

Supplemental Information

Lactone-free ginkgolides *via* regioselective DIBAL-H reduction

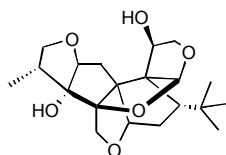
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Materials and Methods: All reagents were used as received. Ginkgolides were isolated from *Ginkgo biloba* extract (*BioGinkgo* 7/27, Pharmanex®, according to published procedures.¹ All reactions were conducted under argon in dry solvents and the yields refer to isolated products. Reactions were monitored by TLC (silica gel 60 F₂₅₄) and spots were visualized by heating and UV (or I₂). Preparatory TLC was performed using silica gel MERCK5715 plates. Column chromatography was performed using silica gel (230-400 mesh). ¹H NMR and ¹³C NMR were recorded on Bruker (300 or 400 MHz) spectrometers. The chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (in CDCl₃) or calibrated to solvent residual peak as an internal standard (MeOH-d₄, δ 3.31). High-resolution mass spectra (HRMS) were measured on JEOL JMS-HX110/100A HF mass spectrometer under FAB conditions with NBA as a matrix.

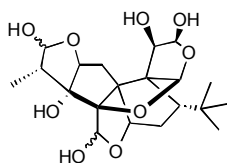
General procedure A – reduction with DIBAL-H: GA (64.5mg, 0.158mmol) was dissolved in dry THF (4.0 ml), cooled to –78°C under argon and 0.5ml of DIBAL-H (1M solution in dichloromethane or hexanes) was added. The mixture was allowed to stir for two hours, warmed to room-temperature and EtOAc (1.0 ml) was added, followed by 3N HCl (0.3 ml) and water (5.0 ml). The mixture was extracted with EtOAc (3 x 20 ml). Organic phase was separated, washed with brine (3 x 20ml), dried (Na₂SO₄), and solvent removed under vacuum. GA F-lactol **3** (3:2 mixture of epimers) was isolated as a white solid by preparative TLC (hexane/acetone–1/1).

General procedure B – deoxygenation with Et₃SiH/BF₃·Et₂O: GA F-lactol **3** (50.3 mg, 0.123 mmol) was dissolved in CH₂Cl₂ (6.0 ml), cooled to –78°C, and Et₃SiH (0.098 ml, 0.61 mmol) was added, followed by BF₃·Et₂O (0.039 ml, 0.304 mmol). The reaction mixture was warmed to room temperature over 12 h, quenched with saturated NaHCO₃ (1.0ml) and water (5.0 ml) and subsequently extracted with EtOAc (3 x 20 ml). Organic layer was separated, washed with brine (3 x 20 ml), dried (Na₂SO₄) and solvent removed under vacuum. GA monoether **4** was isolated by preparative TLC (hexane/acetone–1/1).

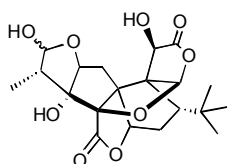


GA-triether (1): *Starting from 2:* GA trilactol **2** (3.1 mg, 0.0075 mmol) was suspended in CH₂Cl₂ (2ml) followed by the addition of Et₃SiH (21 μl, 0.13 mmol). The mixture cooled to –78 °C and BF₃·Et₂O (13 μl, 0.10 mmol) was added, and stirring at room temperature continued for 11 h. NaHCO₃ (sat.) (0.1ml) was added followed by H₂O (5.0 ml) and EtOAc (10ml). The layers were separated and aqueous phase was washed with EtOAc (2 x 10 ml). Organic fractions were combined and washed with brine (3 x 10 ml), dried (Na₂SO₄), and volatiles removed in vacuum. **1** (2.3 mg, 84 % yield) was isolated by prep-TLC (hexane/acetone – 1/1) as a white solid. *Starting from 7:* **1** was obtained according to general procedure B in 84 % yield. ¹H NMR (CDCl₃): 5.58 (s, 1H), 5.02 (t, *J*=8.9Hz, 1H), 4.37 (t, *J*=7.8Hz, 1H), 4.31 (d, *J*=10.5Hz, 1H), 4.18 (t, *J*=8.0Hz, 1H), 4.00 (m, 2H), 3.85 (d, *J*=10.5Hz, 1H), 3.68 (dd, *J*=11.2, 7.8Hz, 1H), 3.04 (m, 1H), 2.55 (dd, *J*=14.9, 9.1Hz, 1H), 2.30 (dd, *J*=13.4, 5.4Hz, 1H), 2.10 (dd, *J*=14.9, 7.5Hz, 1H), 1.91 (m, 2H), 1.09 (s, 9H), 1.01 (d, *J*=6.5Hz, 3H). ¹³C NMR (CDCl₃) 119.84, 108.92, 93.48, 93.11, 89.36, 77.85, 76.81, 74.74, 74.08,

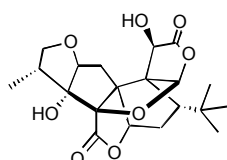
72.08, 69.08, 53.13, 39.89, 38.07, 36.96, 33.39, 29.72, 9.71. HRMS (FAB) m/z : calcd for $C_{20}H_{31}O_6$: 367.2121; found 367.2110 [M+H].



