110. The Synthesis of Racemic *Ambrox*®

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Dedicated to Dr. *Günther Ohloff* on the occasion of his 65th birthday

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(±)-*Ambrox* (**10**), the racemic form of (−)-*Ambrox*®, the commercially most important ambergris odorant has been synthesized from a readily available bicyclic keto ester in five steps. The racemic ether retains the characteristic scent of fine-quality ambergis, and the odor threshold of the racemate and the (−)-enantiomer prepared from natural sclareol were found to be essentially identical.

Introduction. – The remarkably unique, complex, and fascinating odor of ambergris has been given much consideration by both perfumers and chemists. Early work on the nature of the odoriferous constituents of ambergris was summarized in the classic article by *Lederer* [1]. More recent developments, including the discovery of *Ambrox*®[1]) [2], the commercially most important of the ambergris fragrance chemicals, were reviewed by *Ohloff* [3]. *Ambrox*® ((−)-**10**[1]) is produced, on a technical scale, by degradation of natural sclareol, usually of Russian origin, using both CrO_3 and $KMnO_4$ oxidation in a multistep synthesis. An aesthetically more pleasing and more practicable two-step synthesis proceeds *via* β-cleavage of an alkoxy radical [4]. In seeking to expand the availability and the market for *Ambrox*®, we became attracted to the possibility of replacing the optically active material with the previously unknown racemic substance **10**[1]).

Results and Discussion. – The bicyclic β-keto ester **3**, known since 1957 [5a] and subsequently also prepared by others [5b–d], was chosen as starting material. It was synthesized by stannic chloride mediated cyclization of the monocyclic β-keto ester **2** which we prepared by condensation of dihydro-β-ionone **1** [6] with dimethyl carbonate and NaH[2])[3]) rather than by alkylation of the dianion of methyl acetoacetate with β-cyclogeranyl bromide [5b–d]. Attempted *C*-alkylation of **3** failed [5b–d], but we found *O*-allylation to be a facile process. The resulting crude allyl ether **4** when heated in boiling xylene afforded a *C*-substituted β-keto ester **5**, probably with the configuration indicated. Demethoxycarbonylation to a mixture of the desired isomer **6** (86%) and its epimer **7** (14%)[4]) was accomplished in DMSO solution with $CaCl_2 \cdot 2H_2O$ [7][5]). No efforts were

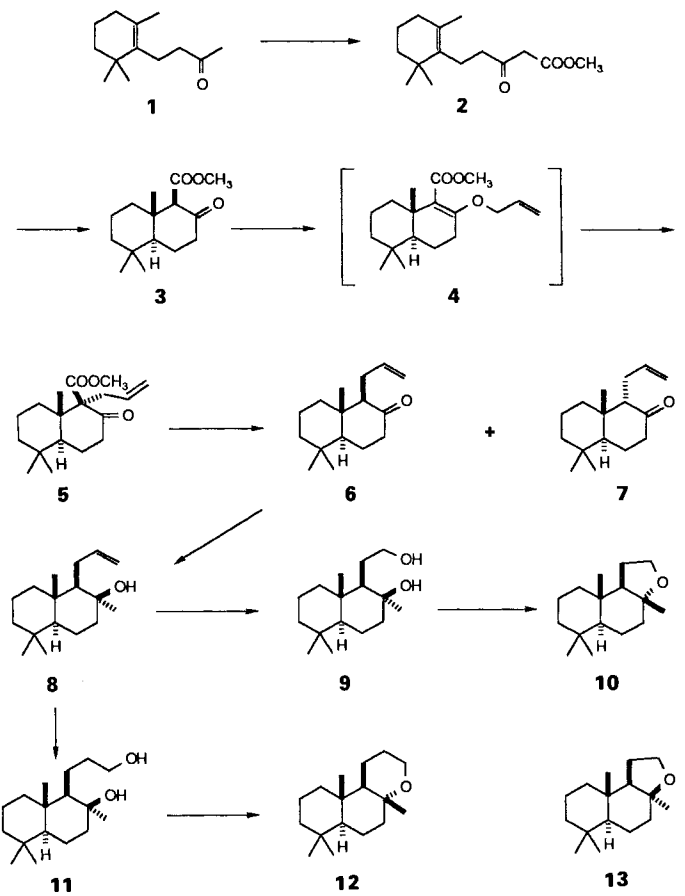
[1]) Trade name of *Firmenich SA*. All compounds synthesized in this work are racemic.

