A Short and Efficient Synthesis of Capnellene

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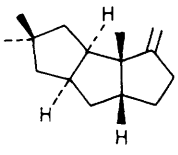
A short synthesis of the marine triquinane sesquiterpene capnell-9(12)-ene based on titanium-induced oxo ester cyclization as the key step for construction of the *cis-transoid-cis*-tricyclo[6.3.0.0^{2,6}]undecane skeleton is described.

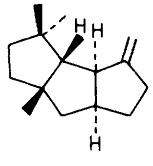
Hirsutene (**1**)[1] and capnellene (**2**)[2] are the presumed biosynthetic precursors to the hirsutane and capnellane families of sesquiterpenes which are known to possess various biological properties.[3,4] Synthesis of their *cis-transoid-cis*-tricyclo[6.3.0.0^{2,6}]undecane skeletal framework has presented a challenge which has aroused much interest recently.[5] We have reported a four-step synthesis of hirsutene (**2**) using the iodotrimethylsilane-induced rearrangement of 4,4-dimethyltricyclo[5.4.0.0^{2,6}]undecane-8,11-dione, followed by reductive methylation of the resultant enedione as the key steps.[6] We describe here a five-step synthesis of capnellene (**2**) from 8,8-dimethylbicyclo[3.3.0]oct-1(5)-en-2-one.

We initially investigated the iodotrimethylsilane-induced rearrangement of the diketone (**3**) based on a synthetic strategy similar to that used for hirsutene[6] [*i.e.* conversion of (**3**) into (**4**), followed by reduction and Wittig reaction]. Thus, (**3**)[†] was prepared by photoaddition of cyclohex-2-ene-1,4-dione to 1,3,3-trimethylcyclopentene.[7] Treatment of (**3**) with Me$_3$SiI in CH$_2$Cl$_2$ or Me$_3$SiCl/NaI in MeCN,[8] however, produced only the undesirable enone (**5**) in 34 or 41% yield, respectively. The formation of (**4**) was not observed, presumably owing to the effect of the *endo*-2-methyl group in (**3**).[8]

The successful approach to the synthesis of capnellene involved the preparation of 3-(2-ethoxycarbonylethyl)-5,8,8-trimethylbicyclo[3.3.0]octan-2-one (**8**), followed by titanium-induced cyclization[9] and Wittig reaction (Scheme 2). Compound (**8**) could be synthesized by the introduction of a propionic ester unit into the 3-position of 8,8-dimethylbicyclo[3.3.0]oct-1(5)-en-2-one (**6**), easily prepared by iodotrimethylsilane-induced rearrangement of 7,7-dimethylbicyclo[4.2.0]octane-2,5-dione.[8]

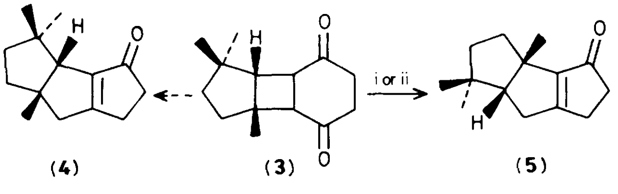


(**1**)

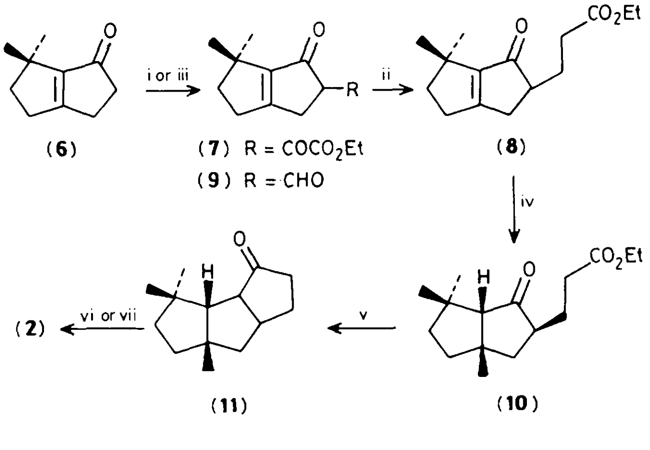


(**2**)

