

Synthesis of Illisimonin A Skeleton by Intramolecular Diels–Alder Reaction of *Ortho*-Benzoquinones and Biomimetic Skeletal Rearrangement of *Allo*-Cedranes

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Supplementary Materials

Table of Contents

General Information for Experimental Details

Experimental Procedure and Compound Characterisation Data

X-ray crystallographic analysis of 20 and 22

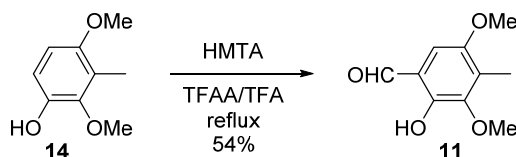
NMR Spectra of 15, 16, 18, 19, 20, 21, 25, 26, and 27

General Information for Experimental Details

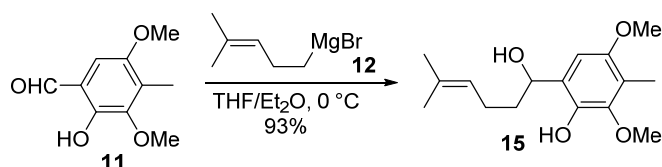
All reactions sensitive to oxygen or moisture were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise noted. DIPEA was distilled from CaH₂ and stored over KOH. Chemical reagents and anhydrous solvents were commercial grades and were used without any purification.

- **Chromatography:** Flash chromatography was performed with Silica Gel 60N (spherical, neutral), purchased from KANTO Chemical Industries Ltd, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using commercial silica gel plates (Merck, Silica Gel 60 F₂₅₄).
- **FT-IR:** Infrared spectra were recorded on a JASCO FT-IR 4100 spectrometer with an ATR unit. Absorbance frequencies are recorded in reciprocal centimetres (cm⁻¹).
- **High-resolution mass spectra (HRMS):** HRMS were obtained from a Thermo Scientific Exactive for electrospray ionization (ESI). HRMS data are reported as m/e (relative intensity), with accurate mass reported for the molecular ion [M+Na]⁺ or [M+H]⁺.
- **NMR:** ¹H and ¹³C NMR spectra were recorded on a JEOL ECA-500 spectrometer operating at either 500 MHz (¹H NMR) or 125 MHz (¹³C NMR) in CDCl₃ as a solvent. Chemical shifts for NMR were reported in ppm relative to the chemical shift of the residual solvent (¹H NMR 7.26 ppm for CDCl₃; ¹³C NMR 77.0 ppm for CDCl₃). Multiplicities are indicated as; br (broad), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Diastereomeric ratio was determined by ¹H NMR analysis.

Experimental Procedure and Compound Characterisation Data

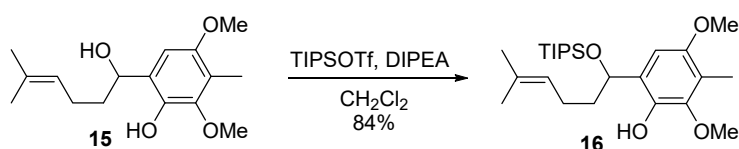


To a solution of **14** (23.7 g, 141 mmol) in TFA (45.45 mL) and TFAA (45.45 mL) was added hexamethylenetetramine (HMTA, 39.51 g, 281.8 mmol) at 0 °C. Then the mixture was heated to reflux and stirred for 24 h. Then the mixture was poured into ice and saturated aqueous NaHCO₃ solution and extracted with Et₂O (×3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by recrystallization (*i*-PrOH / water) before silica gel column chromatography (n-hexane / AcOEt = 1 / 1, short column) to afford aldehyde **11** (14.9 g, 75.9 mmol, 54%). The analytical data are identical to those reported in the previous paper (Kitahara, Y.; Nakahara, S.; Numata, R.; Kubo, A., *Chem. Pharm. Bull.* **1985**, 33, 2122–2128).



To a solution of **11** (1.19 g, 6.05 mmol) in THF (10.1 mL) was added freshly prepared Grignard reagent **12** (0.6 M solution in Et₂O, 41.0 mL) dropwise at 0 °C and stirred for 1.5 h. Then the reaction mixture was quenched with saturated aqueous NH₄Cl solution and acidified with 1 M HCl. The mixture was extracted with Et₂O (×3). The combined organic layers were washed with saturated aqueous NaHCO₃ solution and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane / AcOEt = 2 / 1) to afford diol **15** (1.59 g, 5.65 mmol, 93%).