[2]) Dr. *R.L. Snowden* (*R.L.S.*) and Mr. *S. Linder* (*S.L.*), *Firmenich SA*, Geneva, have scaled up the synthesis of racemic *Ambrox* described in this paper, and made some modifications which led to improved yields. We thank these investigators for their kind exchange of information.

[3]) The β-keto ester **2** was available in > 90% yield when NaH was replaced by NaOMe[2]).

[4]) The undesired epimer **7** was first isolated and characterized by *R.L.S.* and *S.L.*[2]).

[5]) Due to the thermal instability of DMSO, *R.L.S.* and *S.L.* replaced this solvent with *N*-methylpyrrolidin-2-one and obtained the same mixture of **6** and **7** in 91% yield[2]).



made to effect *Claisen* rearrangement and demethoxycarbonylation in a single operation by treating the allyl vinyl ether **4** with $CaCl_2$ in DMSO in view of the result obtained with the corresponding ethyl ester[6]). To continue with the synthesis of (±)-*Ambrox*®, one C-atom had to be added to the decalin ring and a second removed from the side chain. To this end, ketone **6** was condensed with MeMgI, and the resulting alcohol **8** exposed consecutively to ozone and to $NaBH_4$[7]). Racemic diol **9** appears to be identical with a product prepared by a totally different synthesis [8].

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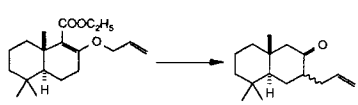
[6]) Interestingly, the ethyl ester **i** when heated in DMSO containing $CaCl_2 \cdot 2H_2O$ afforded ketone **ii**, clearly derived from the isomeric allyl vinyl ether followed by *Claisen* rearrangement and deethoxycarbonylation.



[7]) In larger-scale preparations, *R.L.S.* and *S.L.* found it practical to effect this transformation in two steps. Ozonization in MeOH followed by reduction with $NaBH_4$ at −60° afforded a crystalline lactol (m.p. 83–85°) which was subsequently reduced to diol **9** with $LiAlH_4$ in Et_2O. In this manner, the yield from **8** to **9** was improved from 62 to 88%[2]).

Not surprisingly, the dehydration of diol **9** to (±)-*Ambrox* (**10**) turned out to be the technically most difficult step in the synthesis. In earlier work, it was firmly established that *Ambrox*® ((−)-**10**) with *trans*-fused tetrahydrofuran ring, can be isomerized by acids to *Iso-ambrox* ((+)-**13**) with *cis*-fused heterocyclic ring demonstrating that the latter is the thermodynamically preferred isomer [2]. On the supposition that equatorial rather than axial approach to the tertiary carbenium ion should be favored for steric reasons, conditions for cyclization to the kinetically controlled diastereoisomer had to be found. Consequently, diol **9** was submitted to a number of protic and *Lewis* acids in a variety of solvents. The method of choice involves heating the diol **9** in nitromethane in the presence of a catalytic amount of *p*-toluenesulfonic acid[8]). Under these conditions, the formation of *Iso-ambrox* (**13**) was suppressed to a large measure and (±)-*Ambrox* (**10**) produced in 75% yield.

To prepare the homologous tetrahydropyran, olefin **8** was transformed to diol **11** by hydroboration-oxidation. Cyclization to **12** was again affected with *p*-toluenesulfonic acid in nitromethane. The spectra of the racemic ether **12** were found to be identical with those of the levorotatory substance prepared from natural ambrein [9].

The odor threshold values of the optically active *Ambrox*® (from degradation of sclareol) and of (±)-*Ambrox* were found to be essentially identical (0.26 ppb). The homologous ether **12** displays a much weaker scent, with a threshold value of 15 ppb[9]).

