Cedrenoid Sesquiterpenes. Synthesis of the (±) Stork–Clarke β-Diketone

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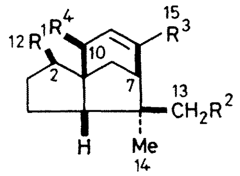
Summary (±)-2β,6,6-Trimethyltricyclo[5.3.1.0^{1,5}]undecane-8,10-dione (**6**) has been synthesized from dimethyl 6,6-dimethyl-5-oxobicyclo[2.2.2]oct-2-ene-2,3-dicarboxylate (**8**).

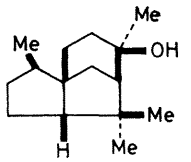
The cedrenoid sesquiterpenes are characterized by the tricyclo[5.3.1.0^{1,5}]undecane skeleton, as in cedrene (**1**) and cedrol (**2**).[1] They differ in their states of oxidation at a variety of ring and substituent carbon atoms, as exemplified by shellolic acid (**3**),[2] laccishellolic acid (**4**),[3] and α-pipitzol (**5**).[4]



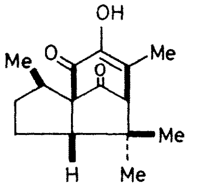
(1) $R^1 = R^3 =$ Me, $R^2 = R^4 =$ H

(3) $R^1 = R^3 = CO_2H$, $R^2 = R^4 =$ OH

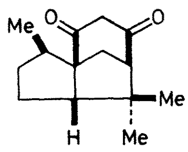
(4) $R^1 = R^3 = CO_2H$, $R^2 =$ H, $R^4 =$ OH



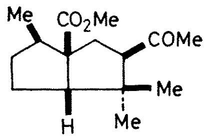
(2)



(5)



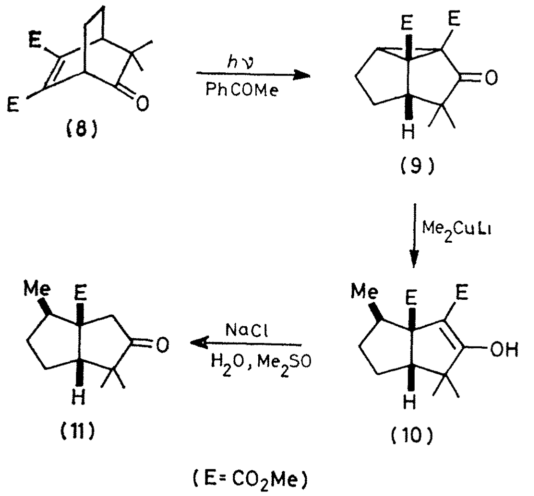
(6)



(7)

Stork and Clarke[5] were the first to achieve the synthesis of a cedrenoid sesquiterpene and their synthesis of (**2**) was followed by several other total syntheses of (**1**) and (**2**).[6] The only more highly oxygenated cedrenoids that have been synthesized are α-pipitzol (**5**) and its stereoisomer, β-pipitzol.[4] We have undertaken a novel approach to the synthesis of (**2**) that is designed to be applicable to the eventual synthesis of many of the more highly oxygenated cedrenoids, a feature that is not shared by most of the previous syntheses of (**1**) and (**2**). We chose as our initial goal the β-diketone (**6**), a key intermediate in the synthesis of Stork and Clarke,[5] which they obtained by base catalysed cyclization of the keto ester (**7**). This intermediate has the potentiality of providing a route to cedrenoids bearing oxygen at C-10 and C-15. We report now a synthesis of (**6**) that is also potentially adaptable to the introduction of substitution at C-12 and C-13, as in (**3**).

Hydrogenation of the Diels-Alder adduct[7] of 6,6-dimethylcyclohexa-2,4-dienone and dimethyl acetylenedicarboxylate gave (**8**).[8]† This on irradiation in acetophenone as solvent and photosensitizer gave the oxa-di-π-methane product[9] (**9**) (76%), m.p. 82—83 °C. Treatment of (**9**) with lithium dimethylcuprate[10] gave (**10**), m.p. 76·5—78·5 °C‡ It was expected that this homoconjugate addition product would have the desired β-configuration of the carbon bearing the entering methyl group as depicted in (**10**),[10] but this was only unambiguously established on completion of the synthesis of (**6**). Demethoxycarbonylation of (**10**) with NaCl in hot, wet Me_2SO[11] gave (**11**) (74%) as a mobile oil.