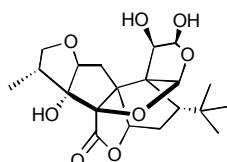
GA trilactol (2): GA (20.1 mg, 0.0496 mmol) was dissolved in THF (5.0 ml) and cooled to $-78\text{ }^{\circ}\text{C}$. 0.80 ml of DIBAL-H (1.0 M in hexane) was added *via* syringe and the stirring continued for 3 h, followed by another 0.40 ml of DIBAL-H and stirring for another 3h. The reaction mixture was brought to room temperature and 0.5 ml of 3N HCL was added, followed by H_2O (10 ml) and EtOAc (20 ml). Layers were separated, and the aqueous layer was washed with EtOAc (2 x 20ml). Organic fractions were combined, washed with brine (3 x 20ml) and dried over Na_2SO_4 , and volatiles removed in vacuum. The residue was subjected to prep-TLC (hexane/acetone – 1/2) to afford **2** (15.3 mg, 70 % yield) as a colorless oil. HRMS (FAB) m/z : calcd for $C_{20}H_{26}O_{11}Na$: 465.1373; found 465.1383 [M+Na].



GA F-lactol (3): Prepared from GA according to general procedure A in 70 % yield as a white solid. 1H NMR (300 MHz, $MeOH-d_4$): major isomer, 5.69 (s, 1H), 5.35 (d, $J=5.0\text{Hz}$, 1H), 4.96 (s, 1H), 4.78 (d, $J=3.4\text{Hz}$, 1H), 4.63 (t, $J=7.7\text{Hz}$, 1H), 2.56 (m, 2H), 2.17 (m, 2H), 1.89 (m, 2H), 1.09 (m, 12H); minor isomer, 5.98 (s, 1H), 5.13 (d, $J=7.7\text{Hz}$, 1H), 4.98 (s, 1H), 4.75 (d, $J=3.5\text{Hz}$, 1H), 4.35 (dd, $J=7.8, 7.1\text{Hz}$, 1H), 2.56 (m, 2H), 2.17 (m, 2H), 1.89 (m, 2H), 1.09 (m, 12H); minor: 5.98 (s, 1H), 5.13 (d, $J=7.7\text{Hz}$, 1H), 4.98 (s, 1H), 4.75 (d, $J=3.5\text{Hz}$, 1H), 4.35 (dd, $J=7.8, 7.1\text{Hz}$, 1H), 2.56 (m, 2H), 2.17 (m, 2H), 1.09 (m, 12H). HRMS (FAB) m/z : calcd for $C_{20}H_{26}O_9Na$: 433.1475; found 433.1494 [M+Na].

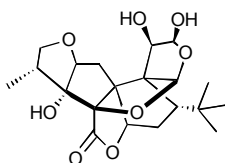


GA monoether (4): Prepared from GA F-lactol **3** according to general procedure B in 95% yield as a white solid. 1H NMR ($MeOH-d_4$): 5.97 (s, 1H), 4.97 (s, 1H), 4.75 (d, $J=3.4\text{Hz}$, 1H), 4.41 (t, $J=7.8\text{Hz}$, 1H), 4.18 (t, $J=7.9\text{Hz}$, 1H), 3.63 (dd, $J=10.5, 8.0\text{Hz}$, 1H), 2.80 (m, 1H), 2.45 (dd, $J=14.9, 7.0\text{Hz}$, 1H), 2.15 (m, 2H), 2.02 (dd, $J=15.0, 8.0\text{Hz}$, 1H), 1.86 (dd, $J=13.3, 5.6\text{Hz}$, 1H), 1.08 (s, 9H), 1.03 (d, $J=6.8\text{Hz}$, 3H); ^{13}C NMR ($MeOH-d_4$): 175.18, 173.66, 110.69, 91.89, 89.38, 87.15, 76.24, 69.60, 69.46, 67.54, 38.80, 37.93, 36.30, 32.27, 28.55, 8.51. HRMS (FAB) m/z : calcd for $C_{20}H_{27}O_8$: 395.1706; found 395.1707 [M+H].

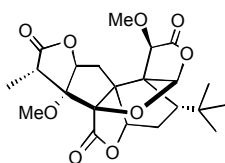


GA monoether C-lactol (5): Prepared for GA monoether **4** according to general procedure A in 80% yield as a white solid. 1H NMR ($MeOH-d_4$): 5.66 (s, 1H), 5.50 (d, $J=5.2\text{Hz}$, 1H), 4.66 (d, $J=3.2\text{Hz}$, 1H), 4.50 (d, $J=5.2\text{Hz}$, 1H), 4.39 (t, $J=6.8\text{Hz}$, 1H), 4.24 (t, $J=7.9\text{Hz}$, 1H), 3.62 (dd, $J=9.6, 8.0\text{Hz}$, 1H),

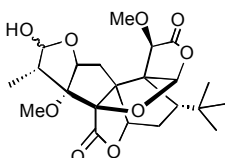
2.96 (m, 1H), 2.48 (dd, $J=6.8, 3.3\text{Hz}$, 2H), 2.10 (m, 2H), 1.80 (dd, $J=13.3, 5.4\text{Hz}$, 1H), 1.10 (s, 9H), 1.01 (d, $J=6.8\text{Hz}$, 3H). HRMS (FAB) m/z : calcd for $\text{C}_{20}\text{H}_{28}\text{O}_8\text{Na}$: 419.1682; found 419.1682 [M+Na].



