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ITERATIVE THREE-CARBON ANNELATIONS. SYNTHESIS OF (±)-HIRSUTENE

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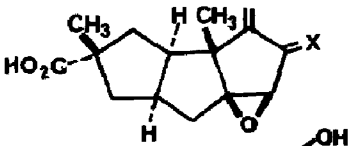
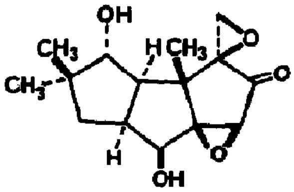
Summary : A short, flexible approach to the tricyclopentanoid carbon skeleton of the hirsutane group is illustrated by the synthesis of (±)-hirsutene (3).

Recent, intense synthetic efforts have led to elegant total syntheses of hirsutic acid (1a)[1], complicatic acid (1b)[1a], and coriolin (2)[2], as well as their proposed biogenetic precursor, hirsutene (3)[3]. There remains, nevertheless, a conspicuous need of simple, general methods for constructing the cis, anti, cis-tricyclo$[6.3.0.0^{2,6}]$undecane carbon skeleton of the hirsutane family, several members of which possess significant antibiotic and antitumor properties[1-3].



1 a,X = <OH H
b,X = O



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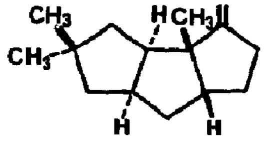

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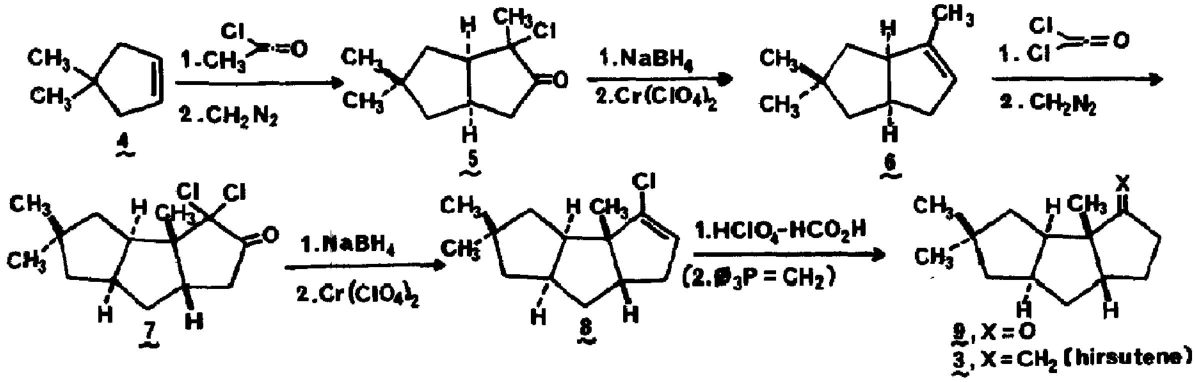
The three-carbon annelation that we recently described[4] offers the possibility of iteration and thus appeared ideally suited for the rapid assemblage of the tricyclopentanoid system. In this communication, the initial application of this approach to a short, selective synthesis of hirsutene, which has been isolated from Coriolus consors[3a], is described.

The known[5] 4,4-dimethylcyclopentene (4) was conveniently converted, albeit in moderate yield[6], to the bicyclo chloro ketone 5 [IR (film) 1750, 1380, 1365 cm^{-1}; NMR δ_{TMS} (CCl_4) 2.83 (m, 2H), 1.45, 1.05, 0.98 ppm (each s, 3H)] through cycloaddition with methylchloroketene, generated in situ from α-chloropropionyl chloride and triethylamine, followed by ring expansion with diazomethane. Sodium borohydride reduction of the chloro ketone 5 engendered in nearly quantitative yield the corresponding chlorohydrin, which was transformed with chromous perchlorate in DMF[5b] in 50-60% isolated yield to the volatile trisubstituted olefin 6 : IR (film) 3035, 1650, 1375, 1360 cm^{-1}; NMR δ_{TMS} (CCl_4) 5.0 (m, 1H),



1.6 (br s, 3H), 1.03 (s, 3H), 0.93 ppm (s, 3H). The third ring was now stereo- and regioselectively joined to **6** by using dichloroketene (CCl_3COCl, Zn-Cu, $POCl_3$, Et_2O)[7] to produce a dichlorocyclobutanone [60% yield. IR (film) 1800, 1380, 1365 cm^{-1}; NMR δ_{TMS} (CCl_4) 3.33 (d, J=8Hz, 1H), 1.46, 1.08, 1.00 ppm (each s, 3H)], which was converted to the vinyl chloride **8** via **7** by sequential treatment with diazomethane, sodium borohydride, and chromous perchlorate (inverse addition). For the hydrolysis of **8**, 70% perchloric acid in formic acid (1:3, 50°C, 8 hr) was clearly the most efficacious of the numerous methods tested and cleanly produced the crystalline ketone **9** [mp 43-44°C (hexane). (lit.[3d] 44-45°C); IR (nujol) 1735, 1365, 1090 cm^{-1}; NMR δ_{TMS} (CCl_4) 1.04, 0.93, 0.88 ppm (each s, 3H)[3d]; MS m/e 206 (M^+, 100%); Anal. ($C_{14}H_{22}O$) : C, H], whose identity was unambiguously confirmed by spectral comparison with an authentic sample[3a,8]. The ketone **9** has been converted to hirsutene ($Ø_3PCH_2$, DMSO, 70%)[3a].

Work directed at extending this straightforward approach to the synthesis of more highly functionalized hirsutanes is planned.

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6. Because of the volatility of several of the compounds in this synthesis, significant loss of material attended a number of these transformations, thus belying their efficiency. However, in the envisaged syntheses of more highly functionalized hirsutanes, this problem will not be present.
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8. The author is very grateful to Prof. Nozoe for providing the spectra of **3** and **9**.

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