Pergamon

Tetrahedron Vol. 51, No. 30, pp. 8333-8338, 1995
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0040-4020/95 $9.50+0.00

0040-4020(95)00444-0

Formal Synthesis of (±)-Ambrox®.

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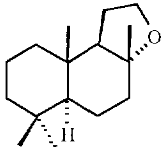
***Abstract*:** The immediate precursor of (±)-Ambrox® **1** has been conveniently prepared in a seven-step sequence starting from the readily available methyl 2-oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate **2**, in turn derived by stannic chloride-mediated cyclization of methyl 3-oxo-5-(2,6,6-trimethylcyclohexen-1-yl)pentanoate.

Ambergris, a metabolite of the blue sperm whale (*Physeter macrocephalus L.*) accumulating as concretions in the gut, is one of the most remarkable animal perfumes.[1] The ageing process of (+)-ambrein, the original major constituent, by the action of sunlight and air proceeds with the formation of odoriferous degradation products that combine to release the ambergris fragrance. The unique olfactive and fixative properties are related principally to (-)-norlabdane oxide **1**, commonly known as Ambrox®, the registered trade-mark of Firmenich SA for (-)-8α-12-epoxy-13,14,15,16-tetranorlabdane, a natural compound also found in trace amounts in several essential oils.



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Its scarcity, a growing demand for ambergris-type odorants coupled with almost complete worldwide whale protection, has encouraged intense preparative efforts towards synthetic substitutes of natural ambergris.
Thus, an impressive synthetic activity has developed around Ambrox® **1**, probably the commercially most important synthetic equivalent of ambergris, which has been successfully synthesized either as racemic or optically active form by different strategies.

Since its first synthesis[2] which dates back 1950, several approaches to **1** as the pure (-)-enantiomer have been reported, taking advantage of the correct stereochemical set up of the four contiguous chiral centers of different sesqui- and diterpenoids, sclareol being the superior starting material[3-16]. Furthermore, total syntheses of **1**, both as racemic[17-18] or optically active forms[19-20], have been developed, including non-enzymatic acid-catalyzed cyclizations of polyenes with different internal nucleophilic terminators.[21]

Not surprisingly, the bicyclic β-ketoester **2**, firstly prepared forty years ago by Eschenmoser et al.[22] during their pioneering work on biogenetic-type cyclizations of polyenes, and later by White et al.[23] through an improved procedure, has been chosen as useful starting point for two successful approaches to (±)-**1**, which retains the characteristic scent of ambergris with an odor threshold essentially identical to the (-)-enantiomer.[17]

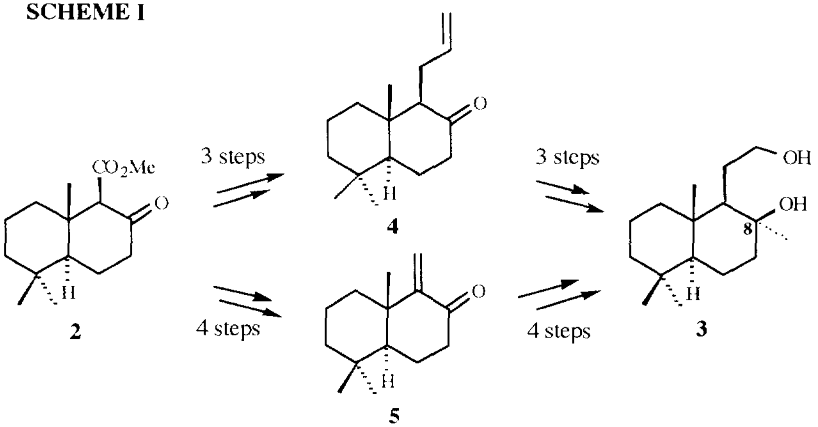
The configurations at the three contiguous chiral centres of **2** are the same as those found at the corresponding centres of **1**; in addition the β-ketoester moiety can be suitably manipulated to obtain the diol **3**, the C-8 epimer of the key intermediate in most of the approaches including the current industrial process.[24]

Since **2** could not be alkylated, indirect solutions have been developed to introduce the required two-carbon chain into the decalin ring system. Thus, Büchi and Wüest[17] were able to prepare **4** inserting an allylic side chain through an easy O-allylation of **2**, followed by Claisen rearrangement and demethoxycarbonylation. Its transformation to **3** required three further steps, with final removal of a carbon atom from the allylic side chain by ozonization combined with reductive treatment.

