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

Anthony J. Pearson,* Avdhoot D. Velankar, and Jung-Nyoung Heo

Department of Chemistry, Case Western Reserve University, Cleveland, OH 44106, USA
E-mail: ajp4@po.cwru.edu

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 \textit{Staphylococcus aureus} infections. However, with rapidly emerging bacterial resistance to these antibiotics, there is a desperate need for stronger antibiotics. Total syntheses of vancomycin and teicoplanin aglycones have already been reported. Ristocetin A, 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. Studies in our group have focused on the application of a ruthenium-promoted S_NAr reaction to the construction of the diaryl ethers. 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.
We have previously reported synthetic studies toward the BCDF\(^6\) and DEF\(^7\) ring systems of ristocetin A, that employ the ruthenium-promoted S\(_{\text{N}}\)Ar 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.

**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.
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 with -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/CH2Cl2 (1:1) at 0 °C removed the Boc group selectively and subsequent reaction with 2-trimethylsilyl-ethyl-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(CH3CN)3]PF6 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 (CH3I, n-Bu4NI, Cs2CO3/DMF, 83%) and the resulting alcohol 13 was oxidized in two steps (Dess-Martin oxidation followed by treatment with NaClO2/NaH2PO4, 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)\(_2\)PHAL, \(K_2\)OsO\(_4\)(OH)\(_2\), n-PrOH/H\(_2\)O, 10 °C, 63%, 93% ee; (b) MEM-Cl, \(i\)-Pr\(_2\)NEt, CH\(_2\)Cl\(_2\), RT, 96%; (c) TFA/ CH\(_2\)Cl\(_2\), 0 °C, then Et\(_3\)N, THF, 2-trimethylsilyl ethyl-\(p\)-nitrophenyl carbonate, 88%; (d) [CpRu(CH\(_3\)CN)\(_3\)]PF\(_6\), 1,2-dichloroethane, reflux, quantitative.

Conclusions

The ruthenium-mediated intermolecular S\(_{\text{N}}\)Ar 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, \(^1\)H frequency), Varian Gemini XL300 (300 MHz, \(^1\)H frequency), or Varian INOVA 600 (600 MHz, \(^1\)H frequency) spectrometer at 25 °C, using CDCl\(_3\) or acetone-\(d_6\) or CD\(_3\)CN 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) Cs₂CO₃, DMF, then hv, CH₃CN, 33%; (b) CH₃I, Cs₂CO₃, DMF, 83%; (c) Dess-Martin reagent, CH₂Cl₂, then NaClO₂, NaH₂PO₄, 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 (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 H₂O (120 mL). The lower aqueous layer was extracted with EtOAc (4 x 60 mL). The combined organic extracts were washed with H₂O (60 mL), aqueous saturated sodium chloride solution (60 mL), dried (Na₂SO₄) and concentrated in vacuo. The product was purified by flash chromatography (1:9 EtOAc:hexanes) to give 9.42 g of pure styrene (93%) as a white solid. mp 52-54 °C; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₃H₂₂O₂, 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 H₂O (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 K₂OsO₂(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 H2O (35 mL), aqueous saturated sodium chloride solution (35 mL), dried (MgSO4) 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; [α]25D + 40.9 (c 1.1, 95% EtOH); 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 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 C28H33NO5Na, 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 CH3OH (16.5 mL) was added 10% Pd/C (0.03 g) and the mixture was hydrogenated under 1 atm of H2 at 38 °C for 8 h. The mixture was filtered through a bed of Celite and washed with CH3OH (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; [α]25D + 31.2 (c 0.85, CHCl3); 1H NMR (acetone-d6, 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); 13C NMR (acetone-d6, 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 C14H21NO5, 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 H2O (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 (1.43 g, 8.5 mmol) in 1-propanol (65 mL) was added, followed by K2OsO2(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 H2O (85 mL), aqueous saturated sodium chloride solution (85 mL), dried (MgSO4) 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; [α]25D-45.3 (c 0.53, CHCl3); 1H NMR (CDCl3, 200 MHz) δ 7.30 (1H, d, J = 2.2 Hz), 6.88 (1H, d, 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); 13C NMR (CDCl3, 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 C14H20ClNO4 301.1080, found, 301.1085.

