Total Synthesis of (±)-Merrilactone A via Catalytic Nazarov Cyclization

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I. General information

a) General Procedures, instruments and reagents. Unless otherwise noted, all reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. TLC Visualization was done with UV light and/or potassium permanganate, *p*-anisaldehyde or ceric ammonium molybdate solution followed by heating. Column chromatograph was performed on EM Science silica gel 60 (230-400 mesh). Methanol-*d*₄, chloroform-*d* and dichloromethane-*d*₂ were purchased from Cambridge Isotope. Diethyl ether, dichloroethane, tetrahydrofuran, and toluene were purchased from Fisher and dispensed using the Glass Contour solvent purification system.

¹H NMR and ¹³C NMR spectra were collected on either a 400 MHz or a 500MHz Avance spectrometer at ambient temperature. Chemical shift δ in ¹H NMR was reported in unit of parts per million (ppm) downfield from tetramethylsilane; Data are reported as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, b = broad, and dd = doublet of doublets with integration and coupling constant(s) given in Hz. High resolution mass spectra was done on a ThermoFinnigan MAT 95XL at the Chemistry Instrumentation Center of the University of Buffalo. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a 8400S Shimadzu FTIR spectrometer.

Ethyl chloroformate was purified as follows¹: It was washed with water (two times), dried over Na₂SO₄, and then distilled at ambient pressure under argon. b.p. = 94 – 95 °C.

Neat NaH was prepared from 60 % NaH dispersed in mineral oil by washing with hexanes (two time), THF (one time) and then drying on vacuum line for 2 hours.

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¹ Purification of Laboratory Chemicals. Armarego, W. L. F.; Perrin, D. D. **1996**, pp. 212, Butterworth-Heinemann, Woburn, MA.

b) Syntheses of known compounds: The following known compounds were synthesized according to literature procedures:

$[\text{IrMeCO}(\text{dppe})(\text{DIB})]^{2+}(\text{BAr}^f)_2$ was synthesized following the procedure of Albietz and Eisenberg² and stored in glove box before use.

Aldehyde **8** was synthesized in two steps from commercially available 4-pentyn-1-ol in 84 % yield following the procedures of Cruciani³.

The acrylate precursor for amide **13** was obtained following the procedures of Baldwin⁴. The obtained E, Z-mixture was used directly in the Weinreb amide formation (see page S-5), as the purification of **13** was easier to achieve using flash chromatography.

II. Experimental procedures for the synthetic intermediates and characterization data

a) Propargyl alcohol 9. To a stirred solution of ethyl propiolate (9052 mg, 89.60 mmol, 1.2 equiv) in THF (200 mL) at $-78\text{ }^{\circ}\text{C}$ under argon was added $n\text{BuLi}$ (1.6 M solution in pentane, 74.60 mL, 89.60 mmol, 1.2 equiv) dropwise over a period of 45 minutes using an addition funnel. The bath temperature was maintained at $-78\text{ }^{\circ}\text{C}$ during the course of the addition. To the resulting yellow anion was then added the aldehyde **8**³ (11488 mg, 74.60 mmol, 1.0 equiv) in THF (15 mL) over 20 minutes. After 20 minutes, TLC indicated complete consumption of the aldehyde **8**. The reaction was quenched with 50 mL saturated NH_4Cl (aq.) at $-78\text{ }^{\circ}\text{C}$. After the mixture was

² Albietz, P.; Cleary, B.; Paw, W.; Eisenberg, R. *J. Am. Chem. Soc.* **2001**, *123*, 12091-12092.

³ Cruciani, P.; Stammer, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699

⁴ Baldwin, I. R.; Whitby, R. J.; *Chem. Commun.* **2003**, 22, 2786 - 2787

warmed up to room temperature, it was extracted with ether (50 mL x 3 times). The extract was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (10 % v/v EtOAc/Hexanes) to furnish **9** as a pale yellow oil (16543 mg, 65.6 mmol, 88 %). **^1H NMR (400 MHz, CDCl_3):** δ 4.65 (m, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 2.76 (d, $J = 6.0$ Hz, 1H), 2.42 (m, 2H), 1.97 (m, 2H), 1.29 (t, $J = 7.2$ Hz, 3H), 0.13 (s, 9H); **^{13}C NMR (100 MHz, CDCl_3):** δ 153.3, 105.3, 87.0, 86.0, 76.7, 62.2, 60.8, 35.3, 15.7, 13.9, 0.0; **IR (neat, cm^{-1})** 3434, 2960, 2900, 2238, 2175, 1703, 1736, 1249, 1043; **HRMS (ES $^+$):** Calculated for $\text{C}_{13}\text{H}_{20}\text{O}_3\text{SiNa}$ ($\text{M} + \text{Na}$) $^+$ 275.1074, Found: 275.1068.

