Supplementary Information

An ortho-quinone methide based strategy towards the rubromycin spiroketal family

Nicky J. Willis\textsuperscript{a} and Christopher D. Bray\textsuperscript{a,*}

\textsuperscript{a} Department of Chemistry, Queen Mary University of London, Mile End Road, London, E1 4NS.

e-mail: \texttt{c.bray@qmul.ac.uk}

Table of Contents:

General Details.................................................................................................................................................. S2
Experimental procedures and spectral data................................................................................................. S3-9
NMR Spectra...................................................................................................................................................... S10-23
X-ray data......................................................................................................................................................... S24
General Details

Unless otherwise stated, commercially available reagents were used as supplied. All reactions requiring anhydrous conditions were conducted in flame-dried apparatus under an inert atmosphere of nitrogen or argon. Microwave heating was conducted in 10 mL thick walled microwave vials fitted with crimp top Teflon seals (CEM). Analytical thin-layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Standard flash chromatography procedures were performed using Kieselgel 60 (40-63 μm) or with a Varian Superflash automated purification system. Petroleum refers to the fraction boiling between 40-60 °C. Infrared spectra were recorded in the range 4000-600 cm\(^{-1}\), using a Bruker Tensor 37 FTIR machine equipped with a PIKE MIRacle ATR accessory. IR signals are reported in wavenumbers (cm\(^{-1}\)) and signal intensity is subjectively denoted br = broad, brs = broad (strong), brm = broad (medium) s = strong, m = medium and w = weak. Both \(^1\)H and \(^{13}\)C NMR spectra were recorded using either a Bruker AV400 NMR or AV600 spectrometer. Chemical shifts \(\delta\) are reported in ppm (relative to \(\delta\)\textsubscript{H} CHCl\(_3\) (7.27) and \(\delta\)\textsubscript{C} CDCl\(_3\) (77.0) unless otherwise stated) and multiplicity of signals denoted: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet respectively with coupling constants \(J\) reported in hertz (Hz). Structural interpretations and assignments were made based upon COSY, HMQC, HMBC, DEPT 135, DEPT 90 and NOESY experiments. High resolution mass spectra (HRMS) were obtained by the EPSRC National Mass Service (Swansea) using a double focussing mass spectrometer (Finnigan MAT 95 XP).
Experimental procedures and spectral data

4-(\textit{tert}-Butyldimethylsilyl)oxy)-3-methoxybenzaldehyde (11).\(^1\) Et\(_3\)N (70 mL, 502 mmol, 1.5 equiv.) was added at 20 °C to a mixture of vanillin (50.0 g, 329 mmol, 1.0 equiv.), TBSCI (54.4 g, 361 mmol, 1.1 equiv.) and DMAP (0.1 g, 0.8 mmol, 0.25 mol%) in CH\(_2\)Cl\(_2\) (750 mL). After stirring at r.t. for 24 h, the organic layer was washed with sat. aq. NH\(_4\)Cl solution (2 × 500 mL). The separated organic layer was dried over MgSO\(_4\), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (25% EtOAc in petrol) afforded the aldehyde 11 as pale yellow oil (84.3 g, 96%); \(R_f = 0.65\) (25% EtOAc in petrol); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2958w and 2930w (C-H), 2857w (OCH\(_3\)), 1696s (C=O, aldehyde), 1593m (C=C), 1284m (SiMe\(_2\)), 1033m (Si-O), and 838m (SiMe\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 9.85\) (s, 1H, CHO), 7.40 (d, \(J = 8.0\) Hz, 1H, ArCH), 7.36 (dd, \(J = 8.0\), 1.8 Hz, 1H, ArCH), 6.96 (d, \(J = 8.0\) Hz, 1H, ArCH), 6.83 (d, \(J = 8.1\) Hz, 1H, ArCH), 5.44 (s, 1H, CHO), 3.87 (s, 3H, OMe), 3.82 (s, 3H, ArOMe), 2.08 (2H, 2 × OCH\(_3\),H\(_3\)), 3.96-3.86 (m, 2H, 2 × OCH\(_3\),H\(_3\)), 3.82 (s, 3H, ArOMe), 2.08-2.22 (m, 1H, OCH\(_2\)CH\(_2\)H\(_3\)), 1.39 (m, 1H, OCH\(_2\)CH\(_2\)H\(_3\)), 0.99 (s, 9H, SiMe\(_2\)Bu); \(^1\)C NMR (100 MHz) \(\delta = 191.1\) (CHO), 151.8 (CO), 151.5 (COMe), 151.5 (COTBS), 126.3 (ArCH), 120.9 (ArCH), 110.3 (ArCH), 55.6 (OMe), 25.7 (SiC(CH\(_3\)_3)), 18.7 (SiC(CH\(_3\)_3)), –4.4 (SiMe\(_2\)); HRMS (CI) calcd for [C\(_{14}\)H\(_{23}\)O\(_3\)Si]^+ 267.1412; found 267.1411 [M+H]^+; these spectroscopic data are in agreement with those previously reported.\(^1\)

