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Synthesis of (+)-totarol

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Abstract—(+)-Totarol, a tricyclic diterpene, has been synthesised from zamoranic acid. The key step is the cyclisation of a 13,14-secototarane using SmI_2.

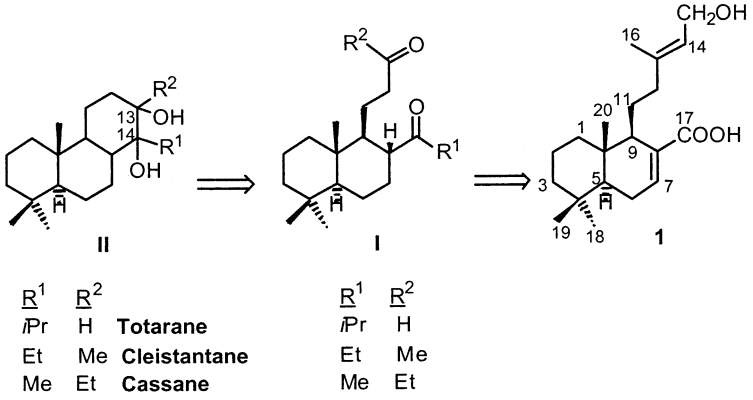
Totaranes, cleistantanes and cassanes are tricyclic diterpenes which are not very common in nature, but which show important biological activities as antiinflammatories, analgesics, antitumour agents, growth regulators and bacteriocides.[1] All of them are characterized by having an alkyl group on C-14 and/or C-13 (methyl, ethyl or isopropyl).

Zamoranic acid[2] **1** is a labdane diterpene used by us for the synthesis of biologically active natural products such as sesquiterpene drimanes,[3] labdenolides such as limonidilactone,[4] diterpenes with the isofregenedane skeleton such as chrysolic acid[5] and tetracyclic diterpenes.[6]

Bearing in mind the following retrosynthetic scheme, biologically active diterpenes with the totarane, cassane or cleistantane skeleton could also be accessible from zamoranic acid. (Scheme 1).

Thus, for the synthesis of tricyclic diterpenes **II**, secoderivatives **I** will be used as intermediates for cyclization via a pinacol coupling promoted by SmI_2.

This strategy will be applied to the synthesis of (+)-totarol, a tricyclic diterpene with an aromatic ring C and a hydroxy group on C-13. (+)-Totarol is the main component of *Podocarpus totara*[7] and *Podocarpus nagi*[8] (Podocarpaceae) and shows potent activity against Gram-positive bacteria such as *Propionibacterium acnes*, *Streptococcus mutans*, *Bacillus subtilis*, *Mycobacterium tuberculosis*, *Brevibacterium ammoniagenes* and *Staphylococcus aureus*[9] (the last two being resistant to penicillin). (+)-Totarol shows synergy with other natu-



R^1	R^2	
*i*Pr	H	**Totarane**
Et	Me	**Cleistantane**
Me	Et	**Cassane**

R^1	R^2
*i*Pr	H
Et	Me
Me	Et

Scheme 1.

