Tandem Diels-Alder/Ene cyclization Project

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Preparation of Triene

Compound

2-methylbut-3-en-2-ol (4.85 mL, 46.4 mmol), ethyl vinyl ether (13.3 mL, 139.3 mmol), and freshly recrystallized $\text{Hg}(\text{OAc})_2$ (2.96 g, 9.29 mmol) were heated in a sealed tube for 5 h at 130°C (*extended reaction time will increase the amount of inseparable side product*). The reaction mixture was concentrated to remove volatiles and then purified via flash column chromatography (hexane: EtOAc = 50:1 to 30:1) to give rather volatile γ,δ -unsaturated aldehyde **9** (3.05 g, 59%) as a pale yellow oil; ^1H NMR (300 MHz, CDCl_3) δ 9.77 (t, $J = 1.5$ Hz 1H), 5.12-5.09 (m, 1H), 2.50-2.32 (m, 4H), 1.61 (s, 3H), 1.56 (s, 3H); R_f (hexane-Et₂O 5:1) = 0.51.

Compound

To a solution of aldehyde **9** (1.87 g, 16.66 mmol) in benzene (40 mL) was added phosphonium salt (3.54 g, 11.10 mmol) at room temperature. The reaction mixture was boiled for 8 h. After cooling, the reaction mixture was concentrated to remove benzene and then the residue was washed with Et₂O. The triphenylphosphine oxide was filtered and the filtrate was concentrated in vacuo. The residue was purified via flash column chromatography to give the enone **11** (1.06 g, 63%) as a pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 6.80 (dt, *J* = 16, 6.4 Hz, 1H), 6.08 (d, *J* = 16 Hz, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 2.29-2.24 (m, 5H), 2.18-2.13 (m, 2H), 1.70 (s, 3H), 1.61 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 198.9, 148.3, 133.1, 131.7, 122.9, 32.9, 27.0, 26.8, 25.9, 17.9; *R_f* (hexane-Et₂O 5:1) = 0.27.

Compound

To a suspension of Ph₃PCH₃Br (4.40 g, 12.3 mmol) in benzene (35 mL) was treated with *t*-BuOK (1.20 g, 10.7 mmol) at room temperature under argon and heated at 60 °C for 4 h, cooled to room temperature, and then a solution of enone **11** (1.25 g, 8.2 mmol) in benzene (5 mL plus 1 mL rinse). The mixture was stirred for 18 h at 25 °C and Ph₃PO was filtered through a pad of silica gel. The filtrate was concentrated in vacuo and the residue was purified via flash column chromatography (silica gel: hexane-Et₂O 20:1) to give compound **13** (772 mg, 63%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 6.18 (d, *J* = 15.6 Hz, 1H), 5.69 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.19-5.14 (m, 1H), 4.89 (bs, 2H), 2.19-2.11 (m, 4H), 1.86 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 142.4, 133.1, 132.0, 130.8, 124.1, 114.4, 33.2, 28.3, 25.9, 18.9, 17.9; *R_f* (hexane-Et₂O 5:1) = 0.88.

Compound

To a -78 °C solution of diethyl allylphosphonate (2.5 mL, 14.3 mmol) in THF (40 mL) was added dropwise *n*-BuLi (5.74 mL, 2.5 M in hexanes, 14.3 mmol). After stirring for 15 min, a solution of the aldehyde (1.34 g, 11.9 mmol) in HMPA (5 mL, 28.9 mmol plus 1 mL THF rinse) was added dropwise via cannula. The resulting solution was stirred for

2 h at $-78\text{ }^{\circ}\text{C}$, and then allowed to warm to $25\text{ }^{\circ}\text{C}$. After 12 h at $25\text{ }^{\circ}\text{C}$, the reaction was quenched by the addition of saturated aqueous NH_4Cl (15 mL). The mixture was extracted with Et_2O ($3 \times 40\text{ mL}$). The combined organic layers were washed with brine (30 mL), dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give triene (861 mg, 53%) as a colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 6.32 (dt, $J = 16.8, 10.4\text{ Hz}$, 1H), 6.07 (dd, $J = 15.3, 10.8\text{ Hz}$, 1H), 5.72 (dt, $J = 15.2, 6.8\text{ Hz}$, 1H), 5.14-5.08 (m, 2H), 4.97 (d, $J = 10.4\text{ Hz}$, 1H), 2.13-2.08 (m, 4H), 1.70 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.5, 135.2, 132.1, 131.2, 124.0, 114.9, 33.0, 28.0, 25.9, 17.9; R_f (hexane) = 0.77; HRMS m/e (EI) for $\text{C}_{10}\text{H}_{16}$ (M) $^+$ calcd 136.1252, measured 136.1255.

