0 °C for extended periods. ¹H NMR (400 MHz, CDCl₃) δ 10.96 (1H, s), 7.40 (1H, dd, *J* = 8.4, 7.2 Hz), 6.88 (1H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 7.2 Hz), 6.46 (1H, dd, *J* = 15.2, 11.2 Hz), 6.16 (1H, d, *J* = 11.2 Hz), 5.82 (1H, dd, *J* = 15.2, 6.4 Hz), 4.96 (1H, d, *J* = 12.8 Hz), 4.40 (1H, br s), 3.17 (1H, dd, *J* = 16.0, 12.8 Hz), 2.87 (1H, d, *J* = 16.0 Hz), 1.89 (3H, s), 1.30 (3H, d, *J* = 6.4 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 162.2, 139.7, 139.5, 136.3, 133.3, 127.8, 124.2, 118.0, 116.3, 108.3, 83.9, 68.3, 31.8, 23.2, 12.6 ppm; IR (thin film) 3019, 1675, 1463, 1215 cm⁻¹; EILRMS *m/e* 274 (*M*⁺), 257, 213, 185, 121, 43; CIHRMS calcd C₁₆H₁₈O₄ 274.1205, found 274.1174.

Macrodilactones 54a and 54b: PPh₃ (68.2 mg, 0.26 mmol) was dissolved in 1.7 mL of distilled THF and DIAD (53.4 mg, 0.26 mmol) was added dropwise. The solution was stirred at rt for 20 min. A white heterogenous suspension was formed. To the suspension was added compound **72** (17 mg, 0.026 mmol) solution in 5 mL of distilled THF at 0 °C over a period of 2 h *via* syringe pump. The resulting mixture was stirred for a further 1 h at 0 °C and quenched with water. The aqueous layer was extracted with EtOAc (3 ×). The organic layers were combined and concentrated *in vacuo*. Purification using a Waters Sep-Pak C18 cartridge (50-70% CH₃CN/water) and silica gel (hexanes : EtOAc = 3 : 1) provided 4.1 mg (26%) of **54a** and 4.1 mg (26%) of **54b** as colorless oil.

54a: [α]_D²³ -14.8° (*c* 0.29, CHCl₃); ¹H NMR (400 MHz, CD₃OD) δ 7.85 (1H, d, *J* = 10.4 Hz), 7.15 (1H, dd, *J* = 8.0, 7.6 Hz), 7.15 (1H, dd, *J* = 15.2, 10.4 Hz), 6.86 (1H, d, *J* = 14.0 Hz), 6.68 (1H, d, *J* = 8.0 Hz), 6.62 (1H, d, *J* = 7.6 Hz), 6.28 (1H, d, *J* = 15.2 Hz), 5.63 (1H, dd, *J* = 15.2, 8.4 Hz), 5.60 (1H, m), 5.43 (1H, dd, *J* = 15.2, 8.4 Hz), 5.36 (1H, dt, *J* = 14.0, 7.2 Hz), 5.21 (1H, m), 5.17 (1H, m), 4.83 (1H, d, *J* = 8.4 Hz), 3.91 (3H, s), 3.20 (1H, dd, *J* = 17.2, 8.8 Hz), 2.98 (1H, d, *J* = 17.2 Hz), 2.69

(1H, dd, $J = 16.8, 2.0$ Hz), 2.60 (1H, dd, $J = 16.8, 10.4$ Hz), 2.49 (2H, m), 1.77 (3H, s), 1.33 (3H, d, $J = 6.8$ Hz), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR (75.0 MHz, CD_3OD) δ 172.0, 170.2, 164.5, 157.4, 149.6, 141.8, 140.0, 135.7, 135.5, 132.3, 131.9, 130.4, 127.2, 125.6, 121.7, 121.2, 114.8, 110.4, 75.0, 73.7, 73.5, 62.9, 39.2, 35.7, 33.5, 26.5, 20.5, 20.2, 19.3, -3.9, -4.5; IR (thin film) 3291, 2927, 2855, 1735, 1654, 1465, 1257, 1103, 1043 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{33}\text{H}_{47}\text{N}_2\text{O}_8\text{Si}$ 627.3102, found 627.3107.

54b: $[\alpha]_D^{23} -15.3^\circ$ (c 0.4, CHCl_3); ^1H NMR (400 MHz, CD_3OD) δ 7.85 (1H, d, $J = 10.4$ Hz), 7.18 (1H, dd, $J = 8.0, 8.0$ Hz), 7.15 (1H, dd, $J = 15.6, 10.4$ Hz), 6.86 (1H, d, $J = 14.0$ Hz), 6.71 (1H, d, $J = 8.0$ Hz), 6.28 (1H, d, $J = 15.6$ Hz), 5.82 (1H, dd, $J = 15.2, 4.0$ Hz), 5.63 (1H, ddd, $J = 15.2, 8.0, 1.6$ Hz), 5.60 (1H, m), 5.40~5.27 (3H, m), 4.68 (1H, dd, $J = 4.0, 1.6$ Hz), 3.90 (3H, s), 3.62 (1H, dd, $J = 18.0, 8.0$ Hz), 3.02 (1H, dd, $J = 18.0, 2.4$ Hz), 2.71 (1H, dd, $J = 16.4, 2.4$ Hz), 2.63 (1H, dd, $J = 16.4, 9.6$ Hz), 2.51 (2H, m), 1.80 (3H, s), 1.33 (3H, d, $J = 6.4$ Hz), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 171.9, 170.8, 164.4, 158.7, 149.5, 142.7, 138.8, 135.9, 135.6, 132.9, 130.3, 129.0, 127.4, 127.1, 121.1, 119.8, 115.0, 110.4, 74.1, 73.6, 73.2, 62.9, 39.1, 35.6, 32.9, 26.5, 22.0, 19.9, 19.2, -4.5, -4.6; IR (neat) 2929, 1734, 1653, 1254, 1043 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{33}\text{H}_{47}\text{N}_2\text{O}_8\text{Si}$ 627.3102, found 627.3154.