b) Bromo-butenolide 11. Part A: To a stirred suspension of CuCN (6123 mg, 68.40 mmol, 1.1 equiv) in THF (200 mL) at -78 $^{\circ}\text{C}$ under argon was added $n\text{BuLi}$ (1.6 M solution in pentane, 85.50 mL, 136.80 mmol, 2.2 equiv) dropwise over 20 minutes using a syringe pump. The suspension turned into a clear solution. To this solution was then added Bu_3SnH (39823 mg, 36.80 mL, 136.8 mmol, 2.2 equiv) dropwise over 20 minutes. The resulting orange solution was stirred for 20 minutes before propargyl alcohol **9** (15680 mg, 62.20 mmol, 1.0 equiv) in THF (20 mL) and methanol (5 mL) was introduced dropwise. After 30 minutes, TLC indicated complete consumption of the alcohol **9**. The reaction was quenched with 150 mL NH_4OH : saturated NH_4Cl (aq.) (v/v = 1 : 9). After the mixture was warmed up to room temperature, it was extracted with ether (100 mL x 3 times). The extract was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (gradient, first

pure hexanes then 15 % v/v EtOAc/Hexanes) to afford **10** as a pale orange red oil (27822 mg, 56.00 mmol, 90 %). **¹H NMR (400 MHz, CDCl₃):** δ 0.16 (s, 9H), 0.81-1.57 (m, 28H), 1.95-2.05 (m, 1H), 2.31-2.58 (m, 2H), 5.20-5.32 (m, 1H), 6.16 (s, 1H); **¹³C NMR (CDCl₃, 100 MHz):** 0.2, 10.2, 13.8, 17.0, 27.4, 29.1, 33.5, 86.4, 88.1, 105.3, 130.1, 173.0, 178.1.

Part B: The as-prepared compound **10** (26200 mg, 52.70 mmol, 1.0 equiv) was taken up in 500 mL CH₂Cl₂, to which a solution of bromine (10120 mg, 3.24 mL, 63.20 mmol, 1.2 equiv) in CH₂Cl₂ (200 mL) was added very slowly using an dropping funnel (*note: The best addition rate was about 50 mL/hr. Faster addition would result in undesired bromination of the alkyne*). When TLC monitoring found absence of the starting material, the addition of bromine was stopped and 50 mL saturated NaHCO₃/NaHSO₃ (aq.) (v/v = 1 : 1) was added to destroy excessive bromine. The aqueous phase was separated and extracted with ether (50 mL x 3 times). The organic phase was combined, washed with brine, dried over MgSO₄, and then concentrated. The crude product was purified by flash chromatography (gradient, first pure Hexanes, then 10 % v/v EtOAc/Hexanes) to offer bromo-butenolide **11** as a clear oil (waxy solid upon refrigeration) (14068 mg, 49.00 mmol, 93 %). **¹H NMR (400 MHz, CDCl₃):** δ 6.32 (s, 1H), 5.09 (m, 1H), 2.45 (m, 2H), 2.31 (m, 1H), 1.79 (m, 1H), 0.15 (s, 9H); **¹³C NMR (100 MHz, CDCl₃):** δ 169.8, 150.3, 122.3, 104.2, 86.7, 83.9, 31.4, 15.6, 0.0; **IR (neat, cm⁻¹)** 3100, 2958, 2175, 1777, 1754, 1603, 1249, 1149; **HRMS (ES⁺):** Calculated for C₁₁H₁₅O₂BrNaSi (M + Na)⁺ 308.9917, Found: 308.9915.

c) **Siloxyfuran 12.** A standard procedure of Et₃N/TIPS·OTf protection was used.⁵

d) **Weinreb amide 13.** To a stirred suspension of N, O-dimethylhydroxylamine hydrochloride (1510 mg, 15.00 mmol, 1.5 equiv) with the 3,3-disubstituted ethylacrylate⁴ (2582 mg, 10.00 mmol, 1.0 equiv) (see I.b) in THF (20 mL) at $-30\text{ }^{\circ}\text{C}$ under argon was added ⁱPrMgCl (2 M solution in THF, 15.0 mL, 30.00 mmol, 3.0 equiv) dropwise over a period of 10 minutes.⁶ The bath temperature was maintained below $-10\text{ }^{\circ}\text{C}$ during the course of the addition. After the addition was completed the reaction was stirred for 40 minutes at $-20\text{ }^{\circ}\text{C}$ to $-10\text{ }^{\circ}\text{C}$ upon when TLC indicated complete consumption of the starting materials. The reaction was quenched with 20 mL saturated NH₄Cl (*aq.*), and then extracted with ether (20 mL x 3 times). The extract was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash chromatography (20 % v/v EtOAc/Hexanes) to offer **13** as a clear oil (2293 mg, 8.4 mmol, 84 %). ¹H NMR (400 MHz, CDCl₃): δ 6.46 (s, 1H), 4.08 (s, 2H), 3.64 (s, 3H), 3.18 (s, 3H), 2.00 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 168.3, 154.4, 111.3, 77.2, 67.1, 61.4, 25.8, 18.2, 15.3, -5.5; IR (neat, cm⁻¹) 2954, 2929, 2895, 2856, 1662, 1641, 1472, 1463, 1361, 1251, 1122; HRMS (ES⁺): Calculated for C₁₃H₂₈O₃NSi (M + H)⁺ 274.1833, Found: 274.1827.

