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Synthesis of Macrocyclic Terpenoids by Intramolecular Cyclization. XI.[1] Total Synthesis of Zerumbone

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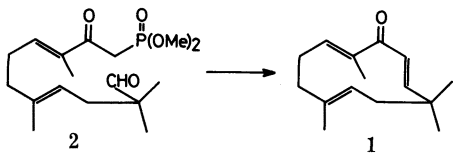
Zerumbone (**1**), an eleven-membered ring sesquiterpene isolated from *Zingiber zerumbet*, was synthesized by means of an intramolecular Wittig-type reaction of the keto-phosphonate **2**.

Keywords——zerumbone; synthesis; humulane sesquiterpene; intramolecular Wittig reaction; eleven-membered ring formation; 2,6,9,9,13,17,20,20-octamethyl-2,6,10,13,17,21-cyclodocosahexaene-1,12-dione

Zerumbone (**1**) is a humulane-type sesquiterpene which is the major component of the essential oil of *Zingiber zerumbet*[2] and is known to exhibit plant growth-regulatory and cytotoxic activities.[3,4] This structurally and biologically interesting compound has been synthesized only by the oxygenation of humulene.[5]

In a previous paper[1] we disclosed that an intramolecular Wittig-type reaction is an effective method of synthesizing oxygenated macrocyclic terpenoids. Considering the α,β-unsaturated ketone functionality in **1**, this compound should be a suitable target for synthesis by this methodology. Furthermore, it is of interest to know whether the intramolecular olefination takes place as expected in the case of medium-sized ring formation, since a severe ring strain would exist in the transition state.

Although the yield was not satisfactory, we achieved the synthesis of **1** by means of the following intramolecular olefination. The present synthesis reveals that the method is applicable to the formation of an eleven-membered ring.



2 1

Chart 1

Reaction of the lithio derivative of methyl isobutyrate with geranyl bromide (**3**) afforded the ester **4** in 60% yield. The Δ^9-double bond in **4** was cleaved by the following sequence in 39% overall yield: (i) reaction of **4** with *N*-bromosuccinimide in aqueous tetrahydrofuran (THF) followed by treatment with potassium carbonate to yield the epoxide **5**; (ii) acid-catalyzed epoxide ring opening to the diol **6**; (iii) reduction with lithium aluminum hydride to the triol **7**, and subsequent cleavage of diol moiety to furnish the aldehyde **8**. An α,β-unsaturated ester group was then introduced by means of a Wittig reaction using (ethoxycarbonylethylidene)triphenylphosphorane to give the *E*-enoate **9** selectively in 83% yield. After oxidation with pyridinium chlorochromate (PCC) to **10**, the resulting aldehyde

group was protected as an acetal and the product **11** was treated with the lithium anion of dimethyl methylphosphonate to afford the keto-phosphonate **12** in 59% overall yield. The key intermediate **2** was obtained by hydrolysis of the acetal group in **12**. The intermediate **2** thus obtained was treated with sodium hydride at high dilution in dimethoxyethane (DME) at 60 °C.[6] The product was a mixture of several compounds from which zerumbone (**1**) was isolated in 3% yield. The identity of the synthetic compound with the natural product was confirmed by infrared (IR), proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectral comparisons and a mixed melting point test. The major product formed in 55% yield was found to be a 22-membered macrocyclic dimer **13** on the basis of the mass spectrum (MS) (M^+, *m/z* 436) and ^{1}H- and ^{13}C-NMR spectra, which closely resembled those of **1**. The formation of the dimer **13** could not be suppressed even under conditions of higher dilution. Other conditions[7] examined so far afforded similar or smaller amounts of **1**. Interestingly, 400 MHz ^{1}H-NMR spectroscopy of the reaction products failed to detect any of the geometrical isomer of **1**.

The present results provide a new entry to the synthesis of humulane-type sesquiterpenes,[8] although they suggest a limitation of the intramolecular Wittig reaction approach with respect to ring size.