27a (lobatamide C): Compound **54a** (9.1 mg, 0.015 mmol) was dissolved in 1.0 mL THF and 0.4 mL of 5.0 M HF-pyridine/pyridine solution was added. The solution was stirred at rt for 2 h, quenched with water, and extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexanes : EtOAc = 1 : 1) provided 4.0 mg (52 %) of product **27a** as a white solid. $[\alpha]_D^{23} -18.8^\circ$ (c 0.17,

MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.85 (1H, d, J = 10.4 Hz), 7.15 (1H, dd, J = 15.6, 10.4 Hz), 7.14 (1H, dd, J = 7.6, 7.6 Hz), 6.86 (1H, d, J = 14.0 Hz), 6.68 (1H, d, J = 7.6 Hz), 6.63 (1H, d, J = 7.6 Hz), 6.28 (1H, d, J = 15.6 Hz), 5.67 (1H, dd, J = 15.2, 8.4 Hz), 5.59 (1H, m), 5.48 (1H, dd, J = 15.2, 8.4 Hz), 5.36 (1H, dt, J = 14.0, 8.0 Hz), 5.22 (1H, dd, J = 8.4, 6.4 Hz), 5.16 (1H, m), 4.78 (1H, d, J = 8.4 Hz), 3.91 (3H, s), 3.20 (1H, dd, J = 16.8, 9.6 Hz), 2.93 (1H, br d, J = 16.8 Hz), 2.69 (1H, dd, J = 16.8, 2.0 Hz), 2.59 (1H, dd, J = 16.8, 10.4 Hz), 2.48 (2H, m), 1.78 (3H, s), 1.34 (3H, d, J = 6.4 Hz); ^{13}C NMR (75.0 MHz, CD_3OD) δ 171.9, 170.2, 164.4, 157.1, 149.5, 141.6, 139.6, 135.6, 135.3, 132.7, 132.1, 130.4, 127.2, 125.8, 121.9, 121.1, 114.7, 110.3, 73.8, 73.5, 73.3, 62.9, 39.1, 35.7, 33.3, 20.2, 19.8; IR (thin film) 3280, 2924, 1733, 1653, 1539, 1457, 1265, 1041 cm^{-1} ; CIHRMS calculated for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_8$: 512.2159, found: 512.2090. TLC R_f 0.25 (hexane/EtOAc=1:1), 0.38 (benzene/acetone=3:1), 0.52 (70% MeOH/ H_2O , C18).

27b (C15-epi lobatamide C): Compound **54b** (9.6 mg, 0.015 mmol) was dissolved in 0.5 mL of THF. To the solution was added 0.24 mL of 5.0 M HF-pyridine pyridine solution. After the reaction mixture was stirred at rt for 2 h, an additional 0.24 mL of 5.0 M HF-pyridine/pyridine solution was added. The mixture was stirred for a further 2 h at room temperature, quenched with water, and extracted with EtOAc (3 $\times$).

The organic layers were combined, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexanes : EtOAc = 1 : 1) provided 6.0 mg (78 %) of **27b** as a white solid. $[\alpha]_D^{23}$ -18° (c 0.2, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.85 (1H, d, J = 10.4 Hz), 7.19 (1H, dd, J = 8.0, 8.0 Hz), 7.15 (1H, dd, J = 15.6, 10.4 Hz), 6.86 (1H, d, J = 14.0 Hz), 6.76 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz), 6.28 (1H, d, J = 15.6 Hz), 5.87 (1H, dd, J = 15.6, 4.8 Hz), 5.62 (1H, ddd, J = 15.6, 8.0, 1.6 Hz), 5.59 (1H, m), 5.42 (1H, m), 5.36 (1H, dt, J = 14.0, 7.2 Hz), 5.29 (1H, m), 4.69 (1H, dd, J = 4.8, 1.6 Hz), 3.91 (3H, s), 3.47 (1H, dd, J = 18.0, 8.0 Hz), 3.08 (1H, dd, J = 18.0, 4.0 Hz), 2.71 (1H, dd, J = 16.4, 2.8 Hz), 2.61 (1H, dd, J = 16.4, 10.0 Hz), 2.50 (2H, m), 1.83 (3H, s), 1.34 (3H, d, J = 6.4

Hz); ^{13}C NMR (75.0 MHz, CD_3OD) δ 171.9, 170.8, 164.4, 158.8, 149.5, 142.5, 139.0, 135.6, 132.9, 130.1, 129.8, 126.9, 126.7, 120.8, 119.6, 115.1, 110.3, 73.6, 73.1, 72.5, 62.8, 39.0, 35.6, 32.9, 21.5, 19.7; IR (thin film) 2923, 1734, 1653, 1540, 1457, 1268, 1041 cm^{-1} ; CIHRMS calculated for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_8$: 512.2159, found: 512.2122.

Mosher ester analysis of 27a (lobatamide C): To a solution of **27a** (1.5 mg, 0.003 mmol) in pyridine (0.25 mL) was added (*S*)-(+)- α -methyl- α -(trifluoromethyl)phenylacetyl chloride (12 μL , 0.064 mmol). The resulting mixture was stirred at rt overnight. To the reaction was added 10 μL of *N,N*-dimethyl-1,3-propanediamine. The solution was

stirred at rt for 10 min, filtered, and the filter cake washed with EtOAc. The filtrate was concentrated and purified by preparative HPLC (Symmetry® C18 5 μm , 40% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 0-10 min, 40-95% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ 10-25 min) to provide the (*R*)-MTPA diester of lobatamide C (R_t = 20.9 min). The (*S*)-MTPA diester of lobatamide C was prepared using (*R*)-(-)- α -methyl- α -(trifluoromethyl)phenylacetyl chloride according to the same procedure. The above figure shows the $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) for *R* and *S* MTPA diesters of lobatamide C.

Alkyne 80. Prepared quantitatively by the procedure reported for alkyne **33** using (*S*)-3-butyne-2-ol and TIPSCl. ^1H NMR (400 MHz, CDCl_3) δ 4.58 (1H, dq, J = 6.4, 2.0 Hz), 2.35 (1H, d, J = 2.0 Hz), 1.44 (3H, d, J = 6.4 Hz), 1.08 (21H, m); ^{13}C NMR (75.0 MHz, CDCl_3) δ 86.6, 71.0, 58.7, 25.5, 17.8, 12.0; IR (neat) 3313, 2944, 2868, 1464, 1122, 1060 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{13}\text{H}_{27}\text{OSi}$ 227.1831, found 227.1821.

Divinylcarbinol 81. To an oven-dried flask was added Cp_2ZrHCl (3333 mg, 12.9 mmol) and 30 mL of distilled CH_2Cl_2 . To the white suspension was added alkyne **80** (2654 mg, 11.7 mmol) dropwise. The resulting mixture was stirred at rt for 60 min. The white

suspension became a pale yellow solution. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and 6.5 mL of 2.0 M Me_2Zn solution in toluene was added. After 10 min of stirring at the same temperature, freshly prepared aldehyde **48** (17.6 mmol dissolved in 5 mL of distilled CH_2Cl_2) was added dropwise. The mixture was warmed to $0\text{ }^{\circ}\text{C}$ and stirred at $0\text{ }^{\circ}\text{C}$ for 3 h. The reaction mixture was quenched with a small amount of saturated NaHCO_3 solution until no more gas evolution. The white suspension was filtered through a pad of silica gel, and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 10 : 1) provided 4.53 g (91 %) of **81** as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 5.95 (1H, s), 5.86 (1H, m), 5.63 (1H, dd, $J = 15.6, 5.6$ Hz), 5.13 (1H, m), 4.40 (1H, m), 1.83 (3H, s), 1.23 (3H, d, $J = 6.4$ Hz), 1.04 (21H, m) ; ^{13}C NMR (75.0 MHz, CDCl_3) δ 147.2, 136.8, 126.4, 76.1, 74.5, 68.5, 24.7, 18.6, 17.9, 12.1; IR (neat) 3383, 2943, 2866, 1464, 1368, 1151, 1091, 1012 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{17}\text{H}_{34}\text{IO}_2\text{Si}$ 425.1373, found 425.1406.

