Enantioselective Synthesis of the [6,6] Spiroketal Core of Reveromycin A

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Supporting Information

General techniques. Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. All nonaqueous reactions were carried out using flame-dried glassware, under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF and Et₂O were distilled from sodium/benzophenone; CH₂Cl₂ and toluene from calcium hydride; and benzene from potassium. Pyridine, triethylamine and boron trifluoride etherate were distilled from calcium hydride prior to use. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and p-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Perkin-Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.
Preparation of iodide 7

Reagents and conditions: (a) 1.5 equiv tBuOK, 1.6 equiv trans-2-buten, 1.5 equiv nBuLi, THF, \(-45 \, ^\circ\text{C}\), 10 min, then 1.6 equiv (-)-ipc$_2$-OMe (1M in THF), 2.0 equiv BF$_3$•Et$_2$O, \(-78 \, ^\circ\text{C}\), 3 h, then 3N NaOH, 30% H$_2$O$_2$, 25 \, ^\circ\text{C}, 18 h, 80%; (b) 1.2 equiv TBAF•THF, THF, 25 \, ^\circ\text{C}, 30 min, 98%; (c) 1.2 equiv PMBCH(OMe)$_2$, 0.1 equiv CSA, CH$_2$Cl$_2$, 25 \, ^\circ\text{C}, 6 h, 98%; (d) 1.5 equiv DIBAL-H (1M in CH$_2$Cl$_2$), CH$_2$Cl$_2$, \(-78 \, \text{to} \, 25 \, ^\circ\text{C}\), 2 h, 91%; (e) 2.5 equiv imid, 1.3 equiv TBSCl, CH$_2$Cl$_2$, 25 \, ^\circ\text{C}, 1 h, 97%; (f) 1.0 equiv BH$_3$•THF, \(-40 \, ^\circ\text{C}\), 10 h, then 3N NaOH, 30% H$_2$O$_2$, 25 \, ^\circ\text{C}, 30 min, 85%; (g) 2.4 equiv imid, 1.2 equiv P$_3$P, 1.2 equiv I$_2$, THF, 0 \, ^\circ\text{C}, 30 min, 96%.

Iodide 7. light yellow oil; $R_f = 0.55$ (10% ether in hexanes); $[^{25}\text{D}]$ +16.1 (c= 1.0, CH$_2$Cl$_2$); IR (film) $\nu_{\text{max}}$ 2957, 2936, 2863, 1614, 1515, 1254, 1092, 836; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.27 (d, 2H, J= 8.0 Hz), 6.88 (d, 2H, J= 8.0 Hz), 4.50 (d, 1H, J= 11.5 Hz), 4.42 (d, 1H, J= 11.5 Hz), 3.80 (s, 3H), 3.69-3.66 (m, 2H), 3.47-3.45 (m, 1H), 3.28-3.27 (m, 1H), 3.18-3.15 (m, 1H), 1.98-1.86 (m, 2H), 1.71-1.55 (m, 3H), 0.91 (d, 3H, J= 7.0 Hz), 0.88 (s, 9H), 0.035 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.2, 131.1, 129.4, 113.8, 78.2, 71.3, 59.8, 55.2, 36.5, 36.0, 33.3, 25.9, 18.2, 13.9, 5.5, -5.4, -5.5; HRMS, calcd for C$_{21}$H$_{37}$IO$_3$Si (M+Cs$^+$) 625.0609, found 625.0631.
Ketone 13. A solution of oxaly chloride (8.0 ml, 91.8 mmol) in CH₂Cl₂ (150 ml) was cooled to -78 °C and treated with dimethylsulfoxide (7.8 ml, 110.1 mmol) added dropwise over 10 minutes. After stirring for 15 minutes, a solution of alcohol 18 (14.0 g, 36.7 mmol) in CH₂Cl₂ (30 ml) was slowly introduced. After additional stirring for 2 h at -78 °C the reaction was quenched with Et₃N (18.6 g, 183.5 mmol) and allowed to warm slowly to 25 °C. The reaction mixture was diluted with brine (300 ml) and CH₂Cl₂ (200 ml) and the aqueous layer was extracted with Et₂O (3 x 400 ml), dried (MgSO₄), filtered concentrated, and chromatographed (0-5% ether in hexanes) to afford ketone 13 (12.6 g, 33.0 mmol, 90%). Ketone 13: light yellow oil; $R_f$ = 0.45 (silica, 20% ether in hexanes); $[a]^{25}_D$: -22.6 (c= 1.1, CH₂Cl₂); IR (film) $\nu$max 2956, 2858, 1717, 1514, 1250, 837; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 7.28 (d, 2H, J= 8.5 Hz), 6.88 (d, 2H, J= 8.5 Hz), 4.50 (d, 2H, J= 4.8 Hz), 3.87-3.84 (m, 3H), 3.83 (s, 3H), 2.58-2.53 (m, 2H), 1.54-1.50 (m, 2H), 1.32-1.27 (m, 2H), 0.91 (t, 3H, J= 6.0 Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl₃) $\delta$ 211.6, 159.1, 129.4, 129.3, 113.7, 84.8, 72.2, 64.1, 55.3, 39.6, 25.9, 25.1, 22.5, 18.4, 14.1, -5.3; HRMS, calcd for C₂₁H₃₆O₄Si (M+Cs⁺) 513.1435, found 513.1442.

