Total Synthesis of the Anti-Angiogenic Agent Luminacin D

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Materials and Methods

Unless otherwise states, reaction were performed under a nitrogen atmosphere using freshly distilled solvents. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone. Methanol was distilled from magnesium. All other commercially obtained reagents were used as received. All reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column or flash chromatography was performed with the indicated solvents using silica gel (particle size 0.32-0.063) purchased from Silicycle. ¹H and ¹³C spectra were recorded on Bruker Advance DPX-500 or Bruker Advance DPX-400 spectrometers. Chemical shifts are reported relative to internal chloroform (¹H, δ 7.27 ppm, ¹³C δ 77.0 ppm). Melting points were obtained on a Gallenkamp variable temperature melting point apparatus and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. High resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

Preparation of Triol 7

To a rapidly stirring suspension of triol **6** (11.4g, 57.6 mmol) and sodium bicarbonate (14.5g, 172.0 mmol) in methanol (200 mL) is added benzyltrimethylammonium dichloroiodate (20g, 57 mmol) portionwise (*ca.* 2g) over 45 minutes. After 2 hours of further stirring, the methanol is removed under reduced pressure and the resulting solid is partitioned between ethyl acetate (500 mL) and water (500 mL). The organic layer is dried over sodium sulfate, filtered, and concentrated *in vacuo* to give **7** as a pale yellow solid, mp = 157°C (14.9g, 80% yield). ^1H NMR (500MHz, acetone d_6) 11.05 (s, 1H), 7.96 (s, 1H), 4.89 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (125MHz, acetone d_6) δ 170.8, 163.3, 160.9, 139.9, 113.0, 107.8, 74.2, 59.5, 53.2; IR (nujol mull, NaCl) 3415 (s), 3066 (m), 2970 (m), 2946 (m), 2920 (s), 2851 (s), 1644 (m), 1612 (m), 1463 (m), 1378 (m), 1241 (m), 1222 (m), 1199 (m), 1076 (w), 981 (m) cm^{-1} ; HRMS (FAB) m/z found: 324.9573 [calc'd for $\text{C}_9\text{H}_8\text{IO}_5$ (M-H): 324.9573].

Preparation of Aryl Iodide 8

To a solution of **7** (2.76g, 8.5 mmol) in acetone (150 mL) was added benzyl bromide (3.26 mL, 27.4 mmol) and potassium carbonate (7.6g, 55.0 mmol). The resulting suspension was rapidly stirred at reflux for 24 hours, cooled, and the acetone removed under reduced pressure. The resulting residue was partitioned between ethyl acetate (300 mL) and 1.0N hydrochloric acid (200 mL). The aqueous layer was washed twice with 200 mL portions of ethyl acetate. Combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was dissolved in 100 mL of dimethylformamide; imidazole (1.45g, 21.3 mmol) and *tert*-butyl dimethylsilyl chloride (1.61g, 10.64mmol) were added as solids and the resulting solution was rapidly stirred for 24 hours. The solution was diluted with 500 mL ethyl acetate and washed twice with 250 mL portions of brine. The combined aqueous phases were washed thrice with 300 mL portions of ethyl acetate. Organic phases were combined, dried over sodium sulfate, and concentrated under reduced pressure. The resulting

residue was purified by flash chromatography (10 % ethyl acetate/hexanes) to furnish **8** (4.30g, 7.0 mmol, 82%) as a white solid, mp = 89°C. ¹H NMR (400MHz, CDCl₃) 8.37 (s, 1H), 7.57 (d, *J* = 6.5Hz, 2H), 7.48 (d, *J* = 7.9Hz, 2H), 7.45-7.33 (m, 6H), 5.15 (s, 2H), 5.12 (s, 2H), 4.74 (s, 2H), 3.85 (s, 3H), 0.83 (s, 9H), -0.02 (s, 6H); ¹³C NMR (100MHz, CDCl₃) δ 164.8, 161.9, 159.8, 141.7, 136.9, 136.5, 131.1, 128.4, 128.4, 128.1, 128.0, 127.8, 127.8, 123.2, 86.3, 78.2, 76.5, 55.4, 52.3, 25.9, 18.1, -5.5; IR (thin film, NaCl) 3090 (w), 3065 (w), 3032 (w), 2951 (m), 2929 (m), 2885 (m), 2855 (m), 1731 (s), 1575 (m), 1498 (w), 1455 (m), 1432 (m), 1373 (m), 1267 (s), 1157 (s), 1086 (s), 1060 (m), 1005 (m), 971 (m), 904 (w), 836 (s) cm⁻¹; HRMS (FAB) *m/z* found: 617.1219 [calc'd for C₂₉H₃₄IO₅Si (M-H): 617.122030].