Diol 82a and 82b. Divinylcarbinol **81** (4000 mg, 9.43 mmol) was dissolved in 20 mL of distilled THF. To the solution was added TBAF solution (1.0 M in THF, 10.4 mL) at rt. The reaction solution was stirred at rt for 4 h, quenched with water, extracted with EtOAc (3 $\times$), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexane/EtOAc=1:1) afforded 2.37 g (94%) diol **82** (dr 1:1) as a white solid.

Diol 82a (>95% de): Obtained by recrystallization of **82** in CHCl_3 at rt (39% yield based on 100% 1:1 mixture of diastereomers). M.p. 80-82 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ 5.98 (1H, d, $J = 0.9$ Hz), 5.92 (1H, ddd, $J = 15.6, 5.6, 1.6$ Hz), 5.65 (1H, ddd, $J = 15.6, 5.6, 1.6$ Hz), 5.16 (1H, br d, $J = 5.6$ Hz), 4.34 (1H, m), 1.83 (3H, d, $J = 0.9$ Hz), 1.27 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (75.0 MHz, CD_3OD) δ 149.4, 136.8, 129.3, 76.9, 74.7, 68.8, 23.7, 18.8; IR (thin film) 3289, 1431, 1069, 1042, 1023 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_8\text{H}_{13}\text{IO}_2$, 267.9960, found 267.9932.

Diol 82b (>95% de): Obtained by recrystallization of **82** in CHCl_3 at $0\text{ }^{\circ}\text{C}$ (40% yield based on 100% 1:1 mixture of diastereomers). M.p. 98-100 $^{\circ}\text{C}$; ^1H NMR (400 MHz,

CDCl₃) δ 5.97 (1H, d, J = 0.8 Hz), 5.92 (1H, ddd, J = 15.6, 5.6, 0.9 Hz), 5.65 (1H, dd, J = 15.6, 5.2 Hz), 5.14 (1H, d, J = 5.2 Hz), 4.34 (1H, m), 1.84 (3H, d, J = 0.8 Hz), 1.27 (3H, d, J = 6.4 Hz); ¹³C NMR (75.0 MHz, CD₃OD) δ 149.5, 136.8, 129.3, 77.0, 74.6, 68.8, 23.7, 18.8; IR (thin film) 3289, 1431, 1069, 1042, 1023 cm⁻¹; CIHRMS [M^+] calculated for C₈H₁₃IO₂, 267.9960, found 268.0018.

Stereochemical Assignment of Diols **82a** and **82b**.

Divinylcarbinol compound **49** (dr=1:1) was desilylated using TBAF according to the similar procedure as diol **82**. The resulting diols **A** and **B** were resolved by recrystallization in CHCl₃. Diols **A** and **B** (>95% de) were then re-silylated with DEIPSCl to afford diastomeric pure divinylcarbinols **49a** and **49b**. The configurations of **49a** and **49b** were assigned by HPLC analysis (*cf.* page S14). At the same time, the configuration of diols **A** and **B** were also assigned based on **49a** and **49b**. The stereochemical assignment of diols **82a** and **82b** were then achieved by comparison of their optical rotations with diols **A** and **B** since they are enantiomers (see Table 1).

Table 1. Stereochemical Assignment of Diols **81a and **81b**.**

compound	$[\alpha]_D^{23}$	Rt ^a (min)	compound	Rt ^b (min)
A	-180.8° (c 1.58, MeOH)	11.4	49a	11.2
B	+165.7° (c 1.19, MeOH)	11.9	49b	12.3
82a	-170.6° (c 1.42, MeOH)	11.3	^a HPLC condition: Chiralcel OD, 5-10% iPrOH/hexane, 10 min, 1.0 mL/min,; ^b HPLC conditions: Chiralcel OD, 2% iPrOH/hexane, 0.5 mL/min.	
82b	+186.7° (c 1.50, MeOH)	12.3		

27c: Prepared from divinylcarbinol **83a** according to the same route employed for the synthesis of **27a**. $[\alpha]_D^{23}$ +2.4° (c 1.0, MeOH); ¹H NMR (400 MHz, CD₃OD) δ 7.85 (1H, d, J = 10.0 Hz), 7.15 (1H, dd, J = 15.6, 10.0 Hz), 7.14 (1H, dd, J = 8.0, 7.6 Hz), 6.87 (1H, d, J

= 14.4 Hz), 6.67 (1H, d, J = 8.0 Hz), 6.65 (1H, d, J = 8.0 Hz), 6.28 (1H, d, J = 15.6 Hz), 5.78 (1H, dd, J = 15.6, 5.2 Hz), 5.62 (1H, dd, J = 15.6, 7.6 Hz), 5.54 (1H, m), 5.43 (1H, dt, J = 14.4, 7.6 Hz), 5.32 (2H, m), 4.78 (1H, d, J = 4.8 Hz), 3.90 (3H, s), 3.21 (1H, dd, J = 18.0, 5.6 Hz), 3.08 (1H, br d, J = 18.0 Hz), 2.76 (1H, dd, J = 15.2, 2.0 Hz), 2.54 (2H, m), 2.51 (1H, dd, J = 15.2, 10.4 Hz), 1.76 (3H, s), 1.36 (3H, d, J = 6.8 Hz); ^{13}C NMR (75.0 MHz, CD_3OD) δ 171.7, 170.7, 164.6, 157.2, 149.8, 141.8, 138.1, 135.9, 133.5, 132.3, 130.8, 130.5, 127.3, 127.2, 122.7, 121.1, 114.7, 110.6, 73.7, 73.4, 72.7, 63.0, 40.2, 35.8, 33.2, 20.5, 19.7; IR (thin film) 3281, 2977, 2938, 1731, 1654, 1450, 1273 1042 cm^{-1} ; CIHRMS calculated for $[\text{M}+1]^+$ $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_8$ 513.2237, found 513.2232.

27d: Prepared from divinylcarbinol **83b** according to the same route employed for the synthesis of **27a**. $[\alpha]_{\text{D}}^{23} +18^\circ$ (c 0.1, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 7.85 (1H, d, J = 10.0 Hz), 7.21 (1H, dd, J = 8.4, 7.6 Hz), 7.15 (1H, dd, J = 15.6, 10.4 Hz), 6.88 (1H, d, J = 14.4 Hz), 6.79 (1H, d, J = 7.6 Hz), 6.70 (1H, d, J = 8.4 Hz), 6.28 (1H, d, J = 15.6 Hz), 5.66 (1H, dd, J = 15.6, 5.6 Hz), 5.60 (1H, m), 5.52 (1H, dd, J = 15.6, 8.0 Hz), 5.41 (1H, dt, J = 14.4, 7.6 Hz), 5.38 (1H, m), 5.31 (1H, m), 4.74 (1H, d, J = 7.6 Hz), 3.90 (3H, s), 3.26 (2H, m), 2.76 (1H, dd, J = 15.2, 2.0 Hz), 2.53 (3H, m), 1.77 (3H, d, J = 0.9 Hz), 1.36 (3H, d, J = 6.8 Hz); ^{13}C NMR (75.0 MHz, CD_3OD) δ 171.4, 170.9, 164.6, 157.9, 149.7, 142.2, 139.6, 135.9, 134.2, 132.9, 131.7, 130.4, 127.3, 125.7, 121.3, 120.7, 114.9, 110.6, 73.9, 73.4, 73.0, 63.0, 40.2, 35.9, 32.2, 20.3, 19.1; IR (thin film) 3295, 2977, 2937, 1731, 1653, 1448, 1273, 1042 cm^{-1} ; CIHRMS calculated for $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_8$: 512.2159, found: 512.2178.

