Supplementary Material for Organic & Biomolecular Chemistry

Supporting Information

Total synthesis of paracentrone, C_{31}-allenic *apo*-carotenoid

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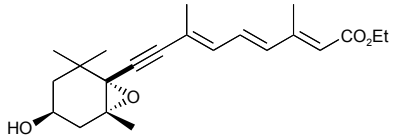
General

All commercially available reagents were used without further purification. All solvents were used after distillation. Tetrahydrofuran (THF), diethyl ether, benzene and toluene were refluxed over and distilled from sodium. Dichloromethane was refluxed over and distilled from CaH_2. Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled from CaH_2 under reduced pressure. Methanol was refluxed over and distilled from magnesium. Triethylamine, diisopropylamine and diisopropylethylamine were refluxed over and distilled from KOH. Preparative separation was usually performed by column chromatography on silica gel (FUJI silysia Ltd., BW-200). IR spectra were recorded on a JASCO FT/IR-8000 MCT-5E spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at JEOL α-400 spectrometer and chemical shifts were represented as δ values relative to the internal standard TMS. IR spectra were recorded with an FT-IR spectrometer. Melting points were uncorrected.

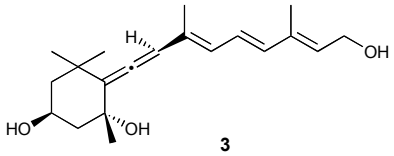
Experimental



11

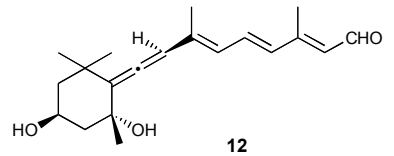
Ethyl (2*E*,4*E*,6*E*)-9-[(1'*R*,2'*R*,4'*S*)-1',2'-epoxy-4'-hydroxy-2',6',6'-trimethylcyclohexyl]-3,7-dimethyl-2,4,6-nonatriene-8-ynoate (11). To a solution of acetylene **5** (60 mg, 0.33 mmol) and vinyl iodide **6** (112 mg, 0.37 mmol) in diisopropylamine (4 mL) was added tetrakis(triphenylphosphine) palladium (38.5 mg, 0.030 mmol) and cuprous iodide (6.3 mg, 0.030 mmol) at room temperature. After being stirred for 4 h at the same temperature, the reaction mixture was poured into a saturated aqueous NH_4Cl solution, and then extracted with diethyl ether. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 20% to 50% ethyl acetate in hexane) afforded coupling product **11** (96 mg, 81%) as a pale yellow oil: $[\alpha]_D^{23}$ –10.16 (*c* 0.90, $CHCl_3$); IR (NaCl, cm^{-1}) 3434, 2965, 2928, 1709, 1613, 1597, 1449; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, 1H, *J* = 15.1, 11.5 Hz), 6.47 (d, 1H, *J* = 11.5 Hz), 6.29 (d, 1H, *J* = 15.1 Hz), 5.81 (s, 1H), 4.16 (q, 2H, *J* = 7.1 Hz), 3.85 (m, 1H), 2.37 (ddd, 1H, *J* = 14.4, 5.1, 1.7 Hz), 2.32 (d, 3H, *J* = 1.2 Hz), 1.98 (q, 3H, *J* = 1.2 Hz), 1.66 (dd,

1H, *J* = 14.4, 8.5 Hz), 1.62 (ddd, 1H, *J* = 12.9, 3.4, 1.7 Hz), 1.52 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.27 (s, 3H), 1.20-1.30 (m, 1H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 151.7, 137.0, 135.6, 129.2, 126.4, 120.3, 89.4, 88.1, 67.2, 63.8, 59.8, 45.9, 39.9, 34.5, 29.9, 25.7, 21.7, 17.9, 14.3, 13.7; EI$^+$ HRMS Found *m/z* 358.2148, Calcd. for $C_{22}H_{30}O_4$ M^+ 358.2144.