Aldehyde 8. A solution of the alkene 24 (5.20 g, 10.3 mmol) in CH₂Cl₂/MeOH/pyridine (100 ml/100 ml/20 ml) at -78 °C was subjected to ozone over a period of 30 min. The reaction mixture was then flushed with argon, treated with triphenylphosphine (5.40 g, 20.6 mmol) and allowed to warm slowly to 25 °C. After stirring for 2 h, the reaction mixture was concentrated, and subjected to flash chromatography (0-15% ether in hexanes) to afford aldehyde 8 (4.42 g, 8.76 mmol, 85% yield). Aldehyde 8: colorless oil; $R_f$ = 0.40 (silica, 15% ether in hexanes); $[a]^{25}_D$: +28.1 (c= 1.25, CH₂Cl₂); IR (film) $\nu$max 2957, 2931, 1729, 1520, 1259, 1097, 841; $^1$H NMR (400 MHz, CDCl₃) $\delta$ 9.72 (d, 1H, J= 1.0 Hz), 7.26 (d, 2H, J= 7.5 Hz), 6.88 (d, 2H, J= 7.5 Hz), 4.75 (d, 1H, J= 11.5 Hz), 4.34 (d, 1H, J= 11.0 Hz), 3.91 (s, 1H), 3.80 (s, 3H), 2.43
Ketone 6. A solution of the iodide 7 (4.83 g, 9.81 mmol) in Et₂O (50 ml) was cooled to -78 °C and treated with tert-butyllithium (11.5 ml of 1.7 M solution in pentane, 19.6 mmol). After stirring for 20 min, a solution of the aldehyde 8 (3.07 g, 6.08 mmol) in Et₂O (30 ml) was added and the mixture was stirred for an additional 0.5 h. The reaction was quenched with aqueous saturated ammonium chloride (10 ml) and the mixture was warmed to 25 °C and diluted with Et₂O (50 ml). The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 x 50 ml). The organic layers were combined, dried (MgSO₄), filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (0-15% ether in hexanes) to afford the C15-alcohol as a colorless oil. This alcohol was redissolved in CH₂Cl₂ (100 ml) and treated at 25 °C with Dess-Martin periodinane (3.87 g, 9.12 mmol). After stirring for 1 h, the reaction was quenched with aqueous saturated sodium thiosulfate (50 ml) and aqueous saturated sodium bicarbonate (50 ml) and diluted with Et₂O (100 ml). The aqueous layer was extracted with Et₂O (3 x 100 ml), the organic layers were combined, dried (MgSO₄), filtered, and concentrated. The residue was subjected to flash chromatography (0-10% ether in hexanes) to afford ketone 6 (4.1 g, 4.74 mmol, 79% over two steps). 