Supplemental Information

Potential Drug Abuse Therapeutics Derived from the Hallucinogenic Natural Product Salvinorin A

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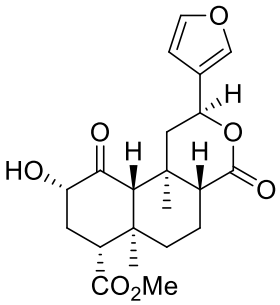
Chemistry

General Procedures. Unless otherwise indicated, all reagents were purchased from commercial suppliers and are used without further purification. NMR spectra were recorded on either a Bruker Avance-300 spectrometer, Bruker DRX-400 with qnp probe and/or a Bruker AV-500 with cryoprobe using δ values in ppm (TMS as internal standard) and *J* (Hz) assignments of ^{1}H resonance coupling. High resolution mass spectrometry data was collected on either a LCT Premier (Waters Corp., Milford, MA) time of flight mass spectrometer or an Agilent 6890 N gas chromatograph in conjuction with a Quatro Micro GC mass spectrometer (Micromass Ltd, Manchester UK). Thin-layer chromatography (TLC) was performed on 0.25 mm plates Analtech GHLF silica gel plates using mixtures of EtOAc/*n*-hexanes as the solvent system. Spots on TLC visualized with phosphomolybdic acid or vanillin in ethanol. Column chromatography was performed with Silica Gel (32–63 μm particle size) from MP Biomedicals (Solon, OH). Analytical HPLC was carried out on an Agilent 1100 Series Capillary HPLC system with diode array detection at 209.4 nm on an Agilent Eclipse XDB-C18 column (4.6 × 150 mm, 5 μm) with isocratic elution in mixtures of CH_3CN/H_2O as noted at a flow rate of 5.0 mL/min unless otherwise detailed.



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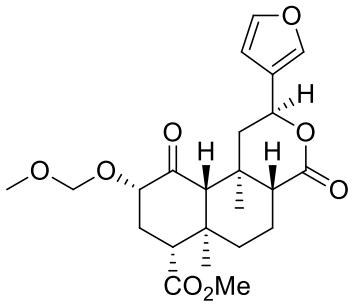
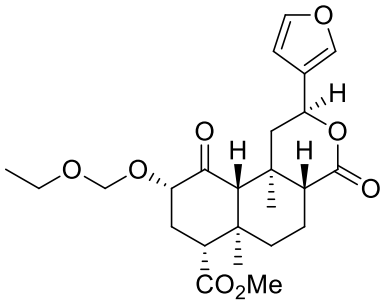


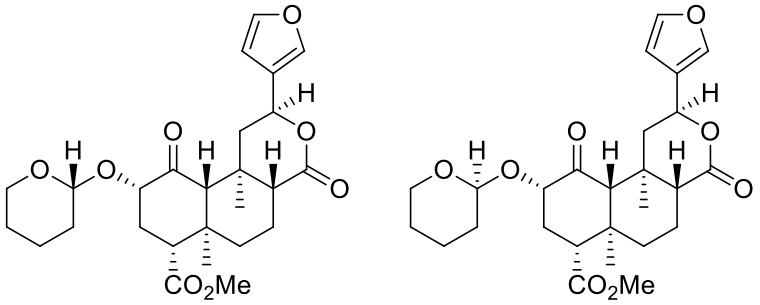
3

(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 2-(furan-3-yl)-9-(methoxymethoxy)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate (**3**). Chloromethyl methyl ether (0.195 mL, 2.56 mmol, 5 equiv.) was added in a dropwise manner to a solution of **2** (0.200g, 0.512 mmol, 1 equiv.) and DIPEA (0.446 mL, 2.56 mmol, 5 equiv.) in anhydrous DCM (10 mL) under an argon atmosphere. The mixture was stirred at room temperature overnight. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL), brine (10 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (1:3) to give 0.0894 g (41% yield) as a white powder. HPLC in 60% MeCN/40% H_2O, t_R = 4.778 min; purity = 99.1%. Spectroscopic information was in agreement with published data.[1, 2]