4-bromophenyl acetic ester 84: Compound **54a** (5 mg, 0.008 mmol), 4-bromophenyl acetic acid (2 mg, 0.0096 mmol), DMAP (0.1 mg, 0.8 μmol) was dissolved in 0.25 mL

CH₂Cl₂. To the solution was added DIC (11 mg, 0.08mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, warmed to rt, stirred for 10 min. The reaction was quenched with water, extracted with EtOAc, dried over Na₂SO₄, and concentrated in vacuo. Purification on silica gel (hexane/EtOAc=2:1) afforded 5 mg (80 %) product **84** as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 7.76 (1H, d, *J* = 10.4 Hz), 7.43 (2H, d, *J* = 8.4 Hz), 7.33 (1H, dd, *J* = 8.4, 7.6 Hz), 7.26 (1H, m), 7.19 (2H, d, *J* = 8.4 Hz), 7.13 (1H, d, *J* = 10.4 Hz), 7.05 (1H, d, *J* = 7.6 Hz), 6.92 (1H, d, *J* = 8.4 Hz), 6.84 (1H, dd, *J* = 14.4, 10.4 Hz), 6.00 (1H, d, *J* = 15.2 Hz), 5.61 (1H, dd, *J* = 15.6, 8.8 Hz), 5.49 (1H, m), 5.29 (1H, dd, *J* = 15.6, 8.8 Hz), 5.17 (2H, m), 5.01 (1H, dt, 14.4, 6.4 Hz), 4.78 (1H, d, *J* = 8.8 Hz), 3.94 (3H, s), 3.74 (2H, s), 3.19 (1H, dd, *J* = 16.8, 9.2 Hz), 2.95 (1H, d, *J* = 16.8 Hz), 2.51 (2H, m), 2.24 (1H, m), 2.16 (1H, m), 1.75 (3H, s), 1.30 (3H, d, *J* = 6.4 Hz), 0.87 (9H, s), 0.05 (3H, s), 0.02 (3H, s); CIHRMS [M+1]⁺ calculated for C₄₁H₅₂BrN₂O₉Si 823.2625, found 823.2611.

Analogue 85. Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 10.72 (1H, s), 7.81 (1H, m), 7.75 (1H, d, *J* = 10.4 Hz), 7.44 (1H, dd, *J* = 8.0, 7.2 Hz), 7.32~7.20 (1H, m), 6.96 (1H, d,

J = 8.4 Hz), 6.86 (1H, dd, *J* = 8.0, 7.2 Hz), 6.80 (1H, d, *J* = 13.2 Hz), 6.58 (1H, d, *J* = 16.0 Hz), 5.10 (1H, m), 4.38 (2H, br s), 3.94 (3H, s), 3.15 (3H, s), 2.57 (2H, br s); ¹³C NMR (75.0 MHz, CDCl₃) δ 170.2, 164.6, 161.9, 148.3, 136.4, 136.0, 130.8, 129.9, 126.2, 119.4, 117.9, 112.6, 108.4, 65.0, 62.7, 30.9, 30.1; IR (thin film) 3186, 2938, 1646, 1614, 1390, 1300, 1250, 1042 cm⁻¹; CIHRMS [M]⁺ calculated for C₁₇H₂₀N₂O₅ 332.1372, found 332.1359.

Salicylate 88. Pd₂(dba)₃CHCl₃ (27 mg, 0.026 mmol) and AsPh₃ (64 mg, 0.21 mmol) were added to a flame-dried Schlenk tube, degassed with high vacuum, refilled with argon, and

suspended in 1 mL of distilled THF. After 15 min of stirring at rt, the suspension became yellow. To the suspension was added a mixture of vinyl stannane **87** (285 mg, 0.521 mmol) and benzylic bromide **76** (200 mg, 0.521 mmol) in 1.5 mL of distilled THF. The resulting solution was refluxed for 2 h, cooled to rt, diluted with EtOAc, and filtered through a pad of silica gel. The filtrate was concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 20 : 1) afforded 157 mg (60 %) of **88**. ^1H NMR (400 MHz, CDCl_3) δ 7.20 (1H, dd, J = 8.0, 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz), 6.69 (1H, d, J = 8.0 Hz), 5.47 (2H, m), 4.84 (2H, s), 3.61 (2H, t, J = 6.4 Hz), 3.33 (2H, d, J = 6.8 Hz), 2.14 (2H, m), 1.58 (2H, m), 0.94 (9H, s), 0.87 (9H, s), 0.22 (6H, s), 0.03 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 167.0, 153.1, 140.7, 131.5, 131.4, 127.2, 123.7, 122.0, 116.8, 114.4, 62.8, 48.8, 32.8, 31.4, 26.2, 25.8, 23.8, 18.6, 18.3, -4.1, -5.1; IR (thin film) 2932, 2859, 1750, 1584, 1466, 1292, 1256, 1098, 1064 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{46}\text{NO}_4\text{Si}_2$ 504.2965, found 504.2944.

Cyanomethyl Ester 89. Compound **88** (176 mg, 0.35 mmol) was dissolved in 5 mL of distilled THF. The solution was cooled to 0 $^\circ\text{C}$ and 0.385 mL of 1.0 M TBAF solution in THF was added dropwise. The reaction mixture was stirred at 0 $^\circ\text{C}$ for 7 min, quenched with water, and extracted with EtOAc (3 $\times$). The organic layers were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on silica gel (hexane : EtOAc = 8:1 -5:1) provided 100 mg (73 %) of **89**. ^1H NMR (400 MHz, CDCl_3) δ 10.50 (1H, s), 7.36 (1H, dd, J = 8.0, 7.6 Hz), 6.88 (1H, d, J = 8.8 Hz), 6.80 (1H, d, J = 7.2 Hz), 5.47 (2H, m), 4.97 (2H, s), 3.66 (2H, d, J = 6.0 Hz), 3.62 (2H, t, J = 6.4 Hz), 2.17 (2H, m), 1.59 (2H, m), 0.88 (9H, s), 0.04 (6H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 170.1, 163.5, 144.6, 135.9, 131.1, 128.1, 122.7, 116.5, 114.0, 110.5, 62.8, 49.1, 34.4, 32.8, 26.2, 24.0, 18.6, -5.0; IR (thin film) 2931, 2857, 1673, 1609, 1449, 1296, 1250, 1207, 1107 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{32}\text{NO}_4\text{Si}$ 390.2101, found 390.2112.