(4-(1,3-Dioxan-2-yl)-2-methoxyphenoxy)\textit{tert}-butyldimethylsilane (12).\(^1\) To a solution of aldehyde 11 (80.0 g, 246 mmol) in CH\(_2\)Cl\(_2\) (210 mL) was added 1,3-propanediol (82 mL, 1.14 mol, 4.6 equiv.), HC(O)Me\(_3\) (49 mL, 477 mmol, 1.9 equiv.) and n-Bu\(_4\)NB\(_3\) (7.6 g, 24.2 mmol, 1.0 equiv.) was added and the resultant mixture was stirred at 20 °C for 60 h. Sat. aq. Na\(_2\)CO\(_3\) solution (250 mL) and H\(_2\)O (250 mL) were added and the layers were separated. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (200 mL) and the combined organic were dried over MgSO\(_4\) and filtered before concentrating under reduced pressure. The residue was purified by flash chromatography (5% EtOAc in n-hexane) furnishing acetal 12\(^1\) as colourless oil (71.7 g, 22.1 mmol, 90%); \(R_f = 0.64\) (5% EtOAc in n-hexane); \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2955w and 2929w (CH), 2855w (OCH\(_3\)), 1696s (C=O, aldehyde), 1593m (C=C), 1284m (SiMe\(_2\)), 1123m (SiO) and 838m (SiMe\(_2\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.03\) (d, \(J = 1.7\) Hz, 1H, ArCH), 6.93 (dd, \(J = 8.2\), 1.7 Hz, 1H, ArCH), 6.83 (d, \(J = 8.1\) Hz, 1H, ArCH), 5.44 (s, 1H, HCO\(_2\)), 4.23 (dd, \(J = 11.2\), 5.0 Hz, 2H, 2 × OCH\(_3\),H\(_3\)), 3.96-3.86 (m, 2H, 2 × OCH\(_3\),H\(_3\)), 3.82 (s, 3H, ArOMe), 2.08-2.22 (m, 1H, OCH\(_2\)CH\(_2\)H\(_3\)), 1.39 (m, 1H, OCH\(_2\)CH\(_2\)H\(_3\)), 0.99 (s, 9H, SiMe\(_2\)Bu), 0.16 (s, 6H, SiMe\(_2\)-Bu); \(^1\)C NMR (100 MHz) \(\delta = 151.1\) (COMe), 145.6 (COTBS), 132.6 (CCHO\(_2\)), 120.8 (ArCH), 118.8 (ArCH), 109.8 (ArCH), 101.9 (CCHO\(_2\)), 67.6 (2 × OCH\(_2\)CH\(_2\)), 55.6 (OMe), 25.9 (SiC(CH\(_3\)_3)), 25.9 (2 × OCH\(_2\)CH\(_2\)), 18.6 (SiC(CH\(_3\)_3)), –4.5 (SiMe\(_2\)); HRMS (CI) calcd for [C\(_{17}\)H\(_{29}\)O\(_4\)Si]^+ 325.1826; found 325.1830 [M+H]^+; these spectroscopic data are in agreement with those previously reported.\(^1\)

\(^1\)M. Brasholz, X. Luan and H. Reißig, Synthesis, 2005, 20, 3571.
Methyl 3-((tert-butyldimethylsilyl)oxy)-6-(1,3-dioxan-2-yl)-2-methoxybenzoate (13). 

Butyllithium (59 mL, 146 mmol, 2.5 M in hexanes, 1.2 equiv.) was added to anhydrous cyclohexane (750 mL) at 2 °C before further cooling to −6 °C (external). Acetal 12 (39 g, 120 mmol, 1.0 equiv) was then added dropwise to the mixture and the reaction mixture was stirred at −6 °C for a further 10 hours. Methyl chloroformate (31 mL, 401 mmol, 3.3 equiv.) was added dropwise and the reaction was allowed to warm slowly to 10 °C over 16 h. The reaction mixture was quenched with sat. aq. Na₂CO₃ solution (200 mL), the layers were separated and the aqueous layer was extracted with Et₂O (3 × 400 mL) and the combined organics were dried over MgSO₄ and concentrated under reduced pressure before the residue was purified by flash column chromatography (17% EtOAc in n-hexane) to give the benzoate 13 as clear colourless solid (33.1 g, 72%); mp. 74-76 °C; [lit. 76-78 °C]; Rᵣ = 0.51 (17% EtOAc in n-hexane); νₑᵣ(max) (film)/cm⁻¹ 2951w and 2930w (CH), 2857w (OCH₃), 1724s (C=O, ester), 1599w (CO-O), 1492w, 1453w and 1437w (C=C), 1271s (SiMe₂), 1143m (SiO) and 838s (SiMe₃); ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, 1H, J = 8.6 Hz, ArCH), 6.87 (d, 1H, J = 8.6 Hz, ArCH), 5.55 (s, 1H, CHO), 4.21 (dd, J = 11.3, 3.8, 2H, 2 × OCH₂H₆), 3.95-3.86 (m, 2H, 2 × ROCH₂H₆), 3.89 (s, 3H, OMe), 3.81 (s, 3H, CO₂Me), 2.21-2.08 (m, 1H, OCH₂CH₂H₆) 1.43-1.35 (m, 1H, OCH₂CH₂H₂), 0.99 (s, 9H, SiMe₂-Bu), 1.16 (s, 6H, SiMe₃-Bu); ¹³C NMR (100 MHz) δ 167.9 (CO₂Me), 149.3 (CO₂Me), 148.3 (CO₂Me), 129.6 (CCH₂O), 127.9 (CCH₂O), 122.2 (ArCH), 122.0 (ArCH), 99.2 (CCH₂O), 67.4 (2 × OCH₂CH₂), 61.4 (OMe), 52.2 (CO₂Me), 25.8 (SiC(CH₃)₃), 25.7 (OCH₂CH₂), 18.5 (SiC(CH₃)₃), −4.7 (SiMe₂); HRMS (CI) calcd for [C₁₉H₁₃O₂Si]⁺ 383.1885; found 383.1884 [M+H]⁺; these spectroscopic data are in agreement with those previously reported.¹