4

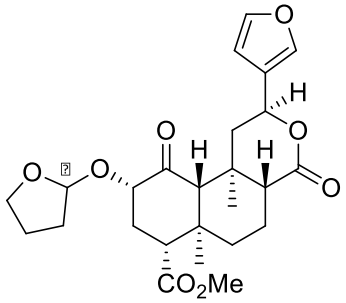
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-(ethoxymethoxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate (**4**). Chloromethyl ethyl ether (0.475 mL, 5.12 mmol, 5 equiv.) was added in a dropwise manner to a solution of **2** (0.400 g, 1.02 mmol, 1 equiv.) and DIPEA (0.890 mL, 5.12 mmol, 5 equiv.) in anhydrous DCM (40 mL) under an argon atmosphere. The mixture was stirred at room temperature overnight. TLC indicated that starting material was still present after 16 h, thus an additional 5 equiv. (0.475 mL, 5.12 mmol) of chloromethyl ethyl ether was added and the mixture stirred for an additional 24 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (3 × 40 mL), brine (40 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (2:3) to afford a brown oil, which was subsequently triturated from DCM/*n*-hexanes to give 0.2487 g (54% yield) as a white powder. HPLC in 60% MeCN/40% H_2O, t_R = 7.151 min; purity = 98.1%. Spectroscopic information was in agreement with reported data.[2]



5 **6**

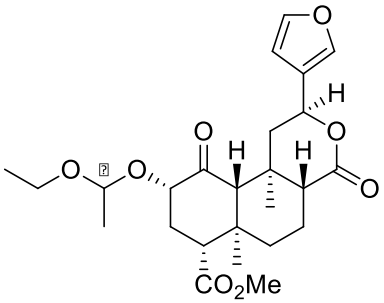
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxo-9-((R)-tetrahydro-2H-pyran-2-yloxy)dodecahydro-1H-benzo[f]isochromene-7-carboxylate (**5**) and **(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxo-9-((S)-tetrahydro-2H-pyran-2-yloxy)dodecahydro-1H-benzo[f]isochromene-7-carboxylate** (**6**). 3,4-dihydro-2H-pyran (0.579 mL, 6.16 mmol, 8 equiv.) was added to a solution of **2** (0.300 g, 0.768 mmol, 1 equiv.) and PPTS (60 mg, cat.) in anhydrous DCM (30 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with TEA (100 μL) and the solvent was removed *in vacuo*. The remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (3:7) to give 0.0939 g (**5**) R_f = 0.56 (EtOAc/*n*-hexanes 1:1) and 0.0560 g (**6**) R_f = 0.48 (EtOAc/*n*-hexanes 1:1) as white powders (41% combined yield). HPLC in 60% MeCN/40% H_2O, t_R =

7.902 min; purity = 99.2% (**5**) and HPLC in 60% MeCN/40% H_2O, t_R = 7.200 min; purity = 98.5% (**6**). Spectroscopic information was in agreement with reported data.[2]



