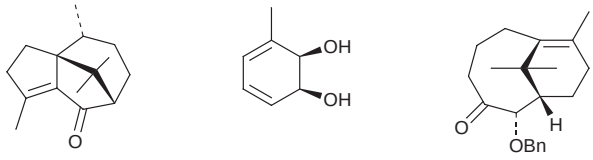
Chemoenzymatic total synthesis of the sesquiterpene (−)-patchoulenone

Martin Banwell*† and Malcolm McLeod

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

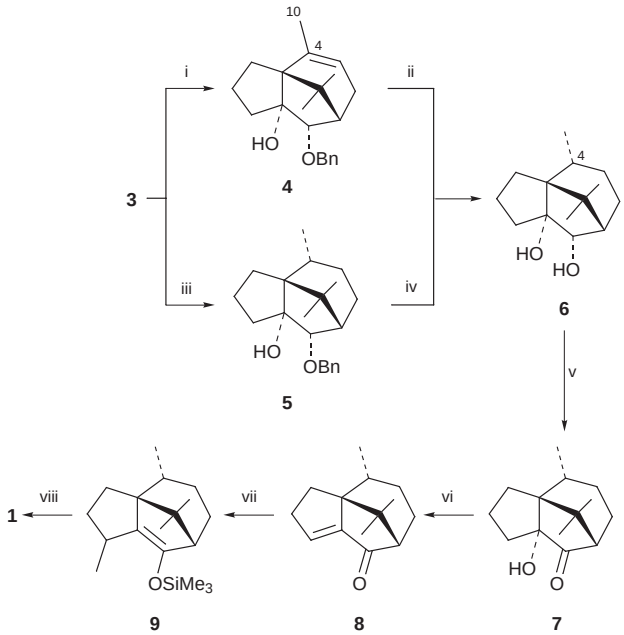
Monochiral *cis*-1,2-dihydrocatechol 2, obtained by microbial oxidation of toluene, has been converted, *via* intermediate 3, into the cyperene-type sesquiterpene 1.

(−)-Patchoulenone **1** is a prominent member of the cyperene class of sesquiterpenes and was first isolated in 1964 from *Cyperus rotundus* Linné (*Cyperaceae*), a plant common in Sudan, India, China, Thailand and Japan.[1,2] The compound has



1 **2** **3**

also been identified as a constituent of, *inter alia*, the root bark of *Uvaria narum* Wall. (*Annonaceae*)[3] and *Piptostigma fugax*.[4] Despite a number of the source plants being used in traditional medicines, only a modest amount is known about the biological properties of (−)-patchoulenone. Thus, compound **1** shows[2] *in vitro* activity (EC_{50} 1.08×10^{-4} M) against the malarial parasite *Plasmodium falciparum*, strong anti-fungal activity against *Rhizoctonia solani* and *Saprolegnia asterophora*,[4] and significant toxicity in a brine shrimp bioassay.[4]



Scheme 1 *Reagents and conditions*: i, $SnCl_2$ (0.25 equiv.), $CHCl_3$, 18 °C, 1 h; ii, H_2 (60 psi), 10% Pd/C, MeOH, 18 °C, 48 h; iii, SmI_2 (1.6 equiv.), HMPA, THF, 0 °C, 0.25 h; iv, H_2 (1 atm), 10% Pd/C, THF, 18 °C, 0.75 h; v, $(COCl)_2$ (3.0 equiv.), DMSO (5.0 equiv.), CH_2Cl_2, −78 °C, 0.25 h, then **6**, 0.25 h then Et_3N (6.0 equiv.) −78 to 0 °C, 0.25 h; vi, $SOCl_2$, pyridine, 40 °C, 1 h; vii, MeLi (10 equiv.), CuBr·DMS (5.0 equiv.), THF, −40 °C, 0.5 h, then **8**, Me_3SiCl (10 equiv.), HMPA, −78 °C, 0.5 h; viii, DDQ (4.0 equiv.), 2,6-lutidine (6.5 equiv.), CH_2Cl_2, 18 °C, 0.1 h

The 1,4,9,9-tetramethyl-2,4,5,6,7,8-hexahydro-3*H*-3a,7-methanoazulene framework associated with the cyperene-type sesquiterpenes has been the subject of a number of synthetic studies[5] and the title compound itself has been synthesised by Hikino *et al*[6] who used (+)-camphor as the starting material. The racemic modification of patchoulenone has also been prepared *via* the Lewis acid catalysed addition of a diazo ketone to a tethered olefin.[7] We now report a quite distinct and chemoenzymatic total synthesis of (−)-patchoulenone which employs the monochiral *cis*-1,2-dihydrocatechol **2**, obtained by microbial oxidation of toluene, as starting material.[8]

In connection with synthetic approaches to taxoids, we have recently described[9] the conversion of compound **2** into the bicyclo[5.3.1]undecenone **3**. As has been observed in a closely related system,[10] the carbon–carbon double-bond and carbonyl group within compound **3** are in close proximity. As a consequence the molecule readily engages in a tin(II) chloride catalysed intramolecular Prins reaction (Scheme 1) to give the tricyclic isomer **4** {97%, $[\alpha]_D$ −32 (*c* 2.0)‡}. Hydrogenation of compound **4** using H_2 at 60 psi and with palladium on carbon as catalyst provided a *ca.* 3:1 mixture of the saturated *cis*-diol **6**§ {59%, mp 209–211 °C (sealed tube), $[\alpha]_D$ −21.4 (*c* 0.6)} and its C4-epimer {21%, mp 207–209 °C (sealed tube), $[\alpha]_D$ +37.2 (*c* 0.7)} which could be separated from one another by flash chromatography. An alternative route to the pivotal compound **6** involved subjecting compound **3** to reductive cyclisation using samarium(II) iodide[11] and a chromatographically separable mixture of **5** {39%, mp 53–54 °C, $[\alpha]_D$ +17.9 (*c* 0.9)} and the $\Delta^{4(10)}$-isomer {54%, $[\alpha]_D$ +65 (*c* 0.4)} of compound **4** was produced. Hydrogenolysis of compound **5** could be achieved under standard conditions and the resulting diol **6** (95%) was oxidised to the acyloin **7** {91%, $[\alpha]_D$ −0.2 (*c* 1.0)} using the Swern reagent. Dehydration of compound **7** to the enone **8** {68%, $[\alpha]_D$ −150 (*c* 0.5)} could be effected using thionyl chloride in pyridine at 40 °C. This latter compound was subjected to reaction with the Gilman reagent derived from methyllithium and copper(I) bromide–dimethyl sulfide (DMS) complex[12] and the ensuing enolate anion trapped with trimethylsilyl chloride to give the unstable silyl enol ether **9**, which was obtained as a single diastereoisomer. Dehydrogenation of compound **9** with DDQ/2,6-lutidine[13] then gave (−)-patchoulenone **1** {77% from **8**, mp 50–51 °C (lit.,[1] 52.5 °C), $[\alpha]_D$ −101 (*c* 0.4) [lit.,[1] −97.1 (*c* 8.0)]}, the ^1H and ^{13}C NMR spectral data for which matched those reported[2] for the natural product.

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Notes and References

† E-mail: mgb@rsc.anu.edu.au

‡ All optical rotations were determined in chloroform solution at 20 °C

§ 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.

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