⁵ Boukouvalas, J.; Cheng, Y.-M.; Robichaud, J. J. *Org. Chem.* 1998, 63, 228.

⁶ Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.; Grabowski, E. J. *Tetrahedron lett.* 1995, 36, 5461

e) Nazarov substrate 5c. To a stirred solution of **12** (1475 mg, 3.33 mmol, 1.0 equiv) in ether (15 mL) at -78°C under argon was added $t\text{BuLi}$ (1.7 M solution in pentane, 4.3 mL, 7.3 mmol, 2.2 equiv) dropwise over 20 minutes (*note: Alternatively the bromofuran could be added into the solution of $t\text{BuLi}$ in ether. Experiments founds this modification did not improve the yield*). The bath temperature was maintained at -78°C during the course of the addition. The reaction was then allowed to warm up slowly to -50°C . After the solution was cooled back to -78°C , the Weinreb amide **13** (neat, 818 mg, 2.99 mmol, 0.9 equiv) was added dropwise via a syringe. (*note: The best yield was achieved with neat 13. The presence of solvent was found to increase the degree of undesired protonation of the resulting 4-lithio-furan*). The reaction was then allowed to warm up slowly in the bath. After 30 minutes at -20°C , TLC indicated complete consumption of the furan **12**. The reaction was then quenched with 10 mL saturated NH_4Cl (aq.) and extracted with ether (20 mL x 3 times). The combined organic phase was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (10 % v/v EtOAc/Hexanes) to offer **5c** as a clear oil (1572 mg, 2.74 mmol, 82 %). ^1H NMR (400 MHz, CDCl_3): δ 6.70 (s, 1H), 5.35 (s, 1H), 4.13 (s, 2H), 3.15 (t, $J = 8$ Hz, 2H), 2.53 (t, $J = 8$ Hz, 2H), 2.06 (s, 3H), 1.24 (m, 3H), 1.08 (d, $J = 7.2$ Hz, 18H), 0.93 (s, 9H), 0.11 (m, 15H); ^{13}C NMR (100 MHz, CDCl_3): δ 187.6, 156.0, 154.8, 149.5, 124.2, 119.3, 105.8, 85.1, 83.5, 67.0, 27.3, 25.8, 18.9, 18.3, 17.7, 17.5, 16.0, 0.0, -5.5; IR (neat, cm^{-1}) 2954, 2867, 2177, 1708, 1463, 1249, 842; HRMS (ES^+): Calculated for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{NaSi}_3$ ($\text{M} + \text{Na}$) $^+$ 599.3379, Found: 599.3389.

f) Nazarov product 14. The Nazarov substrate **5c** (1130 mg, 2 mmol, 1.0 equiv) was taken up in 15 mL CH_2Cl_2 at room temperature, to which the iridium catalyst $[\text{IrMeCO}(\text{dppe})(\text{DIB})]^{2+}(\text{BAr}^f)_2$ (107 mg, 0.04 mmol, 0.02 equiv) (see I.b) was added all at once (*note: in this particular case, the cyclization did not occur with less than 2 mol % catalyst; The reaction was best achieved by manually distilled CH_2Cl_2 over CaH_2*). Vivid color change from pale yellow to burgundy was observed. After 2 hrs, TLC monitoring found absence of the starting material. The reaction was filtered over a short plug of silica eluted with 50 mL 10 % v/v EtOAc/Hexanes to destroy the catalyst. The solvent was then evaporated and the residue was purified by flash chromatography (10 % v/v EtOAc/Hexanes) to offer **14** as a white solid (1002 mg, 1.74 mmol, 87 %) along with the undesired desilylation side product as a greenish yellow flake (100 mg, 0.24 mmol, 12 %). ^1H NMR (400 MHz, CDCl_3): δ 5.85 (s, 1H), 5.38 (s, 1H), 3.64 (dd, $J = 10.8$, 5.2 Hz, 2H), 2.36 (m, 1H), 2.11-2.17 (m, 2H), 1.97-2.02 (m, 1H), 1.24 (m, 3H), 1.17 (m, 18H), 0.96 (s, 9H), 0.84 (s, 3H), 0.12 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 173.9, 173.8, 148.4, 126.7, 108.5, 105.7, 94.0, 84.9, 64.9, 51.4, 33.3, 25.7, 18.0, 17.9, 17.6, 14.2, 12.2, 0.0, -5.7, -5.8; IR (neat, cm^{-1}) 2954, 2929, 2867, 2177, 1770, 1745, 1583, 1463, 1249, 1072, 840; HRMS (ES^+): Calculated for $\text{C}_{31}\text{H}_{56}\text{O}_4\text{NaSi}_3$ ($\text{M} + \text{Na}$) $^+$ 599.3379, Found: 599.3387.

