Synthesis of the F-O-G fragment of ristocetin A via ruthenium-promoted intermolecular S_NAr reaction

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Dedicated to Charles Rees on the occasion of his 75th birthday

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Abstract

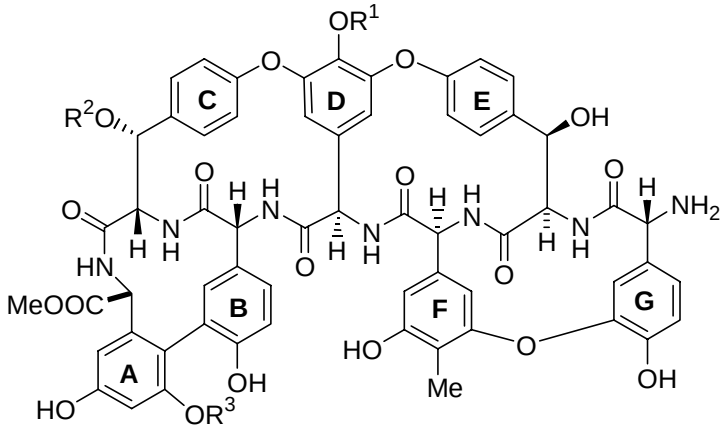
Using the ruthenium-promoted intermolecular S_NAr reaction, a key building block corresponding to the F-O-G fragment of ristocetin A has been synthesized.

Keywords: Ristocetin, ruthenium, nucleophilic, substitution, diaryl, ether, antibiotics

Introduction

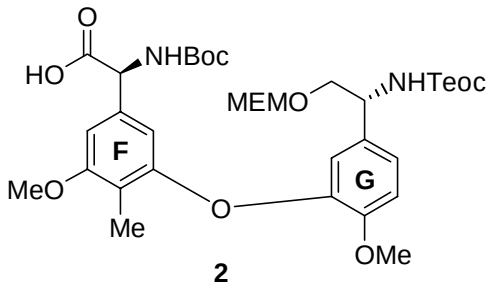
The vancomycin group of antibiotics has recently generated a significant amount of interest among synthetic chemists, due to both their clinical importance and their challenging molecular architecture. Currently vancomycin and teicoplanin are the only members of this group that are waging a lone battle against methicillin-resistant *Staphylococcus aureus* infections. However, with rapidly emerging[1] bacterial resistance to these antibiotics, there is a desperate need for stronger antibiotics. Total syntheses of vancomycin[2] and teicoplanin[3] aglycones have already been reported. Ristocetin A **1**, a member of the vancomycin group of antibiotics, in addition to having structural features similar to vancomycin, incorporates a 14-membered diaryl ether linkage between amino acid residues F and G.

The construction of the diaryl ether linkage in these types of molecules presents a formidable challenge due to the presence of base-sensitive amino acid residues such as aryl glycine derivatives.[4] Studies in our group have focused on the application of a ruthenium-promoted S_NAr reaction to the construction of the diaryl ethers.[5] Complexation of ruthenium to the aromatic subunits takes place under very mild conditions and the subsequent etherification occurs without significant epimerization of arylglycines or phenylalanine residues. Demetalation under simple photolytic conditions furnishes the desired diaryl ether, allowing at the same time recycling of the ruthenium complex precursor.



R^1, R^2, R^3 = sugars Ristocetin A **1**

We have previously reported synthetic studies toward the BCDF[6] and DEF[7] ring systems of ristocetin A, that employ the ruthenium-promoted S_NAr reaction. In this article, we report the synthesis of the F-O-G acid **2** which will serve as a key building block in our efforts to achieve the total synthesis of ristocetin A.