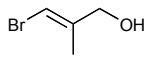
3

(2*E*,4*E*,6*E*)-9-[(1'*R*,2'*R*,4'*S*)-2',4'-Dihydroxy-2',6',6'-trimethylcyclohexylidene]-3,7-dimethyl-2,4,6,8-nonatetraen-1-ol (3). To a solution of coupling product **11** (118 mg, 0.33 mmol) in dichloromethane (3.3 mL) was added dropwise diisobutylaluminum hydride (1.0M in dichloromethane, 3.3 mL, 3.3 mmol) at 0 °C. After the reaction mixture was stirred for 30 min at the same temperature, water and a 2N aqueous HCl solution were added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 50% to 70% ethyl acetate in hexane) afforded allenic triol **3** (84 mg, 80%) as a pale yellow solid: $[\alpha]_D^{23}$ –23.47 (*c* 0.97, $CHCl_3$); IR (KBr, cm^{-1}) 3356, 2961, 2928, 2860, 1930, 1724, 1641, 1454, 1373, 1253, 1157, 1070; ^{1}H NMR (400 MHz, CD_3OD) δ 6.54 (dd, 1H, *J* = 15.1, 11.2 Hz), 6.27 (d, 1H, *J* = 15.1 Hz), 6.07 (d, 1H, *J* = 10.5 Hz), 6.02 (s, 1H), 5.64 (t, 1H, *J* = 6.8 Hz), 4.22 (d, 2H, *J* = 6.8 Hz), 4.20 (m, 1H), 2.18 (ddd, 1H, *J* = 12.7, 3.9, 2.0 Hz), 1.89 (ddd, 1H, *J* = 14.9, 3.9, 2.0 Hz), 1.83 (s, 3H), 1.80 (s, 3H), 1.50-1.20 (m, 2H), 1.33 (s, 3H), 1.33 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 203.4, 137.7, 137.1, 133.1, 131.8, 128.9, 125.8, 118.4, 103.6, 73.1, 64.7, 59.5, 50.6, 50.1, 36.6, 32.9, 31.4, 29.6, 14.2, 12.6; EI$^+$ HRMS Found *m/z* 318.2193, Calcd. for $C_{20}H_{30}O_3$ M^+ 318.2194.



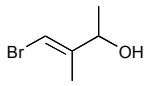
12

(2*E*,4*E*,6*E*)-9-[(1'*R*,2'*R*,4'*S*)-2',4'-Dihydroxy-2',6',6'-trimethylcyclohexylidene]-3,7-dimethylnona-2,4,6,8-tetraen-1-al (12). To a solution of allenic triol **3** (120 mg, 0.38 mmol) in ethyl acetate (10 mL) was added Dess-Martin periodinane (260 mg, 0.62 mmol) at 0 °C. The reaction mixture was stirred for 10 min at room temperature, a saturated aqueous $NaHCO_3$ solution was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude aldehyde **12**, which was used to the next reaction without further purification.



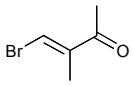
(*E*)-3-Bromo-2-methylprop-2-en-1-ol. To a suspension of lithium aluminum hydride (2.30 g, 60.6 mmol) in diethyl ether (200 mL) was added a solution of methyl bromomethylacrylate **14** (10.0 g, 60.6 mmol) in diethyl ether (100 mL) at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, water and a 2N aqueous HCl solution were added, and then the resulting mixture was extracted with diethyl ether. The organic layers were combined, washed with

brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded alcohol (9.15 g, quant.) as a colorless oil: IR (NaCl, cm^{-1}) 3324, 2965, 2925, 1636; ^1H MNR (400 MHz, $CDCl_3$) δ 6.24 (m, 1H), 4.02 (brd, 2H, *J* = 4.9 Hz), 1.82 (d, 3H, *J* = 1.5 Hz); ^{13}C MNR (100 MHz, $CDCl_3$) δ 140.9, 103.9, 66.2, 16.6.

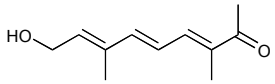


(*E*)-4-Bromo-3-methyl-3-butene-2-ol. To a solution of alcohol obtained above (3.0 g, 20.0 mmol) in acetone (100 mL) was added manganese dioxide (35 g) at room temperature. After being stirred for 12 h at the same temperature, the reaction mixture was filtered through a pad of Celite. The solvents were removed *in vacuo* to afford the crude aldehyde, which was used to the next reaction without further purification.