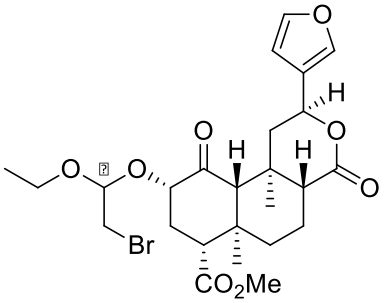
7a,b

(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxo-9-((R)-tetrahydrofuran-2-yloxy)dodecahydro-1H-benzo[f]isochromene-7-carboxylate and **(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxo-9-((S)-tetrahydrofuran-2-yloxy)dodecahydro-1H-benzo[f]isochromene-7-carboxylate** (**7a** and **7b**). 2,3-dihydrofuran (0.465 mL, 6.15 mmol 8 equiv.) was added to a solution of **2** (0.300 g, 0.768 mmol, 1 equiv.) and PPTS (60 mg, cat.) in anhydrous DCM (30 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with TEA (100 μL) and the solvent was removed *in vacuo*. The remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (3:7) to give 0.1497 g (**7a**) R_f = 0.44 (EtOAc/*n*-hexanes 2:5) and 0.0888 g (**7b**) R_f = 0.31 (EtOAc/*n*-hexanes 2:5) as white powders (68% combined yield). **7a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dt, *J* = 0.8, 1.6, 1H), 7.40 (t, *J* = 1.7, 1H), 6.38 (dd, *J* = 0.8, 1.8, 1H), 5.54 (dd, *J* = 5.0, 11.7, 1H), 5.26 (d, *J* = 4.1, 1H), 4.21 (dd, *J* = 7.8, 12.1, 1H), 3.86 (dd, *J* = 6.3, 7.5, 2H), 3.71 (s, 3H), 2.70 (dd, *J* = 3.4, 13.4, 1H), 2.55 (dd, *J* = 5.1, 13.3, 1H), 2.29 (ddd, *J* = 3.4, 7.4, 13.4, 1H), 2.20 – 2.08 (m, 3H), 2.06 – 1.92 (m, 3H), 1.88 – 1.80 (m, 1H), 1.77 (dt, *J* = 3.0, 13.3, 1H), 1.69 – 1.59 (m, 2H), 1.54 (dd, *J* = 8.3, 21.1, 2H), 1.46 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.90, 171.97, 171.29, 143.74, 139.36, 125.34, 108.35, 103.43, 77.19, 71.99, 67.28, 64.25, 53.99, 51.83, 51.52, 43.58, 41.99, 38.19, 35.51, 33.10, 32.29, 23.19, 18.15, 16.44, 15.20. HRMS (*m*/*z*): [M+Na] calcd for $C_{25}H_{32}O_8Na$, 483.1995; found 483.1997 0.4 ppm. HPLC in 60% MeCN/40% H_2O, t_R = 5.013 min; purity = 95.2%. **7b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 0.7, 1H), 7.40 (t, *J* = 1.7, 1H), 6.39 (dd, *J* = 0.7, 1.7, 1H), 5.55 (dd, *J* = 5.1, 11.7, 1H), 5.19 (d, *J* = 4.6, 1H), 4.14 (dd, *J* = 7.3, 12.4, 1H), 3.97 (td, *J* = 6.0, 8.0, 1H), 3.82 (td, *J* = 6.1, 7.8, 1H), 3.71 (s, 3H), 2.66 (dd, *J* = 3.3, 13.5, 1H), 2.55 (dd, *J* = 5.1, 13.4, 1H), 2.40 (ddd, *J* = 3.3, 7.1, 13.3, 1H), 2.17 – 2.02 (m, 6H), 1.98 – 1.90 (m, 1H), 1.90 – 1.83 (m, 1H), 1.78 (dt, *J* = 3.1, 13.3, 1H), 1.67 – 1.57 (m, 2H), 1.53 (d, *J* = 4.3, 1H), 1.47 (s, 3H), 1.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.35, 171.98, 171.35, 143.71, 139.44, 125.37, 108.43, 102.04, 77.43, 72.03, 67.63, 64.35, 53.86, 51.85, 51.54, 43.47, 42.03, 38.23, 35.48, 32.33, 31.82, 23.30, 18.18, 16.39, 15.18. HRMS (*m*/*z*): [M+K] calcd for $C_{25}H_{32}O_8K$, 499.1734; found 499.1731, 0.6 ppm. HPLC in 60% MeCN/40% H_2O, t_R = 4.393 min; purity = 95.2%.



8a,b

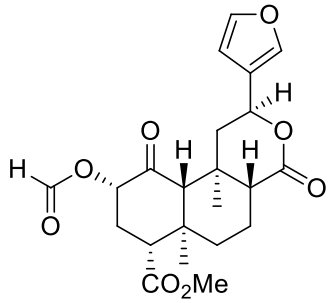
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-((R)-1-ethoxyethoxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate and **(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-((S)-1-ethoxyethoxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate** (**8a** and **8b**). A suspension of **2** (0.200 g, 0.512 mmol) and PPTS (20 mg, cat.) in ethyl vinyl ether (20 mL) was heated to reflux for 2 h. The solvent was removed *in vacuo* and the remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (3:7) to give 0.0350 g (**8a**) R_f = 0.28 (EtOAc/*n*-hexanes 3:7) and 0.0156 g (**8b**) *Rf* = 0.21 (EtOAc/*n*-hexanes 3:7) as white powders (21% combined yield). HPLC in 50% MeCN/50% H_2O, t_R = 10.596 min; purity = 95.0% (**8a**) and HPLC in 50% MeCN/50% H_2O, t_R = 8.769 min; purity = 81.9% (**8b**). Spectroscopic information was in agreement with reported data.[2]