Keywords: diterpenes; zamoranic acid; totarol; samarium iodide.
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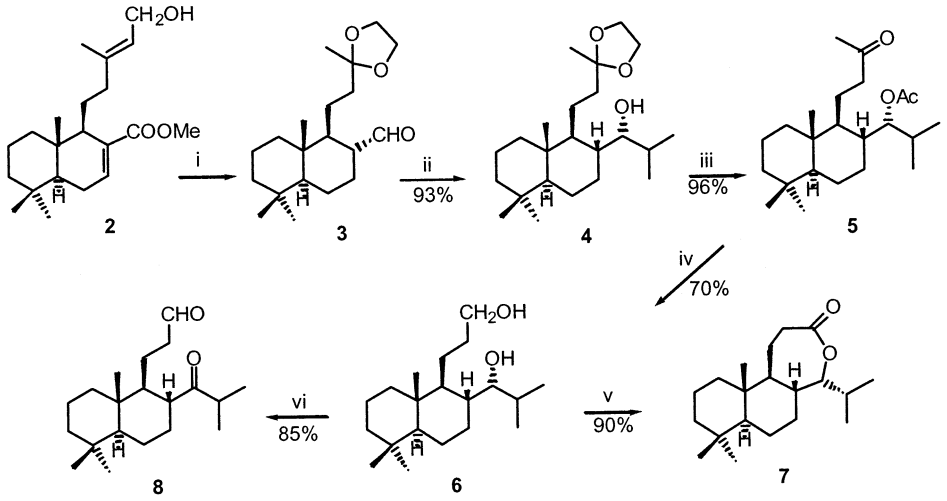
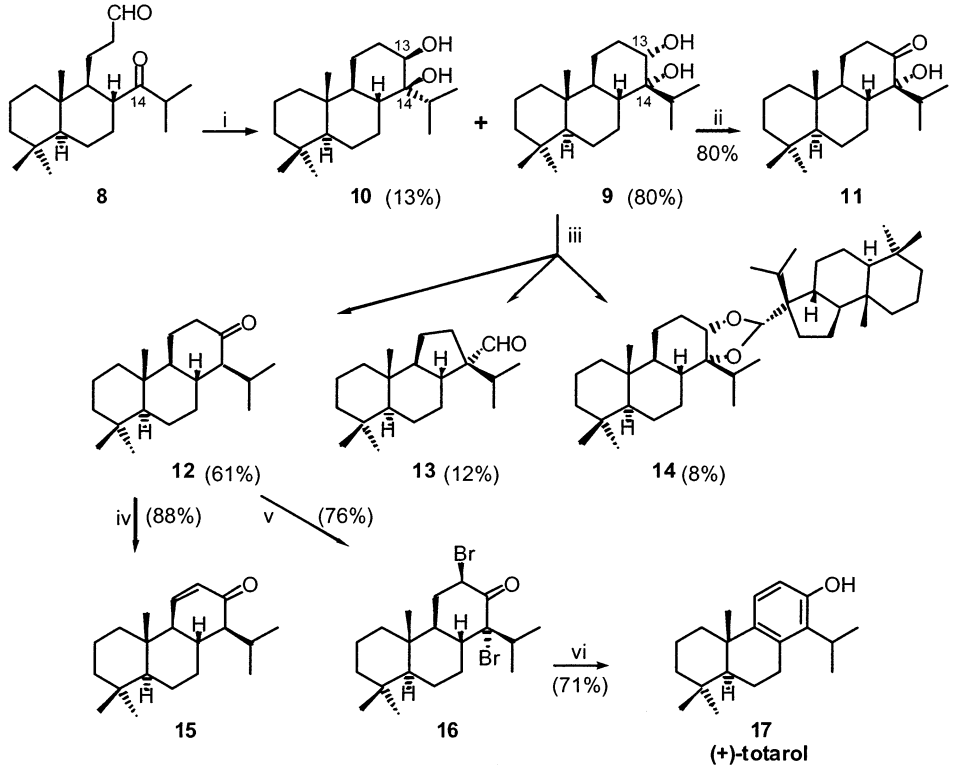
ral products such as anacardic acid, which results in the minimal antibacterial concentration (MBC) decreasing from 15.6 to 0.2 μg/ml.[10] SAR studies with totarol and derivatives have shown totarol to be the most potent agent against *Staphylococcus aureus*.[7,11] To the best of our knowledge there are only two syntheses of totarol;[12] a new approach to (+)-totarol from zamoranic acid is shown in Schemes 2 and 3.

The transformation of the methyl ester of zamoranic acid **2** into the aldehyde **3** was previously reported by our group[6] (Scheme 2). Addition of isopropylmagnesium chloride to aldehyde **3** proceeded with complete stereoselectivity to give exclusively the 14*R*-hydroxy derivative **4**, in excellent yield. The structure of **4** was confirmed by X-ray analysis of one of its derivatives (compound **7**, Scheme 2), showing that reaction of the



Scheme 2. *Reagents and conditions*: (i) Ref. 6; (ii) *i*PrMgCl, THF, 0°C, 1 h; (iii) (a) Ac_2O, py, 70°C, 2 h, (b) *p*-TsOH, Me_2CO, rt, 40 min; (iv) (a) HMDSNa, TMSCl, −78°C, 2 h, (b) OsO_4, NMO, rt, 48 h, (c) H_5IO_6, THF, H_2O, rt, 1 h, (d) $TMSCHN_2$, MeOH, C_6H_6, rt, 12 h, (e) $LiAlH_4$, Et_2O, rt, 1 h; (v) TPAP, NMO, rt, 30 min; (vi) (a) Ac_2O, py, rt, 30 min, (b) TPAP, NMO, rt, 2 h, (c) K_2CO_3, MeOH, rt, 4 h, (d) CrO_3, py, rt, 1 h.



