COMMUNICATION

A chemoenzymatic synthesis of (−)-hirsutene from toluene

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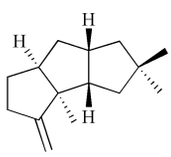
The enantiomerically pure *cis*-1,2-diol 2, which is obtained by microbial oxidation of toluene, has been converted, *via* a sequence of reactions including high-pressure promoted Diels–Alder cycloaddition and oxa-di-π-methane rearrangement steps, into the triquinane (−)-hirsutene (1).

The linear triquinane[1] (+)-hirsutene (*ent*-**1**), a sesquiterpene isolated from the fermented micellium of *Coriolus consors*,[2] is the biogenetic precursor of more highly oxygenated and biologically active congeners such as hirsutic acid (hirsutic acid C),[3] complicatic acid,[3] coriolin,[4] and hypnophilin.[5] 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.[1,6] The vast majority of such work has, however, produced the racemic modification of the natural product. Indeed, only Hua[6a] has achieved a total synthesis of (+)-hirsutene while Greene,[6b] Node[6c] and Leonard[6e] have each claimed formal total syntheses of the same target. It is within this context that we now wish to report a chemoenzymatic total synthesis of (−)-hirsutene (**1**) from the enantiomerically pure *cis*-1,2-dihydrocatechol **2**, a compound obtained in large quantity *via* microbial dihydroxylation of toluene.[7] This work should serve to emphasize the utility of compound **2** as a starting material in the synthesis of terpenoids[8] as well as the high facial selectivities attainable in the reaction of this diene with Diels–Alder dienophiles. Furthermore, since compound *ent*-**2** is available,[9] the present work also constitutes a formal total synthesis of (+)-hirsutene, the naturally occurring form of this sesquiterpene.



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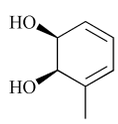

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The reaction sequence leading to target **1** is shown in Scheme 1 and starts with the high pressure (19 kbar) promoted Diels–Alder reaction between compound **2** and cyclopentenone (**3**). In keeping with a previous report,[10] preferential "*syn*-addition"[11] of the dienophile to the diene is observed and the structure of major adduct, **4**† {70% from **2**, mp 93–94 °C, $[\alpha]_D$ −196 (*c* 1.04)‡}, was established by single-crystal X-ray analysis.§ Protection of diol **4** as the corresponding acetonide, **5** {98%, $[\alpha]_D$ −122 (*c* 0.6)}, was achieved under standard conditions and the latter compound could be regioselectively dimethylated, thereby affording compound **6** {100%, mp 70–72 °C, $[\alpha]_D$ −47 (*c* 0.6)}. The now redundant carbonyl group associated with this last compound was deleted by a three step sequence involving initial lithium aluminium hydride-mediated reduction to a *ca*. 12.5 : 1 mixture of alcohols **7** {major epimer: 88%, mp 88–89 °C, $[\alpha]_D$ +18 (*c* 0.4); minor epimer: 7%, mp 57–59 °C, $[\alpha]_D$ +75 (*c* 0.2)}. These were converted into the corresponding xanthates which were immediately subjected to Barton–McCombie deoxygenation[12] using tri-*n*-butyltin hydride. Deprotection of the resulting acetonide **8** {71–82% from **7**, mp 65–66 °C, $[\alpha]_D$ +39 (*c* 0.4)} afforded diol **9** {95% (at 44% conversion), mp 91–92 °C, $[\alpha]_D$ +56 (*c* 0.4)} which could be selectively oxidized at that hydroxy group remote from the bridgehead methyl by the sterically demanding oxammonium salt derived from 4-acetamido-TEMPO.[13] The resulting acyloin **10** {87%, $[\alpha]_D$ −34 (*c* 0.4)} was then protected[14] as the corresponding MEM-ether **11** {91%, $[\alpha]_D$ +28 (*c* 0.4)}. Exploiting a strategy for linear triquinane synthesis first enunciated by Demuth[1c] and later employed by others,[6f] a solution of compound **11** in acetone and containing acetophenone (as triplet sensitizer) was subject to irradiation with a high pressure mercury vapour lamp. Under these conditions the expected oxa-di-π-methane rearrangement product **12** {80% (at 71% conversion), mp 78–79 °C, $[\alpha]_D$ +102 (*c* 0.2)} was obtained and its structure confirmed by single-crystal X-ray analysis¶

