Olefin Metathesis in Polycyclic Frames. A Total Synthesis of Hirsutene

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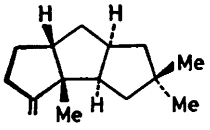
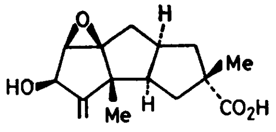
Summary A synthesis of the tricyclic sesquiterpene hydrocarbon (±)-hirsutene, involving a novel photo-thermal metathetic sequence as the key step to generate the linearly fused tricyclopentanoid framework, is reported.

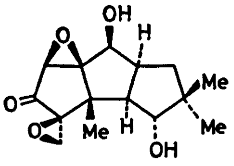
THERE is currently great interest in the linearly fused tricyclopentanoid family, which includes the sesquiterpene hydrocarbon hirsutene (**1**)[2a] and its more complex, oxygenated derivatives like hirsutic acid (**2**)[2b] and coriolin (**3**)[2c], owing to the promising biological activity[3] exhibited by certain members of this family. The interest in the hirsutane group is reflected in the several new and ingenious methods that have been developed for their syntheses in recent years.[4] We report herein a simple, expedient synthesis of (±)-hirsutene (**1**) *via* a novel photo-thermal metathetic sequence[5] whose distinctive features are (a) rapid acquisition of the *cis-syn-cis*-C_{13}-tricyclopentanoid frame (**6**) from cyclopentadiene and 2,5-dimethyl-*p*-benzoquinone in three high-yielding steps employing only heat and light as the reagents, (b) ready and remarkable thermal equilibration of (**6**) with the requisite *cis-anti-cis* system (**8**), and (c) generation of adequate functionality on the tricyclopentanoid frame to permit the synthesis of the more highly oxygenated members of the hirsutane family.



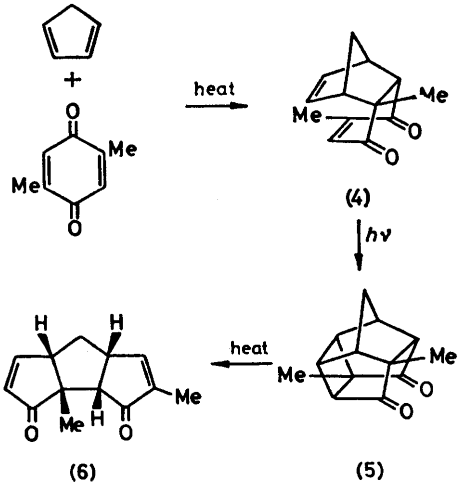
(**1**)



(**2**)

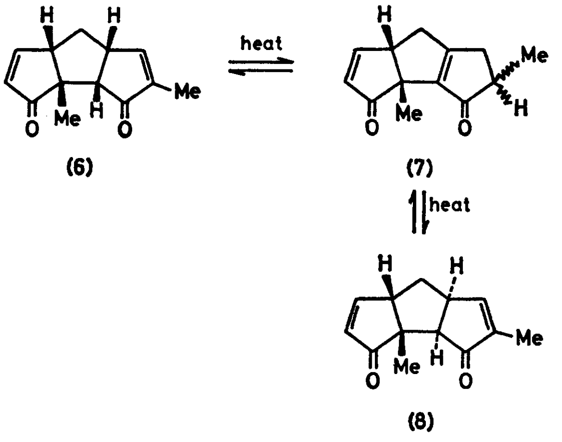


(**3**)