Scheme 3. *Reagents and conditions*: (i) SmI_2, THF, 0.1 M, MeOH, rt, 2 h; (ii) TPAP, NMO, 0°C, 30 min; (iii) *p*-TsOH, C_6H_6, 60°C, 48 h; (iv) (a) LDA, PhSeCl, THF, HMPA, −78 to 0°C, 1 h, (b) *m*-CPBA, DCM, rt, 5 min; (v) $CuBr_2$, MeCN, 72 h, 50°C; (vi) Li_2CO_3, BrLi, DMF, 140°C, 16 h.

nucleophile had taken place from the less hindered *si* face of the carbonyl group.

The transformation of **4** into secototarane **6** through the methyl ketone **5** required acetylation at 70°C due to the hindrance of the hydroxyl group followed by deprotection. Degradation of **5** by the haloform reaction[13] did not work and it was therefore necessary to employ a sequence of reactions. Thus, capture of the kinetic enolate of **5** as a trimethylsilyl enol ether[14] and *cis*-hydroxylation, followed by cleavage with H_5IO_6,[15] esterification[16] of the resulting acid and reduction with LAH gave the diol **6** in excellent overall yield from **4**. TPAP/NMO[17] oxidation of **6** gave the lactone **7**, whose structure was confirmed by single crystal X-ray structure determination (Fig. 1),[18] corroborating the 14*R* configuration in **4**. Due to this unwanted lactonization, the oxidation of **6** to the dicarbonyl system **8** needed for the cyclization was carried out in an indirect way: chemoselective acetylation of the primary hydroxyl group of **6** with Ac_2O in pyridine over 30 min, oxidation of the secondary alcohol of the resulting monoacetyl derivative, hydrolysis of the primary acetoxy group, and subsequent oxidation which gave **8** (Scheme 2).

Treatment of **8** with SmI_2[19] (0.1 M, prepared in situ) gave a mixture of the totarane diastereomers **9** (80%) and **10** (13%), which were separated by column chromatography (Scheme 3). The structures of **9** and **10** were established by NMR, including HMQC, HMBC and nOe experiments. The signal for H-13 of **9** corresponded to an axial hydrogen (δ 3.55, dd, $J=11.1$ and 4.1 Hz) and so the hydroxyl groups are both α. The signal for H-13 in **10** corresponds to an equatorial hydrogen (3.83 ppm, t, $J=2.0$ Hz). The structure for the major diol **9** is that expected from a pinacol coupling with SmI_2.[6]

Transformation of **9** into totarol requires the dehydration of the tertiary hydroxy group and ring C aromatization. Oxidation of **9** with TPAP/NMO gave **11** in good yield, but all attempts to dehydrate and aromatize **11** using different conditions and reagents (DDQ,[20] TsCl/py, $POCl_3$/py, $SOCl_2$/py, $HClO_4$, CF_3COOH, HCOOH, HI) failed to give the desired results.

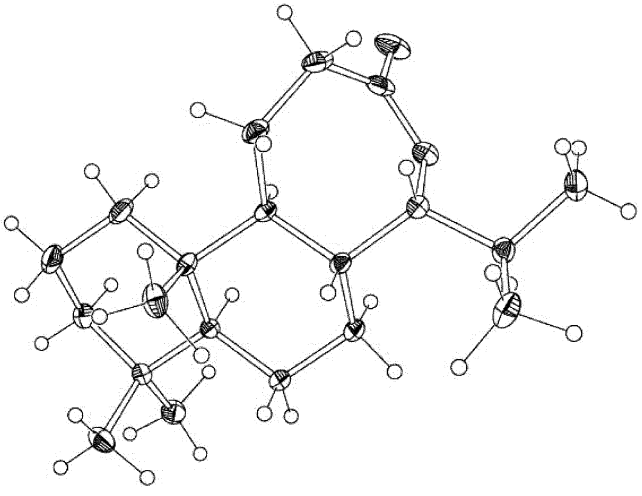


Figure 1. ORTEP view of compound **7**.