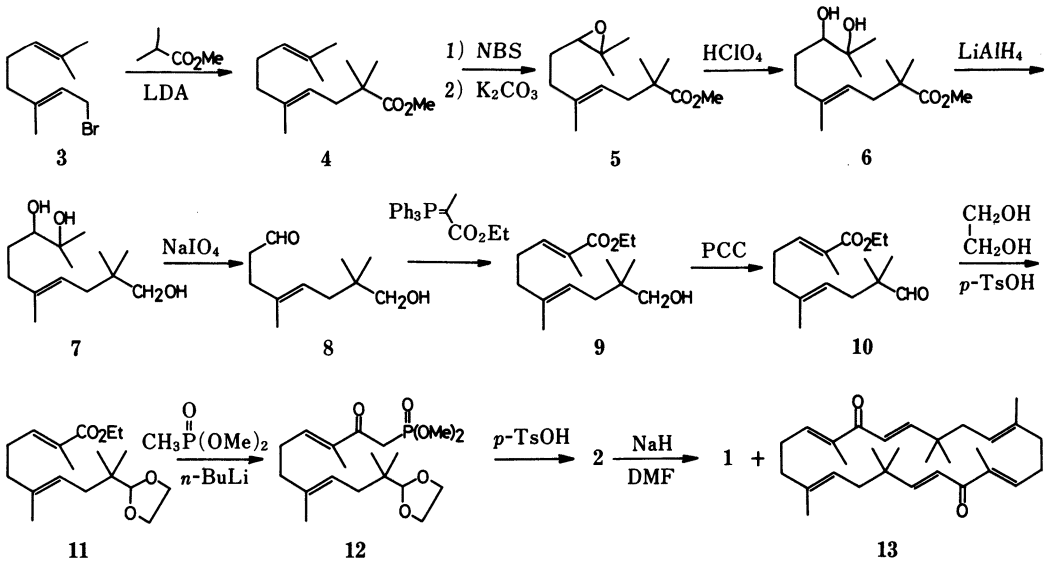


Chart 2

Experimental

^{1}H- and ^{13}C-NMR were recorded on a JEOL GX-400 or JEOL FX90Q spectrometer in $CDCl_3$ solution with $(CH_3)_4Si$ as an internal standard. IR were taken on a Shimadzu IR-27G spectrometer. MS were measured on a Shimadzu LKB-9000 spectrometer. High-resolution mass spectra (HRMS) were obtained on a JEOL HX-100 spectrometer.

Methyl (*E*)-2,2,5,9-Tetramethyl-4,8-decadienoate (4)——A hexane solution of *n*-butyllithium (0.123 mol) was added dropwise to a stirred solution of diisopropylamine (10.5 g, 0.104 mol) in dry THF (300 ml) under argon at −30 °C. After being stirred at 0 °C for 30 min, the mixture was cooled to −70 °C with a dry ice-acetone bath. Methyl isobutyrate (11.9 ml, 0.104 mol) was then added dropwise to the mixture over 1 h, followed by addition of geranyl bromide (**3**) (20.5 g, 0.095 mol) in dry THF (50 ml) over 1 h. The mixture was stirred for 30 min at −70 °C, then the cooling bath was removed and stirring was continued overnight at room temperature. The reaction mixture was concentrated to one-third of its original volume, diluted with water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on 200 g

of silica gel (benzene–hexane, 1 : 1) to give 13.5 g (60%) of **4** as a colorless oil. IR (film): 1738 cm^{-1}. ^{1}H-NMR δ: 1.14 (6H, s), 1.59 (6H, br s), 1.68 (3H, br s), 3.65 (3H, s), 5.08 (2H, m). MS *m/z*: 238 (M^+), 109 (base peak). HRMS *m/z*: 238.1918 (Calcd for $C_{15}H_{26}O_2$, 238.1933).

Methyl (*E*)-8,9-Epoxy-2,2,5,9-tetramethyl-4-decenoate (5)——*N*-Bromosuccinimide (8.97 g, 0.050 mol) was added in small portions over 30 min to an ice-cooled solution of **4** (8.0 g, 0.034 mol) in THF (90 ml) and water (30 ml) with stirring. The reaction mixture was concentrated *in vacuo* to one-third of its original volume, diluted with water and extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on 50 g of silica gel (benzene) to give 6.65 g (59%) of the bromohydrin as a colorless oil, which was immediately used for the next reaction.