General Procedure for Tandem Diels-Alder/Ene reaction

To a $0\text{ }^{\circ}\text{C}$ solution of α,β -unsaturated aldehyde (1.1 mmol) in Et_2O (3.5 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (1.1 mmol) and stirred for 10 min at $0\text{ }^{\circ}\text{C}$ [in case of Et_2AlCl , it was added to aldehyde at $-78\text{ }^{\circ}\text{C}$ and stirred for 10 min at $-78\text{ }^{\circ}\text{C}$]. To the resulting yellow solution was added via cannula a solution of triene (1 mmol) in Et_2O (1. mL plus 0.5 mL rinse). After 1 h at $0\text{ }^{\circ}\text{C}$, the reaction was warmed room temperature and further stirred for 6 to 19 h (monitored by tlc). The reaction was quenched by the addition of saturated aqueous NH_4Cl (3 mL) and extracted by CH_2Cl_2 . The organic layer was dried over MgSO_4 , filtered, and concentrated in vacuo. The residue was purified via flash column chromatography to give Diels-Alder/Ene adduct.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.03 (s, 1H), 4.83 (bs, 1H), 4.81 (s, 1H), 3.28 (d, $J = 10.4\text{ Hz}$, 1H), 3.01 (bs, 1H), 2.86-2.82 (m, 1H), 2.45 (dt, $J = 10.4, 4.0\text{ Hz}$, 1H), 2.28-2.13 (m, 3H), 2.10-1.92 (m, 1H), 1.81-1.73 (m, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 1.52-1.41 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.4, 135.0, 124.8, 112.8, 81.6, 69.0, 50.7, 45.8, 37.2, 29.8, 28.0, 27.0, 23.0, 19.6; R_f (hexane- Et_2O 5:1) = 0.44; HRMS m/e (EI) for $\text{C}_{14}\text{H}_{21}\text{BrO}$ (M) $^+$ calcd 284.0776, measured 284.0780.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.78-5.76 (m, 1H), 5.37 (dd, $J = 10.0, 1.6$ Hz, 1H), 4.87 (s, 1H), 4.85 (s, 1H), 3.34 (bd, $J = 10.0$ Hz, 1H), 3.09 (bs, 1H), 2.92-2.83 (m, 1H), 2.34 (dt, $J = 11.2, 4.0$ Hz, 1H), 2.30-2.12 (m, 4H), 1.75 (bs, 1H), 1.71 (s, 3H), 1.59-1.43 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.4, 130.3, 127.9, 113.1, 81.3, 69.1, 50.8, 45.9, 37.0, 27.8, 27.0, 25.1, 19.6; R_f (hexane- Et_2O 5:1) = 0.46; HRMS m/e (EI) for $\text{C}_{13}\text{H}_{19}\text{BrO}$ (M) $^+$ calcd 270.0619, measured 270.0626.

3:2:1 ratio mixture
Kit-12-112-3

R_f (hexane- Et_2O 5:1) = 0.33; HRMS m/e (EI) for $\text{C}_{14}\text{H}_{22}\text{O}$ (M) $^+$ calcd 206.1671, measured 206.1675.

56%
1:0.4 ratio

^{13}C NMR (100 MHz, CDCl_3) Major isomer δ 147.4, 134.6, 125.7, 112.8, 68.4, 49.0, 43.1, 35.9, 33.3, 27.6, 27.3, 26.8, 23.5, 20.9, 19.1 Minor isomer δ 147.3, 132.2, 124.8, 113.1, 78.5, 48.2, 43.1, 36.8, 30.8, 29.6, 27.7, 23.9, 23.4, 21.0, 18.9; R_f (hexane- Et_2O 5:1) = 0.47; HRMS m/e (EI) for $\text{C}_{15}\text{H}_{24}\text{O}$ (M) $^+$ calcd 220.1827, measured 220.1831.

75% after Dess-Martin Oxidation
1:0.6 ratio

^{13}C NMR (100 MHz, CDCl_3) Major isomer δ 214.1, 144.5, 137.0, 124.7, 113.0, 55.4, 47.1, 43.9, 32.5, 28.0, 27.9, 27.2, 26.6, 23.5, 20.7 Minor isomer δ 215.2, 144.4, 132.4, 124.6, 112.5, 54.7, 47.7, 44.9, 30.0, 29.8, 28.9, 27.2, 23.6, 21.4, 20.5; R_f (hexane- Et_2O 5:1) = 0.63; HRMS m/e (EI) for $\text{C}_{15}\text{H}_{22}\text{O}$ (M) $^+$ calcd 218.1671, measured 218.1675.

