

Supporting Information

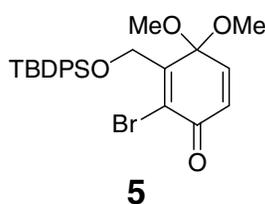
Total Synthesis of the NF- κ B Inhibitor (-)-Cycloepoxydon: Utilization of Tartrate-Mediated Nucleophilic Epoxidation

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Thomas D. Gilmore,[§] and John A. Porco, Jr.*[†]

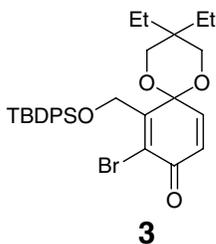
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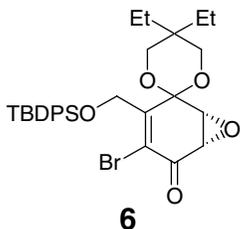
General Information: ¹H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with CDCl₃ as the solvent unless otherwise stated. ¹³C NMR spectra were recorded on a 75.0 MHz spectrometer (unless otherwise stated) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (¹H, δ 7.24; ¹³C, δ 77.23). Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, par obsc = partially obscure, overl = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet,) and coupling constants. All ¹³C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Low and high-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D$ (concentration in grams/100 mL solvent). Chiral HPLC analysis was performed on an Agilent 1100 series (CHIRALCEL OD, Column No. OD00CE-AI015). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Scientific Absorbents, Inc.). Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Potassium hexamethyldisilazide (KHMDS, 0.66 M in toluene) was purchased from Callery Chemical (Pittsburgh, PA). All other reagents were used as supplied by Sigma-Aldrich, Fluka, and Strem Chemicals. Methylene chloride, toluene, hexane, and benzene and 1,2-dichloroethane were distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Ph₃COOH,^{S1} (*E*)-tributyl-1-pentenyl-stannane^{S2} were prepared according to literature procedures. All reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted.



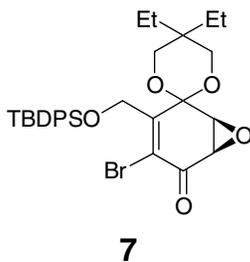
Dimethoxy ketal 5. Compound **4** (8 g, 17 mmol) was dissolved in 100 mL MeOH and cooled to 0°C, PhI(OAc)₂ (6 g, 18.6 mmol) was added over 5 min. The reaction was stirred at 0°C for 30 min. The reaction mixture was quenched with sat. NaHCO₃ and extracted with Et₂O. The organic layers were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification on silica gel (15 % EtOAc in hexane) provided 7.2 g (14.44 mmol, 84 %) of dimethoxy ketal **5** as a yellow solid. mp 98-100 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.81-7.78 (m, 4H), 7.43-7.40 (m, 6H), 6.76 (d, 1H, *J* = 10.4Hz), 6.56 (d, 1H, *J* = 10.4Hz), 4.45 (s, 2H), 3.26 (s, 6H), 1.07 (s, 9H); ¹³C NMR (75.0 MHz, CDCl₃) δ 178.3, 153.8, 144.4, 136.0, 133.0, 130.5, 130.3, 130.0, 127.9, 97.7, 60.9, 51.8, 27.0, 19.6, 19.4; IR (thin film) ν_{max} 2934, 2857, 1682, 1482, 1274, 1113, 1071 cm⁻¹; CILRMS [M⁻¹Bu-MeO]⁺ calculated for C₂₀H₁₈BrO₃Si: 413.3, found: 413.0.



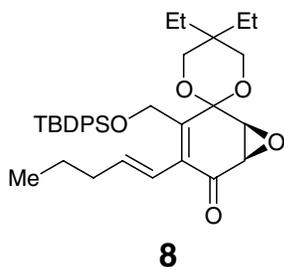
Cyclic ketal 3. A mixture of **5** (600 mg, 1.2 mmol), 2,2-diethyl-1,3-propanediol (500 mg, 3.8 mmol) and pyridinium *p*-toluenesulfonate (45 mg, 0.18 mmol) was placed in a round-bottomed flask fitted with a water condenser and 8 mL anhydrous benzene was added. After stirring at 70 °C for 80 min, pH 7 buffer was added at rt and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (13 % EtOAc in hexane) provided 609 mg (1.07 mmol, 89 %) of cyclic ketal **3** as a white solid. mp 131-133°C; ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.72 (m, 4H), 7.61 (d, 1H, *J* = 10.4 Hz), 7.41-7.34 (m, 6H), 6.34 (d, 1H, *J* = 10.4 Hz), 4.61 (s, 2H), 3.76 (d, 2H, *J* = 12.0 Hz), 3.59 (d, 2H, *J* = 12.0 Hz), 1.40 (q, 2H, *J* = 7.6 Hz), 1.08 (q, 2H, *J* = 7.6 Hz), 1.06 (s, 9H), 0.73 (t, 3H, *J* = 7.6 Hz), 0.57 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (75.0 MHz, CDCl₃) δ 178.4, 153.8, 137.5, 136.2, 133.7, 129.8, 129.0, 127.7, 126.6, 92.8, 68.9, 61.8, 34.5, 27.1, 25.2, 23.2, 19.8, 7.5, 6.6; IR (thin film) ν_{max} 2965, 2859, 1680, 1647, 1145, 1110, 1070, 1002 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₃₀H₃₈BrO₄Si: 569.1724, found: 569.1698.



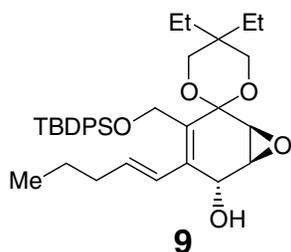
Monoepoxide 6. To 25 mg (0.09 mmol) of Ph₃COOH dissolved in 1 mL toluene was added 22 μL (0.048 mmol) of 2.2 M *n*BuLi in hexane at rt. After 20 min, 4.1 mg (0.018 mmol) *L*-DIPT in 0.2 mL toluene was added, and the mixture was stirred for 30 min at rt. Next, 10 mg (0.018 mmol) cyclic ketal **3** in 0.8 mL toluene was added and the reaction mixture stirred for 24 h at rt. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. 88% conversion (¹H NMR). Chiral HPLC showed 68% ee (HPLC conditions: hexane/2-propanol [85/15], 23 °C, *t*_R = 10.0, 22.2 min for major and minor enantiomers, respectively).