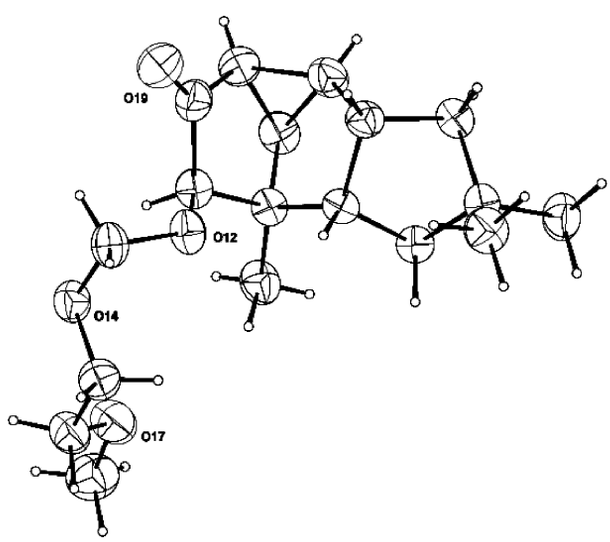

Fig. 1 Anisotropic displacement ellipsoid plot[18] (with 50% probability ellipsoids) of compound **12** derived from X-ray crystallographic data.

(Fig. 1). A number of reagents are available for effecting reductive cleavage of the "carbonyl-conjugated" cyclopropanes[15] but the most useful means for achieving this within photo-products such as **12** is tri-*n*-butyltin hydride.[16] By such means the triquinane **13** {88% (at 81% conversion), $[\alpha]_D$ +20 (*c* 0.4)} was obtained and removal of the now superfluous carbonyl group within this compound carried out by the same means as used earlier, *viz*. sodium borohydride reduction/xanthate ester formation/Barton–McCombie deoxygenation. The ensuing MEM-ether **14** {83% from **13**, $[\alpha]_D$ +32 (*c* 0.6)} was subject to deprotection under conditions defined by Monti[17] and the resulting alcohol **15** {76%, mp 44–46 °C, $[\alpha]_D$ +36 (*c* 0.1)}, previously obtained[14d,e] in racemic form during syntheses of (±)-hirsutene, was oxidized with PCC to the corresponding and volatile ketone **16** {71%, mp 23–24 °C, $[\alpha]_D$ −56 (*c* 0.4); lit.[6a] $[\alpha]_D$ (for *ent*-**16**) +81 (*c* 0.2, hexane)}. Finally, Wittig olefination of compound **16** afforded target **1** {100% at 32% conversion, $[\alpha]_D$ −26 (*c* 0.2, $CDCl_3$); lit.[6a] $[\alpha]_D$ (for *ent*-**1**) +48 (*c* 0.35, pentane)}, the ^1H and ^{13}C NMR spectral data for which were in complete accord with the assigned structure.

