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Synthesis of Norambracetal: A New Ambergris Derivative.

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Abstract: *We describe the synthesis of norambracetal 14 from sclareol 1 using γ -homobicyclo-farnesilic aldehyde10 as a key intermediate.*

Establishing relationship between the structure and fragrance of a product remains a difficult problem: various theories have been proposed by Ohloff, [1] Vlad, [2] Amoore, [3] and more recently Winter.[4] Accordingly, it is of interest to synthetize molecules already known for their fragrance properties in wich the environment of the polar group (which apparently plays an important role on the fixation process on the receptor) has been modified.

Using a strategy previously developed to obtain ambracetal,[6] we report here the synthesis of norambracetal **14** from sclareol **1**. The key intermediate is γ-homobicyclo farnesilic aldehyde **10**, known as one of the most powerful ambergris fragrance but not used as a perfume component probably because of its instability towards dioxygen.[5] It is now possible to degrade the sclareol side chain - at carbon 12 - by oxo ruthenium complexes generated *in situ* from catalytic ruthenium trichloride in presence of stoichiometric amounts of reoxidizing species like sodium periodate which yield a mixture of **2** and **3**. With calcium hypochlorite the active species is the perruthenate; as a consequence, **2** is the only product of the reaction.[7] Reduction of the mixture of **2** and **3** with $LiAlH_4$ yields a single diol **4** in high yield. After selective protection of the primary alcohol as a benzylic ether **5** it is possible to obtain with a good yield a mixture of the two olefins **6** and **7**, which could not be separated by chromatography. A selective epoxidation yields a mixture of unchanged **6** and epoxide **8**, which can now be easily separated from **6** by flash chromatography on SiO_2. The latter compound is reduced to alcohol **9** which is oxidized into key intermediate **10** which is further converted into ambracetal by classical steps. The overall yield of norambracetal **14** from sclareol **1** varies from 25.5%, to 41.6% depending on the nature of the reoxidizing agent used in the ruthenium oxide catalyzed step [respectively $Ca(OCl)_2$ and $NaIO_4$]. Fragrance tests show that **14** has a strong but fugacious ambergris type fragrance.

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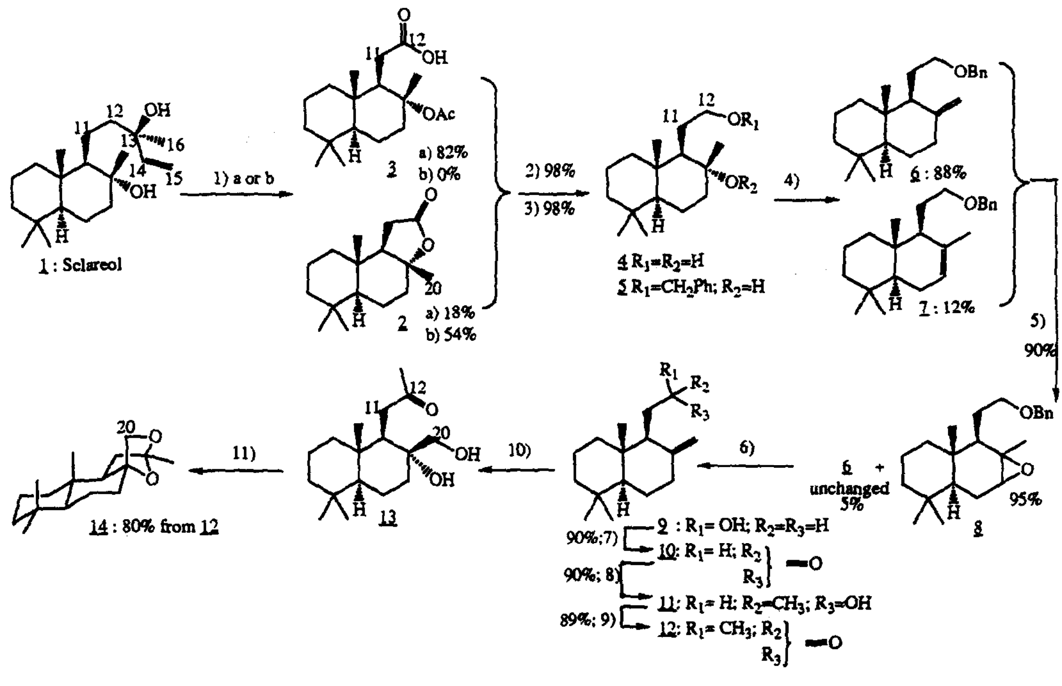

-1) $RuCl_3,3H_2O$, CCl_4 CH_3CN/H_2O; a) $NaIO_4$ or b) $Ca(OCl)_2$ -2) $LiAlH_4$, Et_2O, 25°C -3) $(Bu)_4N^+I^-$, THF, NaH, Benzyl Bromide, 25°C -4) $POCl_3$, Pyr, CH_2Cl_2,-30°C -5) mCPBA 0.35 eq, CH_2Cl_2, 55 min, 25°C -6) $NaNH_3$, Et_2O, -45°C -7) PCC, 25°C, CH_2Cl_2 -8) MeLi, Et_2O, 0°C -9) PCC, CH_2Cl_2, 25°C -10) OsO_4 cat. Trimethyl amine N-oxyde dihydrate, tBuOH, Pyr, H_2O -11) PPTS, CH_2Cl_2.

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7 - French Patent Application n°9105589; May 7th, 1991. The same oxidation procedure has been used in a three step synthesis of Ambrox from sclareol. For a suggested mechanism see:
Martres, P.; Perfetti, P.; Zahra, J. P.; Waegell, B.; Giraudi, E.; Petrzilka, M. *Tetrahedron Lett.* **1993**, *34*, 629-632.

8 - All the compounds reported here have been identified by the usual spectroscopic techniques. We report here the spectral analysis of 14, which is a new product. Norambracetal 14 [12(S)-8 α,12 : 12,20 diepoxy - 5α, 9α, 10β-13, 14, 15-trinorlabdane]. RMN ^{1}H : ($CDCl_3$) δ 0.80 (s, 3H); 0.86 (s, 3H); 0.95 (s, 3H); 1.58 (s, 3H); 3.3 (d, 1H, 9Hz); 4.3 (d, 1H, 9Hz). RMN ^{13}C: ($CDCl_3$) δ 14.8 (q); 18.0 (t); 19.6 (q); 20.3 (t); 21.1 (q); 31.6 (t); 33.0 (s); 33.4 (q); 35.5 (t); 39.3 (t); 39.8 (s); 41.2 (t); 71.8 (t); 56.6 (d); 59.1 (d); 86.2 (s); 110.0 (s); IR $CHCl_3$: 850, 1020, 1340. cm^{-1}
MP = 82-83°C.
Microanalysis $C_{17}H_{28}O_2$: calc. : C 77.27% ; H 10.60% ; found. : C 77.10% ; H 10.70%
MS: m/e= 264.

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