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Experimental Part

Methyl 3-Oxo-5-(2',6',6'-trimethylcyclohex-1'-enyl)pentanoate (**2**). A mixture of 78.4 g (0.4 mol) of **1**, 19.2 g (0.8 mol) of NaH 72 g (0.8 mol) of dimethyl carbonate, and 400 ml of DMF under Ar was stirred for 2 h at 5–10°, followed by 2 h at 20°. The mixture was poured into ice-water containing 60 ml of AcOH extracted with Et_2O, dried (Na_2SO_4), evaporated, and distilled to give 57.7 g (57%) of **2**. B.p. 118–122°/0.05 Torr. IR ($CHCl_3$): 1740, 1710, 1650, 1620. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*s*, 6 H); 1.55 (*s*, 3 H); 1.55 (*s*, 3 H); 1.0–2.8 (*m*, 10 H); 3.25 (*s*, 2 H); 3.6 (*s*, 3 H).

Methyl Perhydro-5,5,8aβ-trimethyl-2-oxo-trans-*naphthalene-1β-carboxylate* (**3**). $SnCl_4$ (29 ml, 0.25 mol) was added, at 5–10°, to a stirred soln. of 57.7 g (0.23 mol) of **2** in 600 ml of CH_2Cl_2. Stirring was continued for 30 min at 5° and 6 h at 20°. The mixture was washed with 1 portion of cold H_2O, dried (Na_2SO_4), and evaporated. The remaining oil in hexane was treated with activated charcoal and allowed to crystallize at −20° to yield 35.2 g (61%) of **3**. M.p. 86–88° ([5b]: 85.5–87°). IR ($CHCl_3$): 1740, 1700. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*s*, 3 H); 0.95 (*s*, 3 H); 1.1 (*s*, 3 H); 1.0–2.5 (*m*, 11 H); 3.0 (*s*, 1 H); 3.6 (*s*, 3 H). ^{13}C-NMR: 205.5 (*s*); 168.7 (*s*); 70.0 (*d*); 53.3 (*d*); 51.4 (*q*); 42.0 (*s*); 41.9 (*t*); 41.3 (*t*); 39.2 (*t*); 33.5 (*s*); 33.5 (*q*); 23.1 (*t*); 21.7 (*q*); 18.6 (*t*); 14.8 (*q*). MS: 252 (8, $C_{15}H_{24}O_3^{+\cdot}$), 234 (21), 219 (23), 205 (27), 136 (100), 129 (57), 123 (54), 116 (88), 109 (48), 95 (60), 81 (60), 69 (88).

Methyl 1-Allylperhydro-5,5,8aβ-trimethyl-2-oxo-trans-*naphthalene-1β-carboxylate* (**5**). To a suspension of 1.2 g (50 mmol) of NaH in 70 ml of DMF, a soln. of 12.27 g (48.7 mmol) of **3** in 30 ml of DMF was added at 5–10°. Then, the stirred mixture was allowed to warm up to 20°. After 30 min, it was cooled to 0°, and 5.2 ml (60 mmol) of allyl bromide were added. The mixture was stirred overnight at 20°, poured into cold H_2O and extracted with Et_2O. Drying (Na_2SO_4) and evaporation left 14.1 g of crude **4**. IR ($CHCl_3$): 1710, 1680. ^{1}H-NMR (60 MHz, CCl_4): 0.85 (*s*, 3 H); 0.9 (*s*, 3 H); 1.15 (*s*, 3 H); 1.0–2.3 (*m*, 11 H); 3.6 (*s*, 3 H); 4.1 (*d*, $J = 6$, 2 H); 4.8–6.1 (*m*, 3 H).

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[8]) Mr. *Christian E. Vial*, *Firmenich SA*, kindly informed us that this crucial cyclization is accomplished preferably at 30°. The resulting *Ambrox* (**10**; 73% yield) was accompanied by less than 1% of *Iso-ambrox* (**13**), and approximately 20% of a mixture of isomeric unsaturated primary alcohols, resulting from dehydration of the tertiary alcohol.

[9]) We thank Dr. *W. Pickenhagen* and his collaborators, *Firmenich SA*, for this information.

