A NEW SYNTHESIS OF AMBROX AND RELATED COMPOUNDS

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Abstract — The cyclic ether **1**, a compounds with an ambergris type odour and related products **(10,11)** have been prepared from (-)-drimenol **(2)**. The synthesis of **1** is accomplished in ten steps with an overall yield of 19%.

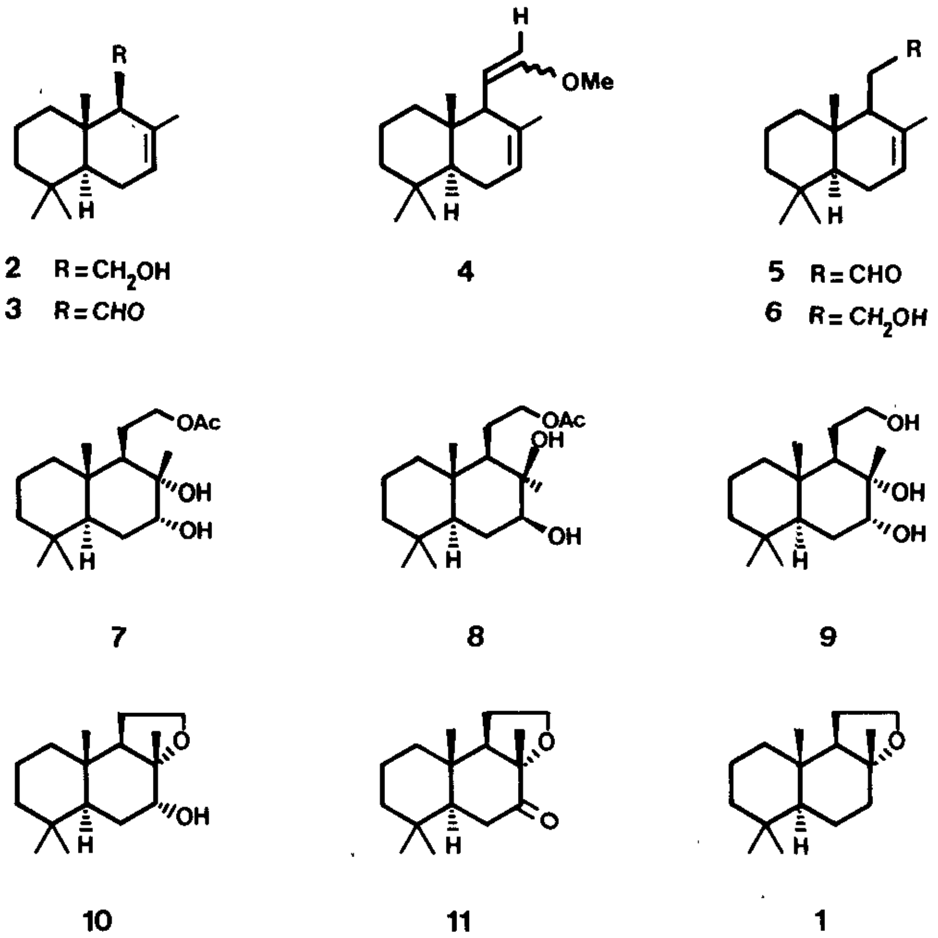
Tinctures obtained from ambergris are highy valued in the perfumery industry, where because of their tenacious odour, they have been used as additives and fixatives in the formulations of perfumes[1]. The analysis of ambergris tincture[2] has demostrated the presence of "ambrox" **(1)**, which has long been used as an aroma chemical of the ambergris type. This compounds has been prepared in its optically active form from sclareol[3], manoyl oxide[4] and labdanolic acid[5].

In a previous work[6] we have reported the preparation of acetals with an ambergris type odour using (-)-drimenol **(2)** as chiral starting material. We describe here an alternative synthesis of chiral ambrox **(1)** and some related compounds from (-)-drimenol **(2)**[7].

Oxidation of alcohol **2** with pyridinium chlorochromate in dichloromethane gave a 72% yield of aldehyde **3**[8]. Compound **3** was condensed with (methoxymethyl) triphenyl phosphonium chloride to give the enol ether **4** in 59% yield (mixture of Z and E isomers).

Hydrolysis of **4** with dioxane-hydrochloric acid and subsequent reduction of aldehyde **5** with $LiAlH_4$ afforded alcohol **6** (82% from **4**). [**6**; ir (neat) 3340, 1460, 1050 cm^{-1}; ^1H-nmr ($CDCl_3$) δ: 0.77(3H,s), 0.86(3H,s), 0.88(3H,s), 1.66(3H,b.s.), 3.4-3.9 (2H,m), 5.42(1H,m)].

Figure 1



Acetylation of **6**, followed by osmylation according to Van Rheenen procedure[9] gave a 96% yield of a 3/1 mixture of the desired diols **7** and **8**. [**7**; ir (KBr) 3540, 3300, 1450 cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ: 0.80 (6H,s), 0.89(3H,s), 1.18(3H,s), 3.30-3.88(3H,)]. This mixture was separated by silica gel chromatography. Saponification of **7** furnished the triol **9** almost quantitatively. Transformation of **9** into **10** was carried out by treatment of **9** with equimolecular amounts of mesyl chloride in pyridine. The monomesylate could not be isolated and the cyclization was occurred spontaneously to give a 95% of the tetrahydropyran derivative **10**. [**10**; ir (KBr) 3440, 1460, 1070, 1040 cm^{-1}; ^{1}H-nmr (CDCl$_3$) δ: 0.84(6H,s), 0.88(3H,s), 1.09(3H,s), 3.75-3.40(3H,m); MS: 252 (M$^+$), 237, 124].

Oxidation of **10** with pyridinium chlorochromate in dichloromethane gave the corresponding ketone **11** in 98% yield. [**11**; ir (KBr) 1720, 1460, 1020 cm^{-1}; ^1H-nmr ($CDCl_3$) δ 0.83(6H,s), 1.02(3H,s), 1.28(3H,s), 2.25-2.69(2H,m), 3.68-3.97(2H,m); MS: 250 (M^+), 222, 207, 124]. Finally Huang-Minlon[10] reduction of **11** afforded the desired ambrox (**1**) in 90% yield, whose physical constant (Table 1) and spectral data were identical with those reported[4].

The overall yield of ambrox in this synthesis from (-)-drimenol was 19%.

It is important to note that this is the first report of the synthesis of 7α-hydroxy and 7-oxo-ambrox. The odoriferous properties of compounds **10** and **11** will be reported afterwards.

Table 1. Physical constants

Substance	Melting point[a]	Optical rotation[b]
5	oil	-18°(c 1.1, $CHCl_3$)
6	oil	-12.2°(c 2.0, $CHCl_3$)
9	152-153°C	-32.5°(c 0.8, EtOH)
10	62-63 °C	-66° (c 0.9, $CHCl_3$)
11	133-134°C	-147° (c 0.9, $CHCl_3$)
1	75-76 °C	-26° (c 0.5, C_6H_6)

a. All solids compounds were crystallized from a mixture of AcOEt hexane; b. Measured at 22°C. Concentrations are expressed in g/ml.

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