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An Efficient Synthesis of (-)-Dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan from (-)-Sclareol.

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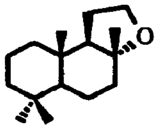
Abstract: *The title compound* **1***was prepared in 74% overall yield (3 steps) from sclareol* **2***. The key step involves osmium tetroxide catalysed rearrangement to* ***4a*** *and* ***b*** *during the oxidative degradation of sclareol.*

Ambergris is a metabolic product of sperm whales, which has been used in the past as a valuable constituent of fine fragrances.[1] Although natural ambergris is no longer used, there is demand for perfume ingredients with ambergris type odors. One of the most commercially important synthetic ingredients is (-)-norlabdane oxide **1**, more commonly known under the trade names Amberlyn (Quest), Ambrox®(Firmenich) and Ambroxan (Henkel).[2]



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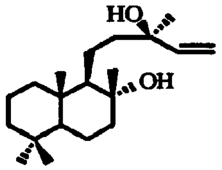

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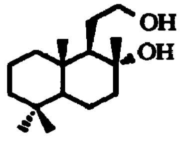

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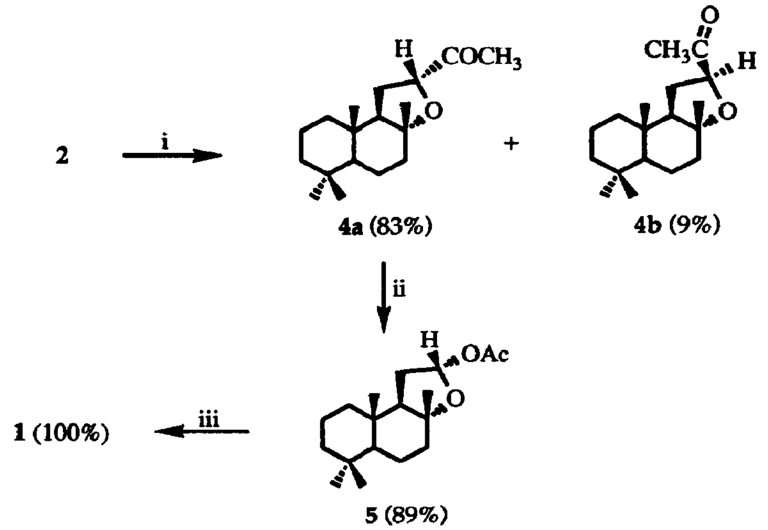
Since the first reported synthesis of **1** in 1950,[3] a number of laborious and low-yielding syntheses have been reported from sesqui- and diterpenoids.[4] Recent reports have shown that naturally occuring (-)-sclareol[5,6] **2** or communic acids[7,8] can be utilized as starting precursors for the preparation of **1**. The reported sequences from **2** to **1**[5,6] are superior to the communic acid pathways as the overall yields are higher due to a decrease in the number of synthetic steps required. All of these latter methods along with the current industrial process[1] lead to the diol **3**. Acid-catalysed cyclisation of **3** to **1** requires some care as the more thermodynamically stable iso-Ambrox (which possesses inferior olfactive properties) may result.[9,10]

Herein we report a simple and efficient synthesis of the title compound **1** from (-)-sclareol **2** which avoids this cyclisation step.

Reaction of **1** in a buffered t-butanol solution (pH $\approx$ 1.0) of osmium tetroxide and sodium periodate at ambient temperature afforded after 5 hrs. an epimeric mixture of the methyl-ketones **4a**[11] and **b** in excellent yield (91%, ratio[12] of **4a** : **b**, 9:1). Baeyer-Villiger oxidation of the major epimer[13] **4a** afforded the acetate **5**[14] in 89%. Quantitative conversion of **5** into **1** was achieved with $LiAlH_4$ in the presence of $BF_3.OEt_2$.[15] Scheme 1.

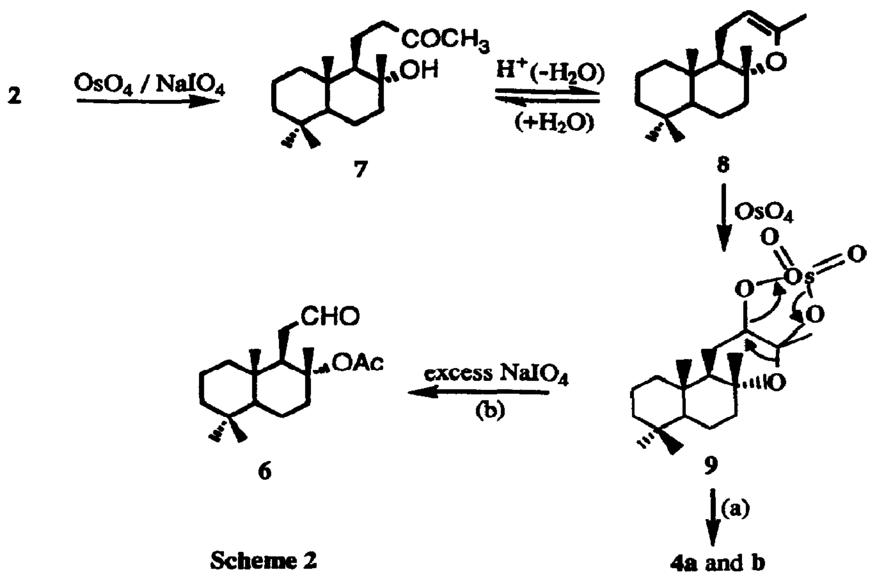


Scheme 1. Reagents and conditions: i; OsO_4 (cat.) / $NaIO_4$, t-butanol, pH=1, r.t. ii; m-CPBA, NaOAc, dioxane, r.t. iii; $LiAlH_4$ / $BF_3.OEt_2$, -78°C.