g) Free alkyne 15. A flask containing the TMS protected alkyne **14** (1870 mg, 3.24 mmol, 1.0 equiv) in THF/EtOH/H₂O (v/v/v = 2 : 1 : 1) co-solvent (84 mL) was cooled down to 0 °C, to which AgNO₃ flakes (1476 mg, 12.98 mmol, 4 equiv) was added portion wise under air. The reaction became turbid with brownish sediment after the addition was complete. After it was stirred at 0 °C for 1.5 hrs, KCN powder (1476 mg, 22.72 mmol, 7 equiv) was added all at once. The suspension was then stirred at room temperature for 1 hr. (*note: It turned into an almost clear brownish solution with floating foam*). After the solvent was evaporated, the residue was dispersed in 50 mL 50 % v/v EtOAc/Hexanes and extracted with EtOAc (30 mL x 3 times). The extract was washed with brine, dried over MgSO₄, and then concentrated. Flash chromatography (10 % v/v EtOAc/Hexanes) offered free alkyne **15** as a white solid (1444 mg, 2.86 mmol, 88 %) along with the side product as a white solid (103 mg, 0.28 mmol, 10 %). **¹H NMR (400 MHz, CDCl₃):** δ 5.91 (s, 1H), 5.40 (s, 1H), 3.67 (s, 2H), 2.38-2.44 (m, 1H), 2.13-2.16 (m, 2H), 1.95-2.02 (m, 2H), 1.20-1.29 (m, 3H), 1.10-1.15 (m, 18H), 0.95 (s, 9H), 0.90 (s, 3H), 0.11 (s, 6H); **¹³C NMR (100 MHz, CDCl₃):** δ 174.0, 148.6, 126.1, 108.6, 94.0, 83.2, 68.9, 64.9, 51.4, 33.2, 25.7, 18.1, 17.9, 17.7, 12.9, 12.3, -5.7, -5.7; **IR (neat, cm⁻¹)** 3313, 2947, 2928, 2866, 1771, 1744, 1583, 1258, 1098, 950; **MS (ES⁺):** Calculated for C₂₈H₄₈O₄Si₂ (M⁺) 504.3, Found: 504.3.

h) Cycloisomerization product 16. Part A: The free alkyne **15** (1440 mg, 2.86 mmol, 1.0 equiv) was taken up in anhydrous PhH (21 mL) at room temperature under air in a 100 mL round bottom flask, to which AIBN flakes (235 mg, 1.43 mmol, 0.5 equiv) was added all at once. After the flask was purged with argon several times, Bu_3SnH (1019 mg, 0.93 mL, 3.43 mmol, 1.2 equiv) was added dropwise via a syringe. After the flask was quickly fitted with a condenser that was purged with argon and protected with an argon balloon, it was lowered into an oil bath preheated to 95 °C. The reaction was refluxed for 1 hr when TLC indicated complete conversion. If the products were isolated at this point, the vinyltin compound (major) and the *exo*-olefin **16** (minor) were obtained. However, this mixture was typically converted into **16** without workup/purification (*vide infra*).

Part B: After the reaction was cooled down to room temperature, *p*-TsOH·H₂O (576 mg, 3.00 mmol, 1.1 equiv) was added all at once. After 2 hrs, TLC indicated complete conversion. The reaction was quenched with 10 mL saturated NaHCO_3 (aq.), and then extracted with ether (10 mL x 3 times). The combined organic phase was concentrated down to 10 mL to which 4 mL 1N KF (aq.) was added. The mixture was stirred for 1 hr before it was extracted again with ether (10 mL x 3 times). The combined organic layer was washed with brine, dried over MgSO_4 , and then concentrated. The crude product was purified by flash chromatography (gradient, first pure hexanes, then 5% → 10 % → 15 % v/v EtOAc/Hexanes) to offer **16** as a white solid (1316 mg, 2.60 mmol, 91 %). ^1H NMR (500 MHz, CDCl_3): δ 5.19 (s, 1H), 5.04 (s, 1H), 4.31 (s, 1H), 3.58 (d, J = 10.0 Hz, 1H), 3.46 (d, J = 10.0, 1H), 2.98 (d, J = 18.5 Hz, 1H), 2.69 (d, J = 18.5, 1H),

2.48-2.56 (m, 3H), 1.90-1.98 (m, 1H), 1.20-1.29 (m, 3H), 1.11-1.17 (m, 21H), 0.97 (s, 9H), 0.08 (s, 6H); **¹³C NMR (125 MHz, CDCl₃)**: δ 176.8, 152.8, 152.6, 108.2, 106.6, 101.6, 68.0, 64.1, 51.1, 41.4, 33.4, 32.9, 25.8, 22.4, 18.2, 17.9, 12.5, -5.6, -5.7; **IR (neat, cm⁻¹)** 2947, 2929, 2893, 2866, 1784, 1652, 1254, 1088; **HRMS (ES⁺)**: Calculated for C₂₈H₅₀O₄Si₂Na (M + Na)⁺ 529.3140, Found: 529.3133.