Hydroxy acid 91. Enamide acid **71** (15 mg, 0.059 mmol) was added to an oven-dried Schlenk flask and dissolved in 1.0 mL of distilled MeOH. To the solution was added 59 μ L of 1.0 M Bu₄NOH solution in MeOH. The solution was stirred at rt for 20 min. The solvent was removed under vacuum and the residue was azeotroped with toluene. A solution of

cyanomethyl ester **89** (22 mg, 0.059 mmol) dissolved in 120 μ L of toluene was added to the flask and the mixture was azeotroped again under high vacuum. Na₂CO₃ (6.4 mg, 0.059 mmol) and 0.6 mL of DMF was added to the flask. The resulting mixture was degassed under high vacuum for 3 min and refilled with argon. To the solution was added 120 μ L of distilled 2-butanone and the mixture was stirred at 80 °C for 2 h. The reaction was quenched with water, extracted with EtOAc. The aqueous layer was acidified to pH 4, extracted with EtOAc (2 $\times$). The organic layers were combined, concentrated *in vacuo*, and purified using a Waters Sep-Pak C18 cartridge (50-60% CH₃CN/H₂O) to afford 20 mg of crude acid **90**, which was advanced to the next step without purification.

Crude **90** (20 mg, 0.034 mmol) was dissolved in 0.9 mL of distilled THF. To the solution was added 136 μ L of 5.0 M of HF-pyridine/pyridine solution. The mixture was stirred at rt for 1 h, quenched with water, and extracted with EtOAc (3 $\times$). The organic layers were combined and concentrated *in vacuo*. Purification using a C18 cartridge (30-40% CH₃CN/H₂O) provided 10 mg (36%, 2 steps) of compound **91** as a yellow oil. ¹H NMR (400 MHz, CD₃OD) δ 7.84 (1H, d, *J* = 10.4 Hz), 7.19 (1H, dd, *J* = 8.0, 8.0 Hz), 7.13 (1H, dd, *J* = 15.6, 10.3 Hz), 6.84 (1H, d, *J* = 14.0 Hz), 6.70 (2H, d, *J* = 8.0 Hz), 6.26 (1H, d, *J* = 15.6 Hz), 5.53 (1H, m), 5.45 (2H, m), 5.39 (1H, dt, *J* = 14.0, 7.2 Hz), 3.89 (3H, s), 3.55 (2H, t, *J* = 6.4 Hz), 3.50 (2H, d, *J* = 5.6 Hz), 2.67-2.50 (4H, m), 2.16 (2H, m), 1.59 (2H, m); ¹³C NMR (75.0 MHz, CDCl₃) δ 174.2, 170.9, 164.3, 159.8, 149.6, 143.2, 135.8, 133.5, 131.2, 130.3, 129.8, 127.1, 122.0, 118.5, 115.6, 110.5, 73.3, 63.0, 62.6, 39.2, 35.7, 33.6, 33.4, 24.8; IR (thin film) 3284, 2936, 1718, 1654, 1525, 1450, 1258, 1214, 1042 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₂₄H₃₁N₂O₈ 475.2080, found 475.2107.

Analogue 86. PPh₃ (44.3 mg, 0.169 mmol) was dissolved in 1.1 mL of distilled THF and diisopropyl azodicarboxylate (DIAD) (34.1 mg, 0.169 mmol) was added dropwise. The solution was stirred at rt for 20 min. A white heterogenous suspension was formed. To the suspension was added compound **91** (8 mg, 0.017 mmol) in 3.4 mL of distilled THF at 0 °C over a period of 2 h *via* syringe pump. The resulting mixture was stirred for a further 1 h at 0 °C and quenched with water. The aqueous layer was extracted with EtOAc (3 ×) and the organic layers were combined and concentrated *in vacuo*. Purification using silica gel (hexanes : EtOAc = 2 : 1) provided 5 mg (65 %) of **86** as a pale yellow solid. $[\alpha]_D^{23} -7.1^\circ$ (*c* 0.31, MeOH); ¹H NMR (400 MHz, CDCl₃) δ 10.33 (1H, s), 7.75 (1H, d, *J* = 10.0 Hz), 7.30 (1H, dd, *J* = 8.0, 8.0 Hz), 7.28 (1H, dd, *J* = 15.2, 10.0 Hz), 7.10 (1H, d, *J* = 10.4 Hz), 6.93 (1H, dd, *J* = 14.4, 10.4 Hz), 6.82 (1H, d, *J* = 8.0 Hz), 6.75 (1H, d, *J* = 8.0 Hz), 6.05 (1H, d, *J* = 15.2 Hz), 5.68 (1H, m), 5.49 (1H, m), 5.42 (1H, m), 5.17 (1H, dt, *J* = 14.4, 7.2 Hz), 4.21 (1H, m), 3.97 (1H, m), 3.94 (3H, s), 3.66 (1H, dd, *J* = 19.2, 8.0 Hz), 3.53 (1H, dd, *J* = 19.2, 4.8 Hz), 2.74~2.56 (4H, m), 2.32 (1H, m), 2.17 (1H, br s), 1.86 (1H, m), 1.66 (1H, br s); ¹³C NMR (75.0 MHz, CDCl₃) δ 171.4, 170.8, 161.7, 161.6, 147.8, 143.7, 135.7, 134.3, 130.4, 129.3, 128.3, 126.1, 120.3, 115.7, 113.4, 107.5, 74.1, 62.9, 62.8, 38.2, 34.0, 32.1, 26.8, 23.2; IR (thin film) 3288, 2927, 1732, 1653, 1524, 1453, 1210, 1042 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₂₄H₂₉N₂O₇ 457.1975, found 457.1953.

Cyanomethyl ester 94: Prepared in 87% yield by the procedure reported for compound **69** from 6-iodosalicylic acid. ¹H NMR (400 MHz, CDCl₃) δ 10.24 (1H, s), 7.62 (1H, dd, *J* = 7.6, 1.2 Hz), 7.06 (1H, dd, *J* = 8.4, 7.6 Hz), 6.99 (1H, dd, *J* = 8.4, 1.2 Hz), 5.00 (2H, s); ¹³C NMR (75.0 MHz, CDCl₃) δ 167.2, 162.4, 136.0, 134.2, 118.2, 115.6, 113.6, 93.5, 48.6; IR (thin film) 3355, 1750, 1684, 1592, 1442, 1288, 1184, 1097 cm⁻¹; CIHRMS [M⁺] calculated for C₉H₆INO₃, 302.9392, found 302.9416.