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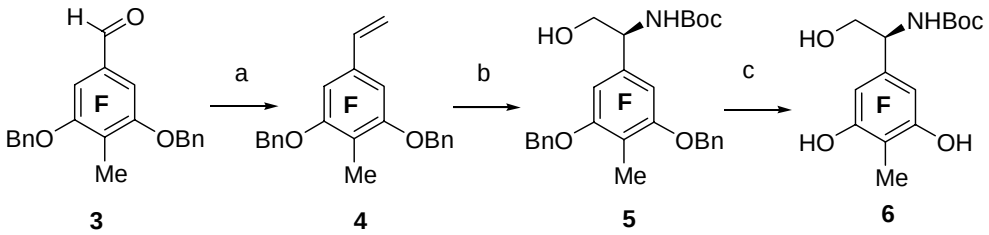
Results and Discussion

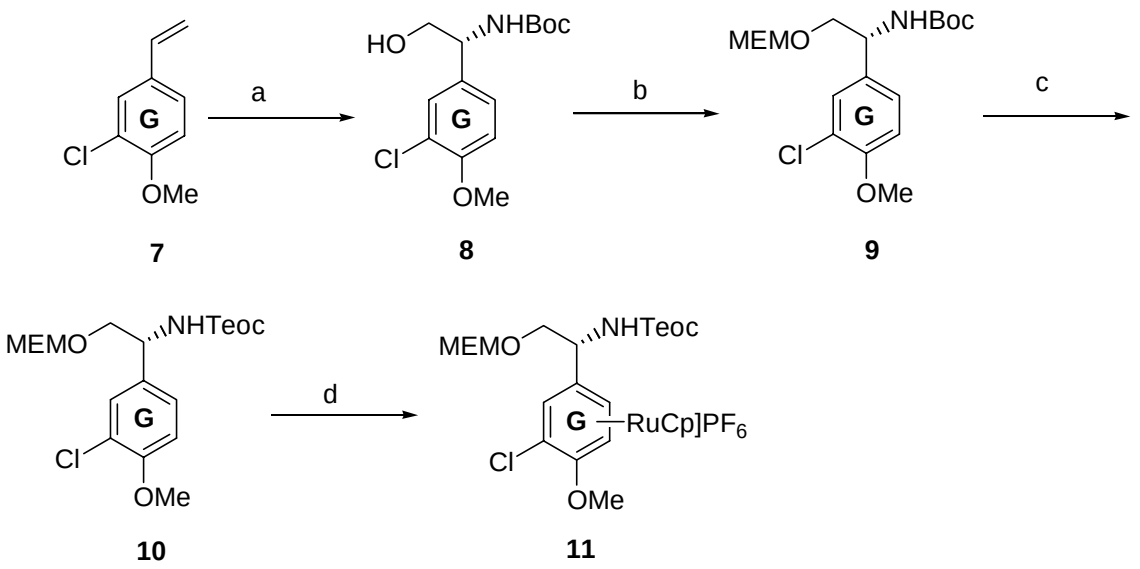
The requisite F and G-ring amino alcohols were synthesized by employing the Sharpless asymmetric aminohydroxylation as a key step. As shown in Scheme 1, 3,5-bis(benzyloxy)-4-methylbenzaldehyde **3**[8] was converted by Wittig olefination to 3,5-bis(benzyloxy)-4-methylstyrene **4** which, when subjected to the Sharpless aminohydroxylation using t-butyl carbamate as a nitrogen source, furnished the desired amino alcohol **5** in 62% yield, with enantioselectivity greater than 99%. The enantiomeric purity was determined by Mosher ester analysis[9] of chromatographically pure **5**. Hydrogenolysis under standard conditions gave the desired F-ring phenol **6** in 80% yield.



Scheme 1. (a) Ph_3PCH_3Br, n-BuLi, -40 °C, 93% (b) *t*-butyl carbamate, *t*-BuOCl, NaOH, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, n-PrOH/H_2O, 10 °C, 62%, >99% ee; (c) H_2 (1atm), 10% Pd/C, CH_3OH, 80%.

The desired G-ring amino alcohol **8** was synthesized in 63% yield with an enantiomeric purity of 93%, by reacting 3-chloro-4-methoxystyrene **7**[10] with *t*-butyl carbamate under standard Sharpless aminohydroxylation reaction conditions (Scheme 2). The primary alcohol in **7** was protected as a 2-methoxyethoxymethyl (MEM) ether **9** (96%). Treatment of **9** with TFA/CH_2Cl_2 (1:1) at 0 °C removed the Boc group selectively and subsequent reaction with 2-trimethylsilylethyl-*p*-nitrophenylcarbonate in the presence of triethylamine installed the required amino-protecting group (NHTeoc), orthogonal to the F-ring Boc group, in 88% yield over two steps. It may be noted that direct introduction of NHTeoc group during the aminohydroxylation step was not successful. Refluxing **10** with $[CpRu(CH_3CN)_3]PF_6$ in 1,2-dichloroethane gave the G-ring ruthenium complex **11** in quantitative yield as a mixture of two diastereomers. The formation of diastereomers is due to introduction of ruthenium on either face of the planar asymmetric molecule and is unimportant because the metal will be removed at a later stage.