Methyl 6-(1,3-dioxan-2-yl)-3-hydroxy-2-methoxybenzoate (14). To a solution of benzoate 13 (70 mg, 0.22 mmol.) in DMSO (1.4 mL) and H₂O (79 µl, 4.4 mmol, 20 equiv.) was heated at 170 °C for 2 h. The reaction mixture was cooled to r.t. diluted with Et₂O (10 mL) and washed with sat. aq. NaCl solution (5 × 6 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc in petro) to give the title compound 14 as white solid (58 mg, 99%). Alternatively, to a solution of benzoate 13 (500 mg, 1.30 mmol) in THF (10 mL) was added TBAF (1 M in THF; 1.4 mL, 1.4 mmol, 1.1 equiv.) and stirred at r.t. for 60 min before addition of saturated aq. NH₄Cl (10 mL). The mixture was extracted with Et₂O (3 × 35 mL), dried over MgSO₄ before concentrating under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc in petrol) to give the title compound 14 as white solid (344 mg, 98%); mp = 174-176 °C; Rᵣ = 0.21 (25% EtOAc in petrol); νₑᵣ(max) (film)/cm⁻¹ 3214br (-OH), 3006w, 2987w and 2924w (CH), 2857w (OCH₃), 1699s (C=O), 1587m (C=C); ¹H NMR (400 MHz, CDCl₃) δ 7.31 (dd, 1H, J = 8.5, 0.5 Hz, ArCH), 7.00 (d, 1H, J = 8.5 Hz, ArCH), 5.70 (brs, 1H, OH), 5.58 (s, 1H, CHO₂), 4.22 (dddd, J = 11.9, 5.0, 1.3 Hz, 2H, 2 × OCH₂H₆CH₂), 3.92 (s, 3H, OMe), 3.91 (dddd, J = 12.3, 2.5, 1.3 Hz, 2H, 2 × ROCH₂H₂CH₂), 3.85 (s, 3H, CO₂Me), 2.16 (ddddd, J = 17.4, 13.2, 12.3, 5.0Hz, 1H, OCH₂CH₂H₆), 1.41 (ddddd, J = 13.5, 4.0, 2.5 Hz, 1.3 Hz, 1H, OCH₂CH₂H₂); ¹³C NMR (100 MHz) δ 167.5 (CO₂Me), 149.2 (COH), 144.3 (CO₂Me), 129.0 (CO₂Me), 126.0 (CO₂Me), 122.9 (ArCH), 116.9 (ArCH), 99.1 (CO₂Me), 67.5 (2 × OCH₂CH₂), 62.6 (OMe), 52.5 (CO₂Me), 25.7 (OCH₂CH₂); HRMS (CI) calcd for [C₁₉H₁₃O₆]⁺ 269.1020; found 269.1023 [M+H]⁺.
Methyl 3-((tert-butyldimethylsilyloxy)-6-formyl-2-methoxybenzoate (15). To a solution of acetal 13 (16.9 g, 44.2 mmol) in reagent grade THF (1.5 L) at −5 °C was added TMSOTf (8.4 mL, 46.4 mmol, 1.05 equiv.) dropwise and left to stir at that temperature for 15 minutes. H₂O (8.8 mL, 489 mmol, 11.1 equiv.) was added dropwise to the reaction over 180 min (at which time TLC analysis indicated complete consumption of the starting material) before diluting the reaction mixture with EtOAc (1.5 L). Sat. aq. Na₂CO₃ solution (1.5 L) was then added to the solution. The layers were separated before further extraction of the aqueous layer with EtOAc (1.5 L). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure at 30 °C. The residue was purified by flash chromatography on silica gel (17% EtOAc in petroleum) to afford the title compound as pale yellow oil (13.2 g, 92%); Rf = 0.41 (17% EtOAc in petroleum); ν_max (film)/cm⁻¹ 2952w and 2933w (CH), 2859w (OCH), 1584m (CO₂Me), 154.9 (ArCH), 7.35 (d, J = 8.5, ArCH), 7.00 (d, J = 8.5, ArCH), 3.97 (s, 3H, OMe), 3.85 (s, 3H, CO₂Me), 3.02 (s, 9H, SiMe₆-Bu), 0.25 (s, 6H, SiMe₂-Bu); ¹³C NMR (100 MHz) δ 167.3 (CO₂Me), 154.8 (COMe), 148.9 (COTBS), 130.3 (CCHO), 128.9 (ArCH), 127.7 (CCO₂Me), 121.9 (ArCH), 61.8 (OMe), 52.9 (CO₂Me), 25.7 (SiC(CH₃)₃), 18.4 (SiC(CH₃)₃), −4.3 (SiMe₂); HRMS (CI) calcd for [C₁₀H₁₂O₃Si]⁺ 325.1466; found 325.1467 [M+H]⁺.

