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SYNTHESIS OF EARTHY-MOULDY SMELLING COMPOUNDS-I STEREOSELECTIVE SYNTHESIS OF (±)-GEOSMIN

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Summary : The strongly earthy-smelling compound (±)-geosmin **1** is obtained stereospecifically in four steps and 42% overall yield from 1,4aβ-Dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one **2**. The key step involves a one-pot double-reduction of an epoxytosylate.

In recent studies aimed at a better understanding of the relationship between chemical structure and earthy odour, some general trends were proposed by Polak *et al.*[1], Mookherjee *et al*[2] and Brunke *et al*[3], *viz* :

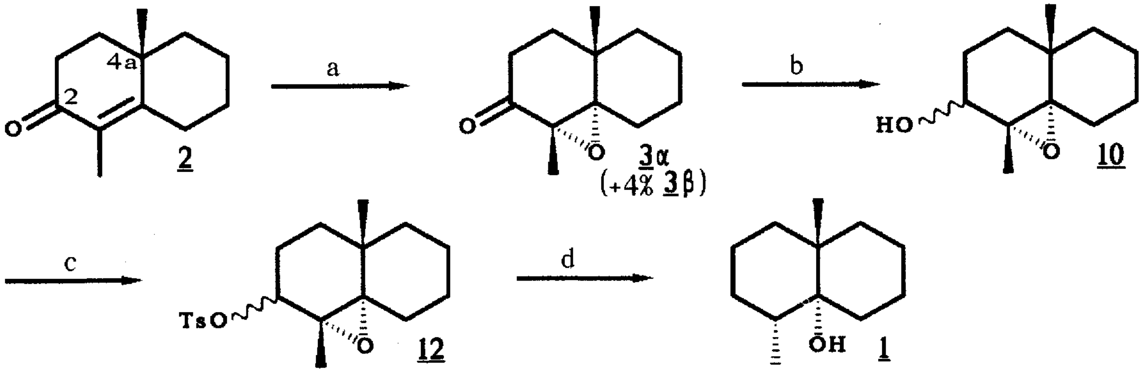
- a rigid bi- or tricyclic structure with 10-15 carbon atoms
- an axial or semi-axial tertiary hydroxyl group
- a methyl or gem-dimethyl group adjacent to the carbinol group.

In view of sensory evaluation, we needed a sample of pure (±)-geosmin **1**, which incorporates all the preceding features.

<u>1</u>

Natural (-)-geosmin is the main odour component of freshly plowed soil and is also frequently responsible, together with 2-methylisoborneol, for the muddy taste in surface water supplies.[4] This norsesquiterpenoid, that is believed to originate from an eudesmane-type precursor, has been first isolated from a culture of Streptomycetes in 1965[5] and its structure established in 1968 through the synthesis of the racemic form by Marshall and Hochstetler.[6] Ayer *et al.*[7] published in 1976 another synthesis of (±)-geosmin, in 24% yield from the readily available dimethyloctalone **2**.

Starting from the same octalone **2**[9], we now report a new stereoselective synthesis of (±)-geosmin in much greater yield (42% overall from **2**, Scheme I).