6: colorless oil; Rf = 0.50 (20% ether in hexanes); [α]²⁵⁺D: +51.5 (c= 1.0, CH₂Cl₂); IR (film) νmax 2962, 2931, 1719, 1614, 1510, 1468, 1254, 1087, 836; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (d, 2H, J= 8.5 Hz), 7.25 (d, 2H, J= 8.5 Hz), 6.87 (d, 2H, J= 8.5 Hz), 6.86 (d, 2H, J= 8.5 Hz), 4.75 (d, 1H, J= 11.5 Hz), 4.47 (d, 1H, J= 10.5 Hz), 4.37 (d, 1H, J= 11.0 Hz), 0.88 (t, 3H, J= 6.5 Hz), 0.84 (s, 9H), 0.18 (s, 9H), 0.055 (s, 3H), 0.035 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.0, 159.3, 129.9, 129.8, 113.7, 102.9, 93.1, 78.8, 74.4, 70.1, 55.2, 38.6, 36.9, 28.7, 26.0, 25.6, 23.2, 18.6, 13.9, -0.27, -2.25, -2.40; HRMS, calcd for C₂₈H₄₈O₄Si₂ (M+Cs⁺) 637.2144, found 637.2161.
Spiroketal 25. A solution of ketone 6 (3.17 g, 3.64 mmol) in CH$_2$Cl$_2$/H$_2$O (25 ml/1 ml) was treated with 2,3-dichloro-4,5-dicyanobenzoquinone (2.48 g, 10.9 mmol) at 25 °C. After stirring for 2 h, the mixture was diluted with aqueous saturated sodium bicarbonate (100 ml) and extracted with CH$_2$Cl$_2$ (3 x 50 ml). The organic layer was collected, dried (MgSO$_4$), filtered and concentrated. The residue was subjected to flash chromatography (0-2% ether in hexanes) to afford spiroketal 25 as a mixture of diastereomers at the C15 carbon center (1.78 g, 2.91 mmol, 81% combined yield). 25 (top diastereomer): colorless gum; $R_f$ = 0.50 (4% ether in hexanes); $[\alpha]_{25}^{25}$: +21.1 (c= 1.25, CH$_2$Cl$_2$); IR (film) $\nu_{max}$ 2962, 2857, 1719, 1614, 1510, 1468, 1254, 836; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.24 (s, 1H), 3.80-3.70 (m, 3H), 2.04-1.67 (m, 6H), 1.55-1.24 (m, 11H), 0.91-0.90 (m, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85-0.84 (m, 3H), 0.11 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 105.1, 95.9, 88.9, 74.8, 73.2, 70.9, 59.0, 37.8, 35.0, 34.3, 33.2, 32.1, 28.4, 27.8, 25.9, 25.8, 24.3, 23.2, 18.5, 18.2, 17.7, 14.0, -0.2, -2.3, -2.5; HRMS, calcd for C$_{33}$H$_{66}$O$_4$Si$_3$ (M+Cs$^+$) 743.3323, found 743.3341. 25 (bottom diastereomer): colorless gum; $R_f$= 0.45 (4% ether in hexanes); $[\alpha]_{25}^{25}$: +38.2 (c= 1.0, CH$_2$Cl$_2$); IR (film) $\nu_{max}$ 2964, 2931, 2857, 1718, 1612, 1510, 1468, 1251, 1085; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.73 (s, 1H), 3.80 (t, 2H, J= 7.0 Hz), 3.26-3.19 (m, 1H), 2.19-2.17 (m, 1H), 1.84-1.60 (m, 8H), 1.43-1.17 (m, 8H), 0.91 (t, 3H, J= 7.5 Hz),
0.88 (s, 9H), 0.87 (s, 9H), 0.82 (d, 3H, J= 6.5 Hz), 0.13 (s, 9H), 0.80 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H); 13C NMR (100 MHz, CDCl₃) δ 103.0, 97.2, 90.6, 75.5, 74.0, 70.3, 59.7, 36.7, 35.8, 34.6, 31.2, 29.6, 29.3, 26.5, 25.81, 25.80, 24.8, 23.1, 18.3, 18.0, 17.4, 14.0, -0.3, -2.0, -2.1; HRMS, calcd for C₃₃H₆₆O₄Si₃ (M+Cs⁺) 743.3323, found 743.3346.

