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A Short Efficient Synthesis of Ambraketal (four steps) and Epiambraketal (five steps) from Sclareol.

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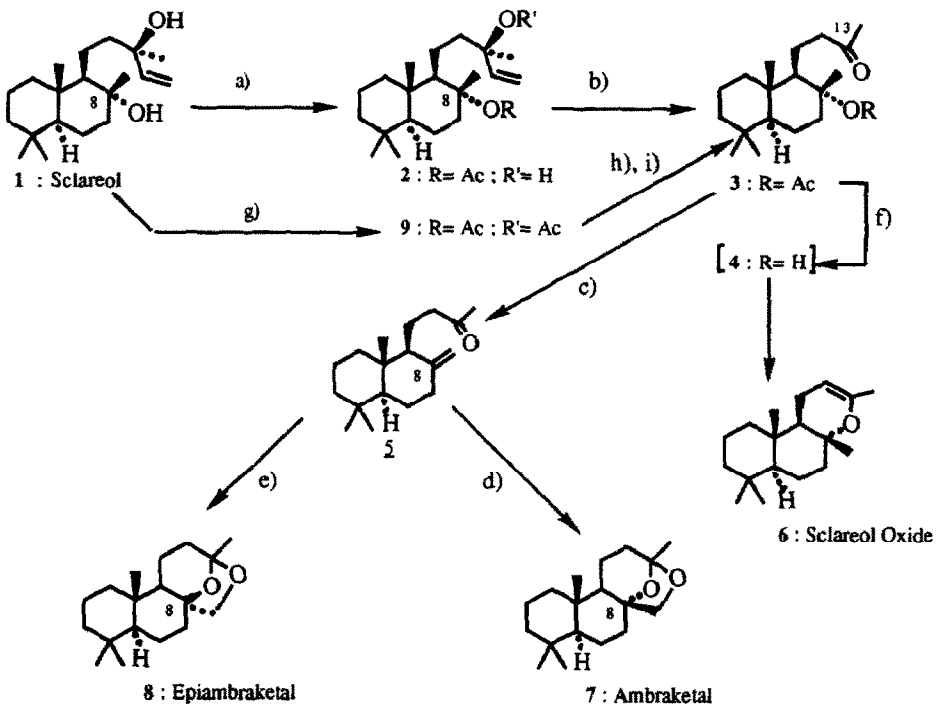
Key Words: Ambraketal, Ambergris Fragrances, Sclareol, Ruthenium tetroxide.

Abstract: *Ambraketal 7 and epiambraketal 8 are synthesized efficiently from sclareol 1. The key intermediate 5 is obtained by a regioselective elimination of ketoacetate 4 resulting from the side chain oxidative degradation of 1 by ruthenim tetroxide generated in situ.*

There is a constant interest in ambergris derivatives as demonstrated by numerous recent publications on this topic.[1] When sclareol **1** is used as starting material and transformed into ambraketal **7**, the major synthetic problems encountered are: i) efficient degradation of the side chain and ii) unequivocal formation of the exo methylene group at the C_8.[2] We describe two approaches to ambraketal **7** and epiambraketal **8** in which these problems have been solved efficiently. These syntheses can be carried out on a > one gram scale, and to our knowledge are the most efficient reported to date, in terms of the number of steps involved and overall yields.

Sclareol **1** was monoacetylated using acetylchloride in N, N-dimethylaniline [3] giving **2** in 60% yield. Ketoacetate **3** was obtained in 95% yield by cleaving the side chain of sclareol monoacetate **2** with catalytic amounts of RuO_4, generated *in situ*. The active catalyst was prepared by reacting $RuCl_3$, $3H_2O$ and stoichiometric amounts of sodium periodate in a ternary mixture of CCl_4, CH_3CN, H_2O, (1: 1: 2).[4] Pyrolysis of ketoacetate **3** at 150°C under modified Vlad conditions [5] yields the ketoolefin **5** (87%). This procedure was reproducible and easier to scale up than the elimination of the acetate **3**.[6] thereby avoiding a carbonyl protection deprotection sequence required to effect the elimination of alcohol **4**[2,7] which could not be isolated as it readily cyclized to sclareol-oxide, **6**. Ambracetal **7** was obtained in 90% yield by treating **5** with catalytic amounts of osmium tetroxide and trimethyl amine oxide dihydrate in a tBuOH, H_2O, Py solvent mixture.[8] Although not attempted, it should be possible to improve the overall yield (44%) of ambraketal **7** from sclareol **1** by increasing the chemoselectivity of the monoacetylation step. The epoxidation of **5** with metachloroperbenzoic acid followed by intramolecular ketalization of the resulting epoxyketone, yields 78% of epiambraketal, **8**. Finally, ketoacetate **3** also can be formed in 88% yield via the palladium catalyzed allylic rearrangement of sclareol diacetate **9**, followed by ozonolysis.[7] In this case, ambraketal, **7**, was obtained using the same steps as described above but with an overall yield of 69% (and five steps altogether instead of four previously).



a) AcCl, $C_6H_5N(CH_3)_2$, 2h, 25°C, 60%; b) $RuCl_3$, $3H_2O$ cat $NaIO_4$, 40°C, 0.3h , 95%; c) DMSO, $NaHCO_3$, 150°C, 6h, 87%; d) OsO_4 cat $[(CH_3)_3NO, 2H_2O]$, tBuOH, H_2O, py, reflux 6h, 90%; e) 1) mCPBA, CH_2Cl_2, 6h 25°C, 78% 2) $CuSO_4$ CH_2Cl_2 2h, 90%; f) K_2CO_3, MeOH; g) AcCl, $C_6H_5N(CH_3)_2$, 12h, 25°C, 98%; h) $PdCl_2(CH_3CN)_2$ cat THF, 25°C, 4h, 100%.

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