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Facile and Practical Total Syntheses of (±)-Mukulol and (±)-Cembrene by Low-valent Titanium-induced Keto Ester Cyclization

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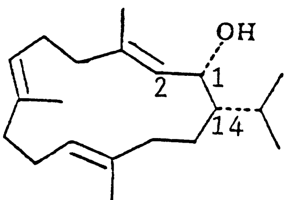
A direct approach of low-valent titanium-induced intramolecular keto ester cyclization was first applied to the total syntheses of macrocyclic diterpenoids, by which (±)-mukulol and (±)-cembrene were synthesized from geranylacetone by a short and efficient route.

In recent years, the interest in the synthesis of cembranes and cembranolides, a novel type of diterpenoids characterized by the presence of a fourteen-membered carbocyclic ring, is ever-increasing as a result of their remarkably wide-range of biological activity and the challenging structure features. Though a number of synthetic strategies have been published,$^{1)}$ the lack of a general method for the construction of the fourteen-membered rings has made an attractive problem for the total synthesis of cembrane natural products. Among the macrocyclizationmethodologies in the literature,$^{1)}$ the low-valent titanium-induced intramolecular cyclization of dicarbonyl precursors developed by *McMurry* and his co-workers$^{2)}$is an extraordinarily effective means of preparing carbocyclic rings of all sizes, by which some total syntheses of natural cembrenoids have been accomplished.$^{2)}$ The intramolecular keto ester coupling reaction induced by low valent titanium was reported as a novel method for cycloalkanone synthesis.$^{3)}$However, the keto α,β-unsaturated ester coupling catalyzed by low valent titanium has not been investigated. Employing this versatile macrocyclization as key step, herein we wish to present facile and practical total syntheses of (±)-mukulol (**1**) and (±)-cembrene (**2**), two naturally occurring cembrane diterpenoids.



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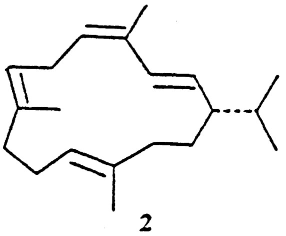

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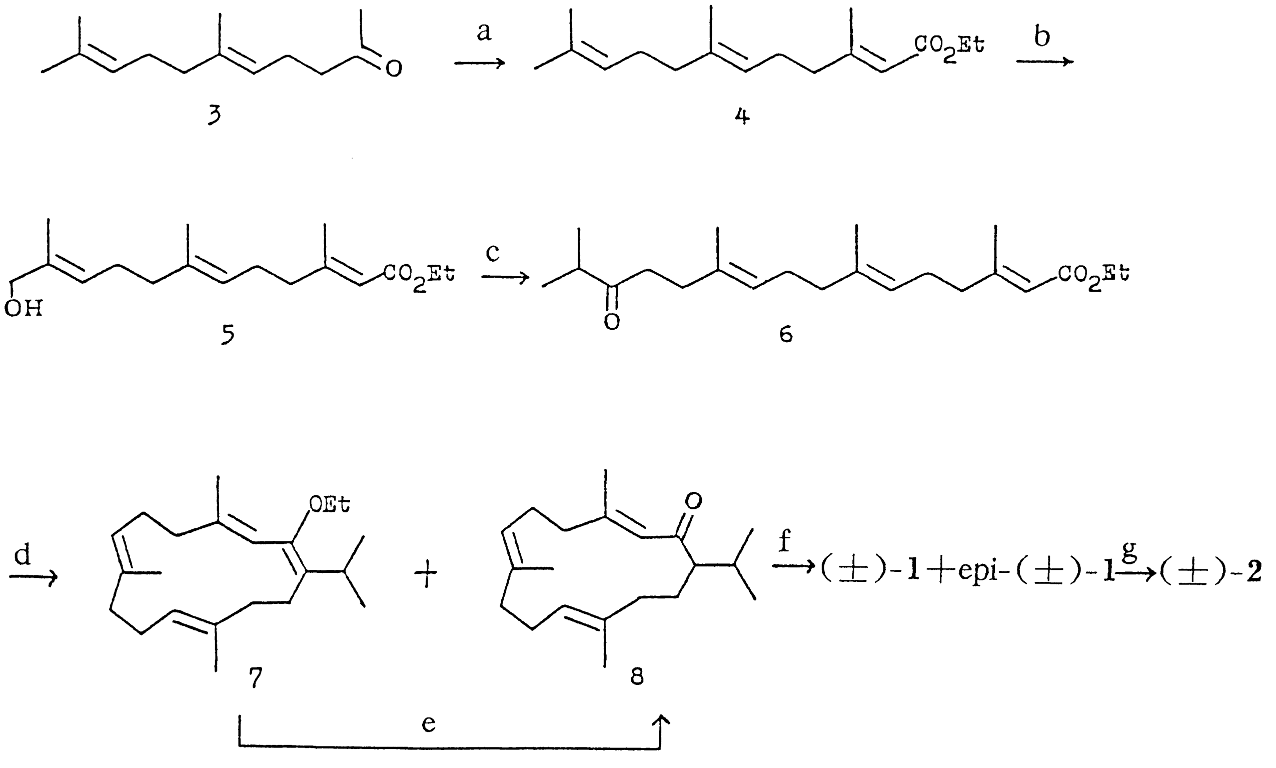
Mukulol (**1**), a cembrane alcohol, was first isolated from the gum-resin of Indian plant (*Commiphora mukul*)4) and its syntheses have been achieved by several groups.5) Furthermore, the conversion of the available cembrane alcohol **1** into some densely oxygen-functionalized cembrenoids, *e. g.* incensole, isoincensole oxide and thunbergol has been reported.6) Cembrene (**2**), the first naturally occurring cembrane hydrocarbon to be characterized,7) was found in many species of pine resins and the synthesis was first achieved by *Dauben*8) and other groups afterwords9) by dehydration of the corresponding cembrane alcohol including mukulol (**1**).