Preparation of Aryl Precursor 9

To a flame-dried roundbottom flask is added **8** (3.5g, 5.65 mmol), *trans*-benzyl(chloro)bis(triphenylphosphine) palladium (II) (431 mg, 0.57 mmol), tri-*o*-tolylphosphine (346 mg, 1.14 mmol), tributylisobutenylstannane (4.87g, 14.1 mmol), and dimethylformamide (55 mL). The resulting yellow suspension is stirred rapidly at 100°C for 24 hours, cooled, and diluted with 300 mL ethyl acetate. The black suspension is washed twice with saturated brine and the organic layer is dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (3.5% ethyl acetate/hexanes, all tin containing fractions are discarded) to give **9** (2.62g, 85%) as a pale yellow oil. ¹H NMR (400MHz, CDCl₃) 7.78 (s, 1H), 7.54 (d, *J*=7.1Hz, 2H), 7.45-7.32 (m, 8H), 6.30 (bs, 1H), 5.15 (s, 2H), 4.99 (s, 2H), 4.76 (s, 2H), 3.86 (s, 3H), 1.92 (d, *J*=1.0Hz, 3H), 1.84 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ¹³C NMR (100MHz, CDCl₃) δ 166.4, 160.3, 157.5, 137.5, 137.3, 136.9, 133.6, 129.3, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 120.3, 120.1, 77.9, 76.1, 55.0, 52.0, 26.3, 25.9, 19.6, 18.2, -5.4; IR (thin film, NaCl) 3051 (w), 2951 (s), 2929 (s), 2885 (s), 2885 (m), 2856 (m), 1729 (s), 1594 (m), 1567 (m), 1497 (m), 1462 (s), 1436 (s), 1416 (w), 1376 (s), 1320 (m), 1287 (s), 1256 (s), 1228 (s), 1193 (s), 1174 (s), 1102 (s), 1070 (s), 1014 (m), 912 (w), 836 (s) cm⁻¹; HRMS (FAB) *m/z* found: 545.2725 [calc'd for C₃₃H₄₁O₅Si (M-H): 545.272328].

Preparation of Aldehyde 4

To a solution of **9** (6.2g, 11.4 mmol) in dichloromethane (300mL) at -78°C is added diisobutylaluminum hydride as a 1.0M solution in dichloromethane (35 mL, 35 mmol). The resulting solution is stirred for three hours, placed in an ice/water bath, and 500 mL of a saturated solution of sodium potassium tartrate is cautiously added. The resulting mixture is stirred rapidly for 8 hours, the aqueous layer is extracted twice with 150 mL portions of dichloromethane, and the combined organic layers are dried over sodium sulfate and concentrated under reduced pressure. The resulting residue is dissolved in dichloromethane (30 mL) and added slowly to a mixture of oxalyl chloride (1.24 mL, 14.16 mmol) and dimethylsulfoxide (2.01 mL, 28.3 mmol) in dichloromethane (100 mL) at -78°C . After 30 minutes, triethylamine (7.9 mL, 56.6 mmol) is added cautiously, the resulting suspension is warmed to room temperature and washed with 1.0N hydrochloric acid (200 mL) and brine (200mL). The combined aqueous layers are washed thrice with 150 mL portions of dichloromethane. Combined organic layers are dried over sodium sulfate, concentrated under reduced pressure, and purified by flash column chromatography (10% ethylacetate/hexanes) to afford **4** (4.65g, 79%) as a pale yellow oil. ¹H NMR (500MHz, CDCl₃) 10.18 (s, 1H), 7.73 (s, 1H), 7.44-7.37 (m, 10H), 6.28 (bs, 1H), 5.20 (s, 2H), 5.01 (s, 2H), 1.92 (d, J = 1Hz, 3 H), 1.82 (d, J = 1 Hz, 3H), 0.86 (s, 9H), 0.05 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 189.3, 162.5, 160.7, 137.3, 137.1, 136.2, 130.4, 129.3, 128.6, 128.6, 128.5, 128.4, 128.1, 127.9, 125.7, 120.0, 79.9, 76.2, 54.8, 26.3, 25.9, 19.6, 18.2, -5.4; IR (thin film, NaCl) 3090 (w), 3065 (w), 3032 (w), 2953 (m), 2929 (m), 2883 (m), 2856 (m), 1686 (s), 1588 (m), 1497 (w), 1454 (m), 1445 (m), 1394 (w), 1374 (m), 1286 (m), 1253 (m), 1215 (w), 1183 (w), 1118 (s), 1067 (s), 1031 (w), 1005 (m), 973 (m), 917 (w), 836 (s), 777 (m), 733 (m), 697 (m), 670 (w) cm⁻¹; HRMS (FAB) *m/z* found: 517.2923 [calc'd for C₃₂H₄₁O₅Si (M+H): 517.2774].

Preparation of Vinyl Iodide i (Structure not pictured in the text)

Two flame-dried roundbottom flasks were charged with dimethylformamide (150 mL), allylic alcohol **10** (33.0g, 0.155 mmol), imidazole (21g, 0.31 mmol), and triisopropylsilyl chloride (36.6 mL, 17.1 mmol) and stirred at room temperature for 24 hours. The resulting solutions were combined, diluted with ethyl acetate (1.5 L) and washed sequentially with 1.0 N hydrochloric acid (400 mL) and saturated brine (400 mL). The aqueous phases were individually washed thrice with 350 mL portions of ethyl acetate, and the combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (2% ethyl acetate/hexanes) to afford **i** (110g, 96%) as a clear oil. ¹H NMR (400MHz, CDCl₃) 6.28 (t, *J*=7.8, 1H), 4.32 (s, 2H), 2.14 (app. quin., *J* = 7.8Hz, 2H), 1.16-1.06 (m, 21H), 1.00 (t, *J*=7.8Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.6, 102.4, 65.0, 24.7, 18.0, 13.8, 12.0 ; IR (thin film, NaCl) 2959 (s), 2942 (s), 2891 (m), 2865 (s), 2724 (w), 1630 (w), 1462 (m), 1383 (w), 1368 (w), 1339 (w), 1289 (w), 1250 (w), 1136 (m), 1104 (s), 1070 (m), 1036 (w), 1014 (m), 996 (m), 919 (w), 882 (m), 804 (m), 684 (m) cm⁻¹; HRMS (FAB) *m/z* found: 367.0954 [calc'd for C₁₄H₂₈IOSi (M+H): 367.0954].