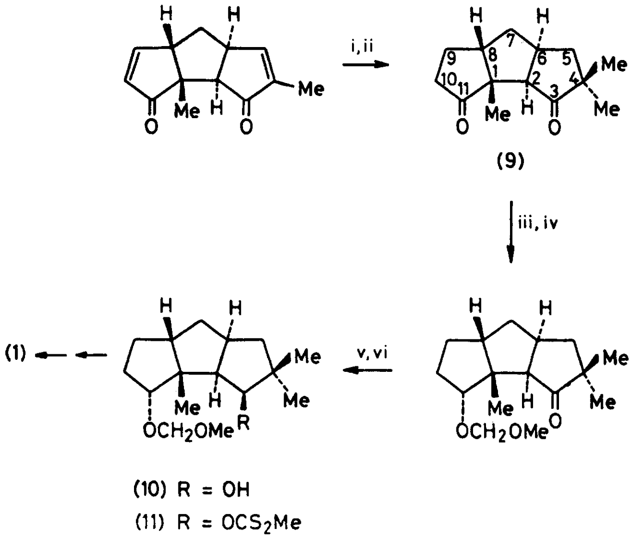
SCHEME 1.

Irradiation of the Diels–Alder adduct [(**4**), Scheme 1][6] in ethyl acetate with a 450 W medium pressure lamp through Pyrex furnished the pentacyclic dione (**5**) [m.p. 72—73 °C (cubic plates, CH_2Cl_2–pentane), ν_{max} 1750 and 1735 cm^{-1}, ^1H n.m.r.: δ 1·04 (s, CH_3) and 1·12 (s, CH_3)] in 85% yield. Sublimation of (**5**) through a Pyrex Vigreux column heated to 500 °C at 1 mm and direct crystallisation of the pyrolysate gave (**6**) [m.p. 113 °C (white, stout needles from CH_2Cl_2–pentane) ^{13}C n.m.r.: δ 208·9(s), 207·6(s), 164·1(d), 159·7(d), 141·2(s), 131·5(d), 60·7(d), 59·5(s), 57·5(d), 47·2(d), 30·9(t), 21·6(q), and 10·1(q) p.p.m.] in quantitative yield. From these ^{13}C n.m.r. and other spectral data the structure of (**6**) was confirmed and contains 13 of the 15 carbon atoms of hirsutene.



Scheme 2.

When a solution of (**6**) was refluxed in benzylbenzoate for 12 min (310 °C), a 14:49:37 (g.l.c.) equilibrium mixture, readily separable by column chromatography, of (**6**), (**7**), and (**8**), respectively, was obtained (Scheme 2). The structure of the *cis-anti-cis*-bisenone (**8**), m.p. 65—66 °C (plates, ether–pentane), having the requisite stereochemical pattern of (**1**), was confirmed by its ^{13}C n.m.r. resonances at δ 211·7(s), 207·7(s), 165·5(d), 159·5(d), 140·2(s), 129·6(d), 57·1(d), 56·5(s), 53·5(d), 46·5(d), 34·9(t), 19·0(q), and 9·7(q) p.p.m. and from the similarity of its ^1H n.m.r., i.r., and u.v. spectra to those of (**6**). Catalytic hydrogenation of (**8**) and regioselective alkylation furnished the C_{14}-dione (**9**), m.p. 65—66 °C (pentane), ν_{max} 1740 cm^{-1}, ^1H n.m.r.: δ 1·02 (s, 9 H) along with a small quantity of C_{10}-methylated product. Readjustment of functionalities (Scheme 3) led to the tricyclic alcohol (**10**) and its *S*-methyl-dithiocarbonate (**11**) both of which were identical (i.r., ^1H n.m.r.) to the compounds reported recently by Tatsuta *et al.*[4b] Since (**11**) has already been converted[4b] into (**1**) *via* a straightforward three-step sequence, our preparation of (**11**) provides a total synthesis of hirsutene (**1**).



Scheme 3. i, 10% Pd–C/H_2 in EtOAc, 100% yield; ii, K^+–Bu^tO^-–tetrahydrofuran (THF)–MeI, room temp., 50%; iii, $NaBH_4$–MeOH, 0 °C, 10 min, 50%; iv, $MeOCH_2Cl$–Pr^i_2NEt–pentane, room temp., 70 h, 80%; (v) $LiAlH_4$–THF, room temp., 100%; (vi) NaH–THF–CS_2–imidazole, MeI, reflux, 100%'

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