**Spiroketal 5 and 26.** A solution of spiroketal 25 (mixture of diastereomers at C15) (0.202 g, 0.328 mmol) in CH₂Cl₂/MeOH (2.5/0.5 ml) at 25 °C was treated with camphorsulphonic acid (8 mg, 0.035 mmol) for 1 h. The reaction mixture was quenched with triethylamine (0.5 ml) and the residue concentrated and subjected to flash chromatography (5-20% ether in hexanes) to afford spiroketals 5 and 26 as a 1.5:1 mixture of diastereomers in favor of 5 (161 mg, 0.321 mmol, 98% combined yield).

**Spiroketal 5** (major diastereomer, 96 mg, 0.193 mmol, 59%); white solid; [α]²⁵°C: +41.2 (c= 1.1, CH₂Cl₂); IR (film) νmax 3364, 2953, 2857, 1719, 1614, 996; ¹H NMR (500 MHz, C₆D₆) δ 4.53 (s, 1H), 4.12-4.10 (m, 1H), 3.94-3.90 (m, 2H), 2.75 (bs, 1H), 2.09-2.06 (m, 2H), 1.86-1.66 (m, 6H), 1.49-1.29 (m, 9H), 0.97 (s, 12H), 0.65 (t, 3H, J= 6.5 Hz), 0.22 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 105.9, 96.1, 89.9, 76.4, 75.1, 71.3, 60.0, 38.9, 35.5, 34.4, 33.5, 32.2, 28.1, 27.6, 26.3, 26.0, 24.6, 23.5, 18.6, 17.6, 14.1, -0.24, -2.42, -2.55; HRMS, calcd for C₂₇H₅₂O₄Si₂ (M+Cs⁺) 629.2455, found 629.2478.
Spiroketal 26 (minor diastereomer, 64 mg, 0.129 mmol, 39%); white solid; \( R_f = 0.22 \) (33% ether in hexanes); \([a]^{25}_D = +30.1 \) (c= 1.1, CH\(_2\)Cl\(_2\)); IR (film) \( \nu_{\text{max}} \) 3364, 2953, 2858, 1719, 1615, 996; \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \( \delta \) 5.05 (s, 1H), 3.73-3.70 (m, 1H), 3.61-3.55 (m, 1H), 3.02-2.98 (m, 1H), 2.16-2.00 (m, 2H), 1.85-1.60 (m, 7H), 1.50-1.30 (m, 9H), 1.09 (s, 9H), 1.01 (t, 3H, J= 7.2 Hz), 0.56 (d, 3H, J= 6.8 Hz), 0.36 (s, 3H), 0.28 (s, 3H), 0.14 (s, 9H); \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)) \( \delta \) 104.4, 97.3, 90.4, 76.8, 74.7, 70.8, 60.0, 36.7, 36.1, 35.3, 32.4, 30.2, 29.7, 27.2, 26.4, 25.7, 24.0, 19.0, 17.7, 14.7, 0.19, -1.3, -1.4; HRMS, calcd for C\(_{27}\)H\(_{52}\)O\(_4\)Si\(_2\) (M+Cs\(^+\)) 629.2455, found 629.2484.