Preparation of Methyl Ketone **ii** (Structure not pictured in the text)

PREP#1: To a flame-dried roundbottom flask under an inert atmosphere (Innovative Technology Glovebox) is added **i** (25 mg, .068 mmol), palladium (II) acetate (3 mg, 0.014 mmol), tri-*o*-tolyl phosphine (4 mg, 0.014 mmol), silver carbonate (20 mg, .068 mmol) and dimethylformamide (1 mL). The resulting suspension is stirred at room temperature for 36 hours, filtered, diluted with ethyl acetate (10 mL) and washed twice with saturated brine (2 mL). The organic phase is dried over sodium sulfate, concentrated, and purified by flash chromatography (5% ethyl acetate/hexanes) to afford **ii** as a clear oil (15 mg, 78%). *It should be noted that the recovered yield decreases significantly if the scale or conditions are altered (see below).*

PREP#2: To a flame-dried roundbottom flask is added **i** (4.5g, 12.2 mmol), palladium (II) acetate (270mg, 1.2 mmol), triphenylphosphine (315 mg, 1.2 mmol), silver carbonate (5.1g, 18.5 mmol) and dimethylformamide (35 mL). The resulting suspension is stirred at room temperature for 48 hours, filtered, diluted with ethyl acetate (200 mL) and washed twice with saturated brine (100 mL). The combined aqueous phases are washed twice with ethyl acetate (150mL) and the combined organic phases are dried over sodium sulfate, concentrated, and purified by flash chromatography (5% ethyl acetate/hexanes) to afford **ii** as a clear oil (1.60g, 46% yield). ¹H NMR (400MHz, CDCl₃) 6.69 (t, *J*=7.5Hz, 1H), 4.48 (s, 2H), 2.39 (app. quin., *J* = 7.5Hz, 2H), 2.32 (s, 3H), 1.14-0.99 (m, 24H); ¹³C NMR (100 MHz, CDCl₃) δ 199.0, 147.7, 139.9, 56.3, 26.0, 22.2, 17.9, 13.4, 12.0 ; IR

(thin film, NaCl) 2961 (s), 2943 (s), 2891 (m), 2867 (m), 2725 (w), 1695 (w), 1672 (s), 1640 (w), 1463 (m), 1390 (w), 1384 (w), 1365 (w), 1347 (w), 1308 (w), 1285 (w), 1239 (m), 1144 (w), 1088 (s), 1067 (s), 1036 (m), 1014 (m), 996 (m), 936 (w), 883 (s), 796 (m) cm^{-1} ; **HRMS** (FAB) m/z found: 285.2251 [calc'd for $\text{C}_{16}\text{H}_{23}\text{O}_2\text{Si}$ (M+H): 285.2250].

Preparation of 11

To a solution of **ii** (2.45g, 8.63 mmol) in tetrahydrofuran (100 mL) at 0°C is added freshly distilled triethylamine (3.60 mL, 26 mmol) followed by freshly distilled trimethylsilyl trifluoromethanesulfonate (2.34 mL, 12.94 mmol). The resulting solution is stirred for 3 hours after which solid *N*-bromosuccinimide (1.69g, 9.5 mmol) is added as a solid portionwise (*ca* 250mg) over 45 minutes. The resulting suspension is immediately diluted with saturated aqueous sodium bicarbonate (50 mL) and the aqueous layer is washed twice with diethyl ether (50 mL). The combined organic layers *are not* dried, they are immediately concentrated under reduced pressure (temperature < 40°C) and flashed through a short plug of silica gel (10% ethyl acetate/hexanes) to afford **11** (3.06g, 98%) as a pale yellow oil. **¹H NMR** (400MHz, CDCl_3) 6.75 (t, $J=7.5$ Hz, 1H), 4.55 (s, 2H), 4.26 (s, 2H), 2.38 (app. quin., $J=7.5$ Hz, 2H), 1.11 (t, $J=7.5$ Hz, 3H), 1.12-1.04 (m, 21H); **¹³C NMR** (100 MHz, CDCl_3) δ 192.4, 148.4, 137.0, 56.9, 31.6, 22.3, 17.9, 13.2, 11.9; **IR** (thin film, NaCl) 2959 (s), 2943 (s), 2890 (m), 2867 (s), 1690 (m), 1670 (m), 1638 (m), 1463 (m), 1431 (w), 1390 (w), 1384 (w), 1311 (w), 1288 (w), 1245 (w), 1206 (w), 1158 (w), 1089 (s), 1067 (s), 1014 (m), 997 (w), 919 (w), 796 (m), 682 (m) cm^{-1} ; **HRMS** (FAB) m/z found: 363.1354 [calc'd for $\text{C}_{16}\text{H}_{30}\text{BrO}_2\text{Si}$ (M-H): 363.1355].

Preparation of 13

To a flame-dried roundbottom flask containing **11** (500mg, 1.37 mmol) neat at 0°C is added samarium diiodide as a 0.1 M solution in tetrahydrofuran (34 mL, 3.4 mmol).

