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Studies on the Total Synthesis of Crotocembreneic Acid and Neocrotocembreneic Acid:A Perchloric Acid-induced Lactonization Reaction of Epoxy Ester

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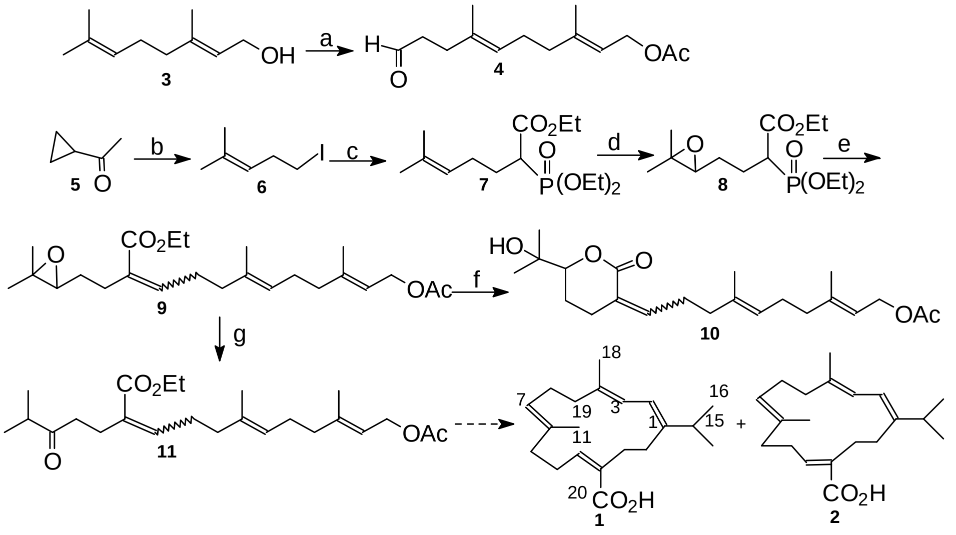
Abstract A perchoric acid-induced lactonization reaction of epoxy ester is described. Using lithium perchlorate, the ketone is obtained in 81% yield.

Keywords Lactonization, crotocembreneic acid, neocrotocembreneic acid, synthesis.

Cembranoids, a large family of diterpenoid natural products characterized by the presence of fourteen-membered ring, have been isolated from various marine sources as well as some terrestrial organisms since the 1960's[1]. Crotocembraneic acid **1** and neocrotocembraneic acid **2** have been isolated from the stem bark of *Croton oblongifolius* Roxb. (Euphorbiaceae)[2]. In our studies on the total synthesis of **1** and **2**, we find a novel perchloric acid-induced lactonization reaction of epoxy ester **9** (**Scheme 1**).

Scheme 1



Reagents and conditions: a) ref. 3; b) i)MeMgI, Et_2O, reflux; ii)30%H_2SO_4, 0 °C, 1 h, 77%; c) NaH, $(Et_2O)P(O)CH_2CO_2Et$, DMF, 60 ^{o}C, 3h, 88%; d) *m*-CPBA, CH_2Cl_2, 0 ^{o}C, 2 h, 93%; e) LDA, -78 ^{o}C, 1h, then aldehyde **4**, -78 ^{o}C~rt, 3h, 73%; f) $HClO_4$, CH_2Cl_2, 0 ^{o}C, 30min., 95%; g)$LiClO_4$, PhH, 80 ^{o}C, 1h, 81%.

Aldehyde **4** was prepared from geraniol **3** according to the reference 3. Using *Juvia* method, the homoprenyl iodide **6** was obtained from methyl cyclopropanyl ketone **5** in 77% yield[4]. The homoprenyl iodide reaction with sodium triethyl phosphonate gave phosphonate **7**. Epoxidation of phosphonate **7** with *m*-CPBA gave the epoxide **8** in 93% yield.

The *Horner-Emmons* reaction of phosphono ester **8** with aldehyde **4** using LDA as base at –78 ^{o}C gave α, β -unstatured ester **9** in 71% yield[5]. The ratio of *E* and *Z* isomers were *ca.* 1:1. As usual[6], we used the perchloric acid to rearrange the epoxide to ketone[7]. To our surprise, the ketone **11** was obtained only in 5% yield, the lactone **10** was obtained in 95% yield, which the *E*, *Z* isomers were separated by silica gel chromatograph[8]. The rearrangement of epoxide **9** to ketone **10** reacted smoothly using lithium perchlorate[9], the ketone **10** was obtained in 81% yield. The transformation of **10** to **1** and **2** is in progress.

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8 Spectral data: Compound **10*E***: IR(film): ν=3458, 2974, 2935, 1730, 1719, 1635, 1448, 1377, 1268, 1235, 1187, 960, cm^{-1}. EIMS (*m/z*): 378 (0.2%, M), 335 (0.2, M-Ac), 318 (1.1), 300 (0.4), 285 (0.3), 250 (0.6), 232 (1.7), 215 (1.3), 184 (10), 166 (16), 138 (16), 135 (14), 96 (16), 93 (22), 67 (25), 59 (58), 43 (100). ^{1}HNMR (400 MHz,$CDCl_3$): δ (ppm) 7.03 (t, J=6.7Hz, 1H, CH=), 5.35(t, J=7.2Hz, 1H, CH=), 5.13 (t, J=6.5Hz, 1H, CH=), 4.58 (d, J=7.2Hz, 2H, CH_2O), 4.03 (dd, J=11.6Hz, J=2.7Hz, 1H, CHO), 2.06 (s, 3H, CH_3), 2.36-2.00 (m, 12H, $6CH_2$), 1.70 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 171.09, 166.51, 146.16, 145.85, 125.76, 124.81, 119.23, 118.41, 85.51, 71.33, 61.33, 39.32, 37.67, 27.06, 26.07, 25.49, 24.40, 22.92, 22.61, 21.02, 16.43, 15.95. Compound **10*Z***: ^{1}HNMR (400 MHz,$CDCl_3$): δ (ppm) 6.04 (t, J=6.7Hz, 1H, CH=), 5.33(t, J=7.2Hz, 1H, CH=), 5.12 (t, J=6.5Hz, 1H, CH=), 4.57 (d, J=7.2Hz, 2H, CH_2O), 4.02 (dd, J=11.7Hz, J=2.7Hz, 1H, CHO), 2.69 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.23-1.96 (m, 10H, $5CH_2$), 1.69 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.22 (s, 3H, CH_3). ^{13}CNMR (100 MHz, $CDCl_3$): δ (ppm) 171.07, 165.41, 147.67, 147.24, 125.19, 124.44, 119.13, 118.30, 85.66, 71.32, 61.31, 39.42, 38.75, 28.64, 27.94, 26.11, 25.57, 24.28, 23.44, 20.99, 16.41, 15.77.

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