A Facile Total Synthesis of (±)-Cembrene by Titanium-Induced Keto Ester Cyclization

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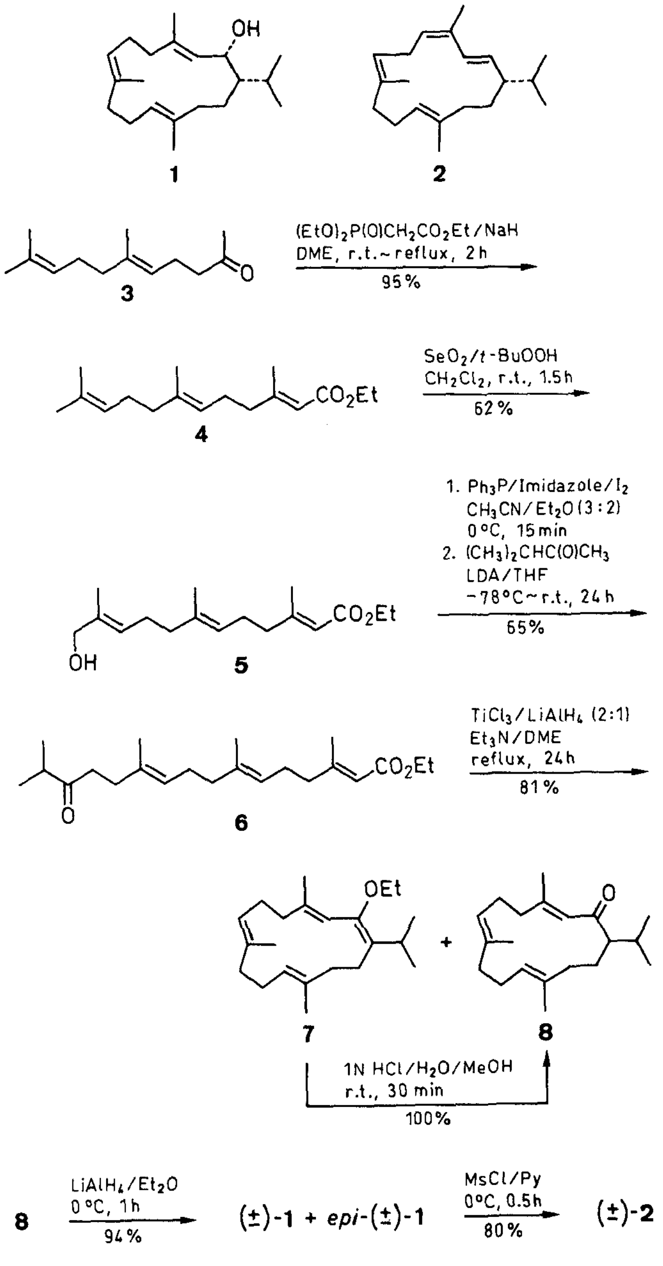
A direct approach of titanium-induced intramolecular keto ester cyclization was applied to the total synthesis of macrocyclic diterpenoids, by which (±)-cembrene was synthesized from geranylacetone by a short and efficient route.

In recent years, interest in the synthesis of cembranes and cembranolides, a new type of diterpenoid characterized by the presence of a fourteen-membered carbocyclic ring, has increased as a result of their remarkably wide range of biological activity, and their challenging structural features. Though a number of synthetic strategies have been published,[1] the lack of a general method for the construction of the fourteen-membered ring has been an intriguing problem in the total synthesis of cembrane natural products.

Among the macrocyclization methodologies in literature,[1] the titanium-induced intramolecular cyclization of dicarbonyl precursors developed by McMurry and coworkers[2] is an extraordinarily effective means for preparing carboxylic 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 a key step, we herein wish to present a facile total syntheses of (±)-mukulol (**1**) and its epimer, and (±)-cembrene (**2**), two naturally occurring cembrane diterpenoids.