After 10 minutes Z-2-bromo-2-pentenal (271 mg, 1.64 mmol) is added as a solution in tetrahydrofuran (2 mL) and the solution is observed to change from a deep Prussian blue to a yellow-brown suspension. Acetaldehyde (1.3 mL, 11 mmol) is immediately added and the solution is stirred for 4 hours and maintained at 0°C. Aqueous saturated ammonium chloride (50 mL) is added at 0°C and allowed to warm to room temperature. The aqueous phase is extracted thrice with diethyl ether (50 mL). Combined organic phases are concentrated, resuspended in methanol (10 mL), and stirred vigorously in the presence of potassium carbonate (1.52g, 11.0 mmol) for 6 hours. The resulting slurry is diluted with diethyl ether (100 mL) and washed twice with saturated brine (50 mL). *The aqueous phase is NOT neutralized.* Combined organic phases are dried over sodium sulfate, concentrated under reduced pressure, and the resulting residue is purified by flash column chromatography (20% ethyl acetate/hexanes) to afford **13** (590 mg, 96%) as a pale yellow oil. ¹H NMR (400MHz, CDCl₃) 6.12 (td, *J* = 7, 1 Hz, 1H), 5.50 (td, *J* = 7.5, 0.7 Hz, 1H), 4.47 (d, *J* = 1.4 Hz, 2H), 4.47-4.39 (m, 2H), 3.72 (d, *J* = 5.9 Hz, 1H), 3.68 (d, *J* = 6.8 Hz, 1H), 2.23 (app. quin., *J* = 7.5 Hz, 2H), 2.17-1.99 (m, 4H), 1.19-1.05 (m, 21H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 136.9, 131.0, 130.4, 129.6, 73.9, 74.1, 60.5, 39.6, 24.2, 20.8, 18.0, 14.1, 12.9, 11.7; IR (thin film, NaCl) 3402 (m), 2963 (s), 2943 (s), 2891 (m), 2867 (s), 1656 (w), 1462 (m), 1384 (w), 1324 (w), 1247 (w), 1208 (m), 1061 (m), 1013 (m), 996 (m), 940 (w), 917 (w), 882 (m), 842 (w), 807 (m), 684 (m), 660 (m) cm⁻¹; HRMS (FAB) *m/z* found: 449.2086 [calc'd for C₂₁H₄₁BrO₃Si (M+H): 449.2087].

Preparation of **5**

To a flame dried roundbottom flask is added **13** (2.42g, 5.38 mmol), 2,2'-dimethoxypropane (1.4mL, 10.9 mmol), and pyridinium-*p*-toluenesulfonate (40mg, 0.16 mmol). The resulting solution is stirred at room temperature for 12 hours, stripped onto silica gel (*ca* 3.0 g), and purified via flash chromatography (2% ethylacetate/hexanes to 20% ethylacetate/hexanes) to afford **5** (2.35g, 89% yield) as a pale yellow oil. ¹H NMR (400MHz, CDCl₃) 6.03 (t, *J* = 7.2 Hz, 1H), 5.56 (t, *J* = 7.4 Hz, 1H), 4.54 (t, *J* = 7.6 Hz, 1H), 4.41 (t, *J* = 7.6 Hz, 1H), 4.33 (dd, *J* = 11.9, 13.7 Hz, 2H), 2.29 (app. quin., *J* = 7.4 Hz, 2H), 2.17-2.08 (m, 4H), 1.45 (s, 3H), 1.43 (s, 3H), 1.16-1.05 (m, 21H), 1.02 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 137.5, 131.2, 129.8, 127.5, 101.0, 71.3, 67.6, 58.7, 36.3, 25.4, 24.9, 24.3, 20.9, 18.1, 14.3, 12.7, 12.0; IR (thin film, NaCl) 2963 (s), 2941 (s), 2891 (m), 2866 (s), 1462 (m), 1378 (m), 1332 (w), 1224 (s), 1170 (m), 1085 (s), 1065 (s), 1013 (m), 997 (m), 908 (w), 882 (m), 805 (w), 682 (m) cm⁻¹; HRMS (FAB) *m/z* found: 487.2245 [calc'd for C₂₄H₄₅BrO₃Si (M-H): 487.2243].

Preparation of Enone **iii** (Structure not pictured in the text)

To a flame-dried roundbottom flask was added **5** (751mg, 1.55 mmol) and 20 mL of freshly distilled benzene. The benzene was removed under reduced pressure, and the process was repeated twice more. After all the benzene had been removed, freshly distilled ether was added (50 mL) and the resulting clear solution was cooled to -78°C . Freshly standardized *t*-BuLi in pentane (1.42 M) was added cautiously in a manner such that the solution ran down the side of the chilled flask before making contact with the reaction solution (1.20 mL, 1.69 mmol). The resulting bright yellow solution was stirred for 35 minutes, and **4** (717mg, 1.39 mmol) was slowly added as a solution in pentane (5 mL). Once the solution lost its color, it was quenched with a saturated aqueous solution of ammonium chloride (35 mL) and allowed to warm to room temperature. The organic phase was collected, dried over sodium sulfate, and the solvents removed under reduced pressure. The crude residue was taken up in methylene chloride (50 mL) and solid Dess Martin Periodinane (960 mg, 2.11 mmol) was added. After 5 minutes, the resulting suspension was extracted vigorously thrice with potassium bicarbonate (25 mL portions) and the organic layer dried over sodium sulfate. The methylene chloride was removed under reduced pressure and the resulting residue was purified by flash column chromatography (3% ethyl acetate/hexanes) to afford **iii** (1.23g, 95% yield) as a pale yellow oil. $^1\text{H NMR}$ (500MHz, CDCl_3) 7.52 (s, 1H), 7.46-7.29 (m, 10H), 6.29 (bs, 1H), 5.88 (td, $J = 7.9, 1.7$ Hz, 1H), 5.53 (t, $J = 7.5$ Hz, 1H), 5.04 (s, 2H), 4.97 (d, $J = 9.6$ Hz, 1H), 4.94 (d, $J = 9.6$ Hz, 1H), 4.82 (t, $J = 7.9$ Hz, 1H), 4.73 (d, $J = 10$ Hz, 1H), 4.67 (d, $J = 10$ Hz, 1H), 4.49 (t, $J = 7.9$ Hz, 1H), 4.31 (s, 2H), 2.11 (m, 6H), 1.91 (d, $J = 1.1$ Hz, 3H), 1.81 (d, $J = 0.9$ Hz, 3H), 1.17-1.04 (m, 21H), 1.00 (t, $J = 7.4$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H), 0.82 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 196.9, 159.9, 156.3, 141.9, 137.8, 137.5, 137.4, 137.1, 136.6, 133.3, 130.0, 129.3, 128.9, 128.4, 128.4, 128.1, 127.9, 127.6, 127.3, 127.3, 120.3, 101.0, 78.2, 76.3, 67.4, 67.0, 58.9, 54.9, 35.8, 26.4, 25.9, 24.6, 24.2, 22.7, 20.9, 19.6, 18.2, 18.1, 14.3, 13.8, 12.0, -5.4, -5.5; **IR** (thin film, NaCl) 3090 (w), 3065 (w), 3031 (w), 2957 (s), 2936 (s), 2890 (s), 2864 (s), 1669 (m), 1588 (m), 1565 (m), 1498 (m), 1461 (m), 1375 (m), 1337 (w), 1314 (w), 1284 (m), 1252 (m), 1224 (s), 1169 (m), 1133 (s), 1067 (s), 1005 (m), 996 (m), 979 (m), 940 (w), 909 (w), 882 (m), 837 (s) cm^{-1} ; **HRMS** (FAB) m/z found: 924.5754 [calc'd for $\text{C}_{56}\text{H}_{84}\text{O}_7\text{Si}_2$ (M): 924.5756].

