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A Convenient Synthesis of Cembrene-C

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ABSTRACT: Cembrene-C (**1**), a natural occurring cembrane hydrocarbon diterpene, was prepared from farnesyl acetate (**3**) *via* four steps in 21% overall yield by titanium-induced macrocyclization as the key step.

Cembrene-C (**1**), a fourteen-membered hydrocarbon diterpene, was first reported as a component of oleoresin of *pinus koraiensis* by Raldugin in 1971, but its structure was not confirmed[1]. In 1978, Vanderah *et al* isolated it from a soft coral (*Nephthea sp.*) and established its structure as (*E*, *E*, *E*, *E*)-1,7,11-trimethyl-4-isopropyl-1,3,7,11-cyclotetradecatetraene[2] which was also found in another sources of soft coral (*Sarcophyton ehrenbergi*) afterwards[3]. Compound **1** was synthesized in trace amounts by isomerization of natural occurring cembrene-A (**2**) with a strong base as catalyst[4]. In previous work[5], we have reported the first total synthesis of **1** from geraniol as starting material *via* 9 steps employing the titanium-induced macrocyclization developed by *McMurry*

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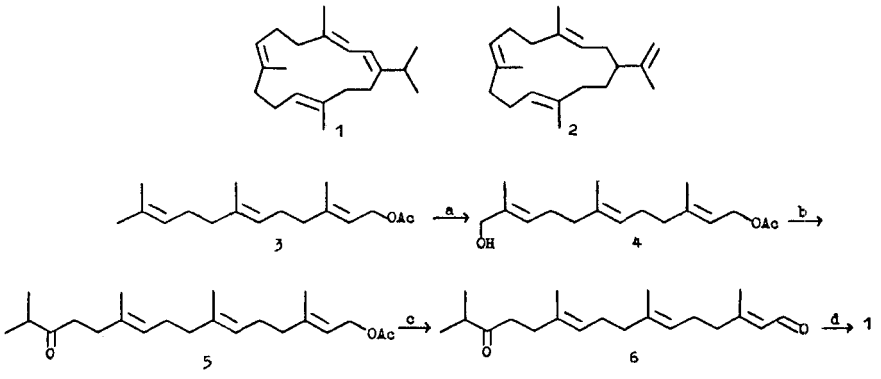
and his co-workers[6]. Herein we wish to present an alternative synthetic route of 1 from farnesyl acetate (3) through four steps to overcome the shortcomings of the time, i. e. , number of steps and low overall yield. The synthetic route is outlined in the scheme:



SCHEME: *Reagents and conditions*: a) SeO_2/t-BuOOH, CH_2Cl_2, r. t. (58%); b) 1. Ph_3P/Imidazole, I_2, CH_3CN-Et_2O(3 : 2), 0℃～r. t. ; 2. i-PrC(O)Me/LDA, THF, -78℃～r. t. (54%); c) 1. K_2CO_3/MeOH, r. t. ; 2. MnO_2/CH_2Cl_2, r. t, (90%); d) $TiCl_4$/Zn, Py, DME, reflux (72%)

Farnesyl acetate (**3**) was exposed to 75% *tert*-butyl hydroperoxide in the presence of a catalytical amount of SeO_2 (10% eq.) in CH_2Cl_2 at room temperature to give the allylic alcohol **4** in 58% yield (based on consumed starting material), which then was converted into the corresponding allylic iodide by standard methodology[7]. Alkylation of the lithium enolate of methyl isopropyl ketone (formed by treatment of the ketone with LDA at -78℃ in THF) with the crude labile iodide from **4** at -78℃ to room temperature afforded the ketone **5** in 54% yield, possessing all the carbon skeleton and the three *trans* double bonds of the target molecule. Base hydrolysis of the ketone **5** was followed by oxidation with active MnO_2 in CH_2Cl_2 at room temperature to give the enal

ketone **6** in 90% yield form **5**. The macrocyclization of **6**, the key step of the synthesis, was conducted by slowly syringing the dilute solution of **6** in anhydrous DME to the refluxing low valent titanium slurry (prepared *in situ* by reduction of $TiCl_4$ with zinc powder in the presence of pyridine in DME) over a period of 16h. After usual work-up (diluting with pet. ether, then filterring) and careful flash column chromatography eluting with *n*-pentane, the title compound **1** was obtained as a colorless oil in good yield (72%) whose spetral data were consistent with those reported in the literature[2].