Analogue 92: Prepared in 10% yield by the procedure reported for compound **68**. ^1H NMR (400 MHz, CDCl_3) δ 10.64 (1H, s), 7.75 (1H, d, $J = 10.4$ Hz), 7.54 (1H, dd, $J = 7.2, 1.2$ Hz), 7.27 (1H, dd, $J = 15.6, 10.4$ Hz), 7.16 (1H, d, $J = 10.4$ Hz), 6.98 (1H, dd, $J = 8.4, 7.2$ Hz), 6.95 (2H, m), 6.05 (1H, d, $J = 15.6$ Hz), 5.61 (1H, m), 5.25 (1H, dt, $J = 14.0, 7.2$ Hz), 3.94 (3H, s), 3.68 (3H, s), 2.88 (1H, dd, $J = 16.4, 8.0$ Hz), 2.72 (1H, dd, $J = 16.4, 4.8$ Hz), 2.57 (2H, m); ^{13}C NMR (75.0 MHz, CDCl_3) δ 170.9, 167.8, 162.2, 161.7, 147.7, 135.6, 135.1, 133.9, 128.2, 125.9, 118.4, 117.0, 107.4, 93.9, 72.7, 62.6, 52.1, 37.8, 34.4; IR (thin film) 3281, 1737, 1651, 1441, 1286, 1042 cm^{-1} ; CIHRMS $[\text{M}+1]^+$ calculated for $\text{C}_{19}\text{H}_{22}\text{IN}_2\text{O}_7$, 517.0472, found 517.0473.

Acetonide 96: Aryl triflate **41** (500 mg, 1.52 mmol) was dissolved with 4.0 mL NMP in a Schlenk flask. To the solution was added LiCl (193 mg, 4.60 mmol), tri-2-furylphosphine (29 mg, 0.12 mmol) and $\text{Pd}_2(\text{dba})_3$ (15 mg, 0.015 mmol). The resulting mixture was stirred at rt for 10 min. Prenyl stannane **95** (568 μL , 1.69 mmol) was added dropwise. The reaction solution was stirred at rt for 72 h, quenched with saturated KF solution, extracted with EtOAc (3 $\times$). The organic layers were combined, dried over Na_2SO_4 , concentrated *in vacuo*. Purification on silica gel (hexane/EtOAc = 10:1) afforded 230 mg (61 %) of **96** as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 7.38 (1H, dd, $J = 8.4, 7.6$ Hz), 6.95 (1H, d, $J = 7.6$ Hz), 6.77 (1H, d, $J = 8.4$ Hz), 5.29 (1H, t, $J = 7.2$ Hz), 3.81 (2H, d, $J = 7.2$ Hz), 1.72 (3H, s), 1.68 (9H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 160.5, 157.1, 147.0, 135.3, 133.4, 124.4, 122.0, 115.1, 112.0, 105.0, 32.5, 25.7, 25.5, 17.8; IR (thin film) 2965, 1726, 1578, 1475, 1296, 1051 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_{15}\text{H}_{18}\text{O}_3$ 246.1256, found 246.1295.

6-prenyl salicylic acid 97: Prepared in 60 % yield from compound **96** by the procedure reported for 6-methyl salicylic acid (page S21). ^1H NMR (400 MHz, CDCl_3) δ 10.92 (1H, s), 7.36 (1H, dd, $J = 8.4, 7.6$ Hz), 6.86 (1H, d, $J = 8.4$ Hz), 6.80 (1H, d, $J = 7.6$ Hz), 5.27 (1H, t, $J = 7.2$ Hz), 3.70

(2H, d, $J = 7.2$ Hz), 1.73 (3H, s), 1.69 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 176.0, 163.7, 146.3, 135.7, 133.0, 122.8, 122.2, 116.1, 110.6, 34.6, 25.7, 17.8; IR (thin film) 2923, 1656, 1605, 1440, 1306, 1248 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_{12}\text{H}_{14}\text{O}_3$ 206.0943, found 206.0923.

Cyanomethyl ester 98: Prepared in 70 % yield by the procedure reported for compound **69**. ^1H NMR (400 MHz, CDCl_3) δ 10.47 (1H, s), 7.35 (1H, dd, $J = 8.0, 8.0$ Hz), 6.86 (1H, d, $J = 8.0$ Hz), 6.78 (1H, d, $J = 8.0$ Hz), 5.15 (1H, t, $J = 6.4$ Hz), 4.96 (2H, s), 3.60 (2H, d, $J = 6.4$ Hz), 1.72 (3H, s), 1.69 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 170.0, 163.2, 145.1, 135.7, 133.3, 122.5, 122.4, 116.1, 113.8, 110.4, 48.7, 34.9, 25.5, 17.8; IR (thin film) 3098, 2932, 1670, 1448, 1373, 1204, 1122 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_{14}\text{H}_{16}\text{NO}_3$ 246.1130, found 246.1123.

Analogue 93: Prepared in 53 % yield by the procedure reported for compound **68**. ^1H NMR (400 MHz, CDCl_3) δ 10.91 (1H, s), 7.75 (1H, d, $J = 10.4$ Hz), 7.27 (1H, dd, $J = 8.4, 7.6$ Hz), 7.26 (1H, m), 7.20 (1H, d, $J = 10.8$ Hz), 6.93 (1H, dd, $J = 14.4, 10.8$ Hz), 6.81 (1H, d, $J = 8.4$ Hz), 6.71 (1H, d, $J = 7.6$ Hz), 6.04 (1H, d, $J = 15.2$ Hz), 5.55 (1H, m), 5.18 (2H, m), 3.93 (3H, s), 3.65 (3H, s), 3.54 (2H, d, $J = 5.6$ Hz), 2.73 (1H, dd, $J = 16.0, 8.0$ Hz), 2.67 (1H, dd, $J = 16.0, 5.2$ Hz), 2.51 (2H, br s), 1.71 (3H, s), 1.67 (3H, s); ^{13}C NMR (75.0 MHz, CDCl_3) δ 166.3, 166.1, 158.0, 157.2, 143.2, 140.1, 131.0, 129.9, 128.0, 123.6, 121.3, 118.8, 117.4, 111.3, 107.7, 103.0, 67.2, 58.0, 47.4, 33.4, 30.04, 29.97, 25.1, 21.1; IR (thin film) 3274, 2925, 1739, 1652, 1450, 1042 cm^{-1} ; CIHRMS $[\text{M}^+]$ calculated for $\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_7$ 458.2053, found 458.2054.

Table 2. HPLC data of natural and synthetic lobatamide C and diastereomers^a

Sample Name	Rt (min)
natural lobatamide C	3.88
synthetic lobatamide C (27a)	3.83
natural lobatamide C plus 27a	3.85
27b	5.51
27c	4.02
27d	4.09

^a Experimental condition: Agilent Zorbax SB-C18 column (4.6mm ID × 7.5cm, 3.5 μ), 40% MeCN/H₂O, 280 nm, 1.0 mL/min.

Table 3. $[\alpha]_D$ of Natural and Synthetic lobatamide C and diastereomers.