Preparation of Diol **14** (Structure not pictured in the text)

To a solution of **iii** (1.23g, 1.33 mmol) in tetrahydrofuran (55 mL) at 0°C was added a 1.0M solution of tetrabutylammonium fluoride in tetrahydrofuran (6.5mL, 6.5 mmol). The solution was maintained at 0°C and stirred until all starting material was consumed (*ca* 10 hrs.). Silica gel was added (*ca* 2 g) and the solvents were removed *in vacuo*. The resulting powder was loaded onto a pre-packed column chromatography column and eluted (35% ethyl acetate/hexanes) to afford **14** (688 mg, 79% yield) as a pale yellow oil. **¹H NMR** (500MHz, CDCl₃) 7.53 (s, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.41-7.32 (m, 8H), 5.97 (td, *J* = 7.7, 0.8 Hz, 1H), 5.52 (t, *J* = 7.3 Hz, 1H), 5.00 (d, *J* = 11 Hz, 1H), 4.95 (d, *J* = 11 Hz, 1H), 4.94 (s, 2H), 4.84 (ddd, *J* = 7.0, 6.0, 1.0 Hz, 1H), 4.60 (m, 2H), 4.47 (dd, *J* = 7.0, 8.6 Hz, 1H), 4.22 (m, 2H), 2.47 (bs, 1H), 2.32 (bs, 1H), 2.20-2.00 (m, 6H), 1.95 (d, *J* = 1.2 Hz, 3H), 1.82 (d, *J* = 1.0 Hz, 3H), 1.33 (s, 3H), 1.15 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 196.5, 159.3, 155.7, 141.1, 137.4, 136.9, 136.7, 136.5, 133.5, 132.6, 129.0, 128.8, 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 120.0, 101.2, 78.3, 76.1, 71.7, 67.2, 58.4, 55.6, 35.4, 26.3, 24.7, 24.4, 22.7, 20.7, 19.6, 14.2, 13.8; **IR** (thin film, NaCl) 3442 (m), 3063 (w), 3031 (w), 2964 (s), 2933 (s), 2873 (s), 2732 (w), 1664 (s), 1586 (m), 1562 (m), 1497 (w), 1454 (s), 1412 (w), 1376 (s), 1337 (w), 1315 (w), 1276 (w), 1222 (s), 1187 (m), 1132 (s), 1068 (s), 1015 (s), 981 (s), 910 (m), 853 (w), 733 (m), 698 (m), 645 (w) cm⁻¹; **HRMS** (FAB) *m/z* found: 654.3557 [calc'd for C₄₁H₅₀O₇ (M): 654.3557].

Preparation of Epoxides **15** and **16**

To a solution of **14** (688 mg, 1.05 mmol) in benzene (25 mL) was added vanadyl acetylacetonate (58mg, 0.22 mmol) and *tert*-butylhydrogenperoxide as a 1.0M solution in toluene (2.2 mL, 2.2 mmol). The resulting blood-red slurry was stirred rapidly for 2 hours, quenched with saturated sodium thiosulfate (25 mL), and the organic layer collected and dried over sodium sulfate. The solvents were removed under reduced