Although this represents a new and efficient synthesis of **1**, it is of interest to mention that Barrero *et. al.* also employed OsO_4 / $NaIO_4$ oxidation of sclareol **2** as the first step in their synthesis.[6] Their oxidative cleavage of **2** in THF at 45°C afforded the aldehyde **6**(73%), as the major product along with a number of other minor products, one of which was **4a** (2%). The difference in outcome was not due to solvent or temperature variations. The most likely explanation is that the formation of **4a** and **b** and/or **6** is strongly dependent on the OsO_4 / $NaIO_4$ ratio. This can be more clearly seen by considering the mechanism for the formation of **4a** and **b** or **6**. Scheme 2.

We propose that oxidative cleavage of **2** affords the uncyclised methyl-ketone **7** which under acidic conditions cylises to enol-ether **8**. Osmylation of the double bond in **8** gives the key intermediate **9**. We feel that because the mole ratio of $NaIO_4$ / OsO_4 used in our studies is lower than that for Barrero's (70 c.f. 558), that intermediate **9** has time to rearrange to the observed epimeric methyl-ketones **4a** and **b**, (pathway a). If the $NaIO_4$ / OsO_4 ratio is high then cleavage to the aldehyde **6**, (pathway b) is favored over rearrangement. To support this rationale we repeated the experiment using 1% OsO_4 and 6 equivalents of $NaIO_4$ (mole ratio, 600) and indeed found the aldehyde **6** to be the major product (62%) along with the methyl-ketone **4a**, 10%.

Furthermore, the relative proportions of **4a,b** and **6** were found to vary with pH. For example, buffering the mixture to pH<4 with H_3PO_4, gave only **4a,b**, while in the pH range (4.6-7.2) the aldehyde **6** was produced in 14% yield along with **4a,b**.



Scheme 2

In summary we describe a simple and high yielding (74% overall) synthesis of the title compound **1** starting from the naturally occuring (-)-sclareol **2**. The key step involves a yet unperceived osmium catalysed rearrangement which is dependent on the ratio of OsO_4 / $NaIO_4$ and the pH of the solution. Also preliminary experiments show that the OsO_4 / $NaIO_4$ system can be replaced by a NaI / H_5IO_6 system, which should make this synthetic sequence very attractive to industry.

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11 To **2** (0.5g, 1.62 mmol) dissolved in a t-butanol / water mixture (21mL, 20:1) was added osmium tetroxide (5 mol%) and the mixture stirred at ambient temp. for 30 min. Sodium meta-periodate (0.35g, 1.62 mmol) was added and the pH adjusted to 1.0 with phosphoric acid. Additional periodate was then added after 15 min. (0.35g, 1.62 mmol) and 45 min. (0.52g, 2.43 mmol) and the mixture stirred for an additional 5 hrs. Column chromatography (hexane/ether 4 : 1) affords pure **4a**. m.p. 71-73°C, $[\alpha]_D$ +44.43, c=1, $CHCl_3$. Anal. Calcd. for $C_{18}H_{30}O_2$: C, 77.65; H, 10.85. Found: C, 78.04, H, 11.02.

12. The stereochemistry of the two epimers was assigned on the basis that none of **4a** isomerised to **4b** on treatment with base. MOPAC6/PM3 optimisation calculations on **4a** and **b** showed **4a** to be 1.04 kcal/mol more thermodynamically stable than **4b**.

13. To **4a** (1.0g, 3.6 mmol) dissolved in anhydrous dioxane (20 mL) was added m-CPBA (0.72g, 4.1 mmol) and anhydrous sodium acetate (0.65g, 7.9 mmol). The mixture was stirred at ambient temperature for 24 hrs. after which time it was poured into saturated aqueous sodium bicarbonate solution (50 mL). The mixture was then extracted with dichloromethane (3 x 50 mL). The combined organic layers were then dried ($MgSO_4$) and the solvent removed in vacuo. Column chromatography (hexane/ether 4 : 1) affords pure **5**. Epimers **4a** and **b** do not need to be separated however the overall yield was not increased.

14 **5**: m.p. 92-94°C, $[\alpha]_D$ -54.26, c=1.21, $CHCl_3$. Anal. Calc. for $C_{18}H_{30}O_3$: C, 73.42; H, 10.27. Found: C, 73.50, H, 10.33.

15. To an ethereal solution (10 mL) of $LiAlH_4$ (0.07g, 1.8 mmol) at 0°C under argon was added borontrifluoride-etherate (0.75 mL, 6.7 mmol). Stirring of the mixture was continued for 30 min. after which time the mixture was cooled to -78°C and a solution of **5** (0.5g, 1.7 mmol) in anhydrous ether (5 mL) added. Stirring was continued for 30 min. and the solution allowed to attain ambient temperature. After 3 hr. the mixture was poured into sat. aqueous bicarbonate solution (20 mL) and extrated with ether (3 x 30 mL) Dessication of the organic layers and removal of the solvent afforded **1**. Column chromatography (hexane/ether 6 : 1) affords pure **1**.Triethylsilane or the borane-THF complex and boron trifluoride-etherate could also be used resulting in near-quantitative yields of **1**.

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