Mukulol (**1**), a cembrane alcohol, was first isolated from the gum-resin of an Indian plant (*Commiphora mukul*)[4] and its synthesis has been achieved by several groups.[5] Furthermore, the conversion of the available cembrane alcohol **1** into some densely oxygen-functionalized cembrenoids, i.e. incensole, isoincensole oxide and thunbergol has been reported.[6] Cembrene (**2**), the first naturally occurring cembrane hydrocarbon to be characterized,[7] is found in many species of pine resins and the synthesis was first achieved by Dauben[8] and later by other groups[9] 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 titanium-induced macrocyclization of the keto α,β-unsaturated ester precursor **6** which was prepared by the selective alkylation of the lithium enolate of isopropyl methyl ketone with the corresponding allylic iodide of alcohol **5**. The synthetic route is outlined in Scheme 1.



Scheme 1

The Horner–Emmons reaction of *trans*-geranylacetone (**3**) with ethyl 2-(diethoxyphosphinyl)-2-sodioacetate in dimethoxyethane at reflux temperature (80°C) 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 catalytic amount of selenium oxide (0.1 equiv) in dichloromethane to give the allylic alcohol **5** in 62% yield, which was then converted quantitatively into the corresponding iodide by standard methodology.[10] Alkylation of the lithium enolate of isopropyl methyl ketone with the labile allylic iodide afforded the keto ester **6** in 65% yield.

Macrocyclization of the keto ester **6** was carried out[11] by slow addition of a dilute solution of **6** in dimethoxyethane to the refluxing low valent titanium slurry, prepared in situ by the reduction of titanium trichloride with lithium aluminum hydride (0.5 equiv) in the presence of triethylamine over 24 h, followed by methanol–water (1:1) workup at 0 °C to give the enone **8** and the macrocyclic enol ether **7** in a ratio of 1:4. Treatment of enol ether **7** with 1 N HCl in methanol gave macrocyclic enone **8** quantitatively, which was reduced with lithium aluminum hydride in diethyl ether at 0 °C to afford (±)-**1** and its epimer in the same ratio (measured by GC) in 94% yield. Dehydration of the mixture of (±)-**1** and its epimer by treatment with methanesulfonyl chloride in pyridine yielded the hydrocarbon product (±)-cembrene (**2**) in 80% yield. The spectral data of the synthetic (±)-**2** were consistent with those in the literature[7] (no authentic sample of cembrene was available for direct comparison).

Thus, (±)-**2** was synthesized by a short and convenient route employing the titanium-induced keto ester cyclization which was used for the first time in the synthesis of cembrane diterpenoids and further studies are underway in our laboratory.

IR spectra were obtained on a FT-170SX spectrometer. ^{1}H NMR spectra were recorded on a FT-80A instrument in $CDCl_3$ solution, chemical shifts are reported in ppm units with TMS as the internal standard. Mass spectra (MS) were measured on a ZAB-HS spectrometer by direct inlet at 70 eV, and signals given in m/z with relative intensity (%) in brackets. All solvents were freshly purified and dried by standard techniques prior to use. All reactions were routinely carried out under an inert atmosphere of argon, and monitored by TLC. Products were purified by flash column chromatography on silica gel (200–300 mesh), purchased from Qing Dao Marine Chemical Co. In the workup, all organic phases were washed with water and brine respectively, then dried over anhydr. $MgSO_4$ and filtered prior to rotary evaporation under reduced pressure.

Ethyl (*E*,*E*)-Farnesenate (4):

To a suspension of NaH (free of oil, 435 mg, 18.1 mmol) in dimethoxyethane (DME, 25 mL) was added triethyl phosphonoacetate (3.6 mL, 4.04 g, 18 mmol) dropwise at 0 °C (ice-water bath) with stirring over 5 min. After being stirred for 0.5 h at r.t., *trans*-geranylacetone (**3**) (3.35 mL, 2.91 g, 15 mmol) was added to the reaction mixture and stirred for 2 h, then refluxed for 1 h to complete the reaction. The cooled reaction mixture was quenched with sat. aq NH_4Cl (10 mL), diluted with Et_2O (60 mL). The organic phase was separated and washed with water and brine (each 15 mL), then dried. Evaporation of the solvent under reduced pressure gave an oily residue which was flash chromatographed on silica gel (petroleum ether/EtOAc/v/v 30:1), yield **4**: 3.76 g (95%) as a colorless oil with a ratio of $E/Z > 8:1$.