To a solution of the crude aldehyde in ether (20 mL) was added methylmagnesium bromide (1.0M in THF, 25.0 mL, 25.0 mmol) at 0 ^oC. After the reaction mixture was stirred for 30 min at room temperature, water was added, and then the resulting mixture was extracted with diethyl ether. The organic layers were combined, washed with a saturated aqueous NH_4Cl solution and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (from 10% to 30% ethyl acetate in hexane) afforded alcohol (2.75 g, 84% for 2 steps) as a colorless oil: IR (NaCl, cm^{-1}) 3344, 2980, 2932, 1634; ^1H MNR (400 MHz, $CDCl_3$) δ 6.27 (brd, 1H), 4.33 (brd, 1H), 1.81 (d, 3H, *J* = 1.2 Hz), 1.31 (d, 3H, *J* = 6.4 Hz); ^{13}C MNR (100 MHz, $CDCl_3$) δ 150.0, 104.0, 71.8, 21.6, 15.0.



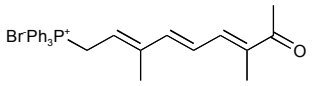
(*E*)-4-Bromo-3-methyl-3-butene-2-one (15). To a solution of alcohol obtained above (1.0 g, 6.10 mmol) in diethyl ether (60 mL) was added manganese dioxide (20 g) at room temperature. After being stirred for 12 h at the same temperature, the reaction mixture was filtered through a pad of Celite, and then the solvents were removed *in vacuo*. Purification by silica gel column chromatography (from 10% to 20% ethyl acetate in hexane) afforded ketone **15** (820 mg, 83%) as a colorless oil: IR (NaCl, cm^{-1}) 3005, 2957, 2876, 1680, 1603, 1427; ^1H MNR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 2.34 (s, 3H), 1.96 (s, 3H); ^{13}C MNR (100 MHz, $CDCl_3$) δ 195.4, 143.3, 124.4, 26.0, 14.8.



4

(3*E*,5*E*,7*E*)-9-Hydroxy-3,7-dimethylnona-3,5,7-triene-2-one (4). To a solution of vinylbromide **15** (303 mg, 1.87 mmol) and vinylstannane **13** (658 mg, 1.87 mmol) in DMF (10.0 mL) was added lithium chloride (144 mg, 3.40 mmol) and tetrakis(triphenylphosphine)palladium (98 mg, 0.090 mmol). After being stirred at 75 ^oC for 1 h, the reaction mixture was poured into a cooled 10% aqueous NH_3 solution, and extracted with ethyl acetate. The organic layers were combined, washed with brain, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (20% ethyl acetate in hexane) afforded **4** (283 mg, 84%) as yellow oil: IR (NaCl, cm^{-1}) 3430, 3054, 3000, 2922, 1647, 1607, 1435, 1366; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, 1H, *J* = 15.1 Hz), 6.62 (d, 1H, *J* = 15.1 Hz), 6.55

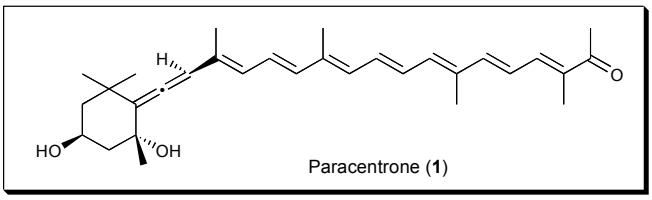
(dd, 1H, J = 15.1, 9.5 Hz), 5.87 (t, 1H, J = 6.6 Hz), 4.36 (d, 2H, J = 6.6 Hz), 2.36 (s, 3H), 1.92 (d, 3H, J = 1.2 Hz), 1.88 (d, 3H, J = 0.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 143.9, 139.6, 136.1, 135.6, 134.9, 123.8, 59.4, 25.5, 12.5, 11.6: EI^+ HRMS Found *m/z* 180.1148, Calcd. for $C_{11}H_{16}O_2$ M^+ 180.1150.



19

(2*E*,4*E*,6*E*)-3,7-dimethyl-8-oxonona-2,4,6-trienyltriphenylphosphonium bromide (19). To a solution of alcohol **4** (500 mg, 2.78 mmol) in dichloromethane (30 mL) was added phosphorous tribromide (0.32 mL, 3.33 mmol) at 0 °C. After being stirred for 10 min at the same temperature, the reaction mixture was poured into a saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layers were combined, washed with brain, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the crude allyl bromide, which was used to the next reaction without further purification.