On the other hand, Snowden and Linder[18] described an alternative approach to **3**, again starting from **2**, the required two carbon side chain being installed by 1,4-addition of a carbon atom through Michael reaction of KCN into a known bicyclic *exo*-methylene ketone **5**. This route has been described as a shorter conversion of **2** to **3** (four steps against six steps), not considering the four-step sequence required to prepare the starting enone.

As summarized in the following Scheme I, in both cases, the one carbon atom to the decalin ring system has been subsequently added by stereoselective equatorial nucleophilic addition at C-8 carbonyl, which takes place from the less hindered α face to produce the tertiary carbinol **3**.

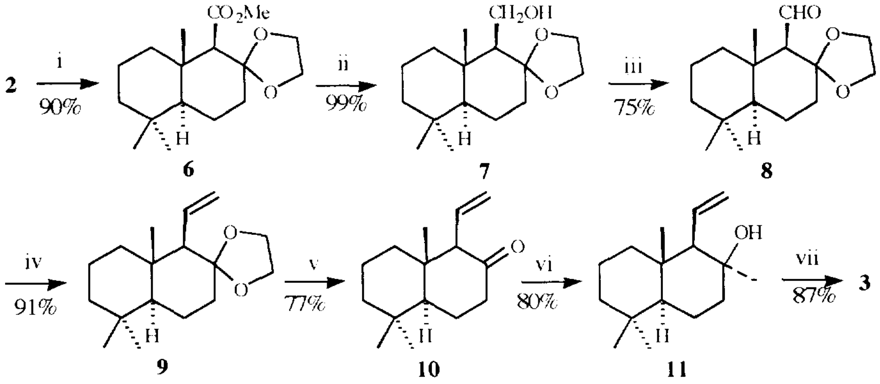
SCHEME I



We describe in this paper a new convenient transformation of **2** to **3**, which takes advantage of our own previous knowledges of the chemistry of **2**. In 1966, in view of the well-established reluctance of **2** to undergo C-alkylation, Traverso et al.[25] discovered a useful device for the introduction of an alkyl side chain through conversion of the β-ketoester moiety into the corresponding more enolized hydromethylene ketone, on which a base-catalyzed addition of ethyl vinyl ketone could be successfully performed. This operation was accomplished through a sequence involving: 1) protection of the carbonyl group of **2** as cyclic ethylene ketal **6** by treatment with ethylene glycol under standard conditions; 2) reduction with $LiAlH_4$ of the ester group to the primary alcohol **7**; 3) oxidation to the corresponding aldehyde **8**[26]; 4) removal of the ketal protecting group by aqueous acid treatment.

We considered the aldehyde **8** an attractive starting material for a convenient alternative synthesis of **3**, and thence for a new formal synthesis of (±)-ambrox® **1**. To this end, our initial task was a careful optimization of the synthetic sequence to secure an abundant source of **8**, which was then submitted to a Wittig reaction with triphenylmethylenephosphorane, generated in situ by action of n-BuLi in THF at 0°C, to afford a 91% yield of the vinylated decalin system **9**, which was then easily transformed in 77% yield to the corresponding ketone **10** by removal of the protecting group by acid treatment. The expected stereoselective equatorial attack on the carbonyl group by treatment with methyl magnesium iodide proceeded uneventfully to produce the tertiary carbinol **11**, the hydroboration of which by means of borane-sulfide complex followed by alkaline hydrogen peroxide oxidation produced the diol **3**, identical in all respects with an authentic sample.

SCHEME II



Reagents: i, $(CH_2OH)_2$, H^+; ii, $LiAlH_4$; iii, PDC; iv, $Ph_3\overset{+}{P}CH_3\ Br^-$, n-BuLi ; v, H_3O^+; vi, MeMgI; vii, B_2H_6, H_2O_2, OH^-

Its transformation to the target **1** has been already accomplished using different protocols, the best results being obtained by p-toluenesulfonic acid catalyzed cyclization in nitromethane solution at room temperature, higher temperatures favouring the formation of the more stable iso-derivative.[11]

In summary, the conversion of the readily available β-keto ester **2** into the immediate precursor **3** of the commecially important Ambrox® **1** has been accomplished using a convenient pathway, which compares well with the known ones in term of number of steps and overall yields.

Experimental.

General remarks. Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel coated plates F_{254} (Merck). Infrared (IR) spectra were measured on a Perkin-Elmer Model 297. Nuclear magnetic resonance (^1H NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted and peak positions are given in parts per millions downfield from tetramethylsilane as an internal standard. Coupling constants are given in Hz. Organic solutions were dried over anhydrous magnesium sulphate and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling range 40-60°C and ether to diethyl ether. Flash-chromatography was carried out with Merck silica gel (230-400 mesh). All reactions were carried out under N_2 atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

Materials. The starting (±)-(1α,4aβ,8aα) methyl 2-oxo-5,5,8a-trimethyldecahydronaphthalene-1-carboxylate **2** has been prepared by stannic chloride mediated cyclization[23] of the monocyclic β-ketoesters prepared by condensation with dimethyl carbonate and NaH of dihydro-α- and β-ionone, in turn obtained by reduction of the commercially available α- and β-ionone by known directions.