A mixture of the bromohydrin (6.65 g, 0.02 mol) and anhydrous potassium carbonate (11.0 g, 0.08 mol) in methanol (100 ml) was vigorously stirred at room temperature for 30 min. The precipitate was filtered off and washed with methanol. The combined filtrates were concentrated *in vacuo* and the residue was taken up in 150 ml of ether. The ether solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford 4.65 g (92%) of **5** as a colorless oil. IR (film): 1746 cm^{-1}. ^{1}H-NMR δ: 1.14 (6H, s), 1.25 (3H, s), 1.30 (3H, s), 1.62 (3H, br s), 2.70 (1H, t, J = 6.4 Hz), 3.63 (3H, s), 5.14 (1H, br t, J = 7.4 Hz). MS *m/z*: 254 (M^+), 109 (base peak). HRMS *m/z*: 254.1872 (Calcd for $C_{15}H_{26}O_3$, 254.1882).

Methyl (*E*)-8,9-Dihydroxy-2,2,5,9-tetramethyl-4-decenoate (6)——A stirred solution of **5** (4.6 g, 0.018 mol) in THF–water (3 : 1, 200 ml) was treated with 0.1 ml of 70% perchloric acid. The mixture was stirred at room temperature for 4 h and then concentrated *in vacuo* to one-third of its original volume. The residue was taken up in 200 ml of ether and the ether solution was washed with brine, dried ($MgSO_4$) and then concentrated *in vacuo*. The residue was chromatographed on 40 g of silica gel ($CHCl_3$) to afford 4.64 g (95%) of the diol **6** as a colorless oil. IR (film): 3450, 1732 cm^{-1}. ^{1}H-NMR δ: 1.16 (12H, s), 1.60 (3H, br s), 3.32 (1H, ddd, J = 9.5, 5.1, 2.5 Hz, changed to dd (J = 9.5, 2.5 Hz) on treatment with D_2O), 3.66 (3H, s), 5.15 (1H, br t, J = 7.4 Hz). MS *m/z*: 254 ($M^+ - H_2O$), 102 (base peak).

(*E*)-8,9-Dihydroxy-2,2,5,9-tetramethyl-4-decenol (7)——A solution of **6** (4.6 g, 0.02 mol) in 20 ml of dry THF was added over 30 min to a suspension of $LiAlH_4$ (0.8 g) in 80 ml of dry THF with stirring at 0 °C. The mixture was stirred overnight at room temperature, and then excess reagent was decomposed by careful addition of water. The mixture was acidified with 2 N HCl and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on 40 g of silica gel ($CHCl_3$–methanol, 96 : 4) to give 3.8 g (92%) of **7** as a colorless oil. IR (film): 3400, 2500 cm^{-1}. ^{1}H-NMR δ: 0.86 (3H, s), 1.15 (3H, s), 1.19 (3H, s), 1.62 (3H, br s), 5.29 (1H, br t, J = 7.7H). MS *m/z*: 226 ($M^+ - H_2O$), 71 (base peak).

(*E*)-8-Hydroxy-4,7,7-trimethyl-4-octenal (8)——Sodium periodate (3.66 g, 0.017 mol) was added in small portions over 1 h to a stirred solution of **7** (3.80 g, 0.016 mol) in THF–water (3 : 1, 80 ml) at room temperature. After being stirred for 3.5 h, the reaction mixture was poured into water and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was chromatographed on 50 g of silica gel (CH_2Cl_2) to afford 2.35 g (82%) of the aldehyde **8** as a colorless oil. IR (film): 3400, 1720 cm^{-1}. ^{1}H-NMR δ: 0.84 (6H, s), 1.62 (3H, br s), 3.30 (2H, br s), 5.25 (1H, br t, J = 7.4 Hz), 9.78 (1H, t, J = 2.6 Hz); MS *m/z*: 166 (M^+), 109 (base peak).