9a,b

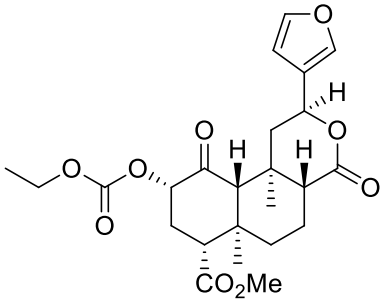
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-((R)-1-bromo-2-ethoxypropan-2-yloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate and **(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-((S)-1-bromo-2-ethoxypropan-2-yloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate** (**9a** and **9b**). Ethyl vinyl ether (0.184 mL, 1.92 mmol, 2.5 equiv) was added in a dropwise fashion to a solution of bromine (0.080 mL, 1.54 mmol, 2 equiv) in DCM (15 mL) at 0° C under an argon atmosphere, turning the solution colorless. The reaction was allowed to stir for 15 minutes. DIPEA (0.535 mL, 3.07 mmol, 4 equiv) was then added to the reaction mixture, followed by the dropwise addition of a suspension of **2** (0.300 g, 0.768 mmol, 1 equiv) in DCM (15 mL). The reaction stirred for 24 h without recharging the ice bath. The reaction mixture was then diluted with DCM (20 mL) and extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL). The combined aqueous layers were washed with DCM (50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The remaining residue was purified by HPLC with an isocratic solvent gradient of 50% MeCN/50% H_2O and a flow rate of 3 mL/min to give 0.0230 g (**9a**) R_f = 0.63 (EtOAc/*n*-hexanes 2:5) and

0.0239 g (**9b**) R_f = 0.56 (EtOAc/*n*-hexanes 2:5) as white powders (11% combined yield). **9a**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.11 – 7.09 (m, 1H), 7.04 (t, *J* = 1.7, 1H), 6.13 (dd, *J* = 0.7, 1.7, 1H), 5.16 (dd, *J* = 5.0, 11.8, 1H), 4.65 (dd, *J* = 4.2, 6.3, 1H), 3.76 – 3.70 (m, 1H), 3.65 – 3.54 (m, 2H), 3.30 (s, 3H), 3.27 (dd, *J* = 4.2, 10.7, 1H), 3.16 (dd, *J* = 6.3, 10.7, 1H), 2.29 (dd, *J* = 5.2, 13.1, 1H), 2.24 – 2.19 (m, 2H), 2.17 – 2.09 (m, 1H), 2.06 (dd, *J* = 7.3, 9.9, 1H), 1.46 (ddd, *J* = 3.3, 5.9, 10.2, 2H), 1.38 (d, *J* = 14.6, 3H), 1.25 (d, *J* = 2.5, 4H), 1.04 (t, *J* = 7.0, 3H), 0.86 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 205.44, 171.96, 170.34, 144.15, 139.69, 126.91, 108.98, 100.90, 77.37, 71.82, 64.19, 62.26, 53.97, 51.66, 51.58, 43.93, 42.04, 38.52, 35.88, 33.40, 32.51, 19.01, 16.54, 15.63, 15.46. HRMS (*m*/*z*): [M+Na] calcd for $C_{25}H_{33}BrO_8Na$, 563.1257; found 563.1265, 1.4 ppm. HPLC in 60% MeCN/40% H_2O, t_R = 9.104 min; purity = >99.9%. **9b**: ^{1}H NMR (500 MHz, C_6D_6) δ 7.10 – 7.07 (m, 1H), 7.05 (t, *J* = 1.7, 1H), 6.12 (dd, *J* = 0.8, 1.8, 1H), 5.17 (dd, *J* = 5.0, 11.7, 1H), 4.92 (dd, *J* = 3.8, 7.4, 1H), 3.85 – 3.79 (m, 1H), 3.55 (dd, *J* = 3.8, 10.9, 1H), 3.41 (dq, *J* = 7.0, 9.0, 1H), 3.33 – 3.23 (m, 5H), 2.29 – 2.18 (m, 3H), 2.10 (ddd, *J* = 6.5, 9.1, 9.5, 2H), 1.46 (dd, *J* = 7.8, 10.4, 3H), 1.24 (s, 3H), 1.23 (s, 1H), 1.12 (dd, *J* = 13.4, 26.2, 2H), 1.04 (t, *J* = 7.0, 3H), 0.85 (s, 3H). ^{13}C NMR (126 MHz, C_6D_6) δ 206.22, 171.92, 170.31, 144.13, 139.76, 126.86, 109.03, 101.22, 77.96, 71.79, 63.99, 60.75, 53.89, 51.61, 51.58, 43.96, 42.05, 38.45, 35.88, 33.32, 31.61, 18.99, 16.56, 15.73, 15.41. HRMS (*m*/*z*): [M+Na] calcd for $C_{25}H_{33}BrO_8Na$, 563.1257; found 563.1265, 1.4 ppm. HPLC in 60% MeCN/40% H_2O, t_R = 9.799 min; purity = 98.5%.