IR (liquid film): $\nu = 1715$ (s), 1637 (s), 1612, 1449, 1368, 1153, 1040, 979, 888 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): $\delta = 1.27$ (t, 3 H, $J = 7.1$ Hz, CH_3), 1.6 (br s, 6 H, CH_3), 1.67 (s, 3 H, CH_3), 2.15 (d, 3 H, $J = 1.2$ Hz, CH_3), 1.70–2.40 (, 8 H, CH_2), 4.14 (q, 2 H, $J = 7.1$ Hz, CH_2O), 4.95–5.20 (br m, 2 H, CH=), 5.66 (br s, 1 H, CH=).

MS (EI): $m/z = 264$ ($M^{+\bullet}$, 5%), 249 (3), 235 (7), 193 (7), 139 (74), 81 (100).

Ethyl (2*E*,6*E*,10*E*)-12-Hydroxy-3,7,11-trimethyldodeca-2,6,10-trienate (5):

To a stirred clear mixture of selenium dioxide (60 mg, 0.54 mmol) and *tert*-butyl hydroperoxide (75%, 1.5 mL, 11.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of ester **4** (1.40 g, 5.3 mmol) in CH_2Cl_2 (5 mL) at 0 °C (ice-water bath) over 15 min. The stirring was continued for 3.5 h at r.t., then the mixture was diluted with Et_2O (30 mL) and washed successively with 10% aq KOH (3 × 15 mL), water and brine, and dried. Evaporation of the solvent under vacuum gave the oily crude product, which was purified by flash column chromatography (petroleum ether/EtOAc, v/v 5:1) to afford the desired primary alcohol **5**: 920 mg (62%) as a colorless oil.

IR (liquid film): $\nu = 3413$ (br s, OH), 1715 (s), 1647 (s), 1445, 1383, 1058, 863 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): $\delta = 1.26$ (t, 3 H, $J = 7.1$ Hz, CH_3), 1.60 and 1.66 (2 s, each 3 H, 2 × CH_3), 2.15 (d, 3 H, $J = 1.2$ Hz, CH_3), 1.70–2.40 (m, 8 H, CH_2), 3.99 (s, 2 H, CH_2O), 4.15 (q, 2 H, $J = 7.1$ Hz, CH_2O), 5.00–5.20 (br m, 1 H, CH=), 5.25–5.50 (br m, 1 H, CH=), 5.65 (br s, 1 H, CH=).

MS (EI): $m/z = 279$ (M − 1, 1%), 263 6 (M − 17, 2), 239 (23), 221 (69), 193 (36), 175 (30), 139 (96), 81 (100).

Ethyl (2*E*,6*E*,10*E*)-3,7,11,15-Tetramethyl-14-oxohexadeca-2,6,10-trienate (6):

To a stirred clear mixture of alcohol **5** (560 mg, 2 mmol), triphenylphosphine (790 mg, 3 mmol) and imidazole (240 mg, 3.5 mmol) in a solvent mixture of MeCN (3 mL) and Et_2O (4 mL) was added iodine crystals (890 mg, 3.5 mmol) portionwise at 0 °C (ice–water bath) over 5 min. Then the resulting mixture was stirred for 0.5 h at r.t. Et_2O (20 mL) was added, and the reaction mixture was filtered. The filtrate was washed with sat. aq $Na_2S_2O_3$, sat. aq $CuSO_4$, water and brine, then dried. Evaporation of the solvent under reduced pressure at 30 °C gave the crude labile iodide which without further purification was taken up in anhydr. THF (5 mL) and used for the following procedure.