Ethyl (*E*,*E*)-10-Hydroxy-2,6,9,9-tetramethyl-2,6-decadienoate (9)——A mixture of **8** (2.30 g, 12.5 mmol) and (ethoxycarbonylethylidene)triphenylphosphorane (4.52 g, 12.5 mmol) in 50 ml of dry benzene was stirred at room temperature for 3 h. The reaction mixture was evaporated *in vacuo* and the residue was chromatographed on 60 g of silica gel (benzene–CH_2Cl_2, 1 : 1) to give 2.80 g (83%) of the ester **9** as a colorless oil. IR (film): 3450, 1710, 1650 cm^{-1}. ^{1}H-NMR δ: 0.85 (6H, s), 1.28 (3H, t, J = 7.2 Hz), 1.62 (3H, br s), 1.82 (3H, br s), 3.32 (2H, br d, J = 5.6 Hz, changed to br s on treatment with D_2O), 4.18 (2H, q, J = 7.2 Hz), 5.23 (1H, br t, J = 7.7 Hz), 6.72 (1H, br t, J = 6.5 Hz). MS *m/z*: 268 (M^+), 128 (base peak). HRMS *m/z*: 268.2033 (Calcd for $C_{16}H_{28}O_3$, 268.2038).

Ethyl (*E*,*E*)-9-Formyl-2,6,9-trimethyl-2,6-decadienoate (10)——Pyridinium chlorochromate (13.0 g, 60.2 mmol) was added to a solution of **9** (2.70 g, 10.1 mmol) in CH_2Cl_2 (150 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture was filtered through a bed of celite and the residue was washed with CH_2Cl_2. The combined filtrates were washed successively with 2 N HCl, saturated $NaHCO_3$ and brine, and then dried ($MgSO_4$). Evaporation of the solvent and chromatography of the residue on 50 g of silica gel (benzene) yielded 1.90 g (70%) of **10** as a colorless oil. IR (film): 1725, 1710, 1650 cm^{-1}. ^{1}H-NMR δ: 0.99 (6H, s), 1.28 (3H, t, J = 7.2 Hz), 1.60 (3H, br s), 1.82 (3H, br s), 4.18 (2H, q, J = 7.2 Hz), 5.10 (1H, br t, J = 7.7 Hz), 6.70 (1H, br t, J = 6.4 Hz), 9.48 (1H, s). MS *m/z*: 266 (M^+), 128 (base peak). HRMS *m/z*: 266.1864 (Calcd for $C_{16}H_{26}O_3$, 266.1882).

Ethyl (*E*,*E*)-9-(1,3-Dioxolan-2-yl)-2,6,9-trimethyl-2,6-decadienoate (11)——A mixture of **10** (1.80 g, 6.8 mmol), ethylene glycol (3.0 g) and *p*-toluenesulfonic acid (20 mg) in 100 ml of benzene was heated under reflux for 1.5 h with stirring, during the time water was removed by a Dean–Stark water separator. After cooling, the reaction mixture was washed with saturated $NaHCO_3$, dried ($MgSO_4$). Evaporation of the solvent yielded the acetal **11** (2.00 g, 95%) as a colorless oil. IR (film): 1710, 1650 cm^{-1}. ^{1}H-NMR δ: 0.86 (6H, s), 1.29 (3H, t, J = 7.2 Hz), 1.62 (3H, br s), 1.84 (3H, br s), 3.90 (4H, m), 4.18 (2H, q, J = 7.2 Hz), 4.54 (1H, s), 5.23 (1H, br t, J = 7.7 Hz), 6.75 (1H, br t, J = 6.5 Hz). MS *m/z*: 310 (M^+), 183 (base peak). HRMS *m/z*: 310.2149 (Calcd for $C_{18}H_{30}O_4$, 310.2144).