The aromatization of ring C was therefore attempted from ketone **12**, obtained by pinacol rearrangement from **9**. Treatment of **9** with *p*-TsOH, and subsequent column chromatography, gave **12** (61%) and the minor compounds **13** and **14**. The formation of the cyclohexanone **12** can be explained by the migration of hydride from C-13 to C-14, although under the acidic conditions of the reaction, epimerization at C-14 takes place to provide the more stable β-isopropyl group. The aldehyde **13** is formed by ring C contraction in the pinacol reaction and compound **14** is a dimer (M^+ *m*/*e*: 580) formed by reaction of the starting material with the aldehyde **13**.

The aromatization of **12** was attempted via enone **15**, obtained by reaction of **12** with PhSeCl/LDA[21] followed by oxidation of the selenide with *m*-CPBA at 0°C. All attempts at aromatization of **15** with DDQ, SeO_2 at 0°C or even Pd/C[22] in refluxing *m*-xylene failed to give totarol.

Aromatization of ring C was finally achieved by a halogenation–dehydrohalogenation sequence via intermediate **16**. Treatment of **12** with $CuBr_2$/MeCN[23] gave the dibromide **16** in moderate yield, and subsequent elimination with Li_2CO_3/LiBr[24] gave a good yield of **17**[25] [mp 129–130°C; $[\alpha]_D^{25}$ +41 (*c* 0.4, $CHCl_3$)], whose spectroscopic properties were coincident with those of (+)-totarol; (lit.[7b]) mp 131–132°C, $[\alpha]_D^{25}$ +42 (*c* 0.8, $CHCl_3$).

With the synthesis of (+)-totarol from zamoranic acid, we have opened a new synthetic route to tricyclic diterpenes with alkyl groups at C-14 (totaranes, cassanes or cleistantanes) using the cyclization of their 13,14-seco derivatives.

Acknowledgements

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18. A suitable single crystal of **7** was subjected to X-ray diffraction studies on a Seifert 3003 SC rotating anode diffractometer with (Cu K_α) radiation (graphite monochromator) using $2\tilde{\theta}\omega$ scans at 293(2) K. Crystal data for **7**: $C_{20}H_{34}O_2$, $M=306.47$, monoclinic, space group $P2_1$ (No. 4), $a=8.816(2)$, $b=8.495(2)$, $c=13.555(3)$ Å, $\alpha=\gamma=90°$, $\beta=105.42(3)°$, $V=908.7(3)$ Å^3, $Z=2$, $D_{calcd}=1.120$ Mg/m^3, $m=$(Cu K_α)$=0.070$ mm^{-1}, $F(000)=340$. 1453 reflections were collected, of which 1315 were considered to be observed with $I>2\sigma(I)$. The structure was determined by direct methods using the SHELXTL™ suite of programs. The positions of the hydrogen atoms were located from difference Fourier method and refined isotropically. Full-matrix least-squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors $R_1=0.0326$ and $wR_2=0.0797$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. CCDC 213752.
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25. Mp: 129–130°C (*n*-hexane); $[\alpha]_D^{25}$ +41 (*c* 0.4, $CHCl_3$); IR ν_{max} (film) cm^{-1}: 3482, 2932, 1458, 1387, 1263, 1103, 665. The assignments for the spectra, ^{1}H and ^{13}C NMR, for

17 were carried out using two-dimensional HMQC and HMBC experiments. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 7.00 (1H, d, $J=8.4$ Hz, H-12), 6.51 (1H, d, $J=8.4$ Hz, H-11), 3.41 (1H, m, H-15), 3.00–2.80 (2H, m, H-7), 2.30–1.20 (9H, m), 1.33 (3H, d, $J=7.0$ Hz, H-16), 1.32 (3H, d, $J=7.0$ Hz, H-17), 1.17 (3H, s, Me-20), 0.94 (3H, s, Me-18) and 0.90 (3H, s, Me-19); ^{13}C NMR (50 MHz, $CDCl_3$, δ ppm): 152.1 (C-13), 143.3 (C-9), 133.9 (C-8), 131.1 (C-14), 123.1 (C-11), 114.5 (C-12), 49.7 (C-5), 42.0 (C-3), 39.8 (C-1), 38.0 (C-10), 33.5 (C-4), 33.4 (C-18), 28.9 (C-7), 27.3 (C-15), 25.4 (C-20), 21.8 (C-19), 20.6 (C-16 and C-17), 19.8 (C-2), 19.6 (C-6); EIHRMS: calcd for $C_{20}H_{30}O$ (M^+): 286.2297, found 286.2292.