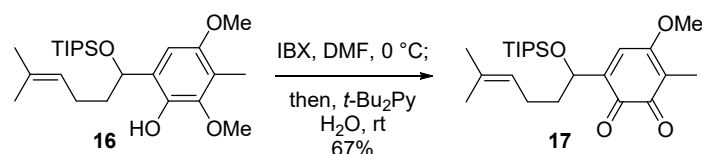
R_f 0.21 (n-hexane/EtOAc = 4/1); White amorphous; ¹H NMR (500 MHz, CDCl₃) δ 6.46 (1H, s), 6.23 (1H, brs), 5.16 (1H, t, *J* = 7.5 Hz), 4.84 (1H, dd, *J* = 7.4, 5.7 Hz), 3.78 (3H, s), 3.76 (3H, s), 2.66 (1H, brs), 2.19–2.04 (5H, m), 1.92–1.78 (2H, m), 1.70 (3H, s), 1.61 (3H, s); ¹³C NMR (125 MHz, CDCl₃) δ 151.2, 146.2, 140.7, 132.3, 126.7, 123.9, 118.9, 104.5, 72.3, 60.7, 56.1, 37.2, 25.7, 24.6, 17.7, 9.1; IR (ATR): ν 3413, 2929, 2856, 1462, 1416, 1377, 1353, 1300, 1220, 1186, 1123, 1084, 1063, 1019, 848, 772 cm^{−1}; HRMS (FD): Calcd for C₁₆H₂₄O₄ [M]⁺: 280.1675; found: 280.1665.



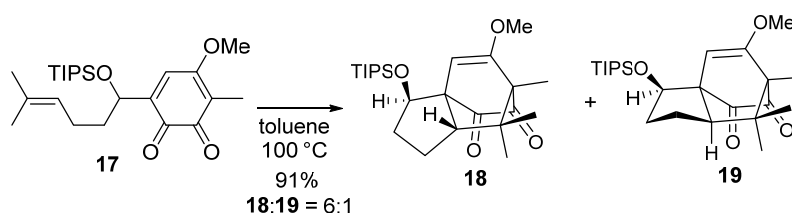
To a solution of **15** (0.836 g, 2.98 mmol) in CH₂Cl₂ (50.0 mL) was added DIPEA (2.22 mL, 5.36 mmol) at 0 °C and stirred for 20 min. Then TIPSOTf (0.719 mL, 4.17 mmol) was added to the mixture, and the mixture was stirred at room temperature for 2 h. Then the reaction mixture was quenched with saturated aqueous NH₄Cl solution and extracted with Et₂O (×3). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (n-hexane / AcOEt = 10 / 1) to afford silyl ether **16** (1.10 g, 2.52 mmol, 84%).

R_f 0.52 (n-hexane/EtOAc = 4/1); colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.23 (brs), 6.29 (1H, s), 5.07 (1H, t, J = 6.9 Hz), 4.87 (1H, dd, J = 6.9, 5.2 Hz), 3.78 (3H, s), 3.74 (3H, s), 2.13 (3H, s), 1.92–1.86 (4H, m), 1.66 (3H, s), 1.54 (3H, s), 1.06–1.00 (21H, m); ^{13}C NMR (125 MHz, CDCl_3) δ 150.6, 146.7, 141.9, 131.8, 126.0, 123.9, 119.1, 104.9, 75.2, 60.2, 56.1, 38.8, 25.6, 23.7, 17.83, 17.81, 17.7, 12.3, 12.1, 8.9; IR (ATR): ν 3384, 2941, 2893, 2866, 1462, 1415, 1378, 1355, 1298, 1248, 1220, 1188, 1125, 1078, 1013, 997, 881, 853, 829, 772, 677, 659 cm^{-1} ; HRMS (FD): Calcd for $\text{C}_{25}\text{H}_{44}\text{O}_4\text{Si}$ $[M]^+$: 436.3009; found: 436.2988.