Compound	$[\alpha]_D$
natural lobatamide C	-15.5° (<i>c</i> 0.113, MeOH)
synthetic lobatamide C (27a)	-18.8 (<i>c</i> 0.17, MeOH)
27b	-18.0° (<i>c</i> 0.2, MeOH)
27c	+2.4° (<i>c</i> 1.0, MeOH)
27d	+18° (<i>c</i> 0.1, MeOH)

Table 4. ¹H NMR Data for Natural and Synthetic Lobatamide C and stereoisomers

¹ H δ (mult, <i>J</i> in Hz)					
No.	natural lobatamide C ^a	27a^a	27b^b	27c^b	27d^b
1	7.86 (d, 10.2)	7.85 (d, 10.1)	7.85 (d, 10.4)	7.85 (d, 10.0)	7.85 (d, 10.0)
2	7.14 (dd, 15.1, 10.2)	7.15 (dd, 15.6, 10.2)	7.15 (dd, 15.6, 10.4)	7.15 (dd, 15.6, 10.0)	7.15 (dd, 15.6, 10.4)
3	6.28 (d, 15.1)	6.28 (d, 15.6)	6.28 (d, 15.6)	6.28 (d, 15.6)	6.28 (d, 15.6)
5	6.87 (d, 14.6)	6.86 (d, 14.4)	6.86 (d, 14.0)	6.87 (d, 14.4)	6.88 (d, 14.4)
6	5.37 (dt, 14.6, 7.8)	5.36 (dt, 14.4, 7.7)	5.36 (dt, 14.0, 7.2)	5.43 (dt, 14.4, 7.6)	5.41 (dt, 14.4, 7.6)
7	2.48 (2H, m)	2.49 (2H, m)	2.50 (2H, m)	2.54 (2H, m)	2.53 (2H, m)
8	5.60 (m)	5.59 (m)	5.59 (m)	5.54 (m)	5.60 (m)
9a	2.67 (dd, 16.6, 2.4)	2.69 (dd, 16.8, 2.2)	2.71 (dd, 16.4, 2.8)	2.76 (dd, 15.2, 2.0)	2.76 (dd, 15.2, 2.0)
9b	2.60 (dd, 16.6, 10.8)	2.59 (dd, 16.8, 10.7)	2.61 (dd, 16.4, 10.0)	2.51 (dd, 15.2, 10.4)	2.53 (m)
11	5.23 (dq, 8.8, 6.4)	5.22 (dq, 8.6, 6.4)	5.42 (m)	5.32 (m)	5.38 (m)
12	1.34 (3H, d, 6.3)	1.34 (3H, d, 6.4)	1.34 (3H, d, 6.4)	1.36 (3H, d, 6.8)	1.36 (3H, d, 6.8)
13	5.50 (dd, 15.1, 8.8)	5.49 (dd, 15.2, 8.6)	5.62 (ddd, 15.2, 8.0, 1.6)	5.62 (dd, 15.6, 7.6)	5.52 (dd, 15.6, 8.0)
14	5.67 (dd, 15.1, 8.8)	5.68 (dd, 15.2, 8.9)	5.87 (dd, 15.6, 4.8)	5.78 (dd, 15.6, 5.2)	5.66 (dd, 15.6, 5.6)
15	4.79 (d, 8.8)	4.78 (d, 8.9)	4.69 (dd, 4.8, 1.6)	4.78 (d, 4.8)	4.74 (d, 7.6)
17	1.79 (3H, s)	1.79 (3H, s)	1.83 (3H, s)	1.76 (3H, s)	1.77 (3H, d, 0.9)
18	5.17 (m)	5.17 (m)	5.29 (m)	5.32 (m)	5.31 (m)
19a	3.21 (dd, 17.6, 8.8)	3.21 (dd, 17.7, 8.5)	3.47 (dd, 18.0, 8.0)	3.21 (dd, 18.0, 5.6)	3.26 (m)
19b	2.95 (br d, 17.6)	2.94 (br d, 17.7)	3.08 (dd, 18.0, 4.0)	2.94 (br d, 18.0)	3.26 (m)
21	6.63 (d, 7.8)	6.63 (d, 7.7)	6.69 (d, 8.0)	6.67 (d, 8.0)	6.70 (d, 8.4)
22	7.14 (dd, 8.3, 7.8)	7.14 (dd, 8.6, 7.9)	7.19 (dd, 8.0, 8.0)	7.14 (dd, 8.0, 7.6)	7.21 (dd, 8.4, 7.6)
23	6.68 (d, 8.3)	6.68 (d, 8.0)	6.76 (d, 8.0)	6.65 (d, 8.0)	6.79 (d, 7.6)
27	3.91 (3H, s)	3.90 (3H, s)	3.91 (3H, s)	3.90 (3H, s)	3.90 (3H, s)

^a 500 MHz, CD₃OD; ^b 400 MHz, CD₃OD.

Table 5. ^{13}C NMR Data of Natural and Synthetic Lobatamide C and diastereomers

C	natural lobatamide C ^a	27a ^b	27b ^b	27c ^b	27d ^b
1	149.3	149.5	149.5	149.8	149.7
2	135.5	135.6	135.6	135.9	135.9
3	130.2	130.4	130.1	130.5	130.4
4	164.1	164.4	164.4	164.6	164.6
5	126.9	127.2	126.9	127.3	127.3
6	110.2	110.3	110.3	110.6	110.6
7	35.5	35.7	35.6	35.8	35.9
8	72.9	73.3	72.5	72.7	73.0
9	38.8	39.1	39.0	40.2	40.2
10	171.7	171.9	171.9	171.7	171.4
11	73.7	73.8	73.6	73.7	73.9
12	20.2	20.2	21.5	20.5	20.3
13	132.6	132.7	132.9	132.3	132.9
14	134.9	135.3	135.6	133.5	134.2
15	73.2	73.5	73.1	73.4	73.4
16	139.4	139.6	139.0	138.1	139.6
17	19.5	19.8	19.7	19.7	19.1
18	125.5	125.8	126.7	127.2	125.7
19	33.0	33.3	32.9	33.2	32.2
20	141.1	141.6	142.5	141.8	142.2
21	120.8	121.1	120.8	121.1	120.7
22	131.7	132.1	129.8	130.8	131.7
23	114.2	114.7	115.1	114.7	114.9
24	156.6	157.1	158.8	157.2	157.9
25	122.2	121.9	119.6	122.7	121.3
26	169.9	170.2	170.8	170.7	170.9
27	62.7	62.9	62.8	63.0	63.0

^a 125 MHz, CD₃OD; ^b 100 MHz, CD₃OD.

X-ray Crystal Structure of lobatamide derivative **84**

Crystals of **84** suitable for x-ray analysis were obtained by slow evaporation from MeOH at -20°C . The structure was solved and refined (R-factor = 5.24 %). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 200364).

Table 6. Crystal data and structure refinement for compound 84.