As shown in Scheme 3, the F-O-G diaryl ether linkage was installed by the ruthenium-promoted intermolecular S_NAr reaction between the F-ring phenol **6** and G-ring ruthenium complex **11** in the presence of cesium carbonate as base and in DMF solvent. Subsequent photolysis gave the desired F-O-G ether **12** in 33% yield over two steps. Other bases such as sodium hydride and sodium-2,6-di-*t*-butylphenoxide were also examined but gave similar yields. Further optimization of this reaction is currently being pursued in our laboratory. The phenolic group on the F-ring in **12** was methylated (CH_3I, n-Bu_4NI, Cs_2CO_3/DMF, 83%) and the resulting alcohol **13** was oxidized in two steps (Dess-Martin oxidation followed by treatment with $NaClO_2/NaH_2PO_4$, 51%) to give the F-O-G acid **2** as a mixture of diastereomers (>2:1), probably epimeric at the α C-H of the F-ring residue. The epimerization likely occurs at the intermediate aldehyde stage (by nmr), and optimization of this oxidation step is currently in progress.



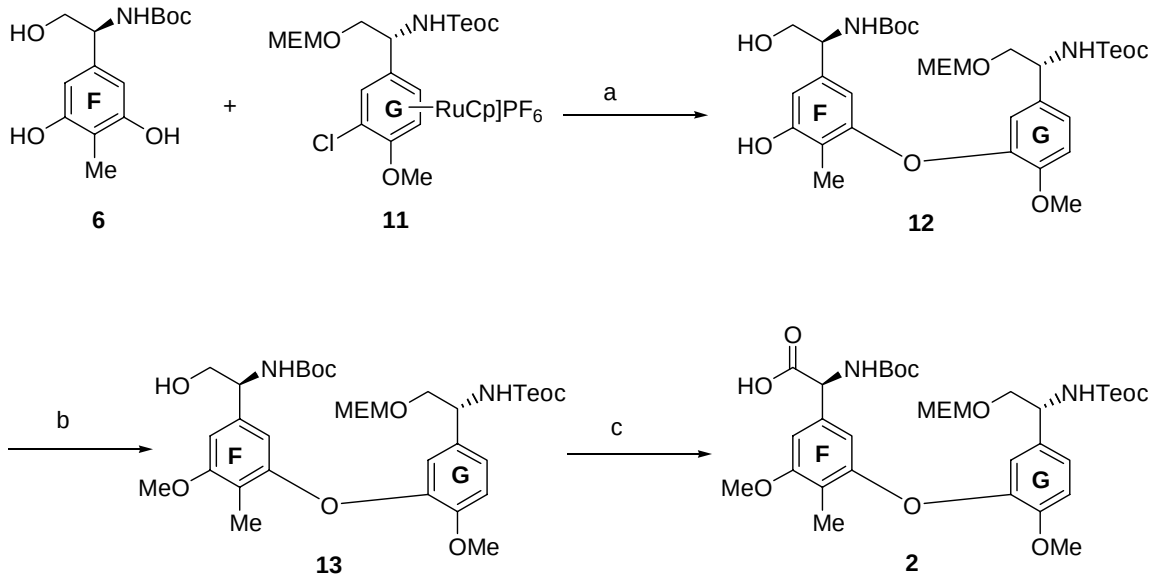
Scheme 2. (a) *t*-butyl carbamate, *t*-BuOCl, NaOH, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, n-PrOH/H_2O, 10 °C, 63%, 93% ee; (b) MEM-Cl, *i*-Pr_2NEt, CH_2Cl_2, RT, 96%; (c) TFA/ CH_2Cl_2, 0 °C, then Et_3N, THF, 2-trimethylsilylethyl-*p*-nitrophenylcarbonate, 88%; (d) $[CpRu(CH_3CN)_3]PF_6$, 1,2-dichloroethane, reflux, quantitative.