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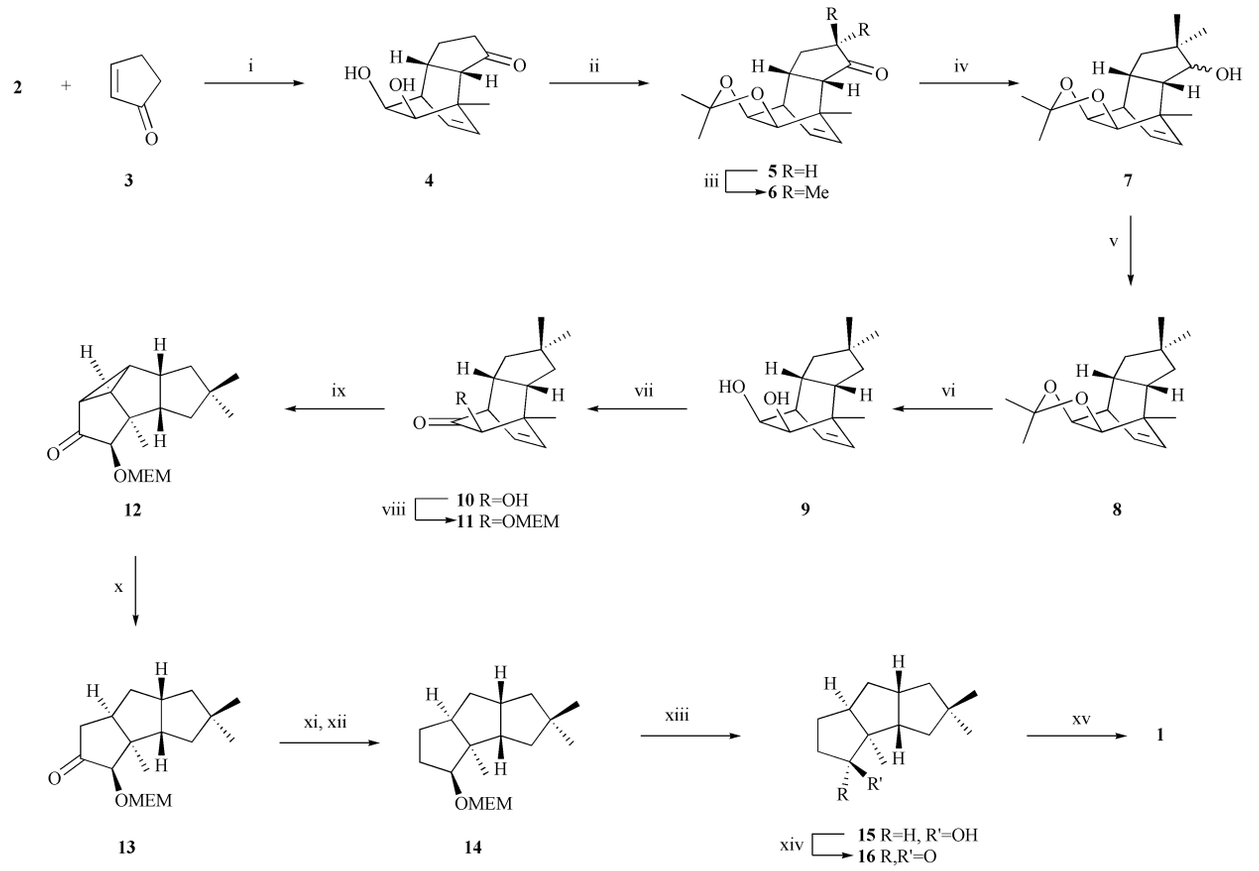

Scheme 1 *Reagents and conditions*: (i) 19 kbar, CH_2Cl_2, 18 °C, 24 h; (ii) 2,2-DMP, *p*-TsOH·H_2O (cat.), 18 °C, 16 h; (iii) MeI (4.2 mol equiv.), LiHMDS (3.15 mol equiv.), THF, 0–18 °C, *ca*. 4 h; (iv) $LiAlH_4$ (1.1 mol equiv.), THF, 0–50 °C, 29 h; (v) (a) NaH (5 mol equiv.), CS_2 (10 mol equiv.), THF, 0–66 °C, 18 h then MeI (20 mol equiv.), 18–66 °C, 56 h; (b) *n*-Bu_3SnH (5 mol equiv.), AIBN (cat.), toluene, 111 °C, 18 h; (vi) 3 : 2 v/v AcOH–H_2O, 60 °C, 96 h; (vii) 4-AcNHTEMPO (2.1 mol equiv.), *p*-TsOH·H_2O (2.1 mol equiv.), CH_2Cl_2, 0–18 °C, 16 h; (viii) MEM-Cl (2 mol equiv.), Hünig's base (2.5 mol equiv.), CH_2Cl_2, 18 °C, 16 h; (ix) see Experimental; (x) *n*-Bu_3SnH (6 mol equiv.), AIBN (cat.), C_6H_6, 80 °C, 8 h; (xi) $NaBH_4$ (2.25 mol equiv.), MeOH, 18 °C, 4 h; (xii) (a) NaH (5 mol equiv.), CS_2 (10 mol equiv.), THF, 0–66 °C, 18 h then MeI (16 mol equiv.), 18–66 °C, 9 h; (b) *n*-Bu_3SnH (2 mol equiv.), AIBN (cat.), toluene, 111 °C, 2 h; (xiii) PPTS (2.6 mol equiv.), *t*-BuOH, 82 °C, 8 h; (xiv) PCC (2 mol equiv.), CH_2Cl_2, 18 °C, 16 h; (xv) $Ph_3P{=}CH_2$ (2 mol equiv.), toluene, 0–66 °C, 1.5 h. 2,2-DMP = 2,2-dimethoxypropane.