pressure and the resulting brown residue was purified by flash chromatography (45% ethylacetate/hexanes) to afford a 1.2:1 mixture of **15** and **16** (605mg, 86% yield) as a mixture of diastereomers. These materials were characterized as *ca* 1.2:1 diastereotopic mixture, however, enriched samples of both could be obtained by preparative thin layer chromatography (25% ethyl acetate, 2% triethylamine/hexanes, 7 elutions). In general the acetonide present in **15/16** is prone to migration and these materials were taken on quickly to **iv**. $^1\text{H NMR}$ (400MHz, CDCl_3) 8.10 (d, $J = 6.9$ Hz, 0.5H), 7.63-7.31 (m, 10.5H), 6.31 (bs, 1H), 5.96 (t, $J = 7.5$ Hz, 0.5H), 5.94 (t, $J = 7.5$ Hz, 0.5H), 4.99-4.91 (m, 4.5 Hz), 4.79 (dd, $J = 8.1, 8.0$ Hz, 0.5H), 4.60 (d, $J = 12.2$ Hz, 1H), 4.57 (d, $J = 12.2$ Hz, 1H), 4.10 (dd, $J = 6.4, 8.7$ Hz, 0.5H), 3.93 (m, 1.5H), 3.70 (dd, $J = 5.2, 13.3$ Hz, 1H), 2.94 (t, $J = 6.4$ Hz, 0.5H), 2.90 (t, $J = 6.9$ Hz, 0.5H), 2.11 (m, 2H), 1.95 (s, 3H), 1.81 (s, 3H), 1.64 (m, 4H), 1.30 (s, 3H), 1.15 (s, 1.5H), 1.13 (s, 1.5H), 1.05 (t, $J = 7.5$ Hz, 1.5H), 1.03 (t, $J = 7.5$ Hz, 1.5H), 0.95 (t, $J = 7.5$ Hz, 3.0H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 196.5, 195.5, 159.2, 155.6, 155.6, 140.8, 140.7, 137.8, 137.6, 137.2, 137.1, 136.7, 136.7, 136.6, 136.5, 133.6, 133.5, 133.4, 130.0, 128.9, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.4, 128.2, 128.0, 127.9, 120.0, 101.3, 78.3, 78.2, 76.0, 70.4, 68.5, 67.0, 67.0, 63.0, 62.4, 62.2, 61.4, 60.7, 60.7, 55.6, 32.1, 31.3, 26.3, 24.4, 24.3, 24.3, 24.2, 24.1, 22.7, 21.1, 21.1, 19.6, 13.7, 10.7; **IR** (thin film, NaCl) 3463 (m), 2089 (w), 2063 (m), 3031 (m), 2969 (s), 2934 (s), 2875 (s), 1720 (m), 1692 (m), 1665 (m), 1585 (m), 1563 (m), 1497 (w), 1453 (s), 1377 (s), 1315 (m), 1276 (m), 1223 (s), 1185 (m), 1133 (s), 1094 (m), 1068 (m), 1052 (m), 1018 (m), 981 (m), 915 (m), 851 (m), 735 (m), 713 (m), 698 (m) cm^{-1} ; **HRMS** (FAB) m/z found: 670.3504 [calc'd for $\text{C}_{41}\text{H}_{50}\text{O}_8$ (M): 670.3506].

Preparation of bis-Aldehyde **iv** (Structure not pictured in the text)

0.92 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 199.3, 199.1, 195.9, 195.8, 189.4, 189.4, 161.1, 161.1, 157.9, 157.8, 140.6, 140.6, 138.3, 138.2, 138.1, 136.1, 136.1, 136.0, 135.9, 130.2, 130.1, 129.5, 128.7, 128.5, 128.4, 128.3, 124.7, 119.1, 101.3, 101.3, 79.2, 79.2, 67.0, 66.8, 66.7, 66.2, 64.2, 63.7, 62.9, 60.8, 32.2, 30.7, 26.4, 24.2, 24.1, 24.0, 23.6, 22.7, 22.7, 21.2, 21.2, 19.6, 13.7, 10.7, 10.5; **IR** (thin film, NaCl) 2971 (m), 2935 (m), 2875 (m), 1725 (m), 1696 (s), 1669 (m), 1557 (m), 1498 (w), 1455 (m), 1405 (w), 1371 (m), 1257 (m), 1222 (m), 1170 (w), 1134 (m), 1094 (w), 1006 (w), 981 (w), 915 (w), 851 (w), 735 (w), 699 (m) cm^{-1} ; **HRMS** (FAB) m/z found: 667.3273 [calc'd for $\text{C}_{41}\text{H}_{47}\text{O}_8$ (M+H): 667.3271].

Preparation of Spiro-epoxy pyranoses **18** and **v** (structure not pictured in the text)

To a solution of **iv** (308 mg, 0.48 mmol) in tetrahydrofuran (5 mL) was added acetic acid (5 mL) and water (3 mL). The resulting solution was warmed to 95°C , stirred rapidly for 3 hours, and then cooled to room temperature and stirred for an additional 15 minutes. The solution was diluted with brine (10 mL) and ethyl acetate (20 mL). The resulting organic phase was concentrated to a residue via azeotropic drying with toluene and purified by flash column chromatography (20% ethyl acetate/hexanes) affording first **18** as a yellow solid, mp = 72°C (130 mg, 44% yield). ^1H NMR (500 MHz, CDCl_3) 10.32 (s, 0.3H), 10.28 (s, 0.7H), 7.68 (s, 1H), 7.48 (d, $J = 7.3$ Hz, 2H), 7.40-7.31 (m, 8H), 6.43 (t, $J = 7.3$ Hz, 0.3H), 6.27 (bs, 0.3H), 6.25 (bs, 0.7H), 6.08 (t, $J = 7.3$ Hz, 0.7H), 5.40 (dd, $J = 12, 2$ Hz, 0.3H), 5.06-4.88 (m, 6.7H), 4.30 (td, $J = 12.3, 4.4$ Hz, 0.7H), 3.34 (t, $J = 6.6$ Hz, 0.3H), 3.29 (t, $J = 7.0$ Hz, 0.7H), 2.67 (d, $J = 3.0$ Hz, 1.3H), 2.62 (d, $J = 2.6$ Hz, 1.7H), 2.59-2.50 (m, 1H), 2.21 (ddd, $J = 12.5, 5.0, 1.5$ Hz, 0.7H), 2.07 (ddd, $J = 12.5, 5.0, 2.0$ Hz, 0.3H), 2.00 (t, $J = 7.5$ Hz, 1H), 1.94 (s, 3H), 1.77 (s, 3H), 1.71-1.56 (m, 4H), 1.10 (t, $J = 7.9$ Hz, 0.9H), 1.06 (t, $J = 7.9$ Hz, 2.1H), 1.00 (t, $J = 7.9$ Hz, 0.9H), 0.90 (t, $J = 7.9$ Hz, 2.1H); ^{13}C NMR (125 MHz, CDCl_3) δ 196.5, 196.2, 189.9, 189.9, 161.7, 160.6, 158.0, 156.9, 155.3, 140.2, 140.0, 139.3, 138.7, 138.7, 138.5, 138.3, 136.8, 136.7, 136.6, 136.4, 131.1, 130.6, 129.9, 129.6, 129.2, 129.1, 129.0, 129.0, 129.0, 128.9, 128.8, 128.8, 128.7,