Conclusions

The ruthenium-mediated intermolecular S_NAr reaction was effectively utilized to synthesize an important building block corresponding to the F-O-G ring system. Future studies involve coupling of the fully functionalized ABCD ring system of ristocetin A with the F-O-G acid 2 and subsequent coupling with the E-ring amino acid, followed by further manipulation to complete the total synthesis of ristocetin A.

Experimental Section

General Procedures. Analytical TLC was performed with aluminium plates precoated with silica gel F_{254} (EMerck) and visualized by UV light and/or phosphomolybdic acid or Verghn′s reagent. Flash chromatography was carried out on silica gel (170-400 μ). Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini XL200 (200 MHz, ^1H frequency), Varian Gemini XL300 (300 MHz, ^1H frequency), or Varian INOVA 600 (600 MHz, ^1H frequency) spectrometer at 25 °C, using $CDCl_3$ or acetone-d_6 or CD_3CN and referenced to the solvent. Infrared spectra were recorded on a Nicolet Impact 400 FTIR spectrometer. Mass spectra were recorded on a Kratos MS25A instrument.



Scheme 3. (a) Cs_2CO_3, DMF, then hν, CH_3CN, 33%; (b) CH_3I, Cs_2CO_3, DMF, 83%; (c) Dess-Martin reagent, CH_2Cl_2, then $NaClO_2$, NaH_2PO_4, t-BuOH, 2-methyl-2-butene, 51%.

3,5-Bis(benzyloxy)-4-methylstyrene (4). To a suspension of methyltriphenylphosphonium bromide (32.7 g, 91.5 mmol) in THF (180 mL) at –40 °C was added *n*-BuLi (2.5 M in hexane, 36 mL, 90 mmol) over 20 minutes. The reaction mixture was then warmed to –10 °C and stirred at –10 °C for 45 minutes. The reaction mixture was then cooled to –30 °C and to it was added a solution of 3,5-bis(benzyloxy)-4-methylbenzaldehyde[8] **3** (10.1 g, 30.5 mmol) in THF (60 mL) over 20 minutes. The reaction mixture was warmed to room temperature and stirred for 3 h before quenching with H_2O (120 mL). The lower aqueous layer was extracted with EtOAc (4 x 60 mL). The combined organic extracts were washed with H_2O (60 mL), aqueous saturated sodium chloride solution (60 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The product was purified by flash chromatography (1:9 EtOAc: hexanes) to give 9.42 g of pure styrene **4** (93%) as a white solid. mp 52-54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45-7.31 (10H), 6.70 (2H, s), 6.66 (1H, dd, *J* = 17.7, 10.8 Hz), 5.68 (1H, d, *J* = 17.7 Hz), 5.21 (1H, d, *J* = 10.8 Hz), 5.11 (4H, s), 2.23 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 137.5, 137.3, 136.1, 128.6, 127.9, 127.3, 115.8, 113.2, 103.5, 70.4, 8.9; HRMS-EI (*m/z*) M^+ calcd for $C_{23}H_{22}O_2$, 330.1620; found, 330.1614.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3,5-dibenzyloxy-4-methylphenyl)-2-hydroxyethylaminutese (5). To a solution of *t*-butyl carbamate (0.61 g, 5.2 mmol) in 1-propanol (6.7 mL) was added a solution of NaOH (0.2 g, 5 mmol) in H_2O (12.5 mL), followed by *t*-butyl hypochlorite (0.6 mL, 5 mmol). After stirring for 5 minutes at room temperature, the solution was cooled to 10 °C and after 5 minutes at 10 °C, a solution of $(DHQD)_2PHAL$ (0.08 g, 0.1 mmol) in 1-propanol (6.7 mL) was added. Then a solution of **4** (0.55 g, 1.7 mmol) in 1-propanol (15 mL) was added, followed by $K_2OsO_2(OH)_4$ (0.027 g, 0.07 mmol). The reaction mixture was stirred at 10 °C for