Our synthetic strategy starting from geranylacetone involves the formation of the conjugated ketone and the 14- membered ring by the low- valent titanium- induced macrocyclization of the keto α, β- unsaturated ester precursor **6** which was prepared by the selective alkylation of the lithium enolate of methyl isopropyl ketone with the corresponding allylic iodide of alcohol **5**. The synthetic route is outlined in the following scheme;



Scheme 1. a) $(EtO)_2P(O)CH_2CO_2Et/NaH$, DME, r. t. ~reflux (95%); b) SeO_2/t-BuOOH, CH_2Cl_2, r. t. (62%); c) 1. Ph_3P/Imidazole, I_2, CH_3CN-Et_2O(3 : 2), 0 ℃~r. t. ; 2. $(CH_3)_2CHCOCH_3$/LDA, THF, -78 ℃~r. t. (65%); d) $TiCl_3-LiAlH_4$(2 : 1)/ Et_3N, DME, reflux (81%); e) 1N $HCl-H_2O$/MeOH, r. t. (100%); f) $LiAlH_4$/ Et_2O, 0 ℃(94%); g) MsCl/Py, 0 ℃(80%)

The Horner-Emmons reaction of *trans*-geranylacetone **3** with ethyl sodio α-[bis-(β,β,β-triethoxy) phosphinyl] acetate in dimethoxyethane at refluxing temperature (80 ℃) afforded the desired *E*-form ethyl farnesenate **4** in 95% yield along with its geometrical isomer **4Z** in a ratio of >8 : 1(determined by GC). Ester **4** was exposed to 75% *tert*-butyl hydroperoxide in the presence of a catalytic amount of selenium dioxide (0. 1 eq.) in methylene chloride to give the allylic alcohol **5** in 62% yield, which was then converted to the corresponding iodide in quantitative yield by standard method.10)Alkylation of the lithium enolate of methyl isopropyl ketone with the labile allylic iodide afforded the keto ester **6**11)in 65% yield. Macrocyclizaton of the keto ester **6** was carried out12) by slow addition of the dilute solution of **6** in dimethoxyethane (DME) to the refluxing low valent titanium slurry (prepared *in situ* by the reduction of titanium trichloride with lithium aluminium hydride (0. 5 eq.)) in the presence of triethylamine over 24 h and followed by methanol-water (1 : 1) workup at 0 ℃ to give the enone **8**11)and the macrocyclic enol ether **7**11)in a ratio of 1 : 4. Treatment of enol ether **7** with 1N HCl in methanol gave macrocyclic enone **8** quantitatively, which was reduced with lithium aluminum hydride in ether at 0℃ to afford the title compound (±)-**1** and its epimer 11)in 94% combined yield with a ratio of ca. 3 : 1 after flash column chromatography on silica gel(eluting with hexane/EtOAc 10 : 1). Dehydration of (±) -**1** and its epimers by treatment with methanesulfonyl chloride in pyridine yielded (±)-cembrene (**2**)11) in 80% yield.