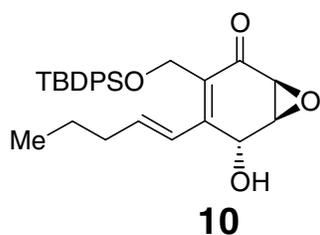
Monoepoxide 7. To 1.5 g (5.4 mmol) of Ph₃COOH dissolved in 10 mL toluene was added 4.35 mL (4.35 mmol) of 1.0 M NaHMDS in THF at rt. After 20 min, 310 mg (1.32 mmol) *L*-DIPT in 2 mL toluene was added, the mixture was stirred for 30 min at rt. The reaction mixture was cooled to -78°C and 480 mg (0.84 mmol) of cyclic ketal **3** in 8 mL toluene was added and the reaction stirred at -50°C for 30 h. The reaction was quenched with water and the mixture extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (10 % EtOAc in hexane) provided 480 mg (0.82 mmol, 97%) of monoepoxide **7** as a white solid. 96% ee (chiral HPLC analysis). mp 105-107°C; ¹H NMR (400 MHz, CDCl₃) δ 7.72-7.70 (m, 4H), 7.41-7.34 (m, 6H), 4.54 (s, 2H), 4.35 (d, 1H, *J* = 4.0 Hz), 3.91 (d, 1H, *J* = 12 Hz), 3.85 (d, 1H, *J* = 12 Hz), 3.70 (d, 1H, *J* = 4.0 Hz), 3.68 (d, 1H, *J* = 12 Hz), 3.59 (d, 1H, *J* = 12 Hz), 1.35 (q, 2H, *J* = 7.6 Hz), 1.12 (q, 2H, *J* = 7.6 Hz), 1.04 (s, 9H), 0.74 (t, 3H, *J* = 7.6 Hz), 0.58 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (75.0 MHz, CDCl₃) δ 187.0, 151.7, 136.2, 133.5, 129.8, 127.8, 126.5, 95.1, 68.7, 62.1, 52.4, 50.4, 34.7, 27.1, 25.2, 23.3, 19.8, 7.4, 6.8; IR (thin film) ν_{max} 3071, 3049, 2965, 2860, 1702, 1427, 1387, 1304, 1276, 1127, 1021 cm⁻¹; CIHRMS [M+H]⁺ calculated for 585.1674, found: 585.1719; [α]_D²³ = +39° (c = 1.0, CHCl₃).



α -Pentenyl enone 8. 30 mg (0.029 mmol) of $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ was placed in a 10 mL Schlenk tube, then 100 mg (0.17 mmol) of **7** in 2 mL anhydrous $\text{CH}_2\text{ClCH}_2\text{Cl}$ was added, followed by addition of 100 mg (0.28 mmol) *E*-tributyl-1-pentenylstannane. The reaction was stirred at 60°C for 20 h. After cooling to rt, a further 30 mg of $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$ was added and the reaction stirred for a further 20 h at 60 °C. After cooling to rt, the reaction mixture was diluted with CH_2Cl_2 and stirred with 20 mL 5 % KF solution for 20 min. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification on silica gel (12 % Et_2O in hexane) provided 80 mg (0.14 mmol, 81%) of α -pentenyl enone **8** as a colorless oil and 10 mg of recovered **7**. ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.67 (m, 4H), 7.41-7.33 (m, 6H), 6.29 (m, 2H), 4.52 (d, 1H, $J = 12$ Hz), 4.47 (d, 1H, $J = 12$ Hz), 4.32 (d, 1H, $J = 4.8$ Hz), 3.88 (d, 1H, $J = 12$ Hz), 3.79 (d, 1H, $J = 12$ Hz), 3.62 (dd, 1H, $J = 2.0, 12$ Hz), 3.56 (d, 1H, $J = 4.8$ Hz), 3.51 (dd, $J = 2.0, 12$ Hz), 2.03 (m, 2H), 1.36 (m, 4H), 1.11 (q, 2H, $J = 7.6$), 0.86 (t, 3H, $J = 7.6$ Hz), 0.73 (t, 3H, $J = 7.6$ Hz), 0.56 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 195.2, 144.6, 140.0, 136.1, 133.8, 129.8, 127.8, 122.2, 95.0, 68.5, 68.4, 59.2, 53.6, 50.1, 36.3, 34.8, 27.1, 25.3, 23.5, 22.4, 19.7, 14.0, 7.4, 6.8; IR (thin film) ν_{max} 2963, 1691, 1427, 1386, 1131, 1092, 1009 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{35}\text{H}_{47}\text{O}_5\text{Si}$: 575.3195, found: 575.3226; $[\alpha]_{\text{D}}^{23} = +51^\circ$ ($c = 1.0, \text{CHCl}_3$).



