Homoenolisation: a Simple Route to Hirsutene

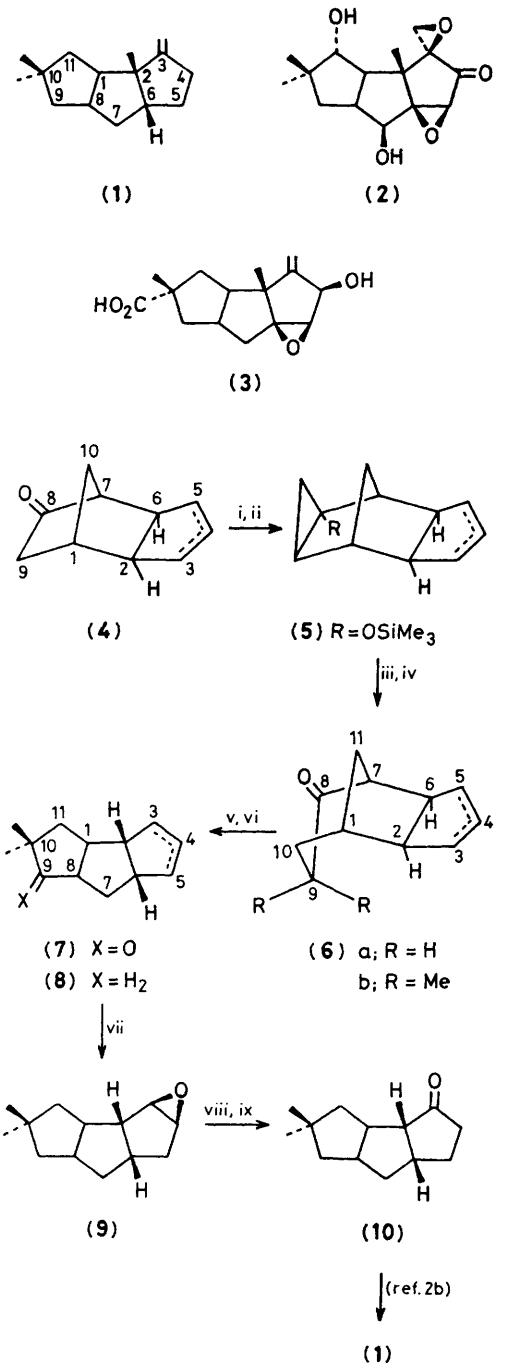
Brian A. Dawson, Ashim K. Ghosh, Jeffrey L. Jurlina, and J. B. Stothers*

Department of Chemistry, University of Western Ontario, London, Canada N6A 5B7

A sequence leading from dicyclopentadiene to the *cis,anti,cis*-tricyclopentane ring system of the hirsutanes is described in which the key step utilizes rearrangement by homoenolisation to generate the carbon skeleton with the requisite stereochemistry.

The linearly fused tricyclopentane ring system of *cis,anti,cis*-tricyclo[6.3.0.$0^{2,6}$]undecane has attracted considerable interest recently because this is the skeleton of several naturally occurring sesquiterpenes having antibiotic and/or antitumour activity.[1] Hirsutene (**1**) and coriolin (**2**) are examples of such compounds and a variety of different syntheses[2] have been developed for (±)-(**1**), which is thought to be the biosynthetic precursor of coriolin (**2**) and hirsutic acid (**3**).[3] We now report a simple stereocontrolled sequence leading from dicyclopentadiene to (**1**) which utilizes ring expansion by homoketonisation of a cyclopropoxide and skeletal rearrangement *via* homoenolisation. A notable feature of this synthesis is the fact that the stereochemistry at three of the four chiral centres is essentially established at the outset of the sequence and the constraints are such that the rearrangement specifically generates the correct configuration at the fourth centre.

Dicyclopentadiene was readily converted into a 30:70 mixture of *exo*-Δ^3- and Δ^4-tricyclo[5.2.1.$0^{2,6}$]decen-8-ones (**4**) by known methods.[4] Thus, at this stage, three of the chiral centres, C-1, C-2, and C-6, have the stereochemistry required for the target skeleton (see Scheme 1). Treatment of (**4**) with lithium di-isopropylamide (LDA) and then with trimethylsilyl chloride and triethylamine gave the trimethylsilyl enol ethers[5] which were converted using a zinc–silver couple and methylene



Scheme 1. *Reagents:* i, LDA, Me_3SiCl, 95%; ii, CH_2I_2–Zn–Ag, 82%; iii, NaOH, MeOH, 0 °C, 90%; iv, $NaNH_2$, Et_2O, MeI, 83%; v, Bu^tO^-–Bu^tOH, 185 °C, 65%; vi, NH_2NH_2, KOH, 185 °C, 90%; vii, *m*-CPBA, CH_2Cl_2, 85%; viii, $LiAlH_4$, Et_2O, quantitative; ix, $K_2Cr_2O_7$–H_2SO_4, Et_2O, 92% (isolated yields indicated).