100% after treatment with NaOH

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.19 (bs, 1H), 2.52-2.47 (m, 1H), 2.35-2.25 (m, 2H), 2.05-1.92 (m, 3H), 1.88-1.85 (m, 4H), 1.76 (s, 3H), 1.63 (s, 3H), 1.57-1.51 (m, 1H), 1.44-1.36 (m, 1H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.5, 141.0, 135.5, 132.3, 124.4, 47.3, 43.3, 30.6, 28.0, 27.6, 27.6, 24.0, 23.6, 23.0, 22.0; R_f (hexane- Et_2O 5:1) = 0.63; HRMS m/e (EI) for $\text{C}_{15}\text{H}_{22}\text{O}$ (M) $^+$ calcd 218.1671, measured 218.1673.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.01 (s, 1H), 4.86 (bs, 1H), 4.83 (s, 1H), 3.52 (d, J = 10.4 Hz, 1H), 2.39 (bd, J = 18.0 Hz, 1H), 2.25-2.19 (m, 2H), 2.12-2.09 (m, 1H), 1.73-1.69 (m, 1H), 1.67 (bs, 6H), 1.59 (bd, J = 18.0 Hz, 1H), 1.46-1.35 (m, 4H), 0.97 (m, 3H), 0.88 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.6, 132.8, 124.8, 112.9, 70.1, 49.2, 38.6, 37.9, 35.4, 32.8, 27.2, 26.7, 23.9, 19.2, 17.8, 15.5; R_f (hexane- Et_2O 5:1) = 0.44; HRMS m/e (EI) for $\text{C}_{16}\text{H}_{26}\text{O}$ (M) $^+$ calcd 234.1984, measured 234.1987.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.06 (s, 1H), 4.88 (bs, 1H), 4.82 (s, 1H), 3.44 (d, J = 10.8 Hz, 1H), 3.18 (d, J = 10.0 Hz, 1H), 2.83-2.79 (m, 1H), 2.73-2.67 (m, 3H), 2.61 (bs, 1H), 2.21 (bd, J = 18.4 Hz, 1H), 2.00 (dt, J = 12.0, 3.6 Hz, 1H), 1.92 (bd, J = 18.4 Hz, 1H), 1.83-1.74 (m, 1H), 1.69-1.67 (m, 7H), 1.57-1.37 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.8, 132.1, 124.3, 113.5, 68.3, 51.4, 49.4, 41.7, 33.8, 33.1, 32.7, 30.2, 27.9, 26.4, 23.6, 19.0; R_f (hexane- Et_2O 2:1) = 0.50; HRMS m/e (EI) for $\text{C}_{16}\text{H}_{24}\text{OS}$ (M) $^+$ calcd 264.1548, measured 264.1552.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.06 (s, 1H), 4.85 (s, 1H), 4.80 (s, 1H), 3.37 (d, J = 10.8 Hz, 1H), 2.30-2.25 (m, 1H), 2.20-2.10 (m, 2H), 1.98 (dt, J = 11.2, 3.2 Hz, 1H), 1.88-1.71

(m, 4H), 1.67-1.59 (m, 9H), 1.52-1.37 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.6, 133.3, 124.4, 112.8, 69.0, 51.6, 47.2, 38.4, 35.2, 30.6, 30.3, 28.0, 27.7, 26.7, 23.7, 20.9, 19.1; R_f (hexane- Et_2O 2:1) = 0.70; HRMS m/e (EI) for $\text{C}_{16}\text{H}_{24}\text{OS}$ (M) $^+$ calcd 246.1984, measured 246.1988.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.69-5.66 (m, 1H), 5.38 (bd, J = 10.0 Hz, 1H), 4.87 (s, 1H), 4.82 (s, 1H), 3.42 (d, J = 10.8 Hz, 1H), 2.28-2.22 (m, 3H), 2.03-1.97 (m, 2H), 1.83-1.72 (m, 2H), 1.71-1.66 (m, 4H), 1.65-1.52 (m, 4H), 1.50-1.37 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 147.5, 130.1, 126.7, 113.0, 68.9, 51.6, 47.0, 37.6, 34.7, 30.0, 27.8, 27.7, 26.7, 25.6, 20.7, 19.0; R_f (hexane- Et_2O 5:1) = 0.57; HRMS m/e (EI) for $\text{C}_{16}\text{H}_{24}\text{O}$ (M) $^+$ calcd 232.1827, measured 232.1831.

Compound

^1H NMR (400 MHz, CDCl_3) δ 5.47-5.46 (m, 1H), 5.02-4.99 (m, 1H), 2.69-2.67 (m, 1H), 2.39 (s, 3H), 2.26-2.16 (m, 1H), 2.08-2.03 (m, 3H), 2.00-1.88 (m, 2H), 1.70 (s, 3H), 1.64 (s, 3H), 1.56 (s, 3H), 1.20-1.14 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 202.5, 133.4, 132.7, 123.3, 120.5, 73.5, 43.7, 34.6, 28.8, 27.4, 25.7, 25.5, 24.9, 23.3, 17.8; R_f (hexane- Et_2O 5:1) = 0.75.