4 h and then quenched by adding aqueous saturated sodium sulfite solution (17 mL). The mixture was extracted with EtOAc (3 x 35 mL). The combined organic extracts were washed with H_2O (35 mL), aqueous saturated sodium chloride solution (35 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (4:6 EtOAc:hexanes) afforded 0.5 g of the amino alcohol **5** as a white solid (62%, 99% ee), mp 151-153 °C; $[\alpha]^{25}_D$ + 40.9 (*c* 1.1, 95% EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46-7.31 (10H), 6.54 (2H, s), 5.13 (1H, brs), 5.08 (4H, s), 4.69 (1H, s), 3.79 (2H, d, *J* = 4.7 Hz), 2.20 (3H, s), 1.92 (1H, brs), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.0, 156.3, 138.1, 137.5, 128.7, 128.1, 127.5, 115.5, 103.9, 80.2, 70.6, 67.2, 57.4, 28.6, 8.9; IR ν (nujol) 3604, 1681, 1592 cm^{-1}; FABHRMS $[M+Na]^+$ calcd for $C_{28}H_{33}NO_5Na$, 486.2256; found, 486.2244.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3,5-dihydroxy-4-methylphenyl)-2-hydroxyethylamine (6). To a solution of **5** (0.3 g, 0.65 mmol) in CH_3OH (16.5 mL) was added 10% Pd/C (0.03 g) and the mixture was hydrogenated under 1 atm of H_2 at 38 °C for 8 h. The mixture was filtered through a bed of Celite and washed with CH_3OH (125 mL). The combined filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (1:1 to 3:1 EtOAc/hexanes, gradient elution) to give 0.145 g (80%) of **5** as a white solid, mp = 65-68 °C; $[\alpha]^{25}_D$ + 31.2 (*c* 0.85, $CHCl_3$); ^{1}H NMR (acetone-d_6, 200 MHz) δ 7.99 (2H, s), 6.38 (2H, s), 6.09 (1H, brs), 4.52-4.48 (1H, m), 3.82 (1H, dd), 3.69-3.62 (2H, m), 2.10 (3H, s), 1.39 (9H, s); ^{13}C NMR (acetone-d_6, 50 MHz) δ 156.9, 156.2, 140.7, 110.0, 105.9, 78.7, 66.5, 57.7, 8.4; IR ν (nujol) 3496, 3268, 1699 cm^{-1}; HRMS-EI M^+ calcd for $C_{14}H_{21}NO_5$, 283.1419; found 283.1410.

(*R*)-*N*-(*tert*-Butyloxycarbonyl)-1-(3-chloro-4-methoxyphenyl)-2-hydroxyethylamine (8). To a solution of *t*-butyl carbamate (3.08 g, 26.3 mmol) in 1-propanol (34 mL) was added a solution of NaOH (1.04 g, 25.9 mmol) in H_2O (65 mL), followed by *t*-butyl hypochlorite (3 mL, 25.9 mmol). After stirring for 5 minutes at room temperature, the solution was cooled to 10 °C and after 5 minutes at 10 °C, a solution of $(DHQD)_2PHAL$ (0.4 g, 0.51 mmol) in 1-propanol (34 mL) was added. Then a solution of 3-chloro-4-methoxystyrene **7**[10] (1.43 g, 8.5 mmol) in 1-propanol (65 mL) was added, followed by $K_2OsO_2(OH)_4$ (0.125 g, 0.34 mmol). The reaction mixture was stirred at 10 °C for 2 h and then quenched by adding aqueous saturated sodium sulfite solution (70 mL). The mixture was extracted with EtOAc (3 x 85 mL). The combined organic extracts were washed with H_2O (85 mL), aqueous saturated sodium chloride solution (85 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (4:6 EtOAc:hexanes) afforded 1.62 g of the amino alcohol **8** as a white solid (63%, 93% ee), mp = 107-108 °C; $[\alpha]^{25}_D$ -45.3 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30 (1H, d, *J* = 2.2 Hz), 7.15 (1H, dd, *J* = 8.4, 2.2 Hz), 6.88 (1H, d, *J* = 8.5 Hz), 5.35 (1H, brs), 4.64 (1H, brs), 3.86 (3H, s), 3.77-3.72 (2H, m), 2.72 (1H, brs), 1.40 (9H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.0, 154.3, 133.0, 128.3, 126.0, 122.5, 112.1, 80.1, 66.2, 56.1, 28.3; IR ν (nujol) 3412, 1681 cm^{-1}; HRMS calcd for $C_{14}H_{20}ClNO_4$ 301.1080, found, 301.1085.