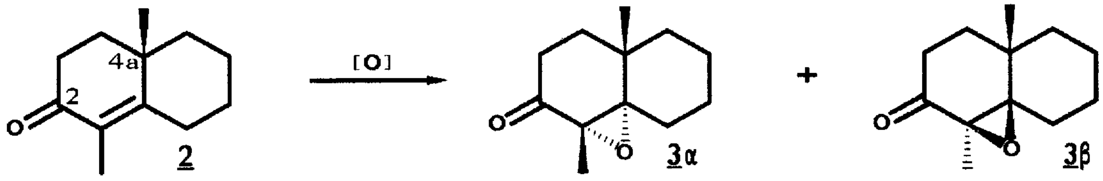
a : m-CPBA, CH_2Cl_2, 20°C, 10 h

b : $NaBH_4$, MeOH, 0°C, 7 h

c : TsCl, pyridine, $CHCl_3$, 5°C, 12 h

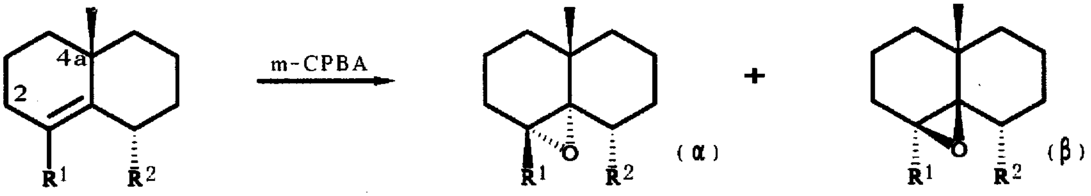
d : $LiAlH_4$, THF, reflux, 3 h

Scheme I



Reagents/ Conditions	3α	3β	Yield	Reference
H_2O_2, NaOH/0°C, 1 day then 20°C, 3 days	55	45	85%	7
H_2O_2, NaOH/15°C, 4 hr then 20°C, 4 days	67	33	77%	3
m-CPBA/CH_2Cl_2, 20°C, 10 hr	96	4	80%	This work

Scheme II



Compound	Conditions	α : β	Yield	Reference
4 ($R^1 = R^2 = H$)	C_6H_6, 10° C then 20° C, 2.5 hr	(5) 57 : 43	83%	11
6 ($R^1 = H, R^2 = CH_3$)	C_6H_6, 25° C, 2.0 hr	(7) 57 : 43	(*)	6
8 ($R^1 = CH_3, R^2 = H$)	(*)	(9) 67 : 33	(*)	3

(*) not reported

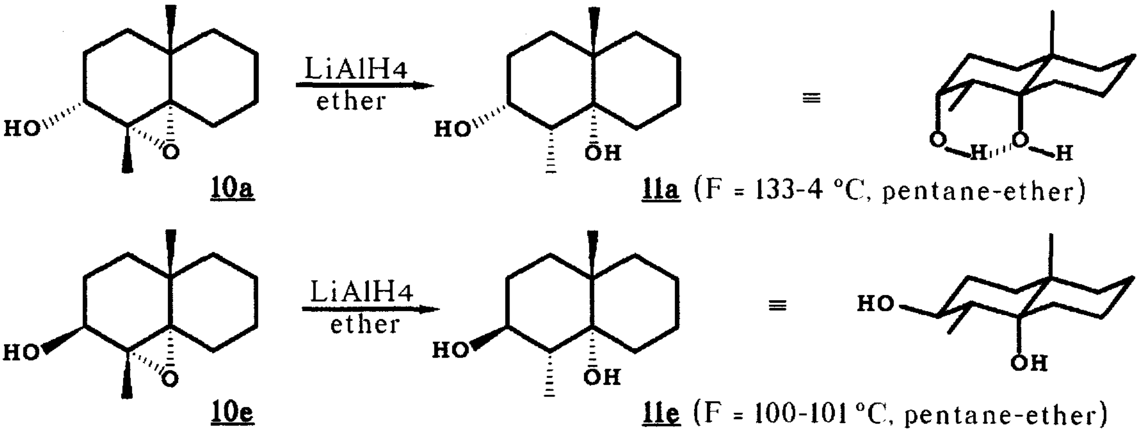
Scheme III

Oxidation of dimethyloctalone **2** with m-chloroperbenzoic acid (m-CPBA) gave a 96:4 mixture of α-and β-epoxyketones **3α** and **3β**. Distillation afforded a 80% yield of pure **3α** ($Eb_{0,1}$ = 77-80°C).[10]

This result is noteworthy : previously reported oxidations of **2** with alkaline hydrogen peroxide yielded 6:5 [7] to 2:1[3] mixtures at best, of **3α** and **3β** respectively. (Scheme II). Furthermore, Marshall and Hochstetler obtained *ca.* 6:4 mixtures of epoxydecalines **5α**/**5β** [11] and **7α**/**7β** [6] through m-CPBA oxidations of octalines **4** and **6** respectively. More recently Brunke *et al* [3] similarly obtained a 2:1 mixture of epoxydecalines **9α** / **9β** from argosmin **8**. (Scheme III).