Thus, two cembrane diterpenoids (±)-**1** and (±)-**2** were synthesized13)with a short and convenient route employing the titanium-induced keto ester cyclization which was first used in the synthesis of cembrane diterpenoids and further studies are undergone in our laboratory.

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11) Spectral data: **6**: ν_{max}(film): 1714(s), 1648(s)cm^{-1}; δ_H(80 MHz, $CDCl_3$/TMS): 1.08 (d, 6H, J=6.8 Hz, $CH(CH_3)_2$), 1.27 (t, 3H, J=7.1 Hz, CH_3), 1.60 and 1.67 (2s, each 3H, 2×CH_3), 2.17 (d, 3H, J=1.2 Hz, CH_3), 1.80-2.80 (m, 13H), 4.15 (q, 2H, J=7.1 Hz, CH_2), 4.95-5.30 (br m, 2H, CH=), 5.65(br s, 1H, CH=)ppm; m/z (EI): 348 ($M^{+\cdot}$, 12%), 217 (9), 153 (24), 121 (37), 71 (100); **7**: δ_H(80 MHz, $CDCl_3$/TMS): 0.85-1.40 (m, 9H, 3×CH_3), 1.52, 1.58 and 1.65 (3s, each 3H, 3×CH_3), 1.80-2.30 (m, 13H), 3.60 (q, 2H, J=7.1 Hz, CH_2O), 4.75-5.30 (br m, 3H, 3×CH=), 5.52 (br s, 1H, CH=)ppm; m/z (EI): 316 ($M^{+\cdot}$, 6%), 301 (M-15, 4), 273 (M-43, 6), 165 (100), 137 (90), 109 (54), 91 (30); **8**: ν_{max}(film): 1683 (s), 1616 (s) cm^{-1}; δ_H(80 MHz, $CDCl_3$ / TMS): 0.87 (d, 6H, J=6.1 Hz, $CH(CH_3)_2$), 1.52 and 1.59 (2s, each 3H, 2×CH_3), 2.10 (s, 3H, CH_3), 1.70-2.40 (m, 14H), 4.70-5.20 (br m, 2H, 2×CH=), 5.88 (br s, 1H, CH=)ppm; m/z (EI): 288 ($M^{+\cdot}$, 93%), 273 (M-15, 30), 245 (M-43, 41), 227 (14), 177 (42), 143 (60), 81 (100); (±)-**1** and its epimer : ν_{max}(film): 3430(s), 1665, 1019 cm^{-1}; δ_H(80 MHz), $CDCl_3$/TMS); 0.93 and 0.97 (2d, 6H, J=7.1 Hz, $CH(CH_3)_2$), 1.53, 1.56 (br s, each 3H, CH_3), 1.62 (d, 3H, J=1.2 Hz, CH_3), 1.68-2.40 (m, 14H), 4.60 (for (±)-mukulol, bd, 1H, J=9 Hz, CH-O), 4.23 (for epi-(±)-mukulol, t, 1H, J=9 Hz), 4.80-5.20 (br m, 2H, CH=), 5.32 (br d, 1H, J=9.1 Hz, CH=) ppm; m/z(EI): 290 ($M^{+\cdot}$, 65%), 272 (M-18, 52), 257(26), 229(71), 121(20), 205(20), 149 (54), 123(100), 109(68), 81(77); (±)-**2**: δ_H(80 MHz, $CDCl_3$/TMS): 0.75-0.95 (m, 6H, $CH(CH_3)_2$), 1.58 (br s, 9H, 3×CH_3), 1.80-2.40 (m, 12H), 4.75-5.20 (br m, 2H, CH=), 5.25-5.65 (br m, 2H, CH=), 6.07 (d, 1H, J=15.6 Hz, *trans* CH=CH) ppm: m/z(EI): 272 ($M^{+\cdot}$, 6%), 257 (M-15, 5), 229(15), 173(13), 145(21), 105(65), 91(88), 41(100).

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13) Their spectral data were consistent with those of literature. No authentic samples of natural (±)-mukulol and (±)-cembrene are available for direct comparison.

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