A solution of freshly distilled anhydr. diisopropylamine (41 mg, 4 mmol) in THF (8 mL) was cooled to − 20 °C under argon and a *n*-hexane solution of BuLi (1.2 N, 3.3 mL, 4 mmol) was introduced via a dry syringe. The resulting mixture was stirred for 0.5 h at that temperature and cooled again to − 78 °C (dry ice-acetone bath), the above solution of allylic iodide in THF was added dropwise with efficient stirring. The stirring was continued for 2 h at − 78 °C, then the reaction mixture was allowed to warm gradually to r.t. overnight. The reaction was quenched by the addition of sat. aq NH_4Cl (10 mL) and Et_2O (30 mL), then the organic phase was separated and the aqueous layer extracted with Et_2O (2 × 10 mL), the combined organic phases were washed with water and brine, and then dried. Evaporation of the solvent under reduced pressure gave the oily residue which was purified by flash column chromatography on silica gel (petroleum ether/EtOAc v/v 15:1) to yield the keto α,β-unsaturated ester **6**: 450 mg (65%) as a colorless oil.

IR (liquid film): $\nu = 1714$ (s), 1648 (s), 1446, 1383, 1145, 863 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): $\delta = 1.08$ [d, 6 H, $J = 6.8$ Hz, $CH(CH_3)_2$], 1.27 (t, 3 H, $J = 7.1$ Hz, CH_3), 1.60 and 1.67 (2 s, each 3 H, 2 × CH_3), 2.17 (d, 3 H, $J = 1.2$ Hz, CH_3), 1.80–2.80 (m, 13 H), 4.15 (q, 2 H, $J = 7.1$ Hz, CH_2O), 4.95–5.30 (br m, 2 H, CH=), 5.65 (br s, 1 H, CH=).

MS (EI): $m/z = 348$ ($M^{+\bullet}$, 12%), 302 (10), 217 (9), 153 (24), 121 (37), 93 (32), 81 (60), 71 (100).

(2*E*,6*E*,10*E*)-14-Isopropyl-3,7,11-trimethylcyclotetradeca-2,6,10-trienone (8) and (1*Z*,3*E*,7*E*,11*E*)-2-Ethoxy-1-isopropyl-4,8,12-trimethylcyclotetradeca-1,3,7,11-tetraene (7):

To a well stirred suspension of titanium trichloride (615 mg, 4 mmol) in freshly distilled anhydr. DME (25 mL) under argon was added lithium aluminum hydride (76 mg, 1.96 mmol) at 0 °C (ice–water bath). After being stirred for 5 min, anhydr. Et_3N (0.3 mL, 2.15 mmol) was added to the slurry mixture, then the resulting mixture was heated under reflux for 2 h to complete the formation of the low-valent titanium reagent. Keto α,β-unsaturated ester **6** (70 mg, 0.2 mmol) in DME (20 mL) was syringed slowly to the above refluxing low-valent titanium slurry over 20 h. After the addition was complete, the reaction mixture was refluxed for an additional 4 h, then cooled to 0 °C, diluted with Et_2O (15 mL), quenched with MeOH (5 mL) and water (5 mL). The resulting mixture was filtered through a short column of silica gel, then the filtrate was washed with brine and dried. Evaporation of the solvent in vacuum gave an oily residue which was purified by flash column chromatography carefully eluting with *n*-hexane/Et_2O (v/v 20:1) to afford macrocyclic enone **8** (10 mg, 18%) and macrocyclic enol ether **7** (40 mg, 63%) in a ratio of 1:4 with 81% combined yield.

To a solution of macrocyclic enol ether **7** (34.5 mg, 0.11 mmol) in wet acetone (2 mL) was added 1 N HCl (0.2 mL) at 0°C with stirring. After 2 h, the solvent (acetone) was removed in vacuum to give an oily residue which is taken up in Et_2O (10 mL), washed with brine, and dried. Evaporation of the solvent under reduced pressure afforded macrocyclic enone **8**: 31.4 mg (100%).

Macrocyclic enol ether **7**, colorless oil.

IR (liquid film): ν = 1625, 1442, 1382, 1179, 1133 (s), 1061 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.85–1.40 (m, 9 H, 3 × CH_3), 1.52, 1.58 and 1.65 (3 s, each 3 H, 3 × CH_3), 1.80–2.30 (br m, 13 H), 3.40–3.80 (q, 2 H, J = 7.1 Hz, CH_2O), 4.75–5.30 (br m, 3 H, 3 × CH=), 5.52 (br s, 1 H, CH=).