(2R)-2-[1,1-dimethylethoxy)carbonyl]amino-2-(3-chloro-4-methoxy) phenoylethoxymethylether (9). To a solution of 8 (0.63 g, 2.1 mmol) in CH2Cl2 (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$_2$SO$_4$) 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$_3$); 1H NMR (CDCl$_3$, 200 MHz) $\delta$ 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); 13C NMR (CDCl$_3$) $\delta$ 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 $\nu$ (neat) 3352, 1711 cm$^{-1}$; HRMS calcd for C$_{18}$H$_{28}$ClNO$_6$ 389.1605, found, 389.1603.

(2R)-2-[(1-trimethylsilylethoxy)carbonyl]amino-2-(3-chloro-4-methoxy) phenylethylmethylether (10). To a solution of 9 (0.79 g, 2.6 mmol) in CH$_2$Cl$_2$ (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$_2$O (70 mL) and extracted with Et$_2$O (2 x 140 mL). The combined Et$_2$O 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. 1H NMR (CDCl$_3$, 200 MHz) $\delta$ 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); 13C NMR (CDCl$_3$, 50 MHz) $\delta$ 156.3, 154.3, 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, 63.3, 59.1, 56.2, 54.0, 17.8, -1.4; IR ν (neat) 3340, 1724 cm$^{-1}$; FABHRMS [M+Na]$^+$ calcd for C$_{19}$H$_{32}$ClNO$_6$Na, 456.1585, found, 456.1580.

Compound 11. A solution of 10 (0.437 g, 1mmol) and [CpRu(CH$_3$CN)$_3$]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. 1H NMR (CD$_3$CN, 200 MHz) $\delta$ 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); 13C NMR (CD$_3$CN, 50 MHz) $\delta$ 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,
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 Cs₂CO₃ (0.116 g, 0.355 mmol). The reaction mixture was stirred for 14 h and then acidified with 1M NaHSO₄ (7.1 mL). The mixture was then extracted with CH₂Cl₂ (20 mL). The organic layer was washed with H₂O (2 x 10 mL), aqueous saturated sodium chloride solution (2 x 10 mL), dried (MgSO₄) and concentrated in vacuo. The residue was dissolved in CH₃CN (20 mL), purged with Ar for 30 min at room temperature and photolyzed with 350 nm UV light using a Rayonet photoreactor. The solution was concentrated in vacuo and the residue was purified by flash chromatography (SiO₂, 3:1 EtOAc:hexanes) to provide 0.016 g (33%) of pure 12. [α]²⁵/D +4.75 (c 0.8, CHCl₃); ¹H NMR (acetone-d₆, 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), 3.10 (3H, s), 1.35 (9H, s), 0.94 (2H, t, J = 8.4 Hz), 0.023 (9H, s); ¹³C NMR (acetone-d₆, 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 C₃₃H₅₂N₂O₁₁SiNa, 703.3238, found, 703.3230.

Compound 13. To a mixture of 12 (17.7 mg, 26 µmol), Cs₂CO₃ (9.3 mg, 28.6 µmol), tetrabutylammonium iodide (2 mg, 5.2 µmol) in dry DMF (0.1 mL) at 0 °C was added CH₃I (2 µL, 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 (MgSO₄) 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. [α]²⁵/D +7.2 (c 0.5, CHCl₃); ¹H NMR (acetone-d₆, 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); ¹³C NMR (acetone-d₆, 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 C₃₃H₅₅N₂O₁₁Si, 695.3575, found 695.3577.

Compound 2. To a solution of 13 (54 mg, 0.078 mmol) in CH₂Cl₂ (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 Na₂S₂O₃ (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 (MgSO₄) 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 NaClO₂ (88 mg, 80%, 0.78 mmol) and NaH₂PO₄·H₂O (80 mg, 0.58 mmol) in 0.72 mL of H₂O and the reaction mixture was stirred at room temperature for 2 h. The volatiles were removed in vacuo, H₂O (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 (MgSO₄) and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 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); ¹H NMR (acetone-d₆, 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 C₃₄H₅₂N₂O₁₂SiK, 747.2927, found, 747.2917.

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References


10. Synthesized from commercially available methyl-3-chloro-4-methoxybenzoate in 3 steps: i) LiAlH₄, THF, 98%, ii) PCC/CH₂Cl₂, 75%, iii) Ph₃PCH₂Br, n-BuLi, -78 °C, THF, 94%.