An Extremely Short Synthesis of Hirsutene

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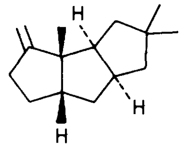
A four-step synthesis of hirsutene is described starting from cyclohex-2-ene-1,4-dione and 4,4-dimethylcyclopentene.

The *cis,anti,cis*-tricyclo[6.3.0.$0^{2,6}$]undecane system is found in the carbon skeleton of the hirsutane group of sesquiterpenes, as for example, hirsutic acid, coriolin, and their biogenetic precursor, hirsutene (**1**). These substances are known to possess remarkable biological properties and have attracted the attention of synthetic chemists.[1] Recently, we have reported the iodotrimethylsilane-induced rearrangement of bicyclo[4.2.0]octane-2,5-diones to bicyclo[3.3.0]oct-1(5)-en-2-ones and have found that the tricyclo[6.3.0.$0^{2,6}$]undecane system can be easily prepared by this reaction.[2] We describe here an extremely short synthesis of hirsutene (**1**) using this rearrangement, followed by reductive methylation of the resultant enedione as the key steps.

Photoaddition of cyclohex-2-ene-1,4-dione (**2**)[3] to 4,4-dimethylcyclopentene (**3**) [CH_2Cl_2–Pyrex][4] afforded the *cis,anti,cis* adduct (**4**) in 80% yield.[†] The iodotrimethylsilane-induced rearrangement of (**4**), as reported previously,[2] proceeded smoothly and selectively to afford the enone (**5**)



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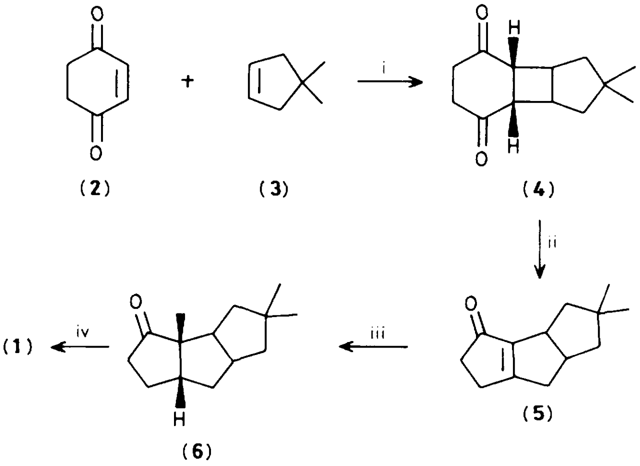
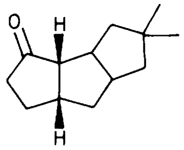


Scheme 1. *Reagents:* i, *h*ν, CH_2Cl_2, room temp., 3 h; ii, Me_3SiI, CH_2Cl_2, room temp., 3 h; iii, Li, liq. NH_3, −78 °C, 3 h; add MeI; iv, $Ph_3P{=}CH_2$, tetrahydrofuran.

[†] All new compounds gave satisfactory analyses and spectral data. (**4**): m.p. 76—78 °C; ^{1}H n.m.r. ($CDCl_3$) δ 0.84 (s, 3H), 1.17 (s, 3H), 1.43—2.06 (m, 4H), 2.82 (m, 4H), 2.94 (m, 2H), and 3.04 (br. s, 2H); *m/z* 206 (M^+); i.r. (KBr) 1710 cm^{-1}; (**5**): b.p. 55 °C at 0.07 mmHg; ^{1}H n.m.r. ($CDCl_3$) δ 0.94 (s, 3H), 1.02 (s, 3H), 1.00—1.32 (m, 2H), 1.64—2.02 (m, 2H), 2.06—2.96 (m, 6H), and 3.06—3.44 (m, 2H); *m/z* 190 (M^+); i.r. (neat) 1695 and 1640 cm^{-1}; (**8**): b.p. 30 °C at 0.15 mmHg; ^{1}H n.m.r. ($CDCl_3$) δ 0.91 (s, 3H), 1.03 (s, 3H), 1.00—3.15 (m, 14H); ^{13}C n.m.r. ($CDCl_3$) δ 25.2, 27.9, 30.1, 38.4, 40.2, 42.8, 43.6, 45.5, 46.3, 47.0, 47.2, 54.7, and 222.7; *m/z* 192 (M^+); i.r. (CCl_4) 1740 cm^{-1}.



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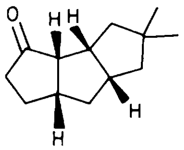

(8)

bearing the hirsutane skeleton. Thus, treatment of (**4**) with Me_3SiI (2.3 equiv.) in CH_2Cl_2 gave (**5**) in 95% yield.

Reduction of the double bond in (**5**) can be carried out stereoselectively using lithium–ammonia reduction or catalytic hydrogenation. Reaction of (**5**) with Li (3 equiv.) in liquid ammonia at −78 °C for 3 h, followed by treatment with NH_4Cl, afforded the *cis,anti,cis* ketone (**7**) in 70% yield [m.p. 35.5—36.0 °C, *m/z* 192 (M^+)]. The ketone (**7**) has previously been converted into hirsutene (**1**) and the spectral data were identical to those reported by Little and Stothers.[5] In contrast to these results, catalytic hydrogenation of (**5**) with 5% Pd–C in ethyl acetate at 50 °C for 16 h gave the *cis,syn,cis* ketone (**8**) in 92% yield. Furthermore, the reductive methylation[6] of (**5**) provided the direct precursor of hirsutene. Treatment of (**5**) with Li in ammonia, in a similar manner as above, followed by quenching the enolate with MeI (4 equiv.) resulted in the formation of the norketone (**6**) in 47% yield [m.p. 42.5—43.0 °C, *m/z* 206 (M^+)], which showed spectroscopic data identical to those reported.[5,7] The norketone (**6**) has previously been converted into hirsutene by reaction with methylenetriphenylphosphorane in good yield.[5,7,8]

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