## Synthesis of ambergris fragrance chemicals from sclareol, involving palladium catalysed key steps\*.

by

I.C.Coste-Manière, J.P.Zahra and B.Waegell.

Laboratoire de Stéréochimie, associé au CNRS, UA 109, Université d'Aix-Marseille III, Faculté des Sciences de St-Jérôme, Avenue Escadrille Normandie Niemen, Case 532, 13397 Marseille Cédex 13.

<u>Abstract</u>: Ambraoxide, Ambrox  $(\mathbb{R})$ , methylambraoxide and ambracetal are synthetised via key steps involving respectively a palladium acetate catalysed elimination and a PdCl<sub>2</sub>(CH<sub>3</sub>CN)<sub>2</sub> catalysed isomerisation of the mixture of sclareol and episclareol acetates.

Ambergris fragrance chemicals raise a constant interest as emphasized by the recent syntheses of Ambrox  $\bigcirc 17$  from sclareol <u>1</u> (la) and from other natural products (lb,c,d). According to Ohloff (2) and Brunke (3) the most interesting ambergris fragrances are due to ambraoxide <u>14</u>, methylambraoxide <u>21</u>, ambracetal <u>24</u> and already mentioned Ambrox  $\bigcirc 17$ . We report here our preliminary results (4) concerning the synthesis of these derivatives from sclareol <u>1</u>, using key steps involving respectively a palladium catalysed elimination of acetic acid from acetates <u>5</u> and <u>6</u> into dienes <u>7</u>, <u>8</u> and <u>9</u>, and a palladium catalysed isomerisation of tertiary acetates <u>5</u> and <u>6</u> into <u>18</u>. The difficulties encountered in the previously described oxidative degradation of sclareol <u>1</u> into sclareolide <u>15</u> for instance, are due to the control of reactivity of the two tertiary alcohols on carbons <u>8</u> and <u>13</u>, during the elimination process occuring on sclareol <u>1</u> (5), yielding the -12,13 double bond which will undergo an oxidative cleavage.

Examination of the  $^{13}$ C NMR spectra of the commercial samples we used (6) showed they were a 90/10 mixture of sclareol <u>1</u> and episclareol <u>2</u> (7). However, as our synthetic scheme leads to a loss of chirality on carbon 13, we used this mixture, throughout the work described here. The action of various acidic media (p.toluene sulfonic acid, BF<sub>3</sub> etherate, sulfuric acid, phosphoric acid, SiO<sub>2</sub> or acetic acid) did not allow to achieve selectively the dehydration of the 13-OH, so as to obtain the abienols <u>10</u>, <u>11</u> and <u>12</u>. Nevertheless, using orthophosphoric acid in refluxing benzene, it was possible to obtain good yields (85%) of a mixture of manoyloxide <u>3</u>, and

\* : Dedicated to the memory of Paul Teisseire.

Ambrox $^{igode{R}}$  : A registered trade-mark of Firmenich, Geneva.



a)  $H_3PO_4$ ,  $C_6H_6$ , reflux, 2h, 85 %; b)  $C_6H_5N(CH_3)_2$ ,  $CH_3COCl$ ,  $25^{\circ}C$ , ld, 98 %; c)  $Pd(OAC)_2$ , dioxane, 100°C, 15mn, 100 %; d) LiAlH<sub>4</sub>,  $Et_2O/H^+$ , 2h, 96 %; e)  $KMnO_4$ , ld, 80 %; f) LiAlH<sub>4</sub>,  $Et_2O/H^+$ ; pTsCl, 2h, 90 %; g) LiAlH<sub>4</sub>, THF, 25°C, 3h, 98 %; h) pTsCl,  $CH_2Cl_2$ , 25°C, 2h, 90 %; i)  $PdCl_2(CH_3CN)_2$ , THF, 25°C, 4h, 100 %; j) LiAlH<sub>4</sub>,  $Et_2O$ ,  $H^+$ , 25°C, 2h, 98 %; k) O<sub>3</sub>, MeOH,  $CH_2Cl_2$ ,  $(CH_3)_2S$ , 70°C, 24h, 75 %; l)  $H_2$ -Pd/C, MeOH, 25°C, 12h, 98 %; m) O<sub>3</sub>, MeOH,  $CH_2Cl_2$ ,  $(CH_3)_2S$ , -70°C, 24h, 90 %; n) vacuum 3mm Hg, 80°C, 82 %; o) OsO<sub>4</sub>, 25°C, mannitol, KOH, EtOH,  $C_6H_6$ , reflux, 75 %.

 $\underline{1}$  : sclareol ;  $\underline{2}$  : episclareol ;  $\underline{3}$  : manoyloxide ;  $\underline{4}$  : 13 epimanoyloxide ;  $\underline{10}$  : neoabienol ;  $\underline{11}$  : isoabienol ;  $\underline{12}$  : abienol ;  $\underline{13}$  : ambreinolide ;  $\underline{14}$  : ambraoxide ;  $\underline{15}$  : sclareolide ;  $\underline{17}$  : Ambrox ;  $\underline{20}$  : sclareol oxide ;  $\underline{21}$  methyl ambraoxide ;  $\underline{24}$  : ambracetal. -13 epi-manoyloxide 4, which are interesting starting material for ambergris derivatives (8).

When acetates 5 and 6 are treated by a catalytic amount of palladium acetate (1 mole %) in presence of phosphine at 100°C (9), the mixture of the three dienic acetates 7, 8, and 9 can be obtained quantitatively. The relative ratio of these dienes depends on the reactions conditions and particularly on the phosphine nature. In a typical experiment using triphenylphosphine for instance, it was possible to obtain a 60/20/20mixture of 7, 8 and 9 (10). The corresponding mixture of neo-abienol 10, isoabienol 11 and abienol 12 was obtained by LiAlH<sub>4</sub> reduction, and further oxidized (11) into ambreinolide 13 and sclareolide 15 (60/40). These two derivatives could easily be separated by column chromatography on silicagel. LiAlH<sub>4</sub> reduction, immediately followed by cyclisation under acidic conditions in presence of tosylchloride gave respectively ambraoxide 14 and Ambrox  $\frac{17}{10}$ . Attempts to modify the relative ratio of abienols 10, 11 and 12, by isomerisation reactions in presence of rhodium chloride for instance (12) were until now unsuccessfull.

Key intermediate 18, on the way to methylambraoxide 21 and ambracetal 24, was obtained by quantitative palladium catalysed isomerisation of 5 and 6(13). No ligand addition is needed, and E isomer of isosclareyl diacetate 18, is the major product. Iso-sclareol 19, which is obtained in practically quantitative yield by LiAlH4 reduction of 18, is ozonolysed into sclareol oxide 20 ; this cyclic enclether is likely to be formed by intramolecular attack of the 8 hydroxy group on the intermediate - but not isolated methylketone 22b - resulting from the oxidative cleavage of the Cl3-Cl4 double bond - followed by dehydratation. Methylambraoxide 21, is then easily formed by catalytic hydrogenation of 20. Ozonolysis of the latter intermediate, followed by LiAlH4 reduction yields diol 16 with 78% overall yield.When the ozonolysis is directly carried out on iso-sclareylacetate 18, the intermediate methylketone 22a can be isolated and transformed into 23 by simple distillation under vacuum. As the transformation of 23 into ambracetal 24, has already been reported (14), this completes the synthesis of our initial target compounds. Full details concerning these syntheses, as well as mechanistic considerations concerning the palladium catalysed transformations, will be reported elsewhere.

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