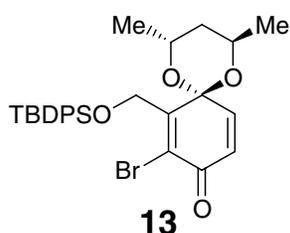
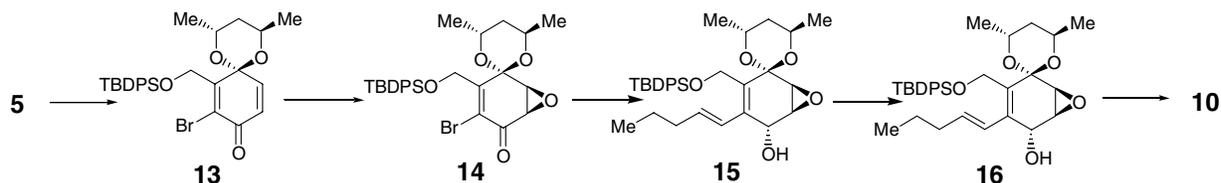
Epoxy alcohol 9. To 50 mg (0.087 mmol) of **8** dissolved in 2 mL THF was added 240 μL (0.24 mmol) of 1.0 M DIBAL-H in hexane at -78°C and the mixture was stirred for 15 min before being quenched with 5% potassium sodium tartrate and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification on silica gel (25% EtOAc in hexane) provided 44 mg (0.076 mmol, 88%) of **9** as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.68 (m, 4H), 7.40-7.32 (m, 6H), 6.46 (d, 1H, $J = 16$ Hz), 6.04 (dt, 1H, $J = 6.8, 16$ Hz), 4.75 (d, 1H, $J = 9.2$ Hz), 4.47 (d, 1H, $J = 11.2$ Hz), 4.44 (d, 1H, $J = 11.2$ Hz), 3.97 (d, 1H, $J = 4$ Hz), 3.88 (d, 1H, $J = 12$ Hz), 3.80 (d, 1H, $J = 12$ Hz), 3.60 (d, 1H, $J = 12$ Hz), 3.55 (d, 1H, $J = 12$ Hz), 3.54 (d, 1H, $J = 4$ Hz), 2.16 (d, 1H, $J = 9.2$ Hz), 2.03 (m, 2H), 1.39 (m, 4H), 1.12 (q, 2H, $J = 7.6$ Hz), 0.73 (t, 3H, $J = 7.6$ Hz), 0.60 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 136.1, 134.3, 134.2, 132.1, 129.6, 127.6, 127.3, 96.1, 68.7, 67.9, 63.7, 60.5, 58.2, 52.8, 52.6, 47.1, 35.7, 34.9, 27.2, 25.2, 23.4, 22.6, 19.6, 14.4, 13.9, 7.4, 6.8; IR (thin film) ν_{max} 3426, 2963, 2931, 2859, 1644, 1428, 1113, 1047 cm^{-1} ; CIHRMS M^+ calculated for $\text{C}_{35}\text{H}_{48}\text{O}_5\text{Si}$: 576.3271, found: 576.3271; $[\alpha]_{\text{D}}^{23} = -30^\circ$ ($c = 1.0, \text{CHCl}_3$).



Epoxy-quinol 10. 45 mg (0.078 mmol) of **9** was dissolved in 1 mL CH_3CN and 0.2 mL 48% HF was added at 0°C . After stirring for 5 min, 2 mL sat. NaHCO_3 was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification on silica gel (25% EtOAc in hexane) provided 33 mg (0.071 mmol, 92%) of **10** as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.63 (m, 4H), 7.43-7.34 (m, 6H), 6.55 (d, 1H, $J = 16$ Hz), 6.43 (dt, 1H, $J = 6.8, 16$ Hz), 5.02 (d, 1H, $J = 8$ Hz), 4.49 (d, 1H, $J = 12$ Hz), 4.46 (d, 1H, $J = 12$ Hz), 3.78 (dd, 1H, $J = 1.6, 4$ Hz), 3.43 (d, 1H, $J = 4$ Hz), 2.15 (m, 2H), 2.05 (d, 1H, $J = 8$ Hz), 1.45 (m, 2H), 1.00 (s, 9H), 0.92 (t, 3H, $J = 7.6$ Hz); ^{13}C

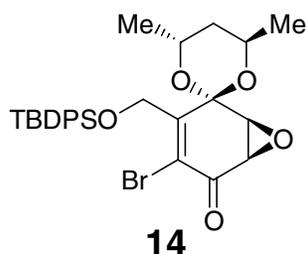
NMR (75.0 MHz, CDCl₃) δ 194.3, 148.7, 141.8, 135.9, 133.4, 130.3, 129.9, 127.8, 126.7, 63.4, 56.5, 55.4, 52.5, 36.1, 27.0, 22.2, 19.4, 13.9; IR (thin film) ν_{max} 3423, 2959, 2931, 2361, 2339, 1663, 1627, 1112, 1043 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₃₀H₃₈BrO₄Si: 463.2306, found: 463.2301; $[\alpha]_{\text{D}}^{23} = -95^{\circ}$ (c = 1.0, CHCl₃).

Absolute Stereochemical Correlation of Compound 10



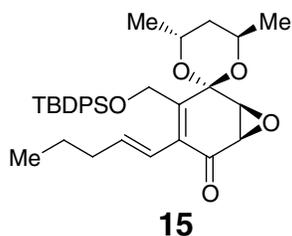
Chiral ketal 13. A mixture of **5** (1.0 g, 2.0 mmol), (2*R*, 4*R*)-(-)-pentanediol (270 mg, 2.6 mmol) and pyridinium *p*-toluenesulfonate (50 mg, 0.2 mmol) was placed in a round-bottomed flask fitted with a water condenser and 20 mL benzene was added. After stirring at 70 °C for 4 h, pH 7 buffer was added at rt and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (15% EtOAc in hexane) provided 900 mg (1.66 mmol, 83%) of chiral ketal **13**

as a yellow solid. mp 103-104 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.74 (m, 4H), 7.43-7.36 (m, 6H), 7.05(d, 1H, *J* = 10.4 Hz), 6.22 (d, 1H, *J* = 10.4 Hz), 4.56(d, 1H, *J* = 11.2 Hz), 4.52 (d, 1H, *J* = 11.2 Hz), 4.23 (m, 1H), 3.97 (m, 1H), 1.67 (m, 1H), 1.47 (m, 1H), 1.15 (d, 3H, *J* = 6 Hz), 1.14 (d, 3H, *J* = 6 Hz), 1.08 (s, 9H); ¹³C NMR (75.0 MHz, CDCl₃) δ 178.7, 154.4, 144.0, 136.3, 136.0, 133.5, 130.0, 127.8, 125.3, 93.8, 66.1, 64.7, 61.8, 37.7, 27.1, 22.5, 22.2, 19.7; IR (thin film) ν_{max} 2931, 2858, 1681, 1473, 1462, 1428, 1275, 1113, 1067 cm⁻¹; CIHRMS [M⁺] calculated for C₂₈H₃₃BrO₄Si: 540.1331, found: 540.1323; $[\alpha]_{\text{D}}^{23} = +12.5^{\circ}$ (c = 1.0, CHCl₃).

