Highly Efficient Synthesis of (+)-Nimbiol and Other Podocarpanes Derivatives from Sclareol

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Abstract: A new access to tricyclic diterpenes of podocarpane skeleton has been opened, in excellent overall yields, and an efficient synthesis of (+)-nimbiol from sclareol has been achieved.

Key words: sclareol, diterpenes, podocarpanes, (+)-nimbiol

Diterpenes such as, abietane, pimarane, totarane or cassane (Figure 1), with the podocarpane tricyclic system, are highly distributed secondary metabolites.[1]

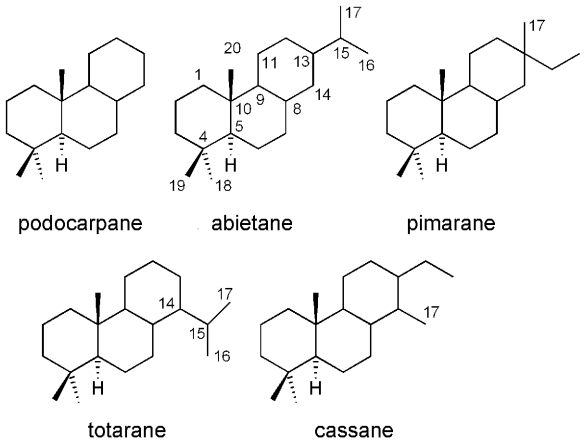


Figure 1 Diterpenes with tricyclic skeleton.

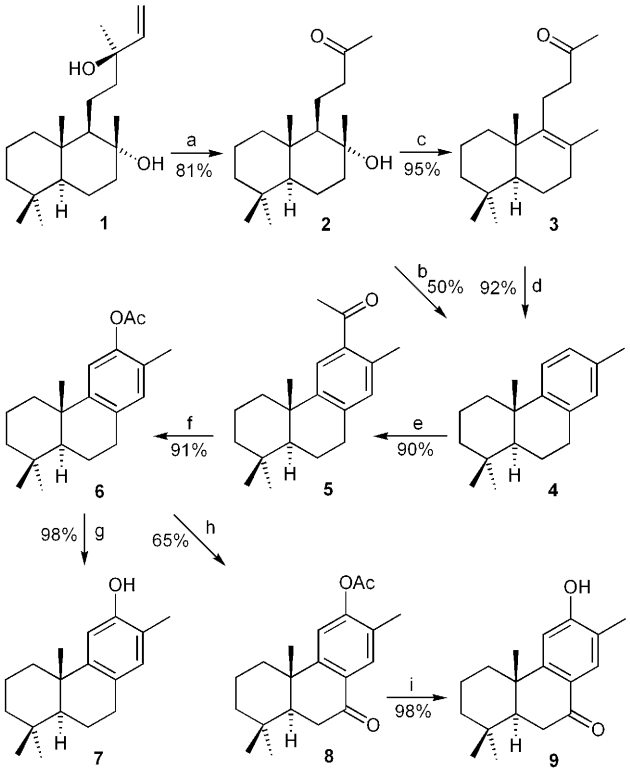
The variety and importance of the biological activities that show these compounds as antitumour,[2] antifungal,[3] antimicrobial,[4] antiinflammatory,[5] antiviral[6] among others, have made them important synthetic objectives for many years.[1b,7]

Easy and direct access to the tricyclic system of these compounds is a very interesting objective that will facilitate the synthesis of several members of these compounds in a straightforward manner.

In this work a three-step synthesis of podocarpanes derivatives starting from commercially available sclareol in nearly quantitative yield is described. We also describe the synthesis of the natural product (+)-nimbiol[8] in six steps from sclareol by a cheap procedure in an excellent global yield requiring only one column chromatography in the whole procedure (Scheme 1).

The transformation of sclareol (**1**) into methylketone **2** has been previously used by us.[9] Starting from hydroxyketone **2**, the podocarpane derivative **4** can be directly obtained in a 50% yield, but the transformation could be achieved in a better yield in two steps. Elimination reaction of **2** by treatment with HI at room temperature gave **3** in a nearly quantitative yield, which on heating at 85 °C with HI led to the podocarpane derivative **4** in an excellent yield. Both reactions were performed on a multigram scale.

The synthesis of the diterpene (+)-nimbiol **9**, known to possess antimicrobial activity,[10] was completed in the following way: Friedel–Crafts acylation of **4** gave **5** that,



Scheme 1 *Reagents and conditions*: a) KMO_4, $MgSO_4$; b) HI, C_6H_6, 85 °C, 6 h; c) HI, C_6H_6, r.t., 6 h; d) HI, C_6H_6, 85 °C, 3 h; e) AcCl, $SnCl_4$, 85 °C, 0.7 h; f) UHP, TFAA, r.t., 24 h; g) K_2CO_3, MeOH, H_2O, 3%, r.t. 0.5 h; h) Na_2CrO_4, Ac_2O, AcOH, 65 °C, 2 h; i) K_2CO_3, MeOH, H_2O, 3%, r.t. 0.7 h.

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under Baeyer–Villiger conditions with urea–hydrogen peroxide (UHP) and TFAA, led to the acetoxy derivative **6**. The benzylic oxidation of **6** produced acetoxynimbiol **8**, that on alkaline hydrolysis led to (+)-nimbiol **9**[11] in an excellent 37% global yield from sclareol. Compound **6** was hydrolyzed to give the known deoxynimbiol **7**[12] as well (Scheme 1).

In conclusion a new straightforward route for the synthesis of diterpenes with podocarpane skeleton starting from sclareol has been accessed. The synthesis of the natural compound (+)-nimbiol **9** corroborates the importance of this new route.

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(11) $[\alpha]_D^{22}$ +31 (*c* = 0.8, $CHCl_3$); mp 245 °C {Lit.[8] $[\alpha]_D^{22}$ +32.3; mp 250 °C}. IR (film): 3291, 2929, 2869, 1655, 1578, 1458, 1287, 1162, 907, 733, 665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H, H-14), 6.75 (s, 1 H, H-11), 5.82 (br s, 1 H, OH), 2.67 (dd, *J* = 4.4, 18.0 Hz, 1 H, H-6α), 2.58 (dd, *J* = 13.6, 18.0 Hz, 1 H, H-6β), 2.23 (s, 3 H, $ArCH_3$), 1.83 (dd, *J* = 4.4, 13.6 Hz, 1 H, H-5), 1.24–1.78 (m, 6 H), 1.20 (s, 3 H, Me-20), 0.98 (s, 3 H, Me-19), 0.92 (s, 3 H, Me-18). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.2 (C-1), 19.1 (C-2), 41.5 (C-3), 33.5 (C-4), 49.8 (C-5), 36.2 (C-6), 199.3 (C-7), 124.4 (C-8), 157.3 (C-9), 38.1 (C-10), 109.8 (C-11), 159.7 (C-12), 122.4 (C-13), 131.0 (C-14), 15.4 ($ArCH_3$), 32.8 (C-18), 21.6 (C-19), 23.5 (C-20). HRMS (ESI): *m*/*z* $[M^+]$ calcd for $C_{18}H_{24}O_2$: 272.1772; found: 272.1776.

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