(2*R*)-2-[(1,1-dimethylethoxy)carbonyl]amino-2-(3-chloro-4-methoxy) phenylethylmethoxymethylether (9). To a solution of **8** (0.63 g, 2.1 mmol) in CH_2Cl_2 (7.5 mL) at 0 °C was added *N*-*N*-diisopropylethylamine (1.1 mL, 6.3 mmol), followed by MEM-Cl (0.72 mL, 6.3 mmol). After

15 minutes, the cooling bath was removed and the reaction mixture was stirred at room temperature for 20 h. Then the reaction mixture was poured into aqueous saturated $NaHCO_3$ solution (7 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with aqueous saturated sodium chloride solution (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (1:1 EtOAc:hexanes) to afford 0.79 g (96%) of **9** as a colorless liquid. $[\alpha]^{25}_D$ –40.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34 (1H, d, *J* = 2.1 Hz), 7.18 (1H, dd, *J* = 8.5, 2.3 Hz), 6.88 (1H, d, *J* = 8.4 Hz), 5.43-5.38 (1H, brd), 4.76-4.72 (1H, brdd), 4.68 (2H, s), 3.88 (3H, s), 3.74 (2H, d, *J* = 4.7), 3.64-3.60 (2H, m), 3.53-3.48 (2H, m), 3.39 (3H, s), 1.40 (9H, s); ^{13}C NMR ($CDCl_3$) δ 155.2, 154.0, 133.6, 128.2, 125.9, 122.1, 111.7, 95.2, 79.4, 71.5, 70.4, 66.9, 58.8, 56.0, 53.4, 28.4; IR ν (neat) 3352, 1711 cm^{-1}; HRMS calcd for $C_{18}H_{28}ClNO_6$ 389.1605, found, 389.1603.

(2*R*)-2-[(1-trimethylsilylethoxy)carbonyl]amino-2-(3-chloro-4-methoxy) phenylethylmethoxy-methylether (10). To a solution of **9** (0.79 g, 2.6 mmol) in CH_2Cl_2 (10.5 mL) at 0 °C was added trifluoroacetic acid (10.5 mL) over 3 minutes. The reaction mixture was stirred at 0 °C for 40 minutes, diluted with EtOAc (130 mL) and then neutralized by adding aqueous saturated $NaHCO_3$ solution (130 mL). The two layers were separated and the lower aqueous layer was extracted with EtOAc (2 x 130 mL). The combined EtOAc layers were dried ($MgSO_4$) and concentrated *in vacuo* to get a yellow semisolid, which was dissolved in THF (7.8 mL). To this solution were added in succession triethylamine (1.1 mL, 7.8 mmol) and 2-trimethylsilylethyl-*p*-nitrophenylcarbonate (2.27 g, 7.8 mmol). The reaction mixture was stirred at room temperature for 3 days, then diluted with H_2O (70 mL) and extracted with Et_2O (2 x 140 mL). The combined Et_2O extracts were washed with aqueous NaOH solution (5% w/v, 140 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (30-50% EtOAc in hexanes, gradient elution) to yield 0.77 g (88%) of **10** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (1H, d, *J* = 2.2 Hz), 7.19 (1H, dd, *J* = 8.5, 2.2 Hz), 6.88 (1H, d, *J* = 8.4 Hz), 5.60 (1H, brd), 4.77 (1H, m), 4.68 (1H, s), 4.18-4.10 (2H, m), 3.88 (3H, s), 3.77 (2H, d, *J* = 5.1 Hz), 3.66-3.61 (2H, m), 3.54-3.49 (2H,m), 3.40 (3H, s), 1.01-0.92 (2H, m), 0.00 (9H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.3, 154.3, 133.6, 128.5, 126.2, 122.5, 112.0, 95.4, 71.8, 70.5, 67.2, 63.3, 59.1, 56.2, 54.0, 17.8, -1.4; IR ν 3340, 1724 cm^{-1}; FABHRMS $[M+Na]^+$ calcd for $C_{19}H_{32}ClNO_6Na$, 456.1585, found, 456.1580.