i) Hydroxylketone 17. To a 50 mL round bottom flask containing the silane **16** (1300 mg, 2.58 mmol, 1.0 equiv) in THF (15 mL) at room temperature under air was added TBAF (1 M solution in THF, 10 mL, 10.00 mmol, 3.9 equiv) dropwise. After 30 minutes, the reaction was quenched with 15 mL saturated NH₄Cl (*aq.*). The organic layer was separated and the aqueous layer was extracted with EtOAc (20 mL x 3 times). The combined organic layer was washed with brine, dried over MgSO₄, and then concentrated. The crude product was purified by flash chromatography (15 % v/v EtOAc/Hexanes) to afford the desired hydroxylketone **17** as a pale yellow oil (608 mg, 2.58 mmol, 99 %). **¹H NMR (400 MHz, CDCl₃)**: δ 5.12 (s, 1H), 5.02 (s, 1H), 3.75 (m, 2H), 3.00 (d, *J* = 19.6, 1H), 2.53-2.67 (m, 4H), 2.18-2.28 (m, 3H), 1.86 (t, *J* = 5.4 Hz, 1H), 1.06 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)**: δ 211.1, 176.6, 151.7, 110.4, 102.7, 68.2, 64.6, 49.9, 46.5, 41.5, 34.5, 33.9, 21.4; **IR (neat, cm⁻¹)** 3466, 2929, 1767, 1733, 1246, 1180, 967; **MS (ES⁺)**: Calculated for C₁₃H₁₆O₆ (M)⁺ 236.10, Found: 236.10.

j) Carbonate 18. To a stirred solution of the hydroxyl ketone **17** (580 mg, 2.45 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at 0 °C was introduced sequentially 4-dimethylaminopyridine (DMAP), pyridine and ethylchloroformate (newly distilled, see I.a) to form a briskly yellow solution. After stirred at 0 °C for 30 min, the ice bath was removed. The reaction was stirred for overnight at room temperature. After quenched with 15 mL saturated NH_4Cl (aq.), the reaction was extracted with ether (20 mL x 3 times). The extract was washed with brine, dried over MgSO_4 , and then concentrated. Flash chromatography (30 % v/v EtOAc/Hexanes) of the residue afforded the carbonate **18** as a clear oil (716 mg, 2.33 mmol, 95 %). ^1H NMR (400 MHz, CDCl_3): δ 5.15 (m, 1H), 5.05 (s, 1H), 4.19-4.30 (m, 4H), 3.02 (d, $J = 19.2$ Hz, 1H), 2.65-2.70 (m, 2H), 2.55-2.59 (m, 2H), 2.25-2.30 (m, 2H), 2.15-2.20 (m, 1H), 1.33 (t, $J = 4$ Hz, 3H), 1.10 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 210.0, 176.3, 156.4, 151.4, 110.7, 101.9, 71.9, 65.9, 64.4, 49.9, 45.0, 41.4, 34.5, 34.1, 21.7, 15.6; IR (neat, cm^{-1}) 2969, 1781, 1772, 1743, 1264, 1244, 1182, 1011; HRMS (ES^+): Calculated for $\text{C}_{16}\text{H}_{20}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 331.1152, Found: 331.1153.

k) Bislactone 20. Part A: To a stirred solution of the carbonate **18** (530 mg, 1.72 mmol, 1.0 equiv) in THF (80 mL) at room temperature under air was introduced NaH (neat, 495 mg, 20.6 mmol, 12.0 equiv) (see I.a) portion wise. The reaction turned turbid. After 20 minutes, TLC indicated complete conversion. The reaction was quenched with 15 mL saturated NH_4Cl (aq.) and extracted with CH_2Cl_2 (20 mL x 3 times) (*note: From this point on, the synthetic intermediates were not very soluble in either ether or EtOAc. They were more soluble in CH_2Cl_2*). The combined organic layer was washed with brine, dried over MgSO_4 , concentrated. ^1H NMR revealed the crude product was a 1 : 1 mixture of bislactone **20** and its open counterpart **19**, which was converged into **20** without further purification (*vide infra*). ^1H NMR (400 MHz, CDCl_3) of **19**: δ 5.17 (s, 1H), 5.08 (s, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.09-4.15 (m, 2H), 3.96 (d, $J = 12.0$ Hz, 1H), 3.42 (d, $J = 19.6$ Hz, 1H), 2.82 (d, $J = 19.6$ Hz, 1H), 2.51-2.56 (m, 3H), 2.06-2.17 (m, 3H), 1.23-1.28 (m, 6H)

Part B: The as-obtained mixture was dispersed in PhH (58 mL) and $p\text{-TsOH}\cdot\text{H}_2\text{O}$ (330 mg, 1.72 mmol, 1.0 equiv) was added all at once. After purged with argon, the reaction was refluxed for 30 minutes. TLC indicated complete conversion. The reaction was then quenched with 10 mL saturated NaHCO_3 (aq.) and extracted with CH_2Cl_2 (30 mL x 3 times). The combined organic layer was washed with brine, dried over MgSO_4 , and then concentrated. The crude product could be purified by either recrystallization in CH_2Cl_2 or by flash chromatography (loaded with CH_2Cl_2 , eluted with 5% v/v EtOAc/ CH_2Cl_2) to offer bislactone **20** as a white solid (405 mg, 1.55 mmol, 90 % from **18**). ^1H NMR (400 MHz, CDCl_3): δ 5.31 (s, 1H), 5.13 (s, 1H), 4.45 (d, $J = 10.0$ Hz,