Treatment of (**6**) with diethyl oxalate–sodium hydride in benzene at room temperature for 2 days gave the adduct (**7**) in 89% yield. Reaction of (**7**) with ethyl acrylate in ethanol–water (1 : 1) containing an excess of triethylamine at room temperature for 3 days resulted in the direct formation of the oxo ester (**8**) in 76% yield. The ester (8) can be also prepared by the reaction of (**6**) with ethyl formate–sodium ethoxide in dimethoxyethane (DME), followed by treatment of the adduct (**9**) with ethyl acrylate–triethylamine in ethanol–water (1 : 1), in 41% overall yield. Conjugate addition of lithium dimethylcuprate to (**8**) proceeded smoothly to give the methylated oxo ester (**10**) in 88% yield. Although the stereochemistry of (**10**) can not be determined spectroscopically, titanium-induced cyclization of (**10**) produced the desired *cis-transoid-cis*-tricycloundecane framework. Thus, a solution of (**10**) in DME was added to the titanium reagent TiCl$_3$/LiAlH$_4$ (2 : 1) in refluxing DME containing triethylamine over a 5 h period, and then the mixture was refluxed for 11 h. After the usual work-up, the nor-ketone (**11**) was obtained in 72% yield [b.p. 45 °C at 0.2 Torr, *m/z* 206 (M^+)], which showed



Scheme 1. *Reagents:* i, Me$_3$SiI, CH$_2$Cl$_2$, room temp, 7 h (34%); ii, Me$_3$SiCl, NaI, MeCN, room temp., 53 h (41%).



Scheme 2. *Reagents:* i, (CO$_2$Et)$_2$ (1.1 equiv.), NaH (1.3 equiv.), benzene, room temp., 2 days; ii, CH$_2$=CH–CO$_2$Et (2 equiv.), Et$_3$N (7 equiv.), EtOH/H$_2$O (1 : 1), room temp., 3 days; iii, HCO$_2$Et (large excess), NaH (2 equiv.), EtOH (2 equiv.), DME, room temp., 1 h; iv, Me$_2$CuLi (4 equiv.), ether, −20 °C, 30 min; v, LiAlH$_4$ (5 equiv.), TiCl$_4$ (10 equiv.), Et$_3$N (5 equiv.), DME, reflux; vi, Ph$_3$P=CH$_2$, THF; vii, (C$_5$H$_5$)TiCH$_2$AlClMe$_2$, 4-dimethylaminopyridine, Et$_2$O.

[†] All new compounds gave satisfactory analytical and spectroscopic data: (**3**), b.p. 75 °C at 0.05 Torr; ^{1}H n.m.r. (CDCl$_3$) δ 0.93 (s, 3H), 1.07 (s, 3H), 1.19 (s, 3H), 1.42—1.82 (m, 4H), 2.10 (m, 1H), 2.78 (br, s, 4H), and 2.91 (m, 2H); *m/z* 220 (M^+); i.r. (neat) 1720 cm^{-1}; (**5**), b.p. 45 °C at 0.1 Torr; ^{1}H n.m.r. (CDCl$_3$) δ 0.88 (s, 3H), 1.02 (s, 3H), 1.30 (s, 3H), 1.13—2.04 (m, 4H), 2.24 (m, 1H), 2.38—2.68 (m, 4H), and 2.68—2.76 (m, 2H); *m/z* 204 (M^+); i.r. (CCl$_4$) 1705 and 1645 cm^{-1}; (**7**) m.p. 55.0—55.5 °C; ^{1}H n.m.r. (CDCl$_3$) δ 1.26 (s, 6H), 1.38 (t, *J* 7.0 Hz, 3H), 2.16 (m, 2H), 2.62 (m, 2H), 3.34 (br, s, 2H), and 4.34 (q, *J* 7.0, 2H); *m/z* 250 (M^+); i.r. (CCl$_4$) 1730 and 1670 cm^{-1}; (**8**) b.p. 75 °C at 0.1 Torr; ^{1}H n.m.r. (CDCl$_3$) δ 1.19 (s, 6H), 1.24 (t, *J* 7.0 Hz, 3H), 1.7—2.8 (m, 11H), and 4.10 (q, *J* 7.0 Hz, 2H); *m/z* 250 (M^+); i.r. (CCl$_4$) 1740, 1700, and 1640 cm^{-1}; (**10**) b.p. 85 °C at 0.15 Torr; ^{1}H n.m.r. (CDCl$_3$) δ 0.93 (s, 3H), 1.14 (s, 3H), 1.21 (s, 3H), 1.23 (t, *J* 7.0 Hz, 3H), 1.9—2.5 (m, 12H), and 4.11 (q, *J* 7.0 Hz, 2H); *m/z* 266 (M^+); i.r. (CCl$_4$) 1740 cm^{-1}.

spectroscopic data identical with those reported.[5b] The nor-ketone (**11**) has previously been converted into capnellene by reaction with methylenetriphenylphosphorane[5a] or the Tebbe reagent.[5h]

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