Compound 11. A solution of **10** (0.437 g, 1mmol) and $[CpRu(CH_3CN)_3]PF_6$ (0.57 g, 1.31 mmol) in 1,2-dichloroethane (52 mL) was purged with dry and oxygen-free argon for 30 minutes and then refluxed for 2 h. It was cooled to room temperature, filtered through a bed of Celite and concentrated *in vacuo* to give 0.750 g of the G-ring ruthenium complex **11** in quantitative yield as a mixture of diastereomers. ^{1}H NMR (CD_3CN, 200 MHz) δ 6.69 (1H, d, *J* = 1.3 Hz), 6.33 (1H, d, *J* = 6.4 Hz), 6.12 (1H, dd, *J* = 6.4, 1.2 Hz), 5.35 (5H, s), 4.74-4.68 (1H, m), 4.64 (2H, s), 4.23-4.13 (2H, m), 3.91 (3H, s), 3.77-3.73 (2H, m), 3.59-3.54 (2H, m), 3.48-3.43 (2H, m), 3.30 (3H, s), 1.06-0.95 (2H, m), 0.05 (9H, s); ^{13}C NMR (CD_3CN, 50 MHz) δ 157.1, 132.8, 103.9, 103.8, 96.9, 96.4, 96.3, 87.1, 85.8, 83.9, 83.5, 82.4, 72.4, 71.5, 71.3, 71.2, 68.1,

68.0, 64.3, 59.1, 59.0, 52.9, 18.4, -1.4; FABHRMS [M – PF_6] calcd for $C_{24}H_{37}ClNO_6RuSi$, 600.1122, found, 600.1102.

Compound 12. To a solution of **6** (0.02 g, 0.07 mmol) and **11** (0.053 g, 0.07 mmol) in anhydrous DMF (1.4 mL) was added Cs_2CO_3 (0.116 g, 0.355 mmol). The reaction mixture was stirred for 14 h and then acidified with 1M $NaHSO_4$ (7.1 mL). The mixture was then extracted with CH_2Cl_2 (20 mL). The organic layer was washed with H_2O (2 x 10 mL), aqueous saturated sodium chloride solution (2 x 10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in CH_3CN (20 mL), purged with Ar for 30 min at room temperature and photolyzed with 350 nm UV light for 60 h using a Rayonet photoreactor. The solution was concentrated *in vacuo* and the residue was purified by flash chromatography (SiO_2, 3:1 EtOAc:hexanes) to provide 0.016 g (33%) of pure **12**. $[\alpha]^{25}_D$ + 4.75 (*c* 0.8, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.29 (1H, s), 7.12 (1H, brdd, *J* = 8.4, 2.4 Hz), 7.06 (1H, d, *J* = 8.4 Hz), 6.99 (1H, s), 6.62 (1H, s), 6.54 (1H, br), 6.26 (1H, s), 6.12 (1H, br), 4.79 (1H, brd), 4.62 (2H, ABq), 4.49 (1H, br), 4.07 (2H, m), 3.80 (3H, s), 3.71-3.69 (2H, m), 3.62-3.56 (4H, overlapping m), 3.45 (2H, t, *J* = 4.8 Hz), 3.27 (3H, s), 2.10 (3H, s), 1.35 (9H, s), 0.94 (2H, t, *J* = 8.4 Hz), 0.023 (9H, s); ^{13}C NMR (acetone-d_6, 50 MHz) δ 157.4, 157.1, 156.9, 156.3, 151.2, 146.6, 141.2, 135.0, 123.3, 119.5, 114.0, 109.2, 107.7, 96.1, 78.8, 72.6, 71.5, 67.7, 66.5, 62.9, 60.6, 58.9, 57.8, 56.5, 55.5, 18.5, 14.6, 9.0, -1.3; IR ν 3516, 3455, 1694 cm^{-1}; FABHRMS $[M+Na]^+$ calcd for $C_{33}H_{52}N_2O_{11}SiNa$, 703.3238, found, 703.3230.

