A chemoenzymatic synthesis of (−)-hirsutene from toluene

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The enantiomerically pure cis-1,2-diol 2, which is obtained by microbial oxidation of toluene, has been converted, via a sequence of reactions including high-pressure promoted Diels–Alder cycloaddition and oxo-di-π-methane rearrangement steps, into the triquinane (−)-hirsutene (1).

The linear triquinane (−)-hirsutene (ent-1), a sesquiterpene isolated from the fermented mycelium of Coriolus consors, is the biogenetic precursor of more highly oxygenated and bioactive congeners such as hirsutic acid (hirsutic acid C),3 complicatic acid,4 coriolin,5 and hypnophilin.6 Whilst biologically inactive itself, hirsutene has been a popular synthetic target used to “showcase” the development of a surprisingly wide variety of ingenious synthetic methodologies and strategies.7,8 The vast majority of such work has, however, produced the racemic modification of the natural product. Indeed, only Hua et al.9 have each claimed formal total syntheses of (−)-hirsutene while Greene,10 Martin G. Banwell,* Alison J. Edwards, Gwion J. Harfoot and Katrina A. Jolliffe

Fig. 1 Anisotropic displacement ellipsoid plot18 (with 50% probability ellipsoids) of compound 12 derived from X-ray crystallographic data.

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Experimental

Compound 12

A deoxygenated solution of compound 11 (254 mg, 0.82 mmol) and acetophenone (240 µL, 2.06 mmol) in acetone (120 mL) contained in a Pyrex™ vessel jacketed by a water-cooled solution of sodium bromide (750 g) and lead(II) nitrate (8 g) in water (1 L) was subjected to irradiation from a Phillips 125 W HPL-N lamp for 32 h whilst being maintained under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure and the resulting clear, colourless oil subjected to flash chromatography (silica, 0–30% v/v ethyl acetate–hexane gradient elution) thereby yielding two major fractions, A and B.

Concentration of fraction A \((R_1, 0.4\) in 30% v/v ethyl acetate–hexane exchange gradient elution 3 thereby yielding two major fractions, A and B.

Concentration of fraction B \((R_2, 0.2\) in 30% v/v ethyl acetate–hexane exchange gradient elution 3 thereby yielding two major fractions, A and B.

References

† All new and stable compounds had spectroscopic data [IR, NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high-resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

‡ Unless otherwise stated, all optical rotations were determined in chloroform solution at 18–26 °C.

§ Details of this analysis will be presented elsewhere and as part of an extended study revealing that syn-addition of dienophiles to...
various cis-1,2-dihydrocatechols is the preferred reaction pathway at 19 kbar.

Crystal data for 12: C₆H₄O₂. M = 308.41, T = 200(1) K, orthorhombic, space group $P2_12_12_1$, Z = 4, $a = 6.08980(10)$, $b = 11.0181(2)$, $c = 25.4436(5)$ Å, $V = 1707.22(5)$ Å³, $D_2 = 1.200$ Mg m⁻³, 1770 unique data (28$^\text{th}_{\text{max}} = 50.86^\circ$), 1268 with $I > 2\sigma(I)$; $R = 0.0297$, $R_w = 0.0334$, $S = 1.0303$.

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, $\lambda = 0.71073$ Å) and data extracted using the DENZO package. Structure solution was by direct methods (SIR97) and refinement was by full matrix least-squares on $F$ using the CRYSTALS program package. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 192411. See http://www.ccdc.cam.ac.uk for crystallographic files in cif or other electronic format.)


7 For an excellent review on the production and general synthetic utility of these types of compounds see T. Hudlicky, D. Gonzalez and D. T. Gibson, Aldrichimica Acta, 1999, 32, 35.