Spiroketal 27. A solution of spiroketal 25 (mixture of diastereomers at C15) (0.35 g, 0.573 mmol) in CH\(_2\)Cl\(_2\) (3 ml) at 0 °C was treated with a solution of HF in pyridine (3.0 ml) and allowed stir for 1 h. The reaction was quenched with Et\(_3\)N (2 ml) and diluted with aqueous saturated sodium bicarbonate (20 ml). The reaction mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 30 ml) and the organic layer was separated, combined, dried (MgSO\(_4\)), filtered and concentrated. The crude residue was carried to the next reaction. A solution of the crude 5,6-spiroketal (18 mg, 0.047 mmol) in THF (0.30 ml) was treated with a 1M solution of TBAF in THF (100 \( \mu\)l) and stirred at 25 °C for 15 minutes. The reaction mixture was quenched with saturated NH\(_4\)Cl (5 ml), diluted with Et\(_2\)O (10 ml). The layers were partitioned and the aqueous layer was extracted with Et\(_2\)O (2x5 ml). The organic layers were combined, washed with brine (5 ml), dried over MgSO\(_4\), filtered, and subjected to flash chromatography (10-25% ether in hexanes) to afford the 5,6-spiroketal 27 (14 mg, 0.046 mmol, 80%). 27: colorless oil; \( R_f = 0.30 \) (70% ether in hexanes); \([a]^{25}_D = +67.8 \) (c= 0.33, CH\(_2\)Cl\(_2\)); IR (film) \( \nu_{\text{max}} \) 3366, 2953, 2929, 2867, 1470, 1377, 1051, 996; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.39 (d, 1H, J= 2.0 Hz), 3.83-3.79 (m, 1H), 3.72-3.65 (m, 2H), 2.54 (bs, 2H), 2.45-2.41 (m, 1H), 2.39 (d, 1H, J= 2.0 Hz), 2.05-1.83 (m, 3H), 1.76-1.50 (m, 7H), 1.41-1.20 (m, 6H), 0.91 (t, 3H, J= 6.5 Hz), 0.86 (d, 3H, J= 6.0 Hz), 0.83 (d, 3H, J= 6.0 Hz), 0.77 (d, 3H, J= 6.0 Hz), 0.70 (d, 3H, J= 6.0 Hz), 0.63 (t, 3H, J= 6.5 Hz), 0.56 (d, 3H, J= 6.0 Hz), 0.49 (t, 3H, J= 6.5 Hz), 0.42 (d, 3H, J= 6.0 Hz), 0.35 (t, 3H, J= 6.5 Hz), 0.28 (d, 3H, J= 6.0 Hz), 0.21 (t, 3H, J= 6.5 Hz), 0.14 (d, 3H, J= 6.0 Hz), 0.07 (t, 3H, J= 6.5 Hz), 0.00 (d, 3H, J= 6.0 Hz).
Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 107.4, 90.7, 82.6, 75.3, 73.4, 67.1, 59.1, 39.1, 36.6, 35.0, 34.4, 28.8, 28.1, 25.3, 23.1, 17.6, 14.0; HRMS, calcd for C$_{18}$H$_{30}$O$_4$ (M+Cs$^+$) 443.1195, found 443.1211.

**Triacetate 29.** A solution of the alkene 28 (6 mg, 0.019 mmol) in MeOH (2 ml) was cooled to -78 °C and treated with ozone until the starting material was consumed (tlc test, ca 2 min). The mixture was then purged with oxygen (2 min) and argon (1 min). The reaction mixture was treated with NaBH$_4$ (4 mg, 0.010 mmol) at -78 °C and stirred to 25 °C. After 1.5 h, the mixture was diluted with a saturated solution of NH$_4$Cl (4 ml), CH$_2$Cl$_2$ (10 ml), and the organic layer was separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 5 ml), dried (MgSO$_4$), concentrated and taken on crude to the next step. A solution of the crude triol in CH$_2$Cl$_2$ (500 $\mu$l) was treated with pyridine (10 $\mu$l, 0.12 mmol) and acetic anhydride (6 $\mu$l, 66 mmol) at 25°C for 2 hours. The reaction mixture was diluted with ether (10 ml) and washed with a saturated solution of NaHCO$_3$ (2 x 5 ml). The organic layer was dried (MgSO$_4$), concentrated and subjected to flash chromatography (silica, 0-25% ether in hexanes) to afford triacetate 29 (7.4 mg, 0.017 mmol, 83% yield). **29:** colorless liquid; $R_f$ = 0.45 (silica, 30% ether in hexanes); $[\alpha]^{25}_D$: +37.5 (c= 1.0, CHCl$_3$); IR (film) $\nu_{\text{max}}$ 2931, 2868, 1745, 1463, 1369, 1238, 1050, 1083, 993, 923; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.19 (dd, 1H, J= 9.0, 2.5 Hz), 4.52 (dd, 1H, J= 12.0, 2.0 Hz), 4.34-4.26 (m, 1H), 4.24 (dd, 1H, J= 12.0, 8.5 Hz), 4.18-4.13 (m, 1H), 3.49 (ddd, 1H, J= 10.8, 8.0, 2.8 Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96-1.50 (m, 11H), 1.31-1.25 (m, 6H), 0.91 (t, 3H, J= 7.0 Hz), 0.87 (d, 3H, J= 6.5 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.27, 171.25, 170.4, 107.0, 86.2, 73.6, 63.9, 61.7, 38.4, 34.5, 34.4, 34.2, 32.1, 31.3, 29.6, 29.0, 25.4, 23.1, 21.0, 20.9, 20.7, 17.6, 14.0; HRMS, calcd for C$_{23}$H$_{38}$O$_8$ (M+Cs$^+$) 575.1619, found 575.1632.
25 (top diastereomer)