1H), 4.14 (d, $J = 10.0$ Hz, 1H), 3.43 (s, 1H), 3.07 (d, $J = 18.8$ Hz, 1H), 2.76-2.84 (m, 2H), 2.60-2.67 (m, 1H), 2.27-2.34 (m, 1H), 2.08-2.16 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 203.1, 174.5, 169.8, 147.9, 113.6, 101.6, 75.5, 67.0, 64.4, 51.1, 41.2, 34.4, 34.1, 21.5; IR (neat, cm^{-1}) 2933, 1783, 1740, 1186, 1159, 960; HRMS (ES^+): Calculated for $\text{C}_{14}\text{H}_{14}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}$) $^+$ 285.0733, Found: 285.0723; m.p. = 217 - 218 $^\circ\text{C}$.

l) α -Quaternized bislactone 21. To a flask containing ketone **20** (262 mg, 1.00 mmol, 1.0 equiv) in THF (10 mL) at room temperature was added NaH (neat, 36 mg, 1.50 mmol, 1.5 equiv). After the flask was purged with argon, first MeI (284 mg, 0.124 mL, 2.00 mmol, 2.0 equiv) then HMPA (358 mg, 0.347 mL, 2.00 mmol, 2.0 equiv) was added. The ice bath was removed. After 30 minutes, the reaction was quenched with 10 mL saturated NH_4Cl (aq.) and extracted with CH_2Cl_2 (20 mL x 3 times). The combined organic layer was washed with brine, dried over MgSO_4 , and then concentrated. The crude product was purified by flash chromatography (loaded with CH_2Cl_2 , eluted with 50 % v/v EtOAc/Hexanes) to afford the desired ketone **21** (530 mg, 1.94 mmol, 97 %) as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 5.30 (m, 1H), 5.12 (m, 1H), 4.29 (d, $J = 10.0$ Hz, 1H), 4.06 (d, $J = 10.0$, 1H), 3.02 (d, $J = 19.2$ Hz, 1H), 2.79-2.87 (m, 2H), 2.64-2.68 (m, 1H), 2.15-2.29 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 206.5, 173.1, 172.3, 146.3, 111.8, 99.8, 72.8, 64.8, 63.3, 52.6, 40.3, 32.9, 32.3, 15.9, 15.7; IR (neat, cm^{-1}) 2917, 1784, 1184, 972; HRMS (ES^+): Calculated for $\text{C}_{15}\text{H}_{16}\text{O}_5\text{Si}$ (M^+) 299.0887, Found: 229.0883; m.p. = 224 - 225 $^\circ\text{C}$.

m) Danishefsky's intermediate 2. Part A: To a flask containing ketone **21** (230 mg, 0.83 mmol, 1.0 equiv) in methanol (5 mL) at 0 °C under air was added NaBH₄ (38 mg, 1.00 mmol, 1.2 equiv) portion wise. Gas evolution was observed. After 30 minutes, TLC indicated complete consumption of the starting material. The reaction was quenched with 10 mL saturated NH₄Cl (aq.) and extracted with CH₂Cl₂ (20 mL x 3 times). The extract was washed with brine, dried over MgSO₄, and concentrated. Flash chromatography of the crude product (loaded with CH₂Cl₂, eluted with 50 % v/v EtOAc/Hexanes) afforded the desired partially purified alcohol **22a** (117 mg, 0.42 mmol, 51 %) as a white solid along with the undesired C-7 epimer **22b**, (97 mg, 0.35 mmol, 42 %) as a white crystalline solid. The partially purified alcohol **22a** was used in part B (*vide infra*) while the C-7 epimer **22b** could be recycled by Dess-Martin oxidation to offer **21** in quantitative yield. Spectra of **22b** are as follows: ¹H NMR (400 MHz, CDCl₃): δ 5.05 (m, 1H), 5.01 (m, 1H), 4.48 (d, *J* = 3.6 Hz, 1H), 4.12 (d, *J* = 9.6 Hz, 1H), 3.90 (d, *J* = 9.6 Hz, 1H), 3.54 (m, 2H), 2.80-2.84 (m, 1H), 2.59-2.61 (m, 1H), 2.42 (d, *J* = 19.6 Hz, 1H), 1.97-2.03 (m, 1H), 1.78-1.84 (m, 1H), 1.20 (s, 3H), 1.11 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 181.4, 177.4, 156.9, 109.5, 105.0, 78.8, 74.4, 65.6, 61.5, 56.2, 38.3, 35.4, 33.6, 17.8, 12.1.