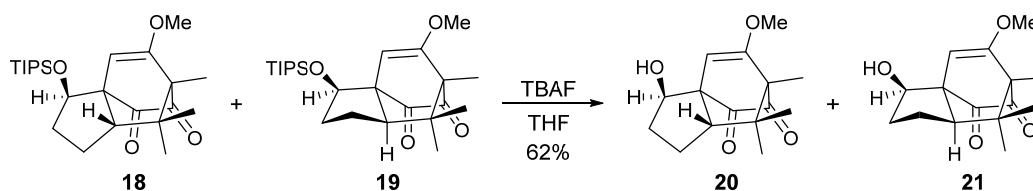


To a solution of **16** (470 mg, 1.08 mmol) in DMF (27.0 mL) was added IBX (525 mg, 1.88 mmol) at 0 °C, and the mixture was stirred for 15 h. After warming to the room temperature, $t\text{-Bu}_2\text{Py}$ (0.725 mL, 3.23 mmol) and water (1.35 mL) was added to the mixture. The resulting mixture was stirred for 2 h. Then the reaction mixture was quenched with saturated aqueous NaHCO_3 solution and extracted with Et_2O ($\times 3$). The combined organic layers were washed with brine, dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane / AcOEt = 5 / 1) to afford ortho-benzoquinone **17** (305 mg, 0.726 mmol, 67%). Since **17** is not stable enough to measure various spectra and physical properties, **17** was used directly for the next reaction.



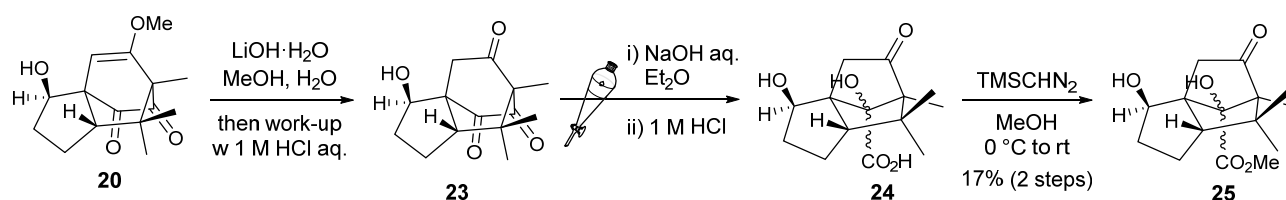
A solution of **17** (211 mg, 0.502 mmol) in toluene (33.5 mL) was stirred at 100 °C for 2.5 h. Then the mixture was cooled to room temperature and filtered through a pad of silica gel which was eluted with AcOEt. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (n-hexane / AcOEt = 5 / 1) to afford cycloadducts **18** and **19** (191 mg, 0.455 mmol, 91%) as an inseparable mixture (6:1).

R_f 0.51 (n-hexane/EtOAc = 5/1); Yellow oil; ^1H NMR (500 MHz, CDCl_3) δ 5.44 (1H of **18**, s), 5.40 (1H of **19**, s), 4.93–4.88 (1H, m), 3.64 (3H of **19**, s), 3.61 (3H of **18**, s), 2.39 (1H of **18**, ddt, J = 14.0, 7.4, 6.3 Hz), 2.14–2.06 (1H, m), 1.80–1.62 (3H, m), 1.21 (3H of **18**, s), 1.18 (3H of **19**, s), 1.10–1.00 (25H, m), 0.78 (3H of **18**, s); ^{13}C NMR (125 MHz, CDCl_3) δ 194.7, 192.4, 189.8, 186.9, 158.4, 157.6, 97.2, 91.8, 69.1, 68.6, 61.7, 61.6, 61.5, 61.4, 56.7, 55.6, 55.5, 53.6, 39.9, 36.4, 35.3, 35.1, 28.2, 26.7, 24.5, 24.4, 21.4, 21.2, 18.1, 18.0, 12.2, 7.02, 6.98; IR (ATR): ν 2942, 2892, 2866, 1732, 1606, 1462, 1369, 1311, 1265, 1242, 1219, 1164, 1111, 1065, 997, 965, 902, 882, 771, 682 cm^{-1} ; HRMS (FD): Calcd for $\text{C}_{24}\text{H}_{40}\text{O}_4\text{Si}$ $[M]^+$: 420.2696; found: 420.2691.