Thus, a short and convenient synthesis of cembrene-C was completed *via* 4 steps from farnesyl acetate with high overall yield (21%).

EXPERIMENTAL

^{1}HNMR spectra were recorded on a FT-80A instrument in $CDCl_3$ solution, chemical shifts were reported in *ppm* units with TMS as the internal standard. FT-IR spectra were obtained on a FT-170SX spectrometer. Mass spectra (MS) were measured on a ZAB-HS spectrometer, direct inlet, 70ev, and signals are given in m/z with relative intensity (%) in brackets. All solvents were purified and dried by standard techniques prior to use. All reactions were routinely carried out under an inert atomsphere of Argon, and monitored by TLC. Products were purified by flash column chromatography (FCG) 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 and dried over anhydrous $MgSO_4$ and filtered prior to rotary evaporation under reduced pressure (20 torr).

3,7,11,15-Tetramethyl-14-oxo-2*E*,6*E*,10*E*-hexadecatrienyl acetate (5)

To a well stirred clear mixture of alcohol **4** (560mg, 2mmol), Ph_3P (790mg, 3mmol) and imidazole (240mg, 3.5mmol) in a solvent

mixture of acetonitrile (3mL) and diethyl ether (4mL) was added portionwise iodine crystals (890mg, 3.5mmol) at 0℃ (ice-water bath) over 5 minutes. After removal of the ice-cooled bath, the reaction mixture was stirred for another 0.5h and then diluted with diethyl ether (30mL). The resulting mixture was filtered and the filterate was washed with saturated $Na_2S_2O_3$, $CuSO_4$ aqueous solution, water, brine and then dried. Evaporation of the solvent under reduced pressure at 35℃ gave the crude allylic iodide, which without further purification was taken in anhydrous THF (5mL), used for the following *procedure*: A solution of freshly distilled anhydrous diisopropylamine (410mg, 4mmol) in THF (8mL) was cooled to -20℃ under argon and a *n*-hexane solution of *n*-BuLi (1.2N, 3.3mL, 4mmol) was introduced by a dry syringe. The resulting mixture was stirred for 0.5h at that temperature, and then cooled to -78℃ by a dry ice-acetone bath. Methyl isopropyl ketone (330mg, 3.8mmol) was added dropwise and the mixture stirred for 40 minutes at -78℃. A clear solution of the crude iodide in THF was added dropwise by a syringe to the above lithium enolate solution with efficient stirring at that temperature. After being stirred for a period of 2h at -78℃, the reaction mixture was allowed to warm gradually to room temperature overnight. Addition of saturated NH_4Cl aqueous solution (5mL) and diethyl ether (30mL) to the mixture was followed by stirring for 15 minutes. The organic phase was separated and the aqueous layer was extracted with ether (2×10mL), then the combined organic phases were washed with water and brine respectively, and dried. Evaporation of the solvent under reduced pressure gave a crude oil which was purified by flash column chromatography eluting with pet. ether/ethyl acetate (16 : 1) to afford the ketone **5** (370mg, 54% two steps) as a colorless oil. ν_{max}: 1739 (s, CO_2Et), 1709 (s, C=O), 1465, 1382, 1233, 1023, 956cm^{-1}; δ_H: 1.07 (6H, d, J=7.2Hz, $CH(CH_3)_2$), 1.60 (6H, br s, $2CH_3$), 1.68 (3H, s, CH_3), 2.03 (3H, s, CH_3CO), 2.0 ~2.8 (13H, m), 4.55 (2H, d, J=7.2Hz, CH_2O), 5.0~5.4 (3H, m, CH=)ppm; *m/z* (EI): 348 ($M^{+\cdot}$, 2%), 288(20), 202(22), 153(8), 71(100), 43(47); *Anal.* Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41; Found: C, 76.11; H, 10.34