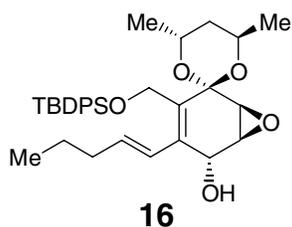


Epoxy enone 14. 51 mg (0.18 mmol) of Ph₃COOH was dissolved in 1 mL THF at -78 °C, then 167 μ L (0.1 mmol) of 0.66 M KHMDS in toluene was added. After 10 min, chiral ketal **13** (40 mg, 0.074 mmol) in 1 mL THF was added. The yellow solution formed was warmed to -10 °C over 5 h and kept at -10°C for a further 1.5 h. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification on silica gel (25 % Et₂O in hexane) provided 35 mg (0.063 mmol, 85%) of **14** as a pale yellow solid.

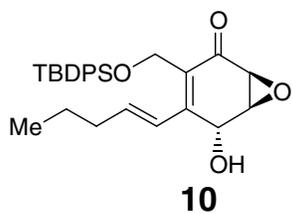
¹H NMR (400 MHz, CDCl₃) δ 7.73-7.69 (m, 4H), 7.44-7.36 (m, 6H), 4.63 (d, 1H, *J* = 10.8 Hz), 4.48 (d, 1H, *J* = 10.8 Hz), 4.28 (m, 1H), 4.09 (m, 1H), 3.87 (d, 1H, *J* = 4Hz), 3.68 (d, 1H, *J* = 4 Hz), 1.64 (m, 1H), 1.35 (m, 1H), 1.16 (d, 3H, *J* = 6 Hz), 1.07 (s, 9H), 1.05 (d, 3H, *J* = 6 Hz); ¹³C NMR (75.0 MHz, CDCl₃) δ 187.7, 152.2, 136.2, 136.1, 133.3, 133.1, 130.1, 127.8, 125.9, 96.7, 65.0, 62.1, 54.2, 52.0, 39.5, 27.1, 22.1, 21.9, 19.6; IR (thin film) ν_{max} 2932, 2858, 1703, 1472, 1428, 1382, 1216, 1114, 1021 cm⁻¹; CIHRMS [M+H]⁺ calculated for C₂₈H₃₄BrO₅Si: 557.1354, found: 557.1361; $[\alpha]_{\text{D}}^{23} = +51^{\circ}$ (c = 1.0, CHCl₃).



α -Pentenyl enone 15. 15 mg (0.014 mmol) of Pd₂dba₃·CHCl₃ was placed in a 10 mL Schlenk tube, then 50 mg (0.09 mmol) of **14** in 3 mL CH₂Cl₂ was added, followed by addition of 50 mg (0.14 mmol) *E*-tributyl-1-pentenylstannane. The reaction was stirred at 35 °C for 15 h. After cooling to rt, another 10 mg Pd₂dba₃·CHCl₃ was added and the reaction stirred for a further 10 h at 35 °C. After cooling to rt, the mixture was diluted with CH₂Cl₂ and stirred with 20 mL 5 % KF solution for 20 min. The organic layer was separated, and the aqueous layer extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (10% Et₂O in hexane) provided 36 mg (0.066 mmol, 73%) of α -pentenyl enone **15** as colorless oil and 9 mg recovered **14**. ¹H NMR (400 MHz, CDCl₃) δ 7.70-7.67 (m, 4H), 7.43-7.37 (m, 6H), 6.12 (m, 2H), 4.56 (d, 1H, *J* = 11.2 Hz), 4.39 (d, 1H, *J* = 11.2 Hz), 4.25 (m, 1H), 4.14 (m, 1H), 3.85 (d, 1H, *J* = 4.4 Hz), 3.56 (d, 1H, *J* = 4.4 Hz), 1.98 (m, 2H), 1.61 (m, 1H), 1.42 (m, 1H), 1.33 (m, 2H), 1.17 (d, 3H, *J* = 6 Hz), 1.06 (s, 9H), 1.05 (d, 3H, *J* = 6 Hz), 0.85 (t, 3H, *J* = 7.2 Hz); ¹³C NMR (75.0 MHz, CDCl₃) δ 196.0, 145.0, 139.9, 136.1, 134.3, 133.4, 130.0, 127.9, 122.2, 96.7, 64.5, 58.5, 53.3, 40.2, 36.2, 27.2, 22.4, 22.0, 19.6, 14.0; IR (thin film) ν_{max} cm⁻¹ 2931, 2859, 1692, 1463, 1428, 1381, 1260, 1217, 1168, 1113; CIHRMS [M+H]⁺ calculated for C₃₃H₄₃O₅Si: 547.2882, found: 547.2887; [α]_D²³ = +76° (c = 1.0, CHCl₃).