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_f 0.4 in 30% v/v ethyl acetate–hexane) afforded starting material **11** (73 mg, 29% recovery) as a clear, colourless oil (Found: $M^{+\bullet}$, 308.1986; C, 69.80; H, 8.75. $C_{18}H_{28}O_4$ requires $M^{+\bullet}$, 308.1988; C, 70.10; H, 9.15%). ν_{max} (NaCl) 3040, 2952, 2931, 2898, 2874, 1736, 1456, 1129, 1111, 1051, 1036, 987, 708 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.10 (1H, dd, *J* 8.4 and 6.0), 6.02 (1H, broad d, *J* 8.4), 5.11 (1H, d, *J* 6.9), 4.80 (1H, d, *J* 6.9), 3.82 (2H, m), 3.58 (2H, m), 3.46 (1H, s), 3.39 (3H, s), 2.99 (1H, broad d, *J* 6.0), 2.65 (2H, m), 1.49 (2H, m), 1.21 (3H, s), 1.16–0.96 (2H, m), 0.99 (3H, s), 0.91 (3H, s); δ_C (75 MHz, $CDCl_3$) 210.0, 140.1, 128.4, 96.4, 76.9, 72.0, 67.7, 59.4, 52.5, 45.5, 44.9, 44.2, 43.4, 42.1, 39.6, 28.8, 27.9, 19.6; *m*/*z* (EI) 308 ($M^{+\bullet}$, 2%), 279 (3), 176 (17), 175 (37), 108 (40), 105 (21), 89 (100), 59 (74).

Concentration of fraction B (R_f 0.2 in 30% v/v ethyl acetate–hexane) afforded triquinane **12** {145 mg, 80% (at 71% conversion)} as a white crystalline solid (Found: $M^{+\bullet}$, 308.1988; C, 70.05; H, 8.86. $C_{18}H_{28}O_4$ requires $M^{+\bullet}$, 308.1988; C, 70.10; H, 9.15%). ν_{max} (NaCl) 2971, 2956, 2933, 2869, 1731, 1110, 1055, 1010 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.99 (1H, d, *J* 6.9), 4.81 (1H, d, *J* 6.9), 3.89–3.73 (3H, complex m), 3.56 (2H, m), 3.39 (3H, s), 2.68 (1H, dt, *J* 12.0 and 7.0), 2.34 (1H, m), 2.10 (1H, t, *J* 5.4), 1.91–1.77 (3H, complex m), 1.64 (1H, dd, *J* 10.3 and 5.6), 1.44 (1H, t, *J* 11.9), 1.36–1.20 (1H, complex m), 1.34 (3H, s), 1.08 (3H, s), 0.86 (3H, s); δ_C (75 MHz, $CDCl_3$) 210.8, 95.6, 88.1, 72.0, 67.5, 59.3, 53.3, 49.9, 48.8, 43.5, 43.3, 40.7, 36.0, 33.7, 32.0, 29.8, 27.7, 21.4; *m*/*z* (EI) 308 ($M^{+\bullet}$, 2%), 279 (9), 219 (53), 108 (70), 89 (88), 59 (100).

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† 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**: $C_{18}H_{28}O_4$, M = 308.418, 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) Å^3, D_x = 1.200 Mg m^{-3}, 1770 unique data ($2\Theta_{max}$ = 50.06°), 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, λ = 0.71073 Å) and data extracted using the DENZO package.[19] Structure solution was by direct methods (SIR97)[20] and refinement was by full matrix least-squares on F using the *CRYSTALS* program package.[21] 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.rsc.org/suppdata/p1/b2/b208778b/ for crystallographic files in .cif or other electronic format.).

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