10

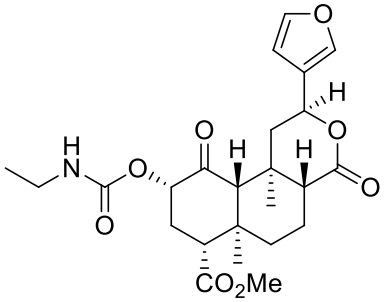
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-(formyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate (**10**). Synthesized according to the procedures of Munro et al.[3] HPLC in 60% MeCN/40% H_2O, t_R = 5.905 min; purity = 95%. Spectroscopic information was in agreement with reported data.[3]



11

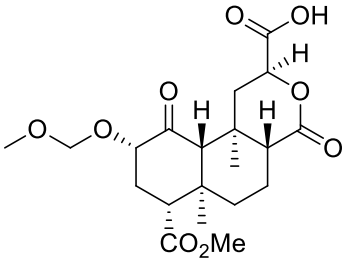
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-(ethoxycarbonyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate (**11**).[1] Ethyl

chloroformate (0.055 mL, 0.576 mmol, 3 equiv) was added in a dropwise fashion to a solution of **2** (0.075 g, 0.192 mmol, 1 equiv), DMAP (0.070 g, 0.576 mmol, 3 equiv), and TEA (0.080 mL, 0.576 mmol, 3 equiv) in DCM (15 mL) under an atmosphere of argon. The reaction stirred at room temperature for 24 h. After TLC indicated completion of the reaction, the mixture was diluted with EtOAc (20 mL) and then extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL), and then dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The remaining residue was purified by flash column chromatography using EtOAC/*n*-hexanes (2:5) to give 0.0681 g (77% yield) R_f = 0.40 (EtOAc/*n*-hexanes 2:5) and as white powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.40 (t, *J* = 1.7, 1H), 6.38 (d, *J* = 1.0, 1H), 5.54 (dd, *J* = 5.1, 11.7, 1H), 4.98 (dd, *J* = 7.7, 12.4, 1H), 4.30 – 4.18 (m, 2H), 3.73 (s, 3H), 2.75 (dd, *J* = 3.7, 13.1, 1H), 2.54 (dd, *J* = 5.2, 13.4, 1H), 2.43 – 2.28 (m, 2H), 2.20 – 2.17 (m, 1H), 2.08 (dd, *J* = 2.9, 11.7, 1H), 1.83 – 1.76 (m, 1H), 1.68 – 1.62 (m, 1H), 1.58 (s, 3H), 1.46 (s, 3H), 1.34 (t, *J* = 7.1, 3H), 1.12 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.77, 171.40, 171.09, 154.19, 143.74, 139.48, 125.18, 108.41, 77.61, 72.01, 64.74, 64.02, 53.43, 52.04, 51.39, 43.34, 42.04, 38.11, 35.46, 30.65, 18.12, 16.40, 15.17, 14.17. HRMS (*m*/*z*): [M+Na] calcd for $C_{24}H_{30}O_9Na$, 485.1788; found 485.1804, 3.3 ppm. HPLC in 60% MeCN/40% H_2O, t_R = 7.645 min; purity = 95.8%.