Part B: The partially purified alcohol **22a** (110 mg, 0.39 mmol, 1.0 equiv) was treated with *p*-TsOH•H₂O (76 mg, 0.39 mmol, 1.0 equiv) in refluxing PhH (5 mL) for 4 hrs when ¹H NMR monitoring found complete isomerization of the *exo*-olefin into the *endo*-olefin. The reaction was

diluted with CH₂Cl₂ (10 mL), quenched with 10 mL NaHCO₃ (aq.) and then extracted with CH₂Cl₂ (10 mL x 3 times). The combined organic layer was washed with brine, dried over MgSO₄ and concentrated. Flash chromatography of the residue (loaded with CH₂Cl₂, eluted with 50 % v/v EtOAc/Hexanes) afforded **2** as a white solid (100 mg, 0.36 mmol, 92 %). **¹H NMR (400 MHz, CDCl₃):** δ 5.40 (m, 1H), 4.21 (d, *J* = 9.2 Hz, 1H), 4.14 (d, *J* = 3.6 Hz, 1H), 3.96 (d, *J* = 8.8 Hz, 1H), 2.90 (m, 1H), 2.85 (d, *J* = 18.8 Hz, 1H), 2.65 (d, *J* = 18.8 Hz, 1H), 2.52 (m, 2H), 1.83 (m, 3H), 1.24 (m, 6H); **¹³C NMR (100 MHz, CDCl₃):** δ 178.4, 175.1, 141.1, 125.1, 104.5, 86.6, 73.6, 69.7, 62.0, 55.3, 41.1, 40.0, 16.8, 15.9, 15.1; **¹H NMR (400 MHz, CD₃OD):** δ 5.34 (m, 1H), 4.16 (d, *J* = 8.8 Hz, 1H), 4.09 (s, 1H), 3.98 (d, *J* = 8.8 Hz, 1H), 2.87 (d, *J* = 19.6 Hz, 1H), 2.77 (d, *J* = 19.6 Hz, 1H), 2.55-2.59 (m, 1H), 2.34-2.39 (m, 1H), 1.80 (t, *J* = 2.0 Hz, 3H), 1.19 (s, 3H), 1.15 (s, 3H); **¹³C NMR (100 MHz, CD₃OD):** δ 180.2, 177.9, 143.8, 125.1, 106.5, 87.0, 74.4, 71.5, 64.0, 57.0, 41.9, 40.6, 16.9, 16.1, 15.1; **IR (neat, cm⁻¹)** 3640 (br.), 2922, 1766, 1750; **MS (ES⁺):** Calculated for C₁₅H₁₉O₅ (M + H)⁺ 279.1, Found: 279.1; m.p. = 190- 192 °C.

n) Merrilactone A 1. (note: The procedure of Birman and Danishefsky was strictly followed.⁷)

Part A: A solution of alcohol **2** (56 mg, 0.201 mmol, 1.0 equiv.) and *m*CPBA (82 mg, 0.473 mmol, 2.3 equiv) in CH₂Cl₂ (5.5 mL) was stirred for 2 days at room temperature. The mixture was treated with 10 mL saturated NaHCO₃ and Na₂SO₃ (v/v = 1 : 1), and extracted with CH₂Cl₂ (10 mL x 3 times). The extract was washed with brine, dried over MgSO₄ and concentrated to give the crude product (60 mg). ¹H NMR of the crude product found it was the epoxide **23** ($\alpha/\beta = 3.2:1$) which matches well with that of Birman's. This mixture was used directly in part B.

Part B: A portion of the mixture obtained in part A (35 mg) was stirred with *p*-TsOH·H₂O (21 mg, 0.11 mmol) in CH₂Cl₂ (6 mL) for a day at room temperature. The *p*-TsOH·H₂O was filtered off using a 0.25 μ m syringe filter and washed with CH₂Cl₂ (3 mL x 3 times). The solvent was evaporated. The crude product was purified by flash chromatography (loaded with CH₂Cl₂, eluted with 25 % $\rightarrow$ 33 % $\rightarrow$ 55 % v/v EtOAc/CH₂Cl₂) to afford Merrilactone A **1** as a white solid (23.4 mg, 0.078 mmol, 68 % calculated from **2**). ¹H NMR (400 MHz, CD₃OD): δ 4.73 (s, 1H), 4.58 (d, *J* = 10.0 Hz, 1H), 4.00 (d, *J* = 10.0 Hz, 1H), 3.93 (dd, *J* = 4.8, 1.6 Hz, 1H), 2.88 (d, *J* = 19.2 Hz, 1H), 2.74 (d, *J* = 5.2 Hz, 1H), 2.70 (d, *J* = 5.2 Hz, 1H), 2.65 (d, *J* = 19.2 Hz, 1H), 2.25 (dd, *J* = 15.2, 1.6 Hz, 1H), 1.48 (s, 3H), 1.23 (s, 3H), 1.07 (s, 3H); ¹³C NMR (100 MHz, CD₃OD): δ 179.3, 177.7, 107.3, 96.2, 90.3, 79.9, 75.5, 66.1, 61.2, 58.5, 44.0, 32.2, 17.5, 17.4, 16.0; IR (neat, cm⁻¹) 3452, 1765; HRMS (ES⁺): Calculated for C₁₅H₁₈O₆Na (M + Na)⁺ 317.0996, Found: 317.0996; m.p. = 233- 234 °C.