MS (EI): m/z = 316 ($M^{+\bullet}$, 6%), 301 (M−15, 4), 273 (M−43, 6), 233 (14), 205 (10), 165 (100), 137 (90), 109 (54), 91 (30), 81 (26).

Macrocyclic enone **8**, colorless oil.

IR (liquid film): ν = 1683 (s), 1616 (s), 1443, 1379, 1083, 802 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.87 [d, 6 H, J = 1 Hz, $CH(CH_3)_2$], 1.52 and 1.59 (2 s, each 3 H, 2 × CH_3), 2.10 (s, 3 H, CH_3), 1.70–2.40 (m, 14 H), 4.70–5.20 (br m, 2 H, 2 × CH=), 5.88 (br s, 1 H, CH=).

MS (EI): m/z = 288 ($M^{+\bullet}$, 93%), 273 (M−15, 30), 345 (M−43, 41), 227 (14), 205 (21), 177 (42), 143 (60), 109 (86), 93 (56), 81 (100).

(±)-Mukulol (1) and Its Epimer:

To a stirred suspension of lithium aluminum hydride (4 mg, 0.103 mmol) in anhydr. Et_2O (5 mL) was added dropwise a solution of enone **8** (43.2 mg, 0.15 mmol) in Et_2O (1 mL) at 0°C. The reaction mixture was then stirred for an additional 0.5 h at that temperature and water (0.2 mL, two drops) was added to quench the reaction. After filtration, the filtrate was washed with water and brine, then dried. Evaporation of the solvent in vacuum gave an oily residue which was purified by FCG on silica gel (n-hexane/Et_2O, 10:1) to yield a mixture of (±)-**1** and its epimer: 40.5 mg (94%), colorless oil.

IR (liquid film): ν = 3430 (br s, OH), 1665, 1447, 1384, 1019 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.93 and 0.97 [2 d, 2 × 3 H, J = 7.1 Hz, $CH(CH_3)_2$], 1.51 and 1.56 (2 s, each 3 H, 2 × CH_3), 1.62 (d, J = 1.2 Hz, CH_3), 1.68–2.40 (m, 14 H), 4.55 (dd, 1 H, J = 5.7, 9.1 Hz, CH−O), 4.80–5.20 (br m, 2 H, CH=), 5.32 (br d, 1 H, J = 9.1 Hz, CH=).

MS (EI): m/z = 290 ($M^{+\bullet}$, 65%), 272 (M−18, 52), 257 (26), 229 (71), 121 (20), 205 (20), 149 (54), 123 (100), 109 (68), 81 (77).

Synthesis of (±)-Cembrene (2):

Methanesulfonyl chloride (23 mg, 0.2 mmol) was added dropwise to a mixture of (±)-mukulol (**1**) and its epimer (29.5 mg, 0.1 mmol) in dry pyridine (0.5 mL) at 0°C with stirring. The stirring was continued for 1 h at ice temperature, then the reaction mixture was diluted with n-hexane (10 mL), washed with 2 N HCl (2 × 5 mL), water, and brine, and dried. Evaporation of the solvent in vacuum afforded the crude oil which was chromatographed on silica gel carefully eluting with n-pentane to yield the hydrocarbon product (±)-**2**: 22 mg (80%), solid wax.

IR (liquid film): ν = 1652 (w), 1455, 1377, 1138, 969, 885, 843 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 0.75–0.95 [m, 6 H, $CH(CH_3)_2$], 1.52–1.65 (br s, 9 H, 3 × CH_3), 1.80–2.40 (m, 12 H), 4.75–5.20 (br m, 2 H, CH=), 5.25–5.65 (br m, 2 H, CH=), 6.07 (d, 1 H, J = 15.6 Hz, CH=CH).

MS (EI): m/z = 272 ($M^{+\bullet}$, 6%), 257 (M−15, 5), 229 (15), 173 (13), 145 (21), 105 (65), 91 (88), 41 (100).

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