GA diether (6): Prepared from **5** according to general procedure B, as a colorless oil in 100% yield. ^1H NMR (MeOH- d_4): 5.52 (s, 1H), 4.94 (t, $J=8.9\text{Hz}$, 1H), 4.67 (m, 1H), 4.40 (t, $J=6.6\text{Hz}$, 1H), 4.25 (t, $J=7.9\text{Hz}$, 1H), 4.11 (t, $J=8.7\text{Hz}$, 1H), 3.94 (t, $J=8.2\text{Hz}$, 1H), 3.62 (dd, $J=9.5, 8.1\text{Hz}$, 1H), 2.91 (m, 1H), 2.82 (dd, $J=15.2, 6.7\text{Hz}$, 1H), 2.41 (dd, $J=15.2, 6.6\text{Hz}$, 1H), 2.10 (m, 1H), 1.89 (m, 1H), 1.09 (s, 9H), 1.01 (d, $J=6.8\text{Hz}$, 3H). ^{13}C NMR (MeOH- d_4) 177.03, 118.94, 101.81, 93.28, 90.63, 89.30, 77.85, 73.79, 72.04, 71.44, 70.03, 39.22, 39.04, 37.11, 33.32, 29.56, 10.79. HRMS (FAB) m/z : calcd for $\text{C}_{20}\text{H}_{29}\text{O}_7$: 381.1913; found 381.1912 [M+H].



Dimethyl GA (8): 0.15g of KH in mineral oil was washed with hexane to give 50mg of white solid, which was placed on dry ice under argon and GA (30.0mg, 0.074mmol) in 4.0ml of THF was added dropwise and the reaction mixture was allowed to stir for 12h at room temperature, before being quenched with H_2O (20ml). The resulting solution was extracted with CH_2Cl_2 (3 x 20ml), dried (MgSO_4) and volatiles removed in vacuum. The residue was washed with hexanes and dried in vacuum to afford **8** (14.7mg, 45% yield) as a white solid. ^1H NMR (CDCl_3): 5.93 (s, 1H), 4.94 (dd, $J=9.4, 7.6\text{Hz}$, 1H), 4.61 (d, $J=3.7\text{Hz}$, 1H), 4.50 (s, 1H), 3.70 (s, 3H), 3.27 (s, 3H), 3.13 (q, $J=7.1\text{Hz}$, 1H), 2.82 (dd, $J=15.1, 7.4\text{Hz}$, 1H), 1.95 (m, 4H), 1.34 (d, $J=7.1\text{Hz}$, 3H), 1.07 (s, 9H). HRMS (FAB) m/z : calcd for $\text{C}_{22}\text{H}_{29}\text{O}_9$: 437.1812; found 437.1819 [M+H].



Dimethyl GA F-lactol (9): Prepared from dimethyl GA **8** according to general procedure A in 41 % yield as an oily solid. ^1H NMR (CDCl_3): major 5.95 (s, 1H), 5.37 (t, $J=6.5\text{Hz}$, 1H), 4.75 (dd, $J=9.3, 7.3\text{Hz}$, 1H), 4.57 (d, $J=3.9\text{Hz}$, 1H), 4.50 (s, 1H), 3.71 (s, 3H), 3.38 (s, 3H), 3.03 (d, $J=6.3\text{Hz}$, 1H), 2.80 (t, $J=6.9\text{Hz}$, 1H), 2.58 (dd, $J=14.8, 7.3\text{Hz}$, 1H), 2.20 (m, 4H), 1.21 (d, $J=7.1\text{Hz}$, 3H), 1.06 (s, 9H); minor 5.92 (s, 1H), 5.39 (t, $J=5.5\text{Hz}$, 1H), 5.04 (t, $J=7.9\text{Hz}$, 1H), 4.63 (d, $J=3.9\text{Hz}$, 1H), 4.48 (s, 1H), 3.70 (s, 3H), 3.45 (s, 3H), 3.15 (d, $J=9.3\text{Hz}$, 1H), 2.78 (m, 1H), 2.53 (dd, $J=15.2, 7.4\text{Hz}$, 1H), 2.20 (m, 4H), 1.21 (d, $J=7.1\text{Hz}$, 3H), 1.06 (s, 9H). HRMS (FAB) m/z : calcd for $\text{C}_{22}\text{H}_{31}\text{O}_9$: 439.1968; found 439.1953 [M+H].

References:

- (a) S. Jaracz, S. Malik, K. Nakanishi, *Phytochemistry* 2004, **65**, 2897; (b) K. Nakanishi, S. Jaracz, S. Malik, H. Ishii, S. V. Dzyuba, *PCT Int. Appl.* 2005, 61 pp. WO 2005046829 A2 20050526.