To a solution of the crude allyl bromide in ethyl acetate (30 mL) was added triphenylphosphine (2.18 g, 8.33 mmol) at room temperature. The reaction mixture was stirred for 15 h at room temperature, and then filtered to afford the corresponding phosphonium salt **19** (1.04 g, 74% for 2 steps) as white solid, which was used to the next reaction without further purification: IR (KBr, cm^{-1}) 3042, 2909, 2826, 2770, 1832, 1645, 1610, 1487, 1439, 1370; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.60 (m, 15H), 7.39 (d, 2H, J = 12.9 Hz), 6.44 (dd, 1H, J = 13.4, 12.4 Hz), 5.38 (td, 1H, J = 7.8, 7.3 Hz), 4.99 (dd, 2H, J = 16.1, 7.8 Hz), 2.40 (s, 3H), 1.85 (d, 3H, J = 5.4 Hz), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 141.7 ($J_{C\text{-}P}$ = 13.2 Hz), 140.3, 135.6 ($J_{C\text{-}P}$ = 5.0 Hz), 134.0 ($J_{C\text{-}P}$ = 9.9 Hz), 130.1 ($J_{C\text{-}P}$ = 12.4 Hz), 127.5 ($J_{C\text{-}P}$ = 2.5 Hz), 118.3, 117.4, 115.6 ($J_{C\text{-}P}$ = 10.8 Hz), 26.1, 24.3 ($J_{C\text{-}P}$ = 49.6 Hz), 20.1 ($J_{C\text{-}P}$ = 3.3 Hz), 11.2.



Paracentrone (1). To a solution of sodium hydride (45 mg, 1.90 mmol) in dimethoxyethane (5 mL) and dichloromethane (5 mL) was added aldehyde **12** and phosphonium salt **19** (400 mg, 0.76 mmol) in dimethoxyethane (5 mL) at 0 °C in dark. The reaction mixture was stirred for 3 h at room temperature, water was added, and then the resulting mixture was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by short silica gel column chromatography (50% ethyl acetate in hexane) in dark afforded a mixture of all-*trans*-paracentrone (**1**), 15-*cis*-congener, and some isomeric compounds (<30% pure of **1**) as a red film.

A solution of mixture in chloroform-d was left at room temperature in dark. After 1 h, a thermodynamic equilibrium was reached (>70% pure of **1**), and then purification and partial separation by preparative HPLC [column, Develosil 60-5 (0.46x25 cm); mobile phase, THF/hexane/*i*PrOH=15/67/3; flow rate, 1 mL/min; UV detection, 450 nm; retention time, 22 min (all-*trans*-isomer)] in dark afforded the desired optically active paracentrone (**1**) as a red film: IR (KBr, cm^{-1}) 3407, 2961, 2924, 2855, 1929, 1721, 1649, 1607, 1530, 1453, 1368, 1321, 1279, 1229, 1157, 1071, 1040, 992,

963; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dq, 1H, *J* = 10.5, 1.0 Hz), 6.73 (dd, 1H, *J* = 14.2, 11.5 Hz), 6.66 (d, 1H, *J* = 14.9 Hz), 6.63 (dd, 1H, *J* = 14.1, 11.5 Hz), 6.60 (dd, 1H, *J* = 14.6, 11.5 Hz), 6.59 (dd, 1H, *J* = 15.4, 10.7 Hz), 6.39 (d, 1H, *J* = 11.5 Hz), 6.34 (d, 1H, *J* = 15.1 Hz), 6.26 (d, 1H, *J* = 11.0 Hz), 6.12 (d, 1H, *J* = 11.3 Hz), 6.03 (s, 1H), 4.32 (m, 1H), 2.36 (s, 3H), 2.27 (ddd, 1H, *J* = 13.3, 4.2, 1.9 Hz), 1.991 (s, 3H), 1.985 (s, 3H), 1.96 (m, 1H), 1.94 (d, 3H, *J* = 1.0 Hz), 1.81 (s, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.33 (s, 3H), 1.35 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 199.4, 144.5, 139.9, 137.9, 137.0, 136.2, 135.5, 132.6, 132.3, 132.1, 129.4, 128.4, 125.6, 123.8, 117.7, 103.2, 73.0, 64.3, 49.5, 48.9, 35.8, 32.2, 31.4, 29.4, 25.6, 14.0, 12.9, 12.8, 11.7; ESI HRMS Found *m/z* 461.3065, Calcd. for $C_{31}H_{42}O_3$ $[M-H]^-$ 461.3056.