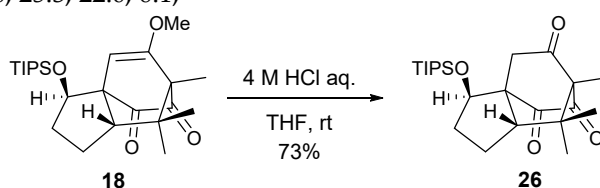
To a solution of **18** and **19** (0.896 g, 2.08 mmol, dr=6: 1) in THF (20 mL) was added a solution of TBAF in THF (1 M, 4.16 mL, 4.16 mmol) at room temperature. The resulting mixture was stirred for 3 h at room temperature. Then saturated aqueous NaHCO_3 was added and the mixture was extracted with Et_2O ($\times 3$). The combined organic layer was dried over MgSO_4 , filtered through cotton plug, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (n -hexane / AcOEt = 5 / 1) to afford a mixture of alcohol **20** and **21** (0.340 g, 1.29 mmol, 62%) as an inseparable mixture (6:1).

R_f 0.36 (n -hexane/ EtOAc = 1/1); Yellow solid; m.p. 130–133 °C; ^1H NMR (500 MHz, CDCl_3) δ 5.36 (1H of **20**, s), 5.27 (1H of **21**, s), 4.77 (1H of **20**, dd, J = 6.9, 2.9 Hz), 4.74 (1H of **21**, dd, J = 9.7, 6.3 Hz), 3.66 (3H of **21**, s), 3.64 (3H of **20**, s), 2.42 (1H of **20**, dddd, J = 16.0, 9.2, 6.9, 1.7 Hz), 2.24–2.15 (1H of **21**, m), 2.12 (1H of **20**, dd, J = 13.7, 6.9 Hz), 1.89–1.61 (2H, m), 1.20 (3H of **20**, s), 1.17 (3H of **21**, s), 1.08–1.00 (4H, m), 0.90 (3H of **21**, s), 0.89 (3H of **21**, s), 0.79 (3H of **20**, s); ^{13}C NMR (125 MHz, CDCl_3) δ 194.5, 192.3, 189.5, 188.1, 159.1, 158.0, 95.9, 90.7, 68.1, 61.4, 61.4, 61.2, 60.6, 60.7, 55.5, 55.1, 51.9, 40.0, 35.3, 34.4, 31.6, 27.9, 26.5, 23.9, 23.1, 21.2, 21.1, 13.9, 6.8, 6.7; IR (ATR): ν 3452, 2966, 2874, 1723, 1601, 1461, 1448, 1397, 1370, 1313, 1265, 1242, 1205, 1142, 1109, 1045, 1006, 994, 963, 871, 843, 820, 754 cm^{-1} ; $\text{C}_{15}\text{H}_{20}\text{O}_4$ [M] $^{+}$: 264.1362; found: 264.1354.



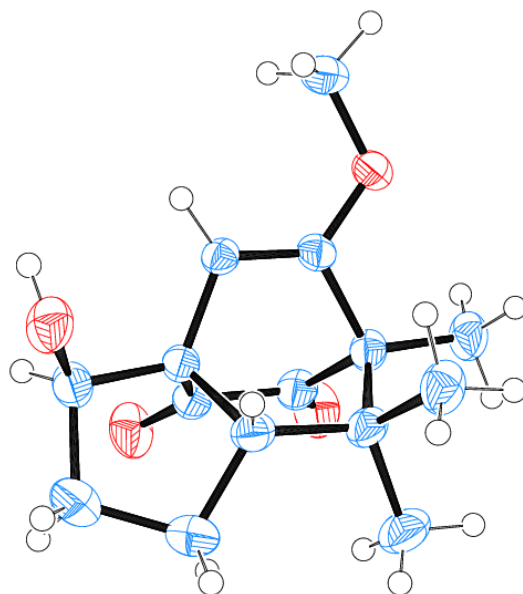
To a solution of **20** (38.9 mg, 0.147 mmol, including **19**) in $\text{MeOH}/\text{H}_2\text{O}$ =1/1 (2.00 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (11.1 mg, 0.265 mmol) at room temperature. The resulting mixture was stirred for 48 h at room temperature. Then the mixture was heated to 50 °C and stirred for 1 h. Then aqueous 1 M HCl solution was added and the mixture was extracted with Et_2O . The combined organic layer was added aqueous 0.1 M NaOH solution until the mixture turned to basic and extracted with Et_2O . Then the organic layer was added aqueous 1 M HCl solution until the mixture turned to acidic and extracted with Et_2O . The organic layer was dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure to afford of crude **24** (30.6 mg). Another batch of the same reaction of **20** (37.2 mg, 0.141 mmol) gave crude **24** (29.0 mg). To a solution of combined **24** in MeOH (2.48 mL) was added 2M TMSCHN_2 in Et_2O (0.622 mL, 0.782 mmol) dropwise at 0 °C. The resulting mixture was stirred for 8 h at 0 °C to room temperature. Then 10% aqueous AcOH was added and the mixture was extracted with Et_2O . The combined organic layer was dried over anhydrous MgSO_4 , filtered through cotton plug, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($\text{hexane} / \text{AcOEt}$ = 1 / 4) to afford of **25** (14.0 mg, 49.6 μmol , 17%).