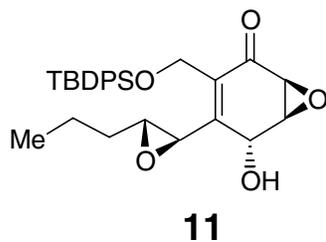


Epoxy alcohol 16. To 130 mg (0.24 mmol) of **15** in 5 mL THF was added 600 μ L (0.6 mmol) of 1.0 M DIBAL-H in hexane at -78°C, the mixture was stirred for 15 min before quenched with 5% potassium sodium tartrate and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification on silica gel (12% EtOAc in hexane) provided 110 mg (0.20 mmol, 85%) of **16** as a pale yellow oil and 10 mg (9%) of the *cis*-epoxy alcohol isomer. ¹H NMR (400 MHz, CDCl₃) δ 7.71-7.67 (m, 4H), 7.42-7.34 (m, 6H), 6.26(d, 1H, *J* = 16 Hz), 6.01 (dt, 1H, *J* = 7.2, 16 Hz), 4.73 (dd, 1H, *J* = 3.2, 11.2 Hz), 4.48 (d, 1H, *J* = 11.2 Hz), 4.31 (m, 1H), 4.27 (d, 1H, *J* = 11.2 Hz), 4.23 (m, 1H), 3.56 (d, 1H, *J* = 4.0 Hz), 3.50 (dd, 1H, *J* = 3.2, 4.0 Hz), 2.45 (d, 1H, *J* = 11.2 Hz), 2.01 (m, 2H), 1.61 (m, 1H), 1.52 (m, 1H), 1.35 (m, 2H), 1.20 (d, 3H, *J* = 6.4 Hz), 1.07 (d, 3H, *J* = 6.4 Hz), 1.04 (s, 9H), 0.86 (t, 3H, *J* = 7.6 Hz); ¹³C NMR (75.0 MHz, CDCl₃) δ 137.6, 136.1, 136.0, 134.1, 133.8, 133.5, 129.8, 127.8, 126.9, 98.8, 64.4, 64.1, 63.9, 56.7, 50.7, 50.4, 40.6, 35.6, 27.1, 22.6, 22.0, 21.8, 19.5, 14.0; IR (thin film) ν_{max} 3422, 2961, 2930, 2858, 1463, 1428, 1381, 1171, 1113, 1039 cm⁻¹; CIHRMS M⁺ calculated for C₃₃H₄₄O₅Si: 548.2958, found: 548.3000; [α]_D²³ = +47.3° (c = 1.0, CHCl₃).



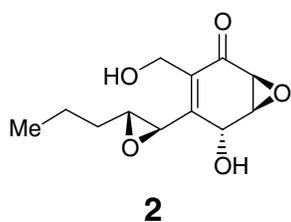
Epoxy-quinol 10. 110 mg (0.2 mmol) of **16** dissolved in 5 mL CH₃CN was added 1 mL 48% HF at 0°C. After stirring for 5 min, 10 mL sat. NaHCO₃ was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification on silica gel (25% EtOAc in hexane) provided 85 mg (0.18 mmol, 92%) of **10'** as a pale yellow oil. ¹H and ¹³C NMR were found to be identical with

10 produced by tartrate-mediated reactions; $[\alpha]_D^{23} = -97.5^\circ$ ($c = 1.2$, CHCl_3). **10** (tartrate-mediated, *cf.* Scheme 1): $[\alpha]_D$ (-95.0° ($c = 1.0$, CHCl_3)).



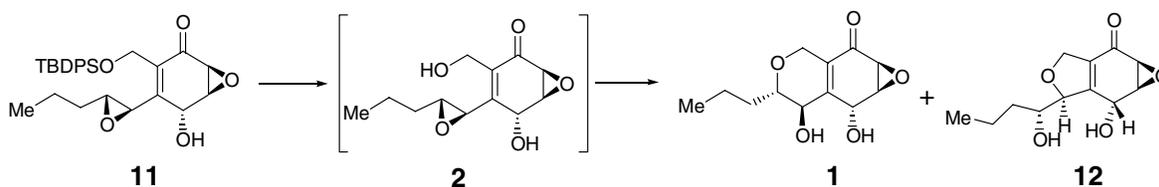
Bis-epoxide 11. Compound **10** (85 mg, 0.18 mmol) was dissolved in 2 mL CH_2Cl_2 containing 0.2 mL pH 7 buffer and 50 mg (0.29 mmol) *m*-CPBA was added. The mixture was stirred at rt for 4 h. After addition of 2 mL 1:1 sat $\text{NaHCO}_3/\text{Na}_2\text{S}_2\text{O}_3$, the mixture was stirred for 10 min and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification on silica gel (14%

EtOAc in hexane) provided 75 mg (0.16 mmol, 85 %) of **11** as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.66-7.60 (m, 4H), 7.40-7.36 (m, 6H), 4.53 (d, 1H, $J = 12$ Hz), 4.47 (d, 1H, $J = 12$ Hz), 4.36 (d, 1H, $J = 3.6$ Hz), 3.87 (d, 1H, $J = 2$ Hz), 3.75 (dd, 1H, $J = 2, 3.6$ Hz), 3.45 (d, 1H, $J = 3.6$ Hz), 3.19 (d, 1H, $J = 3.6$ Hz), 3.14 (m, 1H), 1.43 (m, 4H), 1.01 (s, 9H), 0.92 (t, 3H, $J = 7.6$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 192.0, 150.3, 135.8, 134.3, 133.2, 130.0, 127.9, 61.9, 60.3, 56.5, 56.4, 55.8, 52.9, 34.1, 27.0, 19.3, 14.0; IR (thin film) ν_{max} 3447, 2960, 2932, 2858, 1681, 1428, 1258, 1236, 1112, 1044 cm^{-1} ; CIHRMS M^+ calculated for $\text{C}_{28}\text{H}_{34}\text{O}_5\text{Si}$: 478.2176, found: 478.2207; $[\alpha]_D^{23} = -115^\circ$ ($c = 1.0$, CHCl_3).



Bis-epoxide 2. Compound **11** (52 mg, 0.11 mmol) was dissolved in 2.5 mL THF and 700 μL 1:1 AcOH/TBAF was added (freshly prepared by mixing 60 μL AcOH with 1 mL 1.0 M TBAF in THF). After stirring for 2 h at rt, the reaction mixture was directly subjected to column chromatography. Purification on silica gel (40% EtOAc in hexane) afforded 19 mg (0.079 mmol, 73%) of **2** as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.46 (dd, 1H, $J = 7.2, 12.8$ Hz), 4.38 (dd, 1H, $J = 5.6, 12.8$ Hz), 4.34 (d, 1H, $J = 3.2$ Hz), 3.79 (dd, 1H, $J = 1.6, 3.6$ Hz), 3.76 (d, 1H, $J =$

2.0 Hz), 3.51 (d, 1H, $J = 3.6$ Hz), 3.11 (m, 2H), 2.29 (app t, 1H, $J = 6.8$ Hz), 1.66 (m, 2H), 1.50 (m, 2H), 0.97 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75.0 MHz, CDCl_3) δ 194.4, 150.6, 133.3, 61.7, 60.3, 56.2, 56.1, 56.0, 52.8, 34.0, 19.2, 14.0; IR (thin film) ν_{max} 3420, 2961, 2874, 1676, 1236, 1044 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{17}\text{O}_5$: 241.1078, found: 241.1043.