125.2, 119.6, 119.5, 95.0, 95.0, 79.6, 78.8, 78.2, 65.5, 63.2, 62.9, 62.2, 62.1, 60.3, 60.1, 38.9, 38.8, 26.8, 26.8, 23.3, 23.2, 21.0, 20.1, 20.1, 14.0, 13.8, 11.0, 11.0; **IR** (thin film, NaCl) 3439 (m), 3032 (w), 2969 (m), 2934 (m), 2876 (m), 1696 (s), 1653 (m), 1577 (w), 1557 (m), 1497 (w), 1456 (m), 1404 (w), 1368 (m), 1312 (w), 1260 (m), 1208 (m), 1185 (m), 1132 (s), 1094 (s), 1058 (m), 1032 (s), 971 (w), 931 (w), 853 (w), 827 (w), 737 (m), 699 (m) cm^{-1} ; **HRMS** (FAB) m/z found: 627.2955 [calc'd for $\text{C}_{38}\text{H}_{43}\text{O}_8$ (M+H): 627.2958] and then **v** (100 mg, 34%) as a pale yellow solid, mp = 74°C. **^1H NMR** (500MHz, CDCl_3) 10.28 (s, 1H), 7.68 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.41-7.32 (m, 8H), 6.26 (bs, 1H), 6.01 (t, J = 8.0Hz, 1H), 5.09-4.91 (m, 6H), 4.46 (dd, J = 12.4, 4.0 Hz, 1H), 3.32 (t, J = 6.2 Hz, 1H), 2.78 (bs, 1H), 2.32 (m, 1H), 1.93 (s, 3H), 1.77 (s, 3H), 1.68 (m, 2H), 1.51 (m, 2H), 1.04 (t, J = 8.0Hz, 3H), 0.90 (t, J = 8.0 Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 196.1, 1895., 161.2, 157.8, 139.9, 138.4, 138.1, 137.9, 136.3, 136.0, 130.5, 129.4, 128.7, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 124.8, 119.2, 92.5, 79.2, 68.1, 64.3, 63.1, 59.2, 38.5, 26.4, 22.8, 21.3, 19.6, 13.6, 10.3; **IR** (thin film, NaCl) 3437 (s), 3064 (w), 3032 (w), 2967 (s), 2934 (s), 2858 (s), 1694 (s), 1608 (w), 1581 (m), 1554 (s), 1498 (m), 1455 (m), 1444 (m), 1405 (m), 1368 (s), 1313 (m), 1291 (m), 1260 (m), 1212 (m), 1185 (m), 1132 (s), 1093 (s), 1058 (s), 1029 (s), 936 (m), 919 (m), 851 (m), 783 (w) cm^{-1} ; **HRMS** (FAB) m/z found: 627.2955 [calc'd for $\text{C}_{38}\text{H}_{43}\text{O}_8$ (M+H): 627.2958].

Preparation of Luminacin D (3) and epi-C2'-Luminacin D (20)

To a solution of **18** (33 mg, 0.053 mmol) in ethyl acetate (5 mL) was added 5% palladium on carbon (50 mg). The resulting solution was placed under vacuum, purged with hydrogen, and stirred for 5 hours. The slurry was poured over silica gel and eluted with ethyl acetate. The solvents were removed under reduced pressure, giving *ca* 2:1 mixture of luminacin D and its C2' epimer (20 mg, 84% yield). Separation of **3** and **20** could be effected by preparative thin layer chromatography (30% ethyl acetate/hexanes, 8 elutions), and analytical samples of both materials were prepared in this manner. Luminacin D elutes first: **^1H NMR** (500MHz, CDCl_3) 14.16 (s, 1H), 13.00 (s, 1H), 10.42 (s, 1H), 7.74 (s, 1H), 5.01 (d, J = 2.7 Hz, 1H), 4.39 (dd, J = 8.7, 10.6 Hz, 1H), 4.20 (dt, J = 4.8, 11.6 Hz, 1H), 3.56 (dt, J = 4.5, 9.0 Hz, 1H), 3.30 (t, J = 6.6 Hz, 1H), 2.51 (d, J = 3.4 Hz, 1H), 2.47 (dd, J = 13.8, 7.0 Hz, 1H), 2.42 (dd, J = 13.8, 7.0 Hz, 1H), 2.03 (dd, J = 12.0, 4.5 Hz, 1H), 1.91 (m, 1H), 1.88-1.76 (m, 2H), 1.63 (m, 1H), 1.50 (d, J = 11.6 Hz, 1H), 1.42 (app. quart., J = 11.6 Hz, 1H), 1.31-1.18 (m, 1H), 1.09 (t, J = 7.7 Hz, 3H), 0.93