R_f 0.014 (n -hexane/ EtOAc = 2/1); Colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 4.32 (1H, dd, J = 7.8, 4.6 Hz), 3.78 (3H, s), 3.43 (1H, s), 2.58 (1H, d, J = 18.3 Hz), 2.53–2.45 (1H, m), 2.18–2.13 (2H, m), 2.03–1.94 (1H, m), 1.78–1.69 (2H, m), 1.14 (3H, s), 0.91 (3H, s), 0.87 (3H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 213.1, 173.9, 89.7, 70.8, 68.0, 62.7, 61.8, 53.3, 44.6, 39.5 (2C), 29.0, 25.3, 22.0, 6.1;

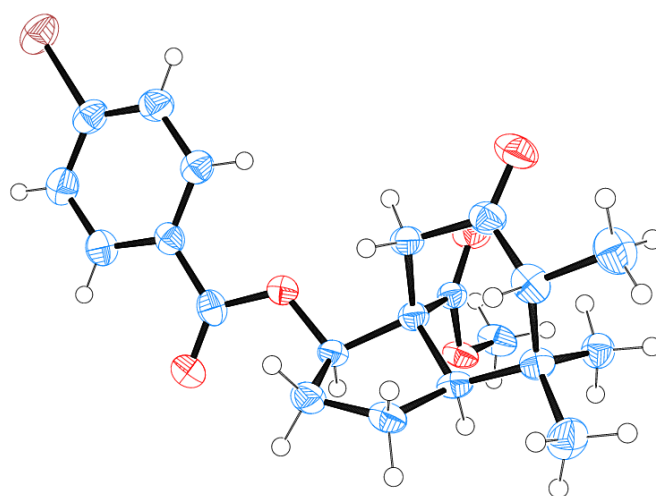


X-ray crystallographic data for compounds 20 and 22

(Thermal ellipsoids are drawn at the 50% probability level)



Crystal data of **20**: CCDC 2095712, $C_{15}H_{20}O_4$, size $0.454 \times 0.237 \times 0.175 \text{ mm}^3$, monoclinic, $P2_1/c$, $a = 7.61980(10) \text{ \AA}$, $b = 12.1533(2) \text{ \AA}$, $c = 14.5819(2) \text{ \AA}$, $\alpha = \gamma = 90^\circ$, $\beta = 94.1070(10)^\circ$, $Z = 4$, $\mu = 0.765 \text{ mm}^{-1}$, Independent reflections 2461, $R(\text{int}) = 0.0342$, Goodness-of-fit on $F^2 = 1.048$, Final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0419$, $wR_2 = 0.1157$.



Crystal data of **22**: CCDC 2095714, $2(C_{21}H_{25}BrO_5)$, size $0.389 \times 0.137 \times 0.132 \text{ mm}^3$, monoclinic, $P2_1/c$, $a = 26.4532(3) \text{ \AA}$, $b = 7.22630(10) \text{ \AA}$, $c = 21.7993(3) \text{ \AA}$, $\alpha = \gamma = 90^\circ$, $\beta = 108.305(2)^\circ$, $Z = 4$, $\mu = 3.079 \text{ mm}^{-1}$, Independent reflections 7243, $R(\text{int}) = 0.0538$, Goodness-of-fit on $F^2 = 1.104$ Final R indices $[I > 2\sigma(I)]$ $R_1 = 0.0798$, $wR_2 = 0.2203$.

NMR Spectra of 15, 16, 18, 19, 20, 21, 25, 26, and 27