Treatment of (**11**) with lithium acetylide in tetrahydrofuran (THF) at −75 °C gave (**12**) (61%), m.p. 95—96 °C; the relative configuration at C-7 is assigned in the expectation that attack of the acetylide occurs at the β-face of (**11**). Compound (**12**) was subjected to Rupe rearrangement (hot $HCO_2H-H_2SO_4$)[12] to give (**13**) (30%) as a mobile oil. At low concentrations of H_2SO_4 this is accompanied by a second product (**14**); increase in the concentration of H_2SO_4 suppresses the formation of (**14**), but gives rise to increased polymerization. Hydrogenation of (**13**) over platinum in ethyl acetate gave (**15**) (80%) as a mobile oil, which is considered to be the C-7 epimer of (**7**), in the expectation that addition of hydrogen occurs at the β-face. Treatment of (**15**) with potassium t-butoxide in t-butyl alcohol [conditions that had been employed previously for the conver-

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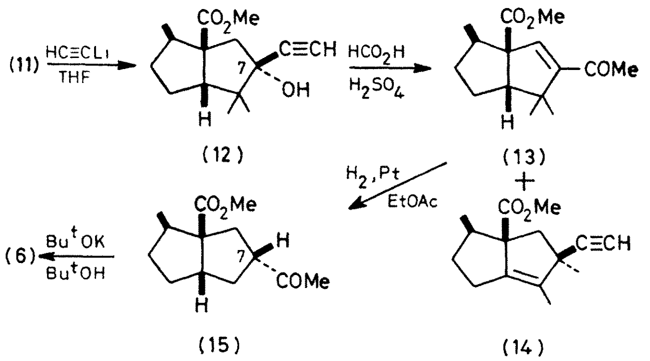
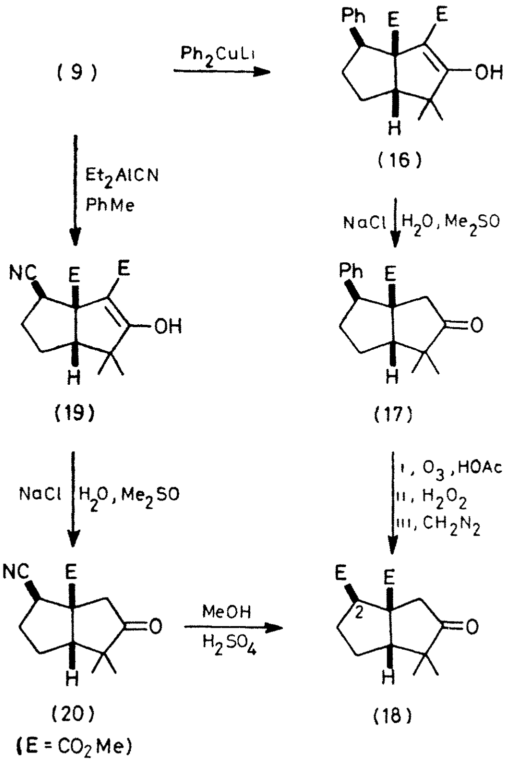
† Satisfactory elemental analytical and spectroscopic data were obtained for compounds (**8**)—(**20**), except (**16**), which was not purified.

‡ Compound (**10**) was accompanied by two bicyclo[3.2 1]octane derivatives as minor products, formed by reductive cleavage of the cyclopropane ring; spectroscopic analysis shows that the yield of (**10**) was *ca.* 80%.

sion of (**7**) into (**6**)[6]] gave a product in 91% yield, shown to be (±)-(**6**) by direct spectroscopic comparison (i.r., mass, ^1H and ^{13}C n.m.r.) with the optically active β-diketone (**6**)§



The viability of this synthetic approach to the introduction of a carboxylic acid function at C-2 has been demonstrated by treatment of (**9**) with lithium diphenylcuprate to give (**16**) as an oil, which was not purified but was subjected to demethoxycarbonylation as before to give (**17**), m.p. 125—127 °C, in 65% overall yield, which on ozonolysis in aqueous acetic acid followed by oxidative work-up[13] and treatment with diazomethane gave (**18**), m.p. 63—65 °C, in 46% overall yield. Also, reaction of (**9**) with diethylaluminium cyanide in toluene[14] gave (**19**) (56%) as a crystalline solid, m.p. 135—137 °C, which on demethoxycarbonylation as before gave (**20**) (69%) as a viscous oil. Treatment of (**20**) with methanolic sulphuric acid gave (**18**) in 41% yield.¶



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§ We are greatly indebted to Professor Gilbert Stork for providing us with a generous sample of optically active (**6**), m.p. 202—204 °C. After recrystallization from dioxan (±)-(**6**) had m.p. 177·5—179 °C.

¶ That (**18**) has the β-configuration assigned at C-2 has been established by the independent synthesis of its α-epimer.

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