Identification code	Compound 84	
Empirical formula	C ₄₁ H ₅₁ Br N ₂ O ₉ S	
Formula weight	827.81	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.8954(15) Å	α = 90°.
	b = 8.8330(13) Å	β = 93.538(5)°.
	c = 24.243(3) Å	γ = 90°.
Volume	2114.9(5) Å ³	
Z	2	
Density (calculated)	1.300 Mg/m ³	
Absorption coefficient	1.075 mm ⁻¹	
F(000)	868	
Crystal size	0.40 x 0.30 x 0.03 mm ³	
Theta range for data collection	2.06 to 24.71°.	
Index ranges	-11 ≤ h ≤ 11, -10 ≤ k ≤ 10, -28 ≤ l ≤ 26	
Reflections collected	13032	
Independent reflections	7052 [R(int) = 0.0324]	
Completeness to theta = 24.71°	99.0 %	
Absorption correction	SADABS	
Max. and min. transmission	0.9736 and 0.6731	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7052 / 1 / 579	
Goodness-of-fit on F ²	0.994	
Final R indices [I > 2σ(I)]	R1 = 0.0524, wR2 = 0.1265	
R indices (all data)	R1 = 0.0750, wR2 = 0.1379	
Absolute structure parameter	0.006(10)	
Largest diff. peak and hole	1.112 and -0.732 e.Å ⁻³	

Table 7. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **84**.U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	8585(1)	2521(1)	2571(1)	62(1)
Si1	12046(2)	-1461(2)	9133(1)	75(1)
O(1)	4096(4)	591(5)	1952(2)	58(1)
O(2)	4526(3)	3322(5)	4360(2)	55(1)
O(3)	8665(3)	4068(4)	7535(1)	39(1)
O(4)	7375(3)	1974(4)	7449(1)	35(1)
O(5)	11755(4)	394(5)	9023(2)	53(1)
O(6)	9896(3)	3516(3)	6367(1)	25(1)
O(7)	11125(3)	5530(4)	6139(2)	38(1)
O(8)	12899(3)	4001(3)	5449(1)	31(1)
O(9)	11145(3)	2599(4)	5113(1)	32(1)
N(1)	3916(4)	1402(5)	2434(2)	42(1)
N(2)	6722(4)	2823(5)	4590(2)	31(1)
C(1)	4858(5)	1152(6)	2797(2)	37(1)
C(2)	4800(5)	1913(6)	3326(2)	36(1)
C(3)	5727(5)	1825(5)	3733(2)	34(1)
C(4)	5573(4)	2705(6)	4250(2)	34(1)
C(5)	6854(5)	3766(5)	5051(2)	29(1)
C(6)	7982(5)	3913(5)	5367(2)	29(1)
C(7)	8155(5)	5037(6)	5820(2)	31(1)
C(8)	8653(4)	4462(5)	6384(2)	28(1)
C(9)	7657(4)	3410(6)	6643(2)	29(1)
C(10)	7974(4)	3217(5)	7255(2)	30(1)
C(11)	7655(5)	1626(7)	8037(2)	37(1)
C(12)	6575(5)	553(7)	8177(2)	51(2)
C(13)	9076(5)	1026(6)	8116(2)	35(1)
C(14)	10048(5)	1606(6)	8435(2)	37(1)
C(15)	11478(5)	1024(6)	8482(2)	39(1)
C(16)	12473(5)	2269(6)	8370(2)	39(1)
C(17)	13340(6)	2849(9)	8861(2)	66(2)
C(18)	12573(6)	2862(6)	7871(2)	40(1)

C(19)	11757(4)	2490(8)	7348(2)	35(1)
C(20)	12593(4)	2418(6)	6845(2)	27(1)
C(21)	13756(4)	1527(5)	6872(2)	32(1)
C(22)	14542(5)	1373(6)	6426(2)	35(1)
C(23)	14228(5)	2153(5)	5943(2)	33(1)
C(24)	13113(4)	3082(5)	5914(2)	25(1)
C(25)	12252(4)	3208(5)	6348(2)	24(1)
C(26)	11053(4)	4219(5)	6282(2)	23(1)
C(27)	3042(7)	972(9)	1555(3)	70(2)
C(28)	10499(8)	-2577(11)	8934(3)	91(2)
C(29)	13522(7)	-2097(11)	8755(3)	87(3)
C(30)	12465(8)	-1568(10)	9889(3)	80(2)
C(31)	11253(9)	-888(14)	10203(3)	112(4)
C(32)	12689(14)	-3262(12)	10047(4)	134(4)
C(33)	13762(8)	-656(14)	10036(3)	110(3)
C(34)	11839(4)	3693(5)	5083(2)	25(1)
C(35)	11644(6)	4956(6)	4668(2)	34(1)
C(36)	10911(4)	4491(5)	4136(2)	26(1)
C(37)	11595(4)	3913(5)	3705(2)	32(1)
C(38)	10932(5)	3385(6)	3230(2)	37(1)
C(39)	9532(5)	3435(6)	3189(2)	35(1)
C(40)	8825(5)	4067(6)	3596(2)	38(1)
C(41)	9501(5)	4588(5)	4066(2)	32(1)

Biology Methods.

Chromaffin granule membranes were prepared from bovine adrenal glands, obtained fresh from a local abattoir, as described.⁴ The membranes had a specific activity for ATP hydrolysis of 0.18 $\mu\text{mol}/\text{min}/\text{mg}$ of protein and were stored in aliquots at -70°C . V-ATPase activity was measured in 0.5 ml of 5 mM Na_2ATP , 5 mM MgSO_4 , 10 mM NH_4Cl , 5 mM KN_3 , 0.1 mM Na_3VO_4 , and 10 mM PIPES buffer adjusted to pH 7.5 with Tris base. Compounds to be tested were dissolved in dimethyl sulfoxide at a concentration of 0.1 or 0.2 M and diluted in the V-ATPase reaction mixture to the desired

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⁴ Nelson, N.; Cidon, S.; Moriyama, Y. *Methods Enzymol.* **1988**, 157, 619.

concentration. In some cases, higher concentrations could not be tested because of limited solubility in the reaction mixture. The reaction was started by addition of chromaffin granule membranes (20 μg protein) and allowed to proceed for 30 min at 37 $^{\circ}\text{C}$. The production of inorganic phosphate was measured as described.⁵

Graph 1. Bovine V-ATPase Activity of Synthetic Lobatamide C and Stereoisomers.

Graph 2. Bovine V-ATPase Activity of Selected Simplified Analogues.

⁵ Bowman, E. J.; Bowman, B. J.; *Methods Enzymol.* **1988**, 157, 562.

^1H NMR (500MHz, CD_3OD) Spectrum of Synthetic lobatamide C (**27a**).

¹H NMR(500MHz, CD₃OD)
of natural lobatamide C

¹H NMR (500MHz, CD₃OD)
of synthetic lobatamide C

^{13}C NMR (75 MHz, CD_3OD) Spectrum of Synthetic lobatamide C (27a).

^1H NMR (400MHz, CD_3OD) Spectrum of C15-epi lobatamide C (**27b**).

^{13}C NMR (75 MHz, CD_3OD) Spectrum of C15-epi lobatamide C (**27b**).

^1H NMR (400MHz, CD_3OD) of 11*R* 15*S* lobatamide C diastereomer (**27c**)

^{13}C NMR (75MHz, CD_3OD) of 11R 15S Lobatmide C diastereomer (27c)

^1H NMR (400MHz, CD_3OD) of 11*R*, 15*R* lobatamide C diastereomer (**27d**)

^{13}C NMR (75MHz, CD_3OD) of 11*R*, 15*R* Lobatamide C diastereomer (**27d**)