Methyl (Dimethylphosphonomethoxy)silylacetate² To methyl bromomethoxyacetate³ (26.3 g, 144 mmol, 1.0 equiv.) was cautiously added trimethyl phosphite (18 mL, 153 mmol, 1.1 equiv.) dropwise at r.t. (CAUTION! This reaction is extremely exothermic, take care to add trimethyl phosphite dropwise at r.t.) and the resultant, gently bubbling mixture was stirred at r.t. for 20 min before heating at 185 °C for 5 h. The cooled reaction mixture was distilled under reduced pressure (111-112 °C/0.1 mbar) to afford the title compound as clear colourless oil (30.5 g, 99%); ν_max (film)/cm⁻¹ 2900w (CO₂C-H₃), 2853w and 2849w (OCH₃), 1750s (C=O), 1262s (P=O); ¹H NMR (400 MHz, CDCl₃) δ = 4.25 (d, J = 19.5 Hz, 1H, PCH), 3.86 (d, J = 5.2 Hz, 3H, POMe), 3.84 (s, 3H, OMe), 3.83 (d, J = 5.2 Hz, 3H, POMe), 3.52 (d, J = 0.5 Hz, 3H, CO₂Me); ¹³C NMR (100 MHz, CDCl₃) δ = 167.3 (CO₂Me), 78.8 (d, J = 158.3 Hz, PCH), 60.3 (d, J = 12.9 Hz, COMe), 54.2 (d, J = 8.0 Hz, POMe), 54.1 (d, J = 8.0 Hz, POMe), 52.8 (CO₂Me); ³¹P (161.9, MHz, CDCl₃) δ = 16.3 (P=O); HRMS (CI) calcd for [C₆H₁₂O₂P]⁺ 213.0528; found 213.0519 [M+H]⁺; these spectroscopic data are in agreement with those previously reported.²

---

(3) Prepared according to S. Gagliardi, G. Nadler, E. Consolandi, C. Parini, M. Morvan, M. Legave, P. Belfiore, A. Zocchetti, G. D. Clarke, I. James, P. Nambi, M. Gowen and C. Farina, J. Med. Chem. 1998, 41, 1568. (CAUTION, this reaction is extremely exothermic, take care to heat the reaction gently in a vessel using methyl methoxyacetate (20.0 g) and CCl₄ (250 mL), a vessel no smaller than 2 litres with extremely efficient vapour release/cooling was needed)
(E/Z)-Methyl-3-((tert-butyldimethylsilyl)oxy)-6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-2-methoxy benzoate (16). To a solution of (MeO)₂P(O)CH(OMe)CO₂Me (3.5 g, 16.5 mmol, 1.3 equiv.) in THF (40 mL) was added NaHMDS (2 M in THF, 8.6 mL, 17.1 mmol, 1.35 equiv.) dropwise at −78 °C over 10 min before stirring at this temperature for 20 min. A solution of aldehyde 15 (4.10 g, 12.7 mmol) in THF (20 mL) was added dropwise and the reaction mixture was allowed to slowly warm to 20 °C and stirred for 16 h. Sat. aq. NH₄Cl (45 mL) was added and the reaction mixture was extracted with Et₂O (3 × 50 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to afford the title compound as pale yellow oil, an inseparable mixture of (E:Z; 1:5) isomers. Rₜ = 0.28 (EtOAc; Petroleum 1:19); νₑₓₘₜ (film)/cm⁻¹ 2953w and 2931w (CH), 2858w (OCH₂), 1722s and 1701s (C=O); HRMS (CI) calcd for [C₁₀H₂₄O₇]⁺ 248.2099; found [M+Na⁺]⁺ 248.099; (Z)-isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, 1H, J = 8.63, ArCH), 6.91 (d, 1H, J = 8.63, ArCH), 6.83 (s, 1H, H=CH₂₄-Bu). 0.22 (s, 6H, SiMe₂-Bu); ¹³C NMR (100 MHz, CDCl₃) δ 167.8 (C=O, Me), 162.9 (C=O, Me), 149.6 (ArC₄), 123.6 (ArC₄), 127.3 (ArC₄), 124.3 (HC=CH₂₄-Bu), 119.4 (HC=CH₂₄-Bu), 61.3 (OMe), 59.3 (OMe), 52.4 (CO₂Me), 52.2 (CO₂Me), 29.5 (Si(C(CH₃)₃), 18.2 (Si(C(CH₃)₃), 4.49 (SiMe₂-Bu); (E)-isomer: ¹H NMR (400 MHz, CDCl₃) δ 6.84-6.79 (m, 2H, 2 × ArCH), 6.11 (s, 1H, H=CH₂₄-Bu), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.69 (s, 3H, CO₂Me), 3.60 (s, 3H, CO₂Me), 1.00 (s, 9H, SiMe₂-Bu), 0.19 (s, 6H, SiMe₂-Bu); ¹³C NMR (100.0 MHz, CDCl₃) δ 167.8 (CO₂Me), 163.9 (CO₂Me), 148.3 (CO₂Me), 147.9 (ArC₄), 147.9 (COTBS), 128.9 (ArC₄), 126.5 (HC=CH₂₄-Bu), 125.2 (ArCH), 122.1 (ArCH), 107.0 (HC=CH₂₄-Bu), 61.3 (OMe), 56.0 (OMe), 52.1 (CO₂Me), 52.0 (CO₂Me), 25.7 (Si(C(CH₃)₃), 18.2 (Si(C(CH₃)₃), 4.6 (SiMe₂).