Compound 13. To a mixture of **12** (17.7 mg, 26 μmol), Cs_2CO_3 (9.3 mg, 28.6 μmol), tetrabutylammonium iodide (2 mg, 5.2 μmol) in dry DMF (0.1 mL) at 0 °C was added CH_3I (2μL, 32.1 μmol). The reaction mixture was then stirred at room temperature for 24 h. Water (4 mL) was added and the reaction mixture was extracted with EtOAc (2 x 4mL). The combined organic extracts were washed with aqueous saturated sodium chloride solution (4mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 to 75:25 EtOAc:Hexanes gradient elution) to afford 15 mg (83%) of pure product as a film. $[\alpha]^{25}_D$ +7.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.13 (1H, dd, *J* = 8.4, 2.4 Hz), 7.07 (1H, d, *J* = 8.4 Hz), 6.94 (1H, s), 6.76 (1H, s), 6.57 (1H, brs), 6.36 (1H, s), 6.24 (1H, brs), 4.79-4.78 (1H, m), 4.62 (2H, ABq), 4.57 (1H, m), 4.08 (2H, m), 3.86 (3H, s), 3.79 (3H, s), 3.71-3.69 (2H, m), 3.65-3.64 (2H, m), 3.57-3.56 (2H, overlapping d), 3.45-3.44 (2H, overlapping dd), 3.27 (3H, s), 2.1 (3H, s), 1.36 (9H, s), 0.96-0.93 (2H, t), -0.023 (9H, s); ^{13}C NMR (acetone-d_6, 50 MHz) δ 159.5, 156.8, 156.2, 151.1, 146.4, 141.4, 134.9, 123.4, 119.5, 115.3, 113.9, 108.8, 104.7, 95.9, 78.8, 72.5, 71.3, 67.6, 66.6, 62.9, 58.8, 58.1, 56.4, 56.1, 55.3, 18.4, 8.9, -1.4; IR ν 3430-3371, 1701 cm^{-1}; FABHRMS $[M+H]^+$, calcd for $C_{34}H_{55}N_2O_{11}Si$, 695.3575, found 695.3577.

Compound 2. To a solution of **13** (54 mg, 0.078 mmol) in CH_2Cl_2 (0.78 mL) at 0 °C was added Dess-Martin periodinane (68 mg, 0.16 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed with aqueous saturated $Na_2S_2O_3$ (34 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with aqueous saturated sodium chloride solution

(40 mL), dried ($MgSO_4$) and concentrated *in vacuo* to provide 54 mg of crude aldehyde which was used without purification for the next reaction.

To a solution of above aldehyde in *t*-BuOH (2.4 mL) and 2-methyl-2-butene (0.54 mL) was added a buffered solution of $NaClO_2$ (88 mg, 80%, 0.78 mmol) and $NaH_2PO_4.H_2O$ (80 mg, 0.58 mmol) in 0.72 mL of H_2O and the reaction mixture was stirred at room temperature for 2 h. The volatiles were removed *in vacuo*, H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with saturated sodium chloride solution (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, EtOAc:hexanes 3:1 to EtOAc:MeOH 9:1, gradient elution) to provide 28 mg (51%) of the F-O-G acid **2** as a mixture of diastereomers (>2:1); ^{1}H NMR (acetone-d_6, 600 MHz) δ 7.15 (1H, d, *J* = 6 Hz), 7.12 (1H, d, *J* = 7.8 Hz), 6.98-6.96 (1H, overlapping d), 6.86, 6.84 (1H, s), 6.49, 6.46 (1H, s), 6.24 (1H, brs), 5.09 (1H, s), 4.79 (1H, br), 4.64 (2H, ABq), 4.1-4.08 (2H, brt, *J* = 7.8 Hz), 3.87, 3.84 (3H, s), 3.78, 3.77 (3H, s), 3.70-3.69 (2H, m), 3.59-3.57 (2H, m), 3.47-3.44 (2H, m), 3.28, 3.27 (3H, s), 2.13, 2.12 (3H, s), 1.38, 1.34 (9H, s), 0.96-0.93, 0.91-0.88 (2H, m), 0.026, 0.024 (9H, s); IR ν (film) 1714 cm^{-1}; FABHRMS $[M+K]^+$ calcd for $C_{34}H_{52}N_2O_{12}SiK$, 747.2927, found, 747.2917.

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10. Synthesized from commercially available methyl-3-chloro-4-methoxybenzoate in 3 steps: i) $LiAlH_4$, THF, 98%, ii) PCC/CH_2Cl_2, 75%, iii) Ph_3PCH_3Br, *n*-BuLi, -78 °C, THF, 94%.