12

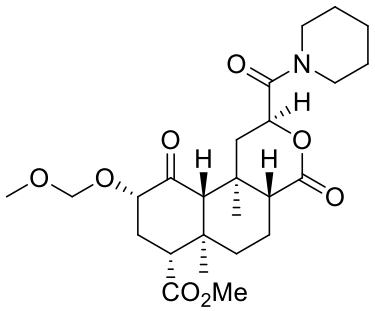
(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-(ethylcarbamoyloxy)-2-(furan-3-yl)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-7-carboxylate (**12**). Synthesized according to the procedures of Beguin et al.[4] HPLC in 60% MeCN/40% H_2O, t_R = 5.074 min; purity = >99.9%. Spectroscopic information was in agreement with reported data.[4]



13

(2S,4aR,6aR,7R,9S,10aS,10bR)-7-(methoxycarbonyl)-9-(methoxymethoxy)-6a,10b-dimethyl-4,10-dioxododecahydro-1H-benzo[f]isochromene-2-carboxylic acid (**13**). To a solution of **3** (51 mg, 0.117 mmol, 1 equiv.) in $CCl_4/CH_3CN/H_2O$ (2:2:3) (3.5 mL) was added $NaIO_4$ (301 mg, 1.41 mmol, 12 equiv.) and $RuCl_3 \cdot 3H_2O$ (1 mg cat.). The mixture was allowed to stir at room temperature for 2 h. The reaction mixture was then filtered through a pad of

celite, washing thoroughly with EtOAc (30 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), and the aqueous layer was collected and subsequently acidified to pH 3 with 4N HCl. The aqueous layer was then extracted with EtOAc (3 × 20 mL) and the organic layers were washed with H_2O (30 mL), brine (30 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give 0.048 g (>99% yield) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (br s, 1H), 5.05 – 4.96 (m, 1H), 4.74 (dd, *J* = 7.0, 25.9, 2H), 4.24 (dd, *J* = 7.4, 12.2, 1H), 3.71 (s, 3H), 3.42 (s, 3H), 2.77 (d, *J* = 10.5, 1H), 2.63 (dd, *J* = 6.8, 13.6, 1H), 2.34 (s, 1H), 2.25 (s, 1H), 2.13 (dd, *J* = 11.8, 40.3, 3H), 1.75 (d, *J* = 9.7, 1H), 1.61 (s, 3H), 1.38 (s, 3H), 1.07 (s, 3H).



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(2S,4aR,6aR,7R,9S,10aS,10bR)-methyl 9-(methoxymethoxy)-6a,10b-dimethyl-4,10-dioxo-2-(piperidine-1-carbonyl)dodecahydro-1H-benzo[f]isochromene-7-carboxylate (**14**). To a solution of **13** (45 mg, 0.109 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) was added piperidine (0.03 mL, 0.273 mmol, 2.5 equiv.), EDCI (52 mg, 0.273 mmol, 2.5 equiv.), HOBt (29 mg, 0.218 mmol, 2 equiv), and TEA (0.06 mL, 0.436 mmol, 4 equiv.). The reaction mixture was stirred at room temperature overnight. The mixture was then washed with saturated aqueous $NaHCO_3$ (3 × 15 mL), H_2O (3 × 15 mL), and brine (15 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The resulting residue was purified by flash column chromatography using EtOAC/*n*-hexanes to give 0.021 g (40% yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (t, *J* = 7.7, 1H), 4.71 (s, 2H), 4.15 (dd, *J* = 7.4, 12.2, 1H), 3.71 (s, 3H), 3.70 – 3.64 (m, 1H), 3.54 (dd, *J* = 7.2, 11.1, 1H), 3.46 – 3.40 (m, 2H), 3.37 (d, *J* = 6.8, 3H), 2.71 (dd, *J* = 3.2, 13.5, 1H), 2.44 – 2.27 (m, 3H), 2.19 (d, *J* = 12.5, 2H), 2.06 (dd, *J* = 3.3, 14.1, 1H), 1.88 (dd, *J* = 7.7, 13.5, 1H), 1.75 – 1.56 (m, 9H), 1.39 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.06, 172.02, 171.37, 166.93, 95.75, 77.92, 71.56, 64.78, 55.81, 53.54, 51.83, 49.19, 46.88, 43.77, 41.88, 37.81, 37.78, 35.12, 32.53, 26.51, 25.49, 24.38, 18.18, 17.01, 16.05. HRMS (*m*/*z*): [M+Na] calcd for $C_{25}H_{37}NO_8Na$, 502.2417; found 502.2169, 49.4 ppm. HPLC in 60% MeCN/40% H_2O, flow rate 2.5 mL/min, t_R = 9.962 min; purity = 98.6%.