Methyl (±)-(1'α,4'aα,8'aβ)-octahydro-5',5',8'a-trimethyl-spiro-[1,3-dioxolane-2,2'(1H)-naphthalene]-1'-carboxylate 6.

A mixture of **2** (0.4g, 1.58mmol), ethylene glycol (3ml), triethyl orthoformate (3ml) and p-toluenesulfonic acid (0.2mg) was left overnight at room temperature. The solution was washed with aqueous $NaHCO_3$ (25ml), dried and evaporated in vacuum. Crystallization of residue from ether gave **6**, (0.41g, 90%), m.p. 110°C. IR: 1740 cm^{-1}; ^1H NMR: δ 0.85 (s, 3H), 0.88 (s, 3H), 1.18-1.97 (m, 14H), 2.51 (s, 1H), 3.63 (s, 3H), 3.68-4.27 (m, 4H). (Found: C, 68.79; H, 9.45. $C_{17}H_{28}O_4$ requires C, 68.89; H, 9.52).

(±)-(1'α,4'aα,8'aβ)-Octahydro-5',5',8'a-trimethyl-spiro-[1,3-dioxolane-2,2'(1H)-naphthalene]-1'-methanol 7.

A solution of **6** (1.2g, 4.05mmol) in dry ether (5ml) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (0.9g) in ether (20ml). After being stirred for 3h, the excess of reducing agent was decomposed by careful addition of water (10ml). The organic phase was decanted and the inorganic salts were washed with ether (3x25ml). The dried organic extracts were evaporated and the solid residue crystallized from ether to give **7** (1.07g, 99%), m.p. 105-106°C. IR: 3530 cm^{-1}; ^1H NMR: δ 0.81 (s, 3H), 0.85 (s, 3H), 0.88 (s, 3H), 1.05-2.11 (m, 11H), 3.02 (d, 1H, J=9Hz), 3.61 (t, 1H, J=11Hz), 3.77-4.30 (m, 5H). (Found: C, 71.49; H, 10.43. $C_{16}H_{28}O_3$ requires C, 71.6; H, 10.52).

(±)-(1'α,4'aα,8'aβ)-Octahydro-5',5',8'a-trimethyl-spiro-[1,3-dioxolane-2,2'(1H)-naphthalene]-1'-carboxaldehyde 8.

To a suspension of pyridinium chlorochromate (0.5g, 2.3mmol) in methylene chloride (15ml) containing sodium acetate (0.13g) was added a solution of **7** (0.3g, 1.12mmol) in methylene chloride (5ml) and the mixture left at room temperature for 4h. Ether (40ml) was added and the resulting suspension filtered through Celite and the salts washed with ether (3x20ml). The filtrate was evaporated in vacuum and the solid residue crystallized from light petroleum to give **8** (0.225g, 75%), m.p. 94°C. IR: 1740 cm^{-1}; ^1H NMR: δ 0.86 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 1.02-2.18 (m, 14H), 3.71-4.15 (m, 5H), 9.82 (d, 1H, J=4.4Hz). (Found: C, 72.09; H, 9.73. $C_{16}H_{26}O_3$ requires C, 72.14; H, 9.84).

(±)-(1'α,4'aβ,8'aα)-Octahydro-1'-ethenyl-5',5',8'a-trimethyl-spiro[1,3-dioxolane-2,2'(1'H)-naphthalene] 9.

A solution of n-BuLi (1.6M in hexane, 1.4ml, 2.25mmol) was added dropwise to a cooled (0°C) slurry of methyltriphenylphosphonium bromide (0.8g, 2.25mmol). The yellow-orange solution was stirred for 15min at room temperature , and a solution of **8** (0.2g, 0.75mmol) in dry THF (5ml) was then added at 0°C. After stirring for 30min, the mixture was poured in water (20ml), extracted with ether (3 x 20ml), dried and evaporated.The residue was purified by column chromatography on silica (eluent ether : light petroleum 1 : 9) to give **9** (0.18g, 91%) as an oil. IR: 3000, 1480, 1100 cm^{-1}; ^{1}H NMR: δ 0.84 (s, 3H), 0.89 (s, 3H), 0.98 (s, 3H), 1.03-1.74 (m, 10H), 1.89 (m, 2H), 3.64-4.08 (m, 4H), 4.94-5.21 (m, 2H), 5.63-5.91 (dt, 1H, J=9.1Hz). (Found: C, 77.09; H, 10.53. $C_{17}H_{28}O_2$ requires C, 77.22; H, 10.67).