Dimethyl (*E*,*E*)-10-(1,3-Dioxolan-2-yl)-3,7,10-trimethyl-2-oxo-3,7-undecadienylphosphonate (12)——A hexane

solution of *n*-butyllithium (6.40 mmol) was added dropwise to a stirred solution of dimethyl methylphosphonate (0.7 ml, 6.45 mmol) in dry THF (20 ml) under argon at −78 °C, and the mixture was stirred for 15 min at −78 °C. A solution of **11** (1.0 g, 3.23 mmol) in dry THF (4 ml) was added over 15 min. After being stirred at −78 °C for 30 min, the mixture was poured into water and extracted with ether. The combined ether layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on 20 g of silica gel. Elution with benzene afforded recovered **11**. Further elution with CH_2Cl_2 gave 0.68 g (89%) of **12** as a colorless oil. IR (film): 1670, 1645 cm^{-1}. ^{1}H-NMR δ: 0.85 (6H, s), 1.62 (3H, br s), 1.80 (3H, br s), 3.35 (2H, d, J=22.8 Hz), 3.76 (6H, d, J=11.0 Hz), 3.89 (4H, m), 4.54 (1H, s), 5.28 (1H, br t, J=7.7 Hz), 6.72 (1H, br t, J=6.5 Hz). MS *m/z*: 388 (M^+), 206 (base peak). HRMS *m/z*: 388.2007 (Calcd for $C_{19}H_{33}O_6P$, 388.2015).

Dimethyl (*E*,*E*)-10-Formyl-3,7,10-trimethyl-2-oxo-3,7-undecadienyl phosphonate (2)——A mixture of **12** (650 mg, 1.68 mmol) and *p*-toluenesulfonic acid (20 mg) in acetone–water (2 : 1, 20 ml) was heated under gentle reflux for 2 h. After cooling, the mixture was diluted with water and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 550 mg (95%) of the aldehyde **2** as a colorless oil. IR (film): 1725, 1665, 1640 cm^{-1}. ^{1}H-NMR δ: 1.04 (6H, s), 1.63 (3H, br s), 1.80 (3H, br s), 3.38 (2H, d, J=22.8 Hz), 3.78 (6H, d, J=11.0 Hz), 5.12 (1H, br t, J=7.7 Hz), 6.67 (1H, br t, J=6.5 Hz), 9.46 (1H, s). MS *m/z*: 344 (M^+), 206 (base peak). HRMS *m/z*: 344.1751 (Calcd for $C_{17}H_{29}O_5P$, 344.1752).

Intramolecular Wadsworth–Emmons Olefination of 2——A solution of **2** (300 mg, 0.87 mmol) in 500 ml of dry DME was heated at 60 °C under argon and 52 mg of sodium hydride (60% mineral oil dispersion, 1.30 mmol) was added with stirring. The mixture was stirred at 60 °C for 16 h, then allowed to cool. The solvent was evaporated off *in vacuo* and the residue was taken up in 200 ml of ether. The ether solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on 30 g of silica gel. Elution with benzene gave a crystalline solid (6 mg, 3%) which was recrystallized from ethanol to yield **1** as colorless needles, mp 64—65 °C (lit.[2] 67—69 °C). The ^{1}H-NMR and ^{13}C-NMR spectra were identical with those of natural zerumbone (**1**). Further elution with benzene–CH_2Cl_2 (1 : 1) afforded a crystalline solid (104 mg, 55%) which was recrystallized from ethanol to give the dimer **13** as colorless needles, mp 123—125 °C. IR (Nujol): 1662, 1616 cm^{-1}. ^{1}H-NMR δ: 1.07 (6H, s), 1.62 (3H, br s), 1.79 (3H, br s), 5.09 (1H, br t, J=7.8 Hz), 6.39 (1H, d, J=15.6 Hz), 6.42 (1H, br t, J=7.2 Hz), 6.66 (1H, d, J=15.6 Hz). ^{13}C-NMR δ: 11.7 (q), 15.8 (q), 26.5 (t), 26.7 (q × 2), 37.9 (s), 38.7 (t), 40.8 (t), 121.9 (d), 122.6 (d), 135.6 (s), 138.1 (s), 142.3 (d), 154.6 (d), 192.8 (s). MS *m/z*: 436 (M^+), 151 (base peak). HRMS *m/z*: 436.3333 (Calcd for $C_{30}H_{44}O_2$, 436.3342).

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