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Synthesis of (R)-(+)-4-Butyl-2,6-cycloheptadienone, a Constituent of Marine Algae

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The title compound was synthesized from (R)-(-)-5-trimethylsilyl-2-cyclohexenone in 19% overall yield.

(+)-4-Butyl-2,6-cycloheptadienone (**1**) was isolated as a minor constituent of the essential oil of Hawaiian Dictyopteris. The unique dihydrotropone derivative is a metabolite of the structurally related dictyopterene C' and the structure was confirmed by the derivatization from natural dictyopterene C'.[1)]

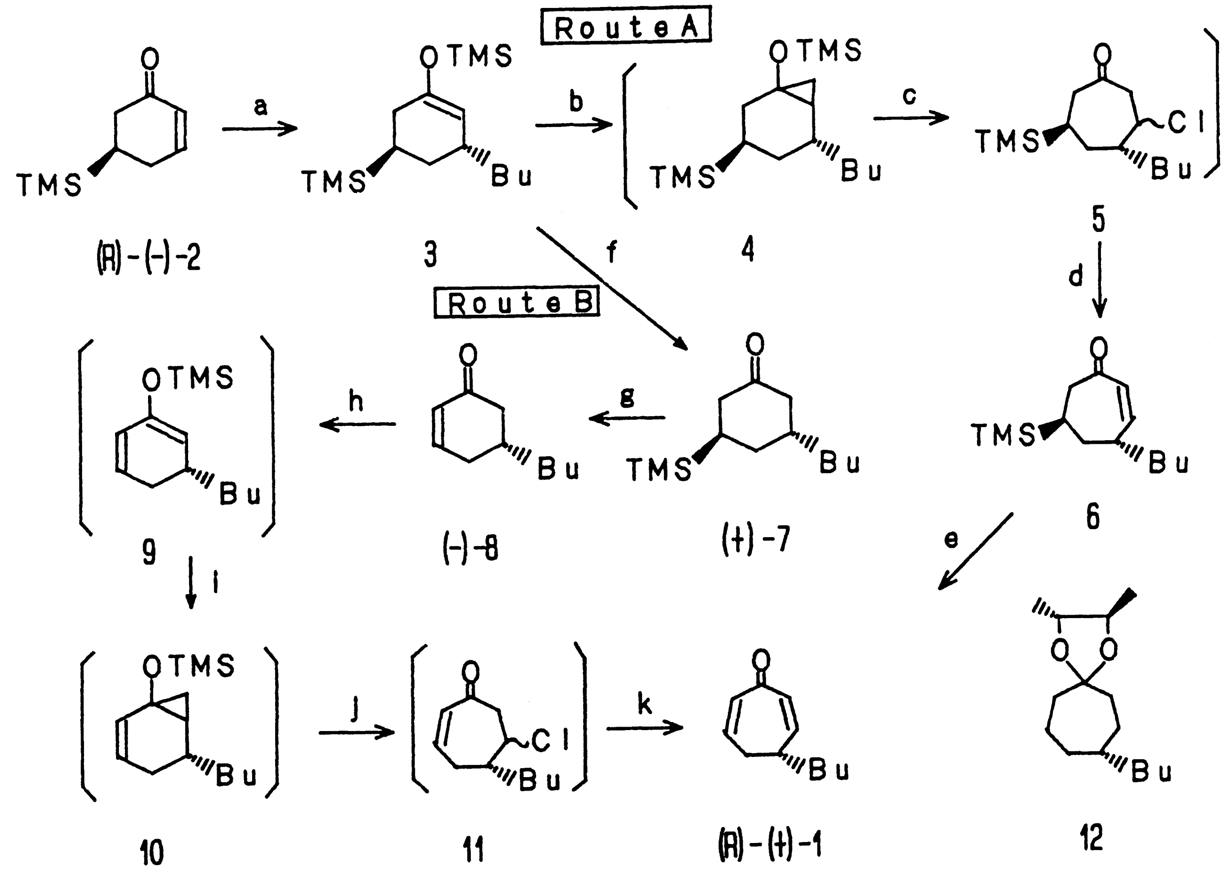
In this paper we will describe a short step synthesis of the above compound by utilizing (R)-(-)-5-trimethylsilyl-2-cyclohexenone (**2**).[2)]

First, the synthetic route A was examined by using racemic **2** (Scheme 1). The route involves the Simmons-Smith type cyclopropanation of enol silyl ether **3**, which was obtained in 93% yield by 1,4-addition of butylmagnesium bromide to **2** in the presence of chlorotrimethylsilane,[2,3)] and subsequent oxidative ring opening as a ring expansion method. Among cyclopropanation conditions of **3** examined, the use of CH_2I_2-Et_2Zn[4)] in benzene at 0 °C-rt gave the best result. Oxidative ring opening of **4** with $FeCl_3$[5)] and dehydrochlorination afforded cycloheptenone derivative **6** in 77% overall yield from **3**.

Disappointingly, oxidative removal of TMS group from **6** under various reported conditions[6)] resulted in a failure. After further trials, the conversion was accomplished by three-step operation to give the desired dienone **1**, but the yield was low (28%). Therefore, alternative route was examined by using ($\pm$)-**2**. The second route (route B) involves the removal of TMS group in an early stage. Hydrolysis of crude enol silyl ether **3** with KF and subsequent removal of TMS group under oxidative conditions ($CuCl_2$ in DMF)[7)] gave enone **8** in 85% overall yield from **2**. After the conversion of **8** to the enol silyl ether **9** (84%), cyclopropanation followed by oxidative ring cleavage and dehydrochlorination gave expected dienone ($\pm$)-**1** in 44% overall yield from **9**.

Thus, the synthesis of (R)-(+)-**1** was carried out by the second route. The 1,4-addition of butylmagnesium bromide to (R)-(-)-**2** proceeded in a stereospecific manner to give ketone (+)-**7** [$[\alpha]_D^{22}$+78.3°(c 2.17, $CHCl_3$)] in 99% yield.[2,7)] Removal of TMS group gave cyclohexenone (-)-**8** [85%, $[\alpha]_D^{22}$-51.2°(c 1.40, $CHCl_3$)] which was converted to enol silyl ether **9**. Cyclopropanation of **9** followed by oxidative ring opening with $FeCl_3$, and dehydrochlorination furnished (R)-(+)-**1**[8)] [22% from (-)-**8**, $[\alpha]_D^{15}$+35.8°(c 3.34, MeOH).[9)] To confirm the optical purity of synthesized (R)-(+)-**1**, it was hydrogenated and converted to acetal derivative of

2(R), 3(R)-butane diol **12** (98% yield). Comparison of the ^{13}C-NMR spectrum of **12** with that of the corresponding acetal derivative obtained from (±)-**1** indicated optical homogeneity of **12**.



a)BuMgBr, cat. CuBr, TMSCl, HMPT; b)CH_2I_2, Et_2Zn; c)$FeCl_3$, DMF; d)AcONa; e)LDA/NCS/TBAF; f)KF, MeOH; g)$CuCl_2$, DMF; h)LDA/TMSCl; i)CH_2I_2, Et_2Zn; j)$FeCl_3$, DMF; k)AcONa.

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