(±)-(1α,4aβ,8aα)-Octahydro-1-ethenyl-5,5,8a-trimethyl-2(1H)-naphthalenone 10.

A solution of **9** (0.55g, 2.08mmol) in acetone (15ml) containing 10%HCl (2.5ml) was heated at 40°C for 2h. Most of the solvent was removed in vacuum, the residue extracted with ether (3 x 20ml), the extracts washed with brine, dried and concentrated. The residue was purified by column chromatography (eluent: ether : light petroleum 1:9) to give **10** (0.35g, 77%) as an oil. IR: 3000, 1735, 1480 cm^{-1}; ^{1}H NMR: δ 0.84 (s, 3H), 0.88 (s, 3H), 0.98 (s, 3H), 1.03-1.88 (m, 8H), 2.01-2.59 (m, 3H), 2.69 (d, 1H, J=9.5Hz), 4.97 (dd, 1H, J=19Hz, J= 2.1Hz), 5.21 (dd, 1H, J=12.5, J=2.1Hz), 5.81-6.03 (dt, 1H, J=9.1Hz).(Found: C, 81.59; H, 10.83. $C_{15}H_{24}O$ requires C, 81.76; H, 10.98).

(±)-(1α,2β,4aβ,8aα)-Decahydro-1-ethenyl-2,5,5,8a-tetramethyl-2-naphthalenol 11.

A solution of **10** (0.35g, 1.59mmol) in dry ether (5ml) was added to the solution of Grignard reagent prepared from Mg (60mg, 2.52mmol) and methyl iodide (0.157ml, 2.52mmol) in dry ether (10ml). The mixture was stirred for 2h at room temperature, then quenched by careful addition of aqueous NH_4Cl and extracted with ether (3 x 20ml). The dried organic extracts were concentrated in vacuum and the residue purified by column chromatography (eluent: ether : light petroleum 1:9) to afford **11** (0.3g, 80%), as a white solid, mp. 40-41°C (n-pentane). IR: 3560, 1650 cm^{-1}; ^{1}H NMR: δ 0.85 (s, 3H), 0.88 (s, 3H), 1.04 (s, 3H), 1.07 (s, 3H), 1.09-1.99 (m, 12H), 4.98 (dd, 1H, J=17Hz, J=2.4Hz), 5.18 (dd, 1H, J=10.3Hz, J= 2.5Hz), 5.77-5.99 (dt, 1H, J=8.1Hz).(Found: C, 81.19; H, 11.83. $C_{16}H_{28}O$ requires C, 81.29; H, 11.94).

(±)-(1α,2β,4aβ,8aα)-Decahydro-2-hydroxy-2,5,5,8a-tetramethyl-1-naphthaleneethanol 12.

A solution of **11** (0.3g, 1.27mmol) in THF (6ml) under argon was cooled to 0°C and treated with borane methyl sulfide (0.6ml, 6mmol). The reaction mixture was allowed to warm to 25°C and was stirred for 3h. The reaction mixture was treated sequentially with water (1.5ml), 2N NaOH (1.5ml), and 30% aqueous hydrogen peroxide (1ml). The reaction mixture was stirred for 16h to room temperature, then poured onto saturated aqueous NaCl (20ml). The mixture was extracted with ether (3x20ml), the combined extracts dried and evaporated in vacuum. The residue was purified by column chromatography (eluent: ether : light petroleum 1:9) to afford **12** (0.28g, 87%), as a white solid, mp. 169-170°C (EtOAc); lit [17]: mp. 168-170°C. IR: 3600, 3450 cm^{-1}; ^{1}H NMR: δ 0.83 (s, 3H), 0.87 (s, 3H), 0.98 (s, 3H), 1.14 (s, 3H), 0.89-1.86 (m, 16H), 3.55-3.65 (m, 2H).(Found: C, 74.89; H, 11.83. $C_{16}H_{30}O_2$ requires C, 75.04; H, 11.89).

Acknowledgment. We gratefully acknowledge the "Progetto Finalizzato Chimica Fine e Secondaria II" and Ministero Pubblica Istruzione (Fondi 40% and 60%) for generous support.

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(*Received in UK* 10 *April* 1995; *revised* 5 *June* 1995; *accepted* 9 *June* 1995)