(d, $J = 6.4$ Hz, 3H), 0.92 (d, $J = 6.3$ Hz, 3H), 0.89 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.6, 194.3, 168.0, 167.5, 139.4, 121.0, 112.5, 109.3, 94.5, 69.8, 62.4, 61.8, 59.8, 49.4, 37.9, 37.3, 32.1, 28.3, 22.3, 22.3, 20.6, 20.6, 14.2, 10.5; **IR** (thin film, NaCl) 3446 (m), 2957 (s), 2927 (s), 2857 (m), 1735 (s), 1632 (m), 1461 (m), 1383 (m), 1262 (m), 1176 (m), 1135 (m), 1075 (m), 1039 (m), 802 (w), 743 (w) cm^{-1} ; **HRMS** (FAB) m/z found: 451.2331 [calc'd for $\text{C}_{24}\text{H}_{34}\text{O}_8(\text{M}+\text{H})$: 451.2331]. Then epi-C2'-Luminacin D: ^1H NMR (500MHz, CDCl_3) 14.03 (s, 1H), 12.82 (s, 1H), 10.28 (s, 1H), 7.60 (s, 1H), 4.72 (s, 1H), 4.37 (t, $J = 9.8$ Hz, 1H), 4.16t (m, 1H), 3.39 (dt, $J = 10.0$, 4.0 Hz, 1H), 3.19 (dd, $J = 7.1$, 5.6 Hz, 1H), 2.42 (dd, $J = 14.3$, 7.1 Hz, 1H), 2.41 (bs, 1H), 2.25 (dd, 13.5Hz, 7.1 Hz), 1.80 (m, 1H), 1.61 (m, 1H), 1.56-1.36 (m, 3H), 1.14 (m, 2H), 1.10 (m, 1H), 0.95 (t, $J = 7.5$ Hz, 3H), 0.82 (d, $J = 6.5$ Hz, 3H), 0.79 (d, $J = 6.5$ Hz, 3H), 0.76 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.6, 194.3, 167.7, 167.0, 139.7, 120.9, 112.8, 109.3, 94.1, 70.1, 62.6, 61.8, 59.8, 49.5, 37.8, 37.1, 31.3, 28.3, 22.4, 22.2, 20.6, 20.4, 14.2, 10.5; **IR** (thin film, NaCl) 3428 (m), 2959 (m), 2932 (m), 2872 (m), 1631 (s), 1461 (m), 1390 (m), 1299 (m), 1264 (m), 1187 (w), 1171 (w), 1054 (m), 1038 (m), 929j (w), 825 (w), 737 (w), 668 (w) cm^{-1} ; **HRMS** (FAB) m/z found: 451.2331 [calc'd for $\text{C}_{24}\text{H}_{34}\text{O}_8(\text{M}+\text{H})$: 451.2331].

Preparation of Spiro-epoxypyranose **19**

To a solution of **18** (20 mg, 0.032 mmol) in ethyl acetate (2 mL) was added 5% palladium on carbon (20 mg). The resulting solution was placed under vacuum, purged with hydrogen, and stirred for 25 minutes. The slurry was poured over silica gel and eluted with ethyl acetate. The solvents were removed under reduced pressure, and the resulting residue was purified by preparative thin layer chromatography (30% ethyl acetate/hexanes, 1 elution, 3 plates) to furnish **19** (7 mg, 49% yield) in addition to **3/20** (3 mg, 21% yield). ^1H NMR (500MHz, CDCl_3) 13.63 (s, 1H), 13.00 (s, 1H), 10.42 (s, 1H), 7.59 (s, 1H), 5.93 (t, $J = 7.5$ Hz, 1H), 4.99 (d, $J = 2.7$ Hz, 1H), 4.91 (d, $J = 11.7$ Hz, 1H), 4.28 (dt, $J = 12.0$, 4.6 Hz, 1H), 3.31 (t, $J = 7.0$ Hz, 1H), 2.56 (d, $J = 2.9$ Hz, 1H), 2.41 (m, 2H), 2.22 (d, $J = 10.0$ Hz, 1H), 1.99-1.56 (m, 9H), 1.08 (t, $J = 7.4$ Hz, 3H), 0.97 (t, $J = 7.4$ Hz, 3H), 0.90 (d, $J = 2.7$ Hz, 3H), 0.89 (d, $J = 2.7$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 194.0, 168.1, 167.0, 142.1, 136.5, 133.7, 121.3, 112.2, 109.1, 94.5, 76.4, 62.6, 61.6, 59.7, 37.8, 28.2, 22.9, 22.3, 22.3, 20.6, 13.6, 10.6; **IR** (thin film, NaCl) 3407 (m), 2959 (m), 2872 (m), 1638 (s), 1451 (m), 1396 (m), 1297 (m), 1269 (m), 1204 (w), 1161

(w), 1093 (m), 1031 (m), 930 (w), 826 (w) cm^{-1} ; **HRMS** (FAB) m/z found: 449.2175 [calc'd for $\text{C}_{24}\text{H}_{33}\text{O}_8$ ($\text{M}+\text{H}$): 449.2175].

Dose Response Data for 3 and 19

● Bovine Aortic Endothelial Cells
● SWISS 3T3 (Mouse Fibroblasts)

Characterization Spectra for Luminacin D