(-)-Cycloepoxydon (1) and "iso"-cycloepoxydon (12). Bis-epoxide **11** (75 mg, 0.016 mmol) was dissolved in 5 mL CH_3CN and 2 mL 48% HF was added. After stirring at rt for 2 h, 5 mL water was added and the solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated *in vacuo*. Purification on silica gel (25% EtOAc in CH_2Cl_2) provided 19.8 mg (0.08 mmol, 53%) of (-)-cycloepoxydon **1** as a white solid and 13 mg (0.05 mmol, 35%) "iso"-cycloepoxydon **12** as a white solid.

1. ^1H NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD}$ 95:5) δ 4.91 (s, 1H), 4.50 (dd, 1H, $J = 2.0, 17.6$ Hz), 4.07-4.02 (m, 1H), 3.77 (dd, 1H, $J = 1.2, 4.0$ Hz), 3.41 (dd, 1H, $J = 0.8, 3.6$ Hz), 3.30 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 1.44-1.32 (m, 2H), 0.90 (t,

3H, $J = 7.2$ Hz); ^{13}C NMR (75.0 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD}$ 95:5) δ 191.8, 150.3, 129.4, 77.7, 65.0, 61.9, 60.0, 57.0, 52.1, 33.8, 18.5, 13.8; IR (thin film) ν_{max} 3397, 2961, 1675, 1457, 1398, 1262, 1108, 1039, 910, 735 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{17}\text{O}_5$: 241.1078, found: 241.1098; $[\alpha]_{\text{D}}^{23} = -139^\circ$ ($c = 1.0$, $\text{CHCl}_3:\text{CH}_3\text{OH}$ 95:5) [literature value:^{S3} $[\alpha]_{\text{D}}^{23} = -145^\circ$ ($c = 1.1$, $\text{CHCl}_3:\text{CH}_3\text{OH}$ 95:5)]. **12.** ^1H NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD}$ 95:5) 4.93 (m, 1H), 4.88 (s, 1H), 4.78 (ddd, 1H, $J = 0.8, 3.6, 12.8$ Hz), 4.60 (ddd, 1H, $J = 2.0, 5.6, 12.8$ Hz), 3.77 (dd, 1H, $J = 0.8, 3.2$ Hz), 3.61 (m, 1H), 3.42 (dd, 1H, $J = 0.8, 3.6$ Hz), 1.55-1.32 (m, 4H), 0.90 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (75.0 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD}$ 95:5) δ 189.5, 155.6, 132.5, 88.9, 73.3, 72.5, 61.6, 59.7, 53.7, 35.2, 18.6, 14.3; IR (thin film) ν_{max} 3396, 2961, 1684, 1457, 1418, 1264, 1107, 1048, 1001, 911, 734 cm^{-1} ; CIHRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{17}\text{O}_5$: 241.1078, found: 241.1103; $[\alpha]_{\text{D}}^{23} = -138^\circ$ ($c = 1.1$, $\text{CHCl}_3:\text{CH}_3\text{OH}$ 95:5).

Experimental Procedures for NF κ B DNA binding and I κ B α degradation

Mouse 3T3 cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum (FBS). Twenty-four hours prior to treatment, cells were fluid changed to DMEM containing 0.5% FBS. Cells were then incubated for 2 h with the indicated concentrations of cycloepoxydon or methanol as a control. Cultures were then treated with 2 ng/ml of TNF α (R&D Systems) for 20 min and cells were lysed in AT buffer (20 mM Hepes, pH 7.9, 1% v/v Triton X-100, 20% v/v glycerol, 1 mM EDTA, 1 mM EGTA, 20 mM NaF, 1 mM $\text{Na}_4\text{P}_2\text{O}_7$, 1 mM dithiothreitol, 1 mM Na_3VO_4 , 1 $\mu\text{g}/\text{ml}$ PMSF, 1 $\mu\text{g}/\text{ml}$ leupeptin, 1 $\mu\text{g}/\text{ml}$ pepstatin). To measure DNA binding, samples containing 20 μg of protein were analyzed in an electrophoretic mobility shift assay using a radiolabelled κB site probe as described previously.^{S4} For Western blotting, samples containing 10 μg of protein were separated on a 12.5% SDS-polyacrylamide gel, transferred to a nitrocellulose membrane, and probed with an anti-I κ B α antiserum (1:500 dilution) directed against C-terminal sequences of I κ B α (Santa Cruz Biotechnology, Inc., Catalog #sc-203); complexes were then detected with horseradish peroxidase-conjugated goat anti-rabbit IgG (1:20,000) and SuperSignal West Dura Extended Substrate (Pierce).