3,7,11,15-Tetramethyl-14-oxo-2*E*,6*E*,10*E*-hexadecatrienal (6)

Powdered anhydrous K_2CO_3 (140mg, 1mmol) was added to a stirred solution of ketone **5** (270mg, 0.78mmol) in methanol (5mL) at room temperature. After being stirred for 1h, the solvent (methanol) was removed in vaccum at room temperature to give an oil residue which was disolved in ether (20mL), then washed with water, brine, and dried. Evaporation of the solvent under reduced pressure afforded the crude alcohol (230mg, 97%), which without further purification, was disolved in methylene chloride (10mL) to give a clear solution, to which active MnO_2 (1.3g, 15mmol) and anhydrous Na_2CO_3 (50mg, 0.47mmol) was added. The resulting mixture was stirred for 4h at room temperature. Ether (20mL) was added the reaction mixture filtered through a short column on silica gel. The filterate was concentrated under reduced pressure to give the crude oil, which was flash chromatographed on silica gel eluting with pet. ether/ethyl acetate (10 : 1) to afford 205mg (90%) of aldehyde **6**. ν_{max}: 1711 (s, C=O), 1674 (s, HC=O), 1632 (w, C=)cm^{-1}; δ_H: 1.09 (6H, d, J=6.9Hz, CH(CH_3)$_2$), 1.59 (6H, br s, 2CH_3), 1.99 (3H, s, CH_3), 1.88~2.50 (13H, m), 5.00~5.30 (2H, m, CH=), 5.84 (1H, d, J=8.1Hz, CH=), 9.98 (1H, d, J=8.1Hz, CHO)ppm; m/z(EI): 304 ($M^{+\cdot}$, 2%), 261(1), 153(30), 71(100); *Anal.* Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; Found: C, 78.63; H, 10.44

4,8,12-Trimethyl-1-isopropyl-1*E*,3*E*,7*E*,11*E*-cyclotetradecatetraene (Cembrene-C, 1)

$TiCl_4$ (1.1mL, 1.9g, 10mmol) was added dropwise by a dry syringe to a cooled (-20℃) solution of anhydrous DME (30mL), followed by addition of zinc powder (1.3g, 20mmol) and pyridine (0.2mL). The resulting mixture was warmed to room temperature, then refluxed for 2h under argon. A solution of dicarbonyl precursor **6** (45mg, 0.15mmol) in DME (20mL) was syringed slowly to the obove

refluxing low valent titanium slurry over 13h. After the addition was complete, the reaction mixture was refluxed for an additional 3h, then cooled to room temperature, diluted with light pet. ether (30～60℃). The slurry mixture was filtered through a short column on silica gel to give a clear filterate which was concentrated in vaccum (40℃, water bath). The oily residue was purified by flash column chromatography carefully eluting with *n*-pentane to afford the desired product **1**, 32mg (72%). ν_{max}: 2959, 2923, 1641, 1444, 1378, 872cm^{-1}; δ_H: 1.04 (6H, d, J=6.7Hz, $CH(CH_3)_2$), 1.52, 1.59, 1.73 (9H, 3s, 3×CH_3), 2.00～2.50 (13H, m), 5.04 (2H, br m, CH=), 5.96 (2H, ABq, J=11.5Hz, CH=CH)ppm; *m/z* (EI): 272 ($M^{+\cdot}$, 31%), 257(2), 229(6), 189(5), 161(14), 136(72), 121(100); *Anal.* Calcd for $C_{20}H_{32}$: C, 88.15; H, 11.84; Found: C, 88.38; H, 11.71

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