X-ray Crystallography. The asymmetric unit contains one $C_{26}H_{34}O_8$ molecule that has two slightly different conformations. All displacement ellipsoids are drawn at the 50% probability level.

Needle-shaped single crystals of $C_{26}H_{34}O_8$ are, at 100(2) K, orthorhombic, space group $P2_12_12_1$ – D_2^4 (No. 19)[5] with **a** = 6.1944(1) Å, **b** = 11.2496(3) Å, **c** = 35.8673(8) Å, V = 2499.4(1) Å^3 and Z = 4 molecules {d_{calcd} = 1.261 g/cm^3; μ_a(CuKα) = 0.767 mm^{-1}}. A full set of unique diffracted intensities was measured[6] (5711 0.50°-wide ω- or ϕ-scan frames with counting times of 1-6 seconds) for a single-domain specimen using monochromated CuKα

radiation (λ= 1.54178 Å) on a Bruker Single Crystal Diffraction System equipped with Helios multilayer optics, an APEX II CCD detector and a Bruker MicroSTAR microfocus rotating anode x-ray source operating at 45kV and 60mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 9928 reflections. A total of 26136 integrated reflection intensities having $2\theta(CuK\alpha) < 127.30°$ were produced using the Bruker program SAINT[7]; 4076 of these were unique and gave $R_{int} = 0.041$ with a coverage which was 99.5% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.905 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.[8]

The initial structure solution revealed that the 6-membered tetrahydropyran ring was disordered with two preferred orientations in the crystal. A second molecule having this conformation was therefore introduced into the model and the structure was refined with "whole molecule disorder" by restraining the bond lengths and angles for nonhydrogen atoms of the two molecules to have similar values. The major conformation is present 64% of the time and the minor conformation is present 36% of the time.

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms except minor-occupancy carbon atoms C1' and C26'. Hydrogen atoms were included with fixed isotropic thermal parameters and carbon atoms C1' and C26' were included with variable isotropic thermal parameters. Mild restraints were applied to the anisotropic thermal parameters for 2 nonhydrogen atoms of the major-ocupancy conformer and 22 nonhydrogen atoms of the minor-occupancy conformer. Identical anisotropic thermal parameters were used for oxygen atoms O4 and O4' which refined to essentially the same position in the unit cell. All methyl groups were incorporated into the structural model as rigid groups (using idealized sp^3-hybridized geometry and a C-H bond length of 0.98 Å) with a "staggered" orientation. The remaining hydrogen atoms were included in the structural model at idealized positions (sp^2- or sp^3-hybridized geometry with C-H bond lengths of 0.95 – 1.00 Å). All hydrogen atoms utilized isotropic thermal parameters that were fixed at values 1.20 (nonmethyl) or 1.50 (methyl) times the equivalent isotropic thermal parameter of the carbon atom to which they were covalently bonded. A total of 598 parameters were refined using 240 restraints, 4076 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0785\ P)^2 + (0.9339\ P)]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.046 for 3704 independent absorption-corrected "observed" reflections having $2\theta(CuK\alpha) < 127.30°$ and $I > 2\sigma(I)$; R_1(unweighted, based on F) = 0.052 and wR_2(weighted, based on F^2) = 0.126 for all 4076 independent absorption-corrected reflections having $2\theta(CuK\alpha) < 127.30°$. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference map had maxima and minima of 0.38 and -0.34 $e^-/Å^3$, respectively. Since oxygen was the "heaviest" element present, the absolute configuration could not be reliably established using anomalous dispersion of the x-rays; the "Flack" absolute structure parameter refined to a final value of 0.0(2).

Animal Experiments. All experimental procedures were approved by The Animal Ethics Committee of Victoria University of Wellington.

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7. Data Reduction: SAINT Software in APEX2 v2010.3-0 Suite. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.
8. Refinement: SHELXTL v2010.3-0. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.