The steric hindrance induced by the angular methyl group (on C^{4a}) over the β face in **2**, **4**, **6** and **8**, should explain the preferential attack of the bulky m-CPBA molecule on the α face, the small hydroperoxide ion being unaffected. Although very high in **2**, *the stereoselectivity of this epoxidation is but poor in octalines* **4** *and* **6**, *or only* moderate in **8**, probably due to the presence of a pseudo-axial hydrogen on C^2 (sp^3 in **4**, **6** and **8**, sp^2 in **2**), which also hinder the α face.

$NaBH_4$ reduction of **3α** afforded a 3:1 mixture of equatorial **10e** and axial **10a** epoxyalcohols which were readily separated by flash-chromatography (SiO_2, 95:5 cyclohexane:ethylacetate) in 64% yield for **10e** (oil) and 22% yield for **10a** (F = 64-65°C, pentane). Stereochemistry of each epimer was deduced from ^1H NMR spectroscopy and further secured by $LiAlH_4$ reduction to the cristalline diols **11e** and **11a** (Scheme IV).



Scheme IV

X-Ray diffraction spectroscopy established the proposed structure for **11a**.[12] Furthermore, the infrared spectra of 0.01 M and 0.05 M CCl_4 solutions of diols **11a** and **11e** clearly showed a strong absorption band at 3513 cm^{-1} for **11a**, due to intramolecular hydrogen bonding, which was missing in the infrared spectra of **11e**.[13]

Assuming an anti-attack of the hydride ion in the reduction of epoxides **10** (Scheme IV), structure elucidation of diols **11** also confirms the α stereochemistry of epoxyketone **3α**.[10]

The mixture of epimeric epoxyalcohols **10** was routinely converted to the tosylates **12** , using a 1:1.5:2 ratio of **10** /p-toluenesulfonylchloride/pyridine in chloroform solution, as recently reported.[14] One recrystallization from pentane-ether afforded a 75% yield of tosylates **12**, free of excess tosyl chloride.

One-pot double-reduction of the epoxytosylates **12** with $LiAlH_4$ was readily performed in refluxing THF,[15] affording a 72% yield of (±)-geosmin (> 97% pure by capillary GLC)[16] after flash chromatography (SiO_2, 99:1 cyclohexane:ethylacetate). HPLC monitoring of the reaction (RP18, MeOH : H_2O 8:2, R.I. detection) clearly showed the rapid disappearance of the more reactive axial tosylate **12a** whereas reduction of equatorial **12e** was only fulfiled after 3h refluxing in THF.

This sequence was readily applied at a semi-preparative level affording routinely 2 g of geosmin in 42% overall yield.

Work is now in progress to examine the scope of this interesting double reduction of α-epoxytosylates.[17]

References and Notes

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12 Structural parameters will be reported in a forthcoming communication. We thank D^r M. Leblanc for resolving the structure.

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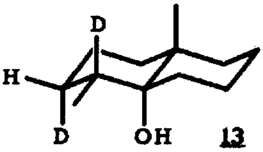
15 Reductions of the tosylates **12** and of the corresponding mesylates were also performed using various reducing agents and conditions. Results will be reported elsewhere.

16 GLC analysis were carried out using a single injection into two 0.32 mm x 50 m fused silica capillary columns coated with SE 30 and Carbowax 20M respectively; temperature program was 3°C/mn from 60°C to 200°C.

17 Stereochemistry of the reaction is now being studied through $LiAlD_4$ reduction of the equatorial tosylate which should afford dideuterogeosmin **13**. 500 MHz - ^1H NMR spectra of geosmin **1** and D_2-geosmin **13** are in progress (300 MHz insufficient).



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