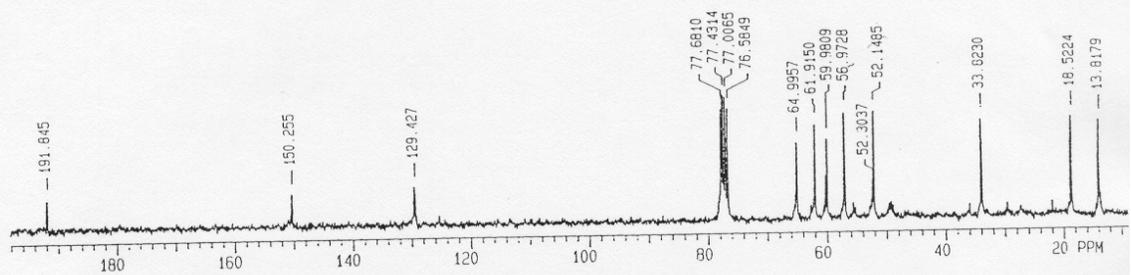
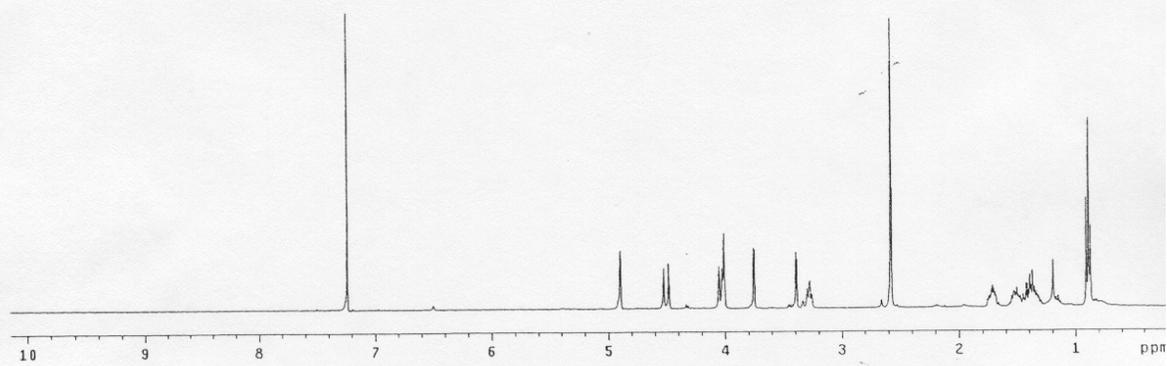
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- (S1) Bissing, D. E.; Matuszac, C. A.; McEwen, W. E. *J. Am. Chem. Soc.* **1964**, *86*, 3824-3828.
- (S2) Prepared according to: (a) Eisch J. J.; Galle J. E. *J. Organomet. Chem.* **1988**, *341*, 293-313. (b) Zweifel, G.; Miller, J. A. *Organic Reactions*, Vol. 32, John Wiley & Sons, New York, **1984**, p. 430.
- (S3) Gehrt, A.; Erkel, G.; Anke, H.; Anke, T.; Sterner, O. *Nat. Prod. Lett.* **1997**, *9*, 259-264.
- (S4) (a) Capobianco, A. J.; Gilmore, T. D. *Oncogene* **1991**, *6*, 2203-2210. (b) Sif, S.; Capobianco, A. J. Gilmore, T. D. *Oncogene* **1993**, *8*, 2501-2509.

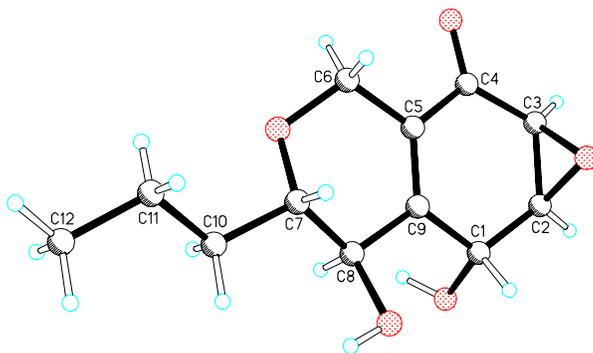
Table 1. NMR data (in CDCl₃:CD₃OD 95:5) comparison of natural and synthetic (-)-cycloepoxydon 1

¹ H NMR (Hz)		¹³ C NMR (Hz)	
Natural (500 MHz)	Synthetic (400 MHz)	Natural (125 MHz)	Synthetic (75.0 MHz)
4.90 (m, 1H)	4.91 (s, 1H)	191.9	191.8
4.49 (dd, 1H, 2.2, 17.1)	4.50 (dd, 1H, 2.0, 17.6)	150.4	150.3
4.03 (ddd, 1H, 2, 2, 17.1)	4.07 – 4.02 (m, 2H)	129.3	129.4
4.02 (m, 1H)		77.7	77.7
3.75 (dd, 1H, 1.4, 3.6)	3.77 (dd, 1H, 1.2, 4.0)	64.9	65.0
3.38 (dd, 1H, 1.0, 3.6)	3.41 (dd, 1H, 0.8, 3.6)	62.0	61.9
3.28 (ddd, 1H, 2.8, 7.6, 10.3)	3.30 (m, 1H)	59.9	60.0
1.71 (m, 1H)	1.72 (m, 1H)	57.0	57.0
1.51 (m, 1H)	1.52 (m, 1H)	52.1	52.1
1.40 (m, 1H)	1.44 – 1.32 (m, 2H)	33.8	33.8
1.35 (m, 1H)		18.5	18.5
0.88 (t, 3H, 7.2)	0.90 (t, 3H, 7.2)	13.8	13.8

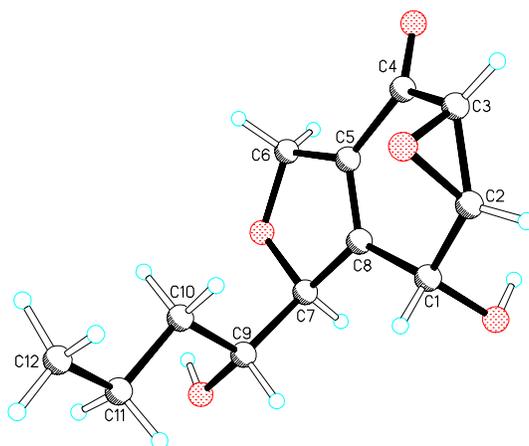
NMR spectra of synthetic (-)-cycloepoxydon (in CDCl₃:CD₃OD 95:5)



X-ray Crystal Structure of Cycloepoxydon 1



X-ray Crystal Structure of “iso”-cycloepoxydon 12



Crystals of **1** and **12** suitable for x-ray analysis were obtained by slow evaporation from $\text{CHCl}_3/\text{MeOH}$ (95:5). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (**1**: CCDC-168199; **12**: CCDC-168200). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 1. Crystal data and structure refinement for **1**