(E/Z)-Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-3-hydroxy-2-methoxybenzoate (17). To a solution of phenoxysilane 16 (340 mg, 0.82 mmol) in THF (3.5 mL) was added TBAF (1 M in THF; 1.05 mL, 1.05 mmol, 1.28 equiv) and the reaction was stirred at 20 °C for 30 min before addition of sat. aq. NH₄Cl solution (5 mL). The mixture was extracted with Et₂O (3 × 20 mL), dried over MgSO₄ and filtered before being concentrated under reduced pressure. The residue purified by flash column chromatography (25% EtOAc in petrol) to give the title compound, an inseparable mixture of (E:Z; 1:5) isomers. Rₜ = 0.23 (11% EtOAc in petrol); νₑₓₘₜ (film)/cm⁻¹ 3283br (OH), 2998w and 2939w (CH), 2834w (OCH₃), 1730s and 1701s (C=O, ester), 1629 (C=C, conj.) 1573m (C=C), 1275s and 1063 (C-O-CH₃); HRMS (CI) calcd for [C₁₄H₁₀O₇]⁺ 297.0972; found 297.0696 [M+H⁺]; (Z)-isomer: ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d, 1H, J = 7.50, ArCH), 7.03 (d, 1H, J = 7.5, ArCH), 6.88 (s, 1H, H=CH₂₄-Bu) 5.89 (brs, 1H, OH), 3.97 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.83 (s, 3H, CO₂Me), 3.71 (s, 3H, CO₂Me); ¹³C NMR (100 MHz, CDCl₃) δ 167.8 (CO₂Me), 165.2 (CO₂Me), 149.7 (COH), 146.0 (COMe), 127.6 (ArCH), 124.2 (HC=CH₂₄-Bu), 120.0 (ArCH).

(4) Stereochemical assignments were made on the basis of NOESY experiments and correlation of chemical shifts of the closely related compounds found in reference 1 (SI).
117.8 (HC=C quat.), 62.9 (OMe), 59.9 (OMe), 53.2 (CO2Me), 52.7 (CO2Me); (E)-isomer: 1H NMR (400 MHz, CDCl3) δ 6.85-6.78 (m, 2H, ArCH), 6.12 (s, 1H, HC=C quat.), 5.85 (brs, 1H, OH), 3.87 (s, 3H,OMe), 3.84 (s, 3H, OMe), 3.70 (s, 3H, CO2Me), 3.61 (s, 3H, CO2Me); 13C NMR (100 MHz, CDCl3) δ 167.8 (CO2Me), 164.1 (CO2Me), 148.2 (COH), 147.0 (COMe), 128.76 (ArC quat.), 128.2 (CH=C quat.), 125.7 (ArCH), 122.7 (ArCH), 107.1 (HC=C quat.), 63.0 (OMe), 56.3 (OMe), 52.4 (CO2Me), 52.0 (CO2Me).

Methyl 7-hydroxy-8-methoxy-1-oxo-1H-isochromene-3-carboxylate (18). A solution of phenol 17 (100 mg, 0.34 mmol) and p-TSA monohydrate (66 mg, 0.35 mmol, 1.02 equiv.) in PhMe (2 ml) was heated in a crimp sealed microwave vial at 135 °C for 21 h. The reaction mixture was then slowly cooled to −25 °C and the duly formed creamy precipitate was filtered and washed with cold Et2O (15 mL). The resultant white solid was purified by flash column chromatography (20% EtOAc in petrol) to give the title compound 18 as pale white powder (80 mg, 94%); mp = 136-138 °C; Rf = 0.21 (20% EtOAc in petrol); v max (film)/cm⁻¹ 3241br (-OH), 3083w (CH), 2944w (OCH), 2841w (OCH); HRMS (EI) calcd for [C17H17O5]⁺251.0550; found [M+H]⁺ 251.0552.

Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-3-hydroxy-2-methoxy-4-(morpholinomethyl) benzoate (20). To a solution of phenol 17 (50 mg, 0.17 mmol) in MeCN (1 mL) was added 4-methylenemorpholin-4-ium chloride 5 (46 mg, 0.34 mmol, 2.0 equiv.), the vial was crimp sealed and then heated at 150 °C for 16 h. The resultant clear yellow solution was allowed to cool to r.t. and then diluted with EtOAc (10 mL) and filtered before being concentrated under reduced pressure. The residue, a pale yellow oil, was purified by flash column chromatography (33% EtOAc in petroleum) to give the title compound 20 (E:Z: 16:84)⁶ as clear colourless oil which solidified to a clear wax upon storage at −5 °C (61 mg, 91%). Alternatively, a solution of paraformaldehyde (101 mg, 3.9 mmol, 2.0 equiv.) and morpholine (0.3 mL, 3.9 mmol, 2.0 equiv.) in acetic acid (6 mL) was stirred at 20 °C for 24 h before addition of phenol 17 (574 mg, 1.9 mmol, 1.0 equiv.). The vial was crimp sealed then heated at 130 °C for 16 h. The clear yellow solution was allowed to cool to r.t. and filtered before being concentrated under reduced pressure. The residue, a pale yellow oil, was purified by flash column chromatography (33% EtOAc in petroleum) to give the title compound 20 (E:Z; 13:87) as clear colourless oil which solidified to a clear wax upon storage at −5 °C (76.5 mg, quant); mp = 22-23 °C; Rf = 0.23 (10% MeCN in CH2Cl2); v max (film)/cm⁻¹ 2948w (CH), 2841w (OCH3), 1726s (C=O, ester), 1636m (C=C, 1676). (5) (a) H. Sliwa and D. Blondeau, Heterocycles, 1981, 16, 2159-2167. (b). R. Hernández-Altamirano, V. Y. Mena-Cervantes, S. Perez-Miranda, F. J. Fernández, C. A. Flores-Sandoval, V. Barba, H. I. Beltrán and L. S. Zamudio-Rivera, Green Chem., 2010, 12, 1036-1048. (6) Stereochemical assignments were made on the basis of nOe experiments.
Methyl 3-acetoxy-4-(acetoxy methyl)-6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-2-methoxy benzoate (21). To a solution of 20 (100 mg, 0.25 mmol, 1.0 equiv.) in Ac₂O (2 mL, 21.2 mmol, 84.6 equiv.), the reaction was crimp sealed then heated at 155 °C for 24 h. Once cooled the solution was added to MeOH (10 mL) and concentrated under reduced pressure. The residue, a light brown oil was purified by flash column chromatography (5% MeCN in CH₂Cl₂) to give the title compound 21 (E/Z; 1:4)⁶ as pale yellow oil (89 mg, 84%); Rᵣ = 0.26 (5% MeCN in CH₂Cl₂); $ν_{max}$ (film)/cm⁻¹ 2953w (CH), a 2851w (OCH₃), 1770m (C=O, ester), 1727s (C=O, ester), 1635m (C=O, conj.), 1454m (C-H), 1221s, 1183s and 1154s (C-O-CH₃); HRMS (Cl) calcd for [C₁₉H₂₈O₁₀N₁⁺] 428.1551; found 428.1551 [M+NH₄⁺]; (Z)-isomer: $^1$H NMR (400 MHz, CDCl₃) δ = 7.11 (s, 1H, ArCH), 6.13 (s, H, CH=C quat.), 5.02 (s, 2H, CH₂OAc), 3.85 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.72 (s, 3H, CO₂Me), 3.61 (s, 3H, CO₂Me), 2.33 (s, 3H, OAc), 2.06 (s, 3H, OAc); $^{13}$C NMR (100 MHz) δ = 171.1 (OCOMe), 168.8 (OCOMe), 167.3 (CO₂Me), 164.8 (CO₂Me), 150.2 (COMe), 147.8 (CH=C quat.), 142.9 (COAc), 132.3 (ArCH), 131.9 (Ar quat.), 130.4 (Ar quat.), 127.1 (Ar quat.), 118.8 (CH=C quat.), 62.9 (OMe), 61.6 (CH₂OAc), 60.3 (OMe), 53.3 (CO₂Me), 53.0 (CO₂Me), 21.4 (OCOMe), 21.1 (OCOMe); (E)-isomer: $^1$H NMR (400 MHz, CDCl₃) δ = 7.91 (s, 1H, ArCH), 6.86 (s, H, CH=C quat.), 5.05 (s, 2H, CH₂OAc), 3.93 (s, 3H, OMe), 3.83 (s, 6H, 1 × OMe, 1 × CO₂Me), 3.74 (s, 3H, CO₂Me), 2.35 (s, 3H, OAc), 2.09 (s, 3H, OAc); $^{13}$C NMR (100 MHz) δ = 171.1 (OCOMe), 168.9 (OCOMe), 167.4 (CO₂Me), 164.1 (CO₂Me), 150.3 (COMe), 149.2 (CH=C quat.), 141.9 (COAc), 133.0 (ArCH), 130.2 (CH₂), 128.8 (Ar quat.), 127.1 (Ar quat.), 118.8 (CH=C quat.), 62.8 (OMe), 61.4 (ArCH₂), 56.7 (OMe), 53.0 (CO₂Me), 52.8 (CO₂Me), 21.4 (COMe), 21.1 (COMe).