di-iodide into the cyclopropane derivative (**5**)[6] (isolated by bulb-to-bulb distillation in 78% yield). Reaction of (**5**) with methanolic NaOH effected ether cleavage and homoketonisation of the resulting cyclopropoxides[7] to give the *exo*-tricyclo[5.3.1.$0^{2,6}$]undecen-8-ones (**6a**) which were methylated using $NaNH_2$–MeI to afford (**6b**) in 75% yield.

† The i.r., ^1H and ^{13}C n.m.r. spectra for all new compounds were in agreement with the assigned structures.

Rearrangement of (**6b**) to a 1:1 mixture of Δ^3- and Δ^4-tricyclo[6.3.0.$0^{2,6}$]undecen-9-ones (**7**) under homoenolisation conditions (Bu^tO^-–Bu^tOH, 185 °C) proceeded smoothly as anticipated from our conversion of the bicyclo[3.2.1]octan-2-one system into its bicyclo[3.3.0]octan-2-one analogue.[8] The generation of (**7**) is the key step in the sequence since this produces the desired *cis,anti,cis*-ring system of the hirsutane family. The stereochemistry of the rearrangement is constrained to give the correct configuration at C-8 because the alternative is too strained. *gem*-Dimethyl substitution, required to block condensation of (**6b**) under the strong basic conditions of the rearrangement, leads directly to the correct positioning of these groups in the target skeleton. It should be noted that under the homoenolisation conditions, the allylic methylene carbon undergoes exchange, thereby equilibrating the double bond isomers to furnish a 1:1 mixture of ketones (**7**). Separation of the isomeric mixtures (**4**)–(**6b**) is therefore unwarranted.

Wolff–Kishner reduction of (**7**) gave (**8**) in 90% yield after isolation by bulb-to-bulb distillation. Upon treatment with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2, (**8**) gave (**9**) and its 4,5-epoxy-isomer in 85% yield. The mixture of epoxides was treated with lithium aluminium hydride in Et_2O to generate a 1:1 mixture of the 3- and 5-alcohols which was subsequently oxidized to the corresponding mixture of ketones with acidic potassium dichromate in 92% overall yield. The ketone (**10**) was separated from the 5-oxo-isomer by preparative h.p.l.c. Spectral data (i.r., ^1H and ^{13}C n.m.r.) for (**10**) were identical with data kindly provided by Prof. R. D. Little. Since (**10**) has previously been converted into (±)-hirsutene,[2b] the synthesis is complete.

With this demonstration of the utility of a stereocontrolled homoenolate rearrangement for the generation of the tricyclopentane-ring system of the hirsutanes, another route to these natural products is available. It should be noted that, in principle, resolution of enantiomeric intermediates could be accomplished at an early stage thereby providing an asymmetric synthesis of these compounds. This feature and other variations on the general scheme are under investigation as is its extension to more highly substituted derivatives.

We are grateful for financial support from the Natural Sciences and Engineering Research Council of Canada.

Received, 8th November 1982; Com. 1270

References

1 W. A. Ayer and L. M. Browne, *Tetrahedron*, 1981, **37**, 2199; R. D. Little and G. W. Muller, *J. Am. Chem. Soc.*, 1979, **101**, 7129, which contains references concerning biological activities
2 (a) P. A. Wender and J. J. Howbert, *Tetrahedron Lett.*, 1982, **23**, 3983; (b) R. D. Little and G. W. Muller, *J. Am. Chem. Soc.*, 1981, **103**, 2744, and references therein; (c) G. Mehta and A. V. Reddy, *J. Chem. Soc., Chem. Commun.*, 1981, 756.
3 S. Nozoe, J. Furukawa, U. Sankawa, and S. Shibata, *Tetrahedron Lett.*, 1976, 195.
4 S. J. Cristol, W. K. Seifert, and S. B. Solway, *J. Am. Chem. Soc.*, 1960, **82**, 2351; H. C. Brown, C. P. Garg, and K. T. Liu, *J. Org. Chem.*, 1971, **36**, 387.
5 H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
6 C. Girard and J.-M. Conia, *J. Chem. Res.* (*S*), 1978, 182; (*M*) 2351.
7 Y. Hoyano, V. Patel, and J. B. Stothers, *Can. J. Chem.*, 1980, **58**, 2730.
8 A. L. Johnson, N. O. Petersen, M. B. Rampersad, and J. B. Stothers, *Can. J. Chem.*, 1974, **52**, 4143.