Identification code	cycloepoxydon	
Empirical formula	C ₁₂ H ₁₆ O ₅	
Formula weight	240.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 7.1459(10) Å	α = 90°.
	b = 4.5094(7) Å	β = 92.890(5)°.
	c = 17.904(3) Å	γ = 90°.
Volume	576.22(14) Å ³	
Z	2	
Density (calculated)	1.385 Mg/m ³	
Absorption coefficient	0.108 mm ⁻¹	
F(000)	256	
Crystal size	0.60 x 0.10 x 0.02 mm ³	
Theta range for data collection	3.02 to 23.25°.	
Index ranges	-7 ≤ h ≤ 7, -5 ≤ k ≤ 4, -19 ≤ l ≤ 15	
Reflections collected	2626	
Independent reflections	1540 [R(int) = 0.0471]	
Completeness to theta = 23.25°	98.9 %	
Absorption correction	SADABS	
Max. and min. transmission	0.9978 and 0.4849	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	1540 / 1 / 207	
Goodness-of-fit on F ²	1.046	
Final R indices [I > 2σ(I)]	R1 = 0.0519, wR2 = 0.1186	
R indices (all data)	R1 = 0.0695, wR2 = 0.1268	
Absolute structure parameter	0(3)	
Largest diff. peak and hole	0.229 and -0.207 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **1**. $U(\text{eq})$ is defined as 1/3 of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5536(4)	7101(8)	9299(2)	23(1)
O(2)	705(4)	9989(7)	9323(2)	29(1)
O(3)	-490(4)	5449(8)	7818(2)	32(1)
O(4)	3865(4)	8884(7)	6693(2)	22(1)
O(5)	6219(4)	12855(7)	8260(2)	23(1)
C(1)	4015(6)	9000(11)	9075(2)	21(1)
C(2)	2276(6)	8020(11)	9456(2)	22(1)
C(3)	589(6)	7029(11)	9022(2)	21(1)
C(4)	668(5)	6890(11)	8196(2)	21(1)
C(5)	2239(5)	8351(10)	7836(2)	19(1)
C(6)	2081(6)	8591(14)	7006(3)	24(1)
C(7)	4951(6)	11255(11)	7036(2)	21(1)
C(8)	5437(6)	10405(11)	7838(2)	19(1)
C(9)	3778(5)	9251(10)	8241(2)	17(1)
C(10)	6648(6)	11665(13)	6578(3)	24(1)
C(11)	6216(7)	12700(14)	5781(3)	28(1)
C(12)	7967(7)	13105(18)	5350(3)	54(2)

Table 3. Crystal data and structure refinement for **12**

Identification code	"iso"-cycloepoxydon	
Empirical formula	C ₁₂ H ₁₆ O ₅	
Formula weight	240.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.8454(8) Å	α = 90°.
	b = 18.7240(16) Å	β = 90.216(4)°.
	c = 13.6620(11) Å	γ = 90°.
Volume	2262.7(3) Å ³	
Z	8	
Density (calculated)	1.410 Mg/m ³	
Absorption coefficient	0.110 mm ⁻¹	
F(000)	1024	
Crystal size	0.30 x 0.15 x 0.10 mm ³	
Theta range for data collection	2.30 to 24.71°.	
Index ranges	-10 ≤ h ≤ 10, -15 ≤ k ≤ 22, -16 ≤ l ≤ 15	
Reflections collected	10587	
Independent reflections	3847 [R(int) = 0.0471]	
Completeness to theta = 24.71°	99.8 %	
Absorption correction	SADABS	
Max. and min. transmission	0.9891 and 0.81939	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3847 / 0 / 435	
Goodness-of-fit on F ²	1.044	
Final R indices [I > 2σ(I)]	R1 = 0.0472, wR2 = 0.1006	
R indices (all data)	R1 = 0.0739, wR2 = 0.1114	
Largest diff. peak and hole	0.222 and -0.218 e.Å ⁻³	

Table 4. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **12**. U(eq) is defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	982(2)	7770(1)	443(1)	22(1)
O(2)	1603(2)	9711(1)	62(1)	29(1)
O(3)	5163(2)	9153(1)	-755(1)	25(1)
O(4)	2053(2)	8016(1)	-2672(1)	26(1)
O(5)	-1017(2)	7590(1)	-3030(1)	22(1)
C(1)	864(3)	8430(1)	-72(2)	19(1)
C(2)	1563(3)	9022(1)	519(2)	23(1)
C(3)	3019(3)	9349(1)	231(2)	24(1)
C(4)	3801(3)	9079(1)	-654(2)	19(1)
C(5)	2851(2)	8679(1)	-1342(2)	17(1)
C(6)	3272(3)	8468(1)	-2356(2)	21(1)
C(7)	986(3)	7907(1)	-1895(2)	20(1)
C(8)	1561(2)	8370(1)	-1076(2)	17(1)
C(9)	-608(2)	8069(1)	-2252(2)	19(1)
C(10)	-888(3)	8842(1)	-2528(2)	23(1)
C(11)	-2540(3)	8988(1)	-2770(2)	24(1)
C(12)	-2920(3)	9773(2)	-2841(2)	34(1)
O(1')	5944(2)	7323(1)	-3207(1)	22(1)
O(2')	6573(2)	5380(1)	-2880(1)	30(1)
O(3')	10130(2)	5918(1)	-2035(1)	33(1)
O(4')	7093(2)	7082(1)	-126(1)	24(1)
O(5')	3996(2)	7495(1)	240(1)	20(1)
C(1')	5829(3)	6656(1)	-2706(2)	20(1)
C(2')	6527(3)	6073(1)	-3316(2)	24(1)
C(3')	7988(3)	5749(1)	-3043(2)	24(1)
C(4')	8780(3)	6006(1)	-2147(2)	21(1)
C(5')	7843(2)	6409(1)	-1456(2)	17(1)
C(6')	8302(3)	6632(1)	-447(2)	19(1)
C(7')	5981(2)	7169(1)	-890(2)	18(1)
C(8')	6544(2)	6708(1)	-1706(2)	18(1)
C(9')	4408(2)	6989(1)	-500(2)	18(1)
C(10')	4236(3)	6230(1)	-144(2)	21(1)

C(11)	2602(3)	6033(1)	89(2)	22(1)
C(12)	2432(4)	5276(2)	468(2)	34(1)