Methyl 6-((Z)-2,3-dimethoxy-3-oxoprop-1-en-1-yl)-8-methoxy-3,3a,4,9a-tetrahydro-2H-furo[2,3-b]chromene-7-carboxylate ((±)-24). To a solution of amine 20 (20 mg, 51 µmol, 1.0 equiv.) dissolved in PhMe (0.2 ml) was added Mel (0.1 M in PhMe, 0.5 ml, 50 µmol, 0.99 equiv). The reaction was stirred at r.t. for 2 h, at which time TLC analysis indicated complete consumption of the starting material. 2,3-Dihydrofuran (0.38 µl, 0.5 mmol, 10.0 equiv.) was added and the crimp sealed reaction mixture was heated at 130 °C for 16 h in a microwave reactor. The reaction mixture was cooled to r.t., diluted with EtOAc (3 mL) and filtered through a short pad of silica (d = 1 cm × h = 0.5 cm). The filtrate was concentrated under reduced
pressure and the residue purified by flash column chromatography (25% EtOAc in petrol) to give the title compound 24 as clear colourless oil (12.4 mg, 0.033 mmol, 65%). Alternatively, a solution of amine 20 (20 mg, 51 μmol, 1.0 equiv.) was dissolved in 2,3-dihydrofuran (0.10 mL, 6.81 mmol). The crimp sealed mixture was heated at 130 °C for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue purified by flash column chromatography (1→10% Et2O in petrol) to give the title compound 24 as clear colourless oil (14.0 mg, 35 μmol, 70%); Rf = 0.19 (25% EtOAc in petrol); vmax (film)/cm⁻¹ 2938w and 2924w (CH), 2854 (O-C-H₃), 1724s (2 × C=O, ester), 1645w (O-CO), 1452m, and 1438m (C=O). ¹H NMR (400 MHz, CDCl₃) δ 7.58 (s, 1H, ArCH), 6.78 (s, 1H, CH=C=O), 5.71 (d, J = 5.3 Hz, 1H, O₂CH), 3.98-3.88 (m, 2H, OCH₂), 3.87 (s, 3H, OMe), 3.84 (s, 3H, OMe), 3.75 (s, 3H, CO₂Me), 3.66 (s, 3H, CO₂Me), 3.01 (dd, J = 15.9, 5.3 Hz, 1H, O₂CHCH), 2.78-2.72 (m, 1H, ArH₃H₅b), 2.68 (dd, J = 15.9, 2.6 Hz, 1H, ArH₃H₇b), 2.03-1.96 (m, 1H, OCH₂CH₃H₆b), 1.62-1.57 (m, 1H, OCH₂CH₂H₇b); ¹³C NMR (100 MHz) δ 164.5 (CO₂Me), 163.5 (CO₂Me), 153.1 (COME), 148.3 (CH=CMet), 142.0 (ArC quat.), 129.8 (ArC quat.), 127.2 (ArC quat.), 119.0 (ArC quat.), 103.6 (CH=CMet), 103.2 (O₂CH), 74.5 (OCH₂), 67.0 (OME), 66.1 (OME), 61.9 (CO₂Me), 59.6 (CO₂Me), 52.8 (O₂CHCH), 30.7 (OCH₂CH₂), 29.8 (CH₂); The ¹³C NMR spectrum could not be clearly distinguished from the major (Z)-isomer. HRMS (EI) calcd for [C₁₀H₂₀O₈N⁺] 396.1653; found 396.1654 [M+NH₄⁺].