⁷ Birman, V.B.; Danishefsky, S. *J. Am. Chem. Soc.* **2002**, *124*, 2080

Propargyl Alcohol 9

Cl3 of Propargyl alcohol 9
in CDCl3

9

Cl3 of 4-Bromo-Butenolide 11
in CDCl3

11

13

¹H Nazarov Product 14
in CDCl₃

14

173.873
173.779

148.385

126.665

108.516
105.667

94.053

84.860

77.329
77.010
76.692

64.873

51.370

33.253

25.696

18.008
17.883
17.630
14.182
12.218

-0.054

-5.712
-5.767

C13 of Nazarov product 14
in CDCl3

14

15

¹H of Free Alkyne 15
in CDCl₃

7.312

5.907

5.399

3.669
2.444
2.430
2.422
2.397
2.385
2.166
2.143
2.132
2.026
2.015
1.995
1.988
1.963
1.956
1.950
1.684
1.295
1.278
1.275
1.260
1.256
1.242
1.238
1.227
1.221
1.205
1.154
1.141
1.136
1.123
1.103
0.983
0.955
0.948
0.941

174.011
148.554
126.127
108.594
94.004
83.214
77.285
76.968
76.650
68.920
64.860
51.374
33.174
25.701
18.068
17.909
17.656
12.857
12.263
-5.669
-5.707

¹³C of free alkyne 15
in CDCl₃

15

¹H of Cycloisomerization Product 16
in CDCl₃

16

7.312

5.193

5.038

4.315

3.594

3.574

3.469

3.449

3.004

2.967

2.713

2.676

2.565

2.526

2.520

2.513

2.506

2.500

2.490

2.475

1.635

1.289

1.274

1.259

1.244

1.230

1.222

1.216

1.202

1.173

1.166

1.158

1.133

1.126

1.121

1.118

1.111

0.984

0.970

0.943

0.917

0.085

¹³C of Cycloisomerization Product 16
in CDCl₃

16

7.256

5.119
5.023

3.761
3.750
3.739
3.037
2.988
2.672
2.634
2.623
2.592
2.562
2.560
2.552
2.550
2.546
2.538
2.534
2.279
2.265
2.256
2.247
2.239
2.223
2.182
1.879
1.866
1.853
1.689
1.058

¹H of hydroxylketone 17

17

7.270

¹H of Carbonate 18
in CDCl₃

18

5.152
5.150
5.147
5.144
5.056

4.301
4.273
4.251
4.232
4.224
4.214
4.197

3.056
3.008
2.696
2.688
2.647
2.588
2.580
2.574
2.570
2.563
2.559
2.553
2.303
2.274
2.268
2.261
2.252
2.198
2.178
2.168
2.148
1.582
1.349
1.331
1.321
1.313
1.101

1.000
1.001

4.071

1.001

2.044
1.968

2.031
1.101

3.395

3.294

7.270

5.318
5.315
5.153

4.468
4.443
4.159
4.133
3.426
3.095
3.048
2.836
2.828
2.821
2.811
2.804
2.789
2.780
2.762
2.669
2.664
2.660
2.648
2.644
2.639
2.628
2.619
2.607
2.598
2.344
2.336
2.321
2.312
2.308
2.299
2.284
2.275
2.162
2.141
2.138
2.126
2.117
2.104
2.101
2.080

¹H of Bislactone 20
in CDCl₃

20

1.013
0.989

1.000

1.004

0.923

0.996

2.032

1.031

1.006

1.030

3.039

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

7.270

5.307
5.303
5.300
5.296
5.129
5.126
5.121

4.308
4.283
4.072
4.047

3.772
3.045
2.997
2.874
2.868
2.850
2.840
2.826
2.792
2.680
2.670
2.659
2.649

2.293
2.265
2.255
2.240
2.230
2.217
2.195
2.179
2.172
2.157
1.578
1.444
1.358
1.302
1.292

¹H of Quaternized Bislactone 21
in CDCl₃

21

7.270

1H of the undesired C-7 Epimer 22b
in CDCl₃

22b

5.056
5.052
5.048
5.024
5.019
5.016

4.488
4.479

4.137
4.113

3.916
3.892
3.765
3.588
3.554
3.539

2.842
2.824
2.801
2.615
2.605
2.594
2.455
2.406
2.042
2.031
2.018
2.006
1.994
1.981
1.971
1.846
1.824
1.809
1.802
1.787
1.202
1.128
1.114

1.000
1.034

1.005

1.040

1.046

1.999

1.086

1.085

1.061

1.135

1.070

3.194
3.041

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

178.440
175.078

141.148

125.128

104.504

86.636

77.333
77.219
77.016
76.698
73.655
69.677

61.996

55.335

41.079
40.062

16.759
15.924
15.126

C13 of Danishefsky's Intermediate 2
in CDCl₃

2

2

¹H of Danishefsky's intermediate 2
in CD₃OD

180.212
177.947

143.755

125.130

106.526

87.025

74.438
71.534

63.988

56.967
49.636
49.423
49.210
48.998
48.785
48.572
48.359
41.884
40.548

16.912
16.083
15.062

¹³C of Danishefsky's intermediate 2
in CD₃OD

2