Methyl 6-(2,3-dimethoxy-3-oxoprop-1-en-1-yl)-8-methoxy-5'o-oxo-4',5'-dihydro-3'H-spiro[chroman-2,2',furan]-7-carboxylate ((±)-26). Amine 20 (20 mg, 51 μmol) was dissolved in γ-methylene-γ-butyro lactone (0.10 mL, 1.12 mmol) and the crimp sealed reaction mixture was heated at 130 °C for 16 h in a microwave reactor. The reaction mixture was then cooled to r.t., and purified by flash column chromatography (1→10% EtOAc in petrol) to give spiroketal 26 (E:Z; 1:3) as clear colourless oil (14.2 mg, 64%); Rf = 0.15 (10% EtOAc in petrol); vmax (film)/cm⁻¹ 2939w and 2930w (CH), 2854 (O-C-H₃), 1792s and 1725s (C=O, ester), 1645w (O-CO), 1567m, 1475m, 1440m, 1436m (C=C); 1H NMR (400 MHz, CDCl₃) δ 7.67 (s, 1H, ArCH), 6.81 (s, 1H, CH=CMet), 3.96 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.82 (s, 3H, CO₂Me), 3.74 (s, 3H, CO₂Me), 3.09-2.94 (m, 2H, CH₂), 2.72-2.52 (m, 2H, CH₂), 2.41-2.23 (m, 2H, CH₂), 2.19-2.08 (m, 1H, CH₃H₅b), 2.04 (m, 1H, CH₃H₇b); ¹³C NMR (100 MHz) δ 173.5 (CO₂), 167.2 (CO₂Me), 164.3 (CO₂Me), 147.3 (RH=CMet), 146.2 (COME), 142.2 (ArC quat.), 125.5 (ArC quat.), 125.4 (ArC quat.), 124.9 (ArCH), 118.6 (CH=CMet), 109.0 (spiro-C), 61.9 (OME), 59.4 (OME), 52.6 (CO₂Me), 52.3 (CO₂Me), 38.8 (CH₂), 32.9 (CH₂), 26.9 (CH₂), 25.7 (CH₂); (E)-isomer: ¹H NMR (400 MHz, CDCl₃) δ = 7.65 (s, 1H, ArCH), 6.84 (s, 1H, CH=CMet), 3.93 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.81 (s, 3H, CO₂Me), 3.72 (s, 3H, CO₂Me), 3.09-2.94 (m, 2H, CH₂), 2.72-2.52 (m, 2H, CH₂), 2.41-2.23 (m, 2H, CH₂), 2.19-2.08 (m, 1H, CH₃H₅b), 2.04 (m, 1H, CH₃H₇b); The ¹³C NMR spectrum could not be clearly distinguished from the major (Z)-isomer. HRMS (EI) calcd for [C₂₀H₂₃O₉⁺] 407.1337; found 407.1339 [M+H⁺].
NMR Spectra

$^1$H NMR Spectrum (Compound 11)

$^{13}$C NMR Spectrum (Compound 11)
$^1$H NMR Spectrum (Compound 12)

$^{13}$C NMR Spectrum (Compound 12)
$^1$H NMR Spectrum (Compound 13)

$^{13}$C NMR Spectrum (Compound 13)
$^1$H NMR Spectrum (Compound 14)

$^{13}$C NMR Spectrum (Compound 14)
**$^1$H NMR Spectrum (Compound 15)**

![H NMR Spectrum](image)

**$^{13}$C NMR Spectrum (Compound 15)**

![C NMR Spectrum](image)
$^1$H NMR Spectrum

\[
\begin{array}{c}
\text{O} \\
\text{(MeO)$_2$P} \\
\text{O} \\
\text{OMe} \\
\text{O} \\
\end{array}
\]

$^{13}$C NMR Spectrum
$^{31}$P NMR Spectrum
$^1$H NMR Spectrum (Compound 16; Z-isomer highlighted)

$^{13}$C NMR Spectrum (Compound 16; Z-isomer highlighted)
$^{1}H$ NMR Spectrum (Compound 17; Z-isomer highlighted)

$^{13}C$ NMR Spectrum (Compound 17; Z-isomer highlighted)
$^{1}H$ NMR Spectrum (Compound 18)

$^{13}C$ NMR Spectrum (Compound 18)
$^{1}H$ NMR Spectrum (Compound 20; Z-isomer highlighted)

$^{13}C$ NMR Spectrum (Compound 20)
$^1$H NMR Spectrum (Compound 21; Z-isomer highlighted)

-$^1$H NMR Spectrum (Compound 21; Z-isomer highlighted)

$^{13}$C NMR Spectrum (Compound 21; Z-isomer highlighted)
$^1$H NMR Spectrum (Compound (±)-24)

$^{13}$C NMR Spectrum (Compound (±)-24)
$^1$H NMR Spectrum (Compound (±)-26)

$^{13}$C NMR Spectrum (Compound (±)-26)
X-ray data
Ortep plot of compound 13 with ellipsoids shown at 30% probability. Data for this compound is available via the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk) as CCDC 1420253.

<table>
<thead>
<tr>
<th>Empirical formula</th>
<th>C19 H30 O6 Si</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula weight</td>
<td>382.52</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>-P 2ybc</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 14.6051(10)Å, a = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 15.8731(11)Å, b = 97.9860(10)°</td>
</tr>
<tr>
<td></td>
<td>c = 8.9463(6)Å, g = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2053.9(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density</td>
<td>1.237 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.145 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>824</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.40 × 0.10 × 0.10 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.57 to 34.99°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-23≤h≤23, 25≤k≤24, -14≤l≤7</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>8987</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>43509 [R(int) = 0.0304]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>99.3%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Multiscan</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>8987/0/242</td>
</tr>
<tr>
<td>Goodness-of-fit F²</td>
<td>1.025</td>
</tr>
<tr>
<td>Final R indices [I.2sigma(I)]</td>
<td>R1 = 0.0421, wR2 = 0.1192</td>
</tr>
</tbody>
</table>
R indices (all data)  \( R_1 = 0.0590, \ wR_2 = 0.1329 \)
Largest diff. peak and hole  \( 1.474 \text{ and } -0.383 \text{e.Å}^{-3} \)