Crude **4** (14.1 g) in 80 ml of xylene was heated at reflux for 3.5 h. The solvent was evaporated, the remaining oil (GLC: 2 peaks, ratio 1:9) dissolved in 40 ml of hexane and then allowed to crystallize at −20°, yielding 8.85 g (62%) of **5**. A sample was recrystallized from AcOEt. M.p. 100–101°. IR ($CHCl_3$): 1740, 1705, 1630, 970, 920. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*s*, 3 H); 1.0 (*s*, 3 H); 1.05 (*s*, 3 H); 0.8–3.2 (*m*, 13 H); 3.6 (*s*, 3 H); 4.7–5.8 (*m*, 3 H). ^{13}C-NMR: 206.6 (*s*); 170.0 (*s*); 133.9 (*d*); 117.6 (*t*); 70.9 (*s*); 51.4 (*q*); 45.0 (*d*); 42.5 (*s*); 41.6 (*t*); 39.4 (*t*); 35.4 (*t*); 34.7 (*t*); 34.3 (*q*); 33.8 (*s*); 22.4 (*q*); 22.0 (*t*); 19.8 (*q*); 18.4 (*t*). MS: 292 (7, $C_{18}H_{28}O_3^{+\cdot}$), 259 (19), 169 (43), 156 (27), 137 (69), 123 (67), 109 (67), 95 (61), 81 (71), 55 (72), 41 (100).

*1β-Allyl-3,4,4a,5,6,7,8,8a-octahydro-5,5,8aβ-trimethyl-*trans*-naphthalen-2(1H)-one* (**6**). A stirred mixture of 7.30 g (25 mmol) of **5**, 9.4 g (62 mmol) of $CaCl_2 \cdot 2H_2O$, and 90 ml of DMSO was heated at reflux for 75 min. It was poured into H_2O, extracted with Et_2O, dried (Na_2SO_4), and evaporated. Distillation of the remaining oil gave 5.39 g of **5**/**6**/7, b.p. 100–115°/0.07 Torr. Yield of **6**: *ca.* 70%. Purification was achieved by silica-gel chromatography using hexane/AcOEt 98:2. IR ($CHCl_3$): 1700, 1630, 990, 910. ^{1}H-NMR (60 MHz, CCl_4): 0.7 (*s*, 3 H); 0.85 (*s*, 3 H); 0.95 (*s*, 3 H); 1.1–2.6 (*m*, 14 H); 4.6–5.0 (*m*, 2 H); 5.1–6.0 (*m*, 1 H). ^{13}C-NMR: 211.4 (*s*); 138.7 (*d*); 114.9 (*t*); 64.3 (*d*); 54.3 (*d*); 42.7 (*s*); 42.5 (*t*); 42.0 (*t*); 39.3 (*t*); 33.7 (*s*); 33.5 (*q*); 26.3 (*t*); 24.0 (*t*); 21.7 (*q*); 19.0 (*t*); 14.6 (*q*). MS: 234 (27, $C_{16}H_{26}O^{+\cdot}$), 219 (7), 201 (7.5), 137 (11), 123 (14), 109 (19), 96 (100).

*1β-Allylperhydro-2α,5,5,8aβ-tetramethyl-*trans*-naphthalen-2β-ol* (**8**). Ketone **6** (2.34 g, 10 mmol) in 5 ml of Et_2O was added to the *Grignard* reagent prepared from 0.36 g (15 mmol) of Mg and 0.9 ml (15 mmol) of CH_3I in 20 ml of Et_2O. The mixture was heated at reflux for 30 min, then it was decomposed with aq. NH_4Cl soln. and extracted with Et_2O. Drying (Na_2SO_4), evaporation, and distillation of the residue afforded 2.47 g (98%) of **8**. B.p. 105°/0.1 Torr. IR ($CHCl_3$): 3600, 1630, 910. ^{1}H-NMR (60 MHz, CCl_4): 0.85 (*s*, 6 H); 0.9 (*s*, 3 H); 1.05 (*s*, 3 H); 0.7–2.2 (*m*, 15 H); 4.6–5.0 (*m*, 2 H); 5.2–5.9 (*m*, 1 H). ^{13}C-NMR: 142.0 (*d*); 113.7 (*t*); 73.4 (*s*); 58.6 (*d*); 56.0 (*d*); 42.5 (*t*); 42.0 (*t*); 39.4 (*t*); 39.0 (*s*); 33.5 (*q*); 33.3 (*s*); 31.0 (*q*); 29.4 (*t*); 21.7 (*q*); 18.3 (*t*); 18.2 (*t*); 15.1 (*q*). MS: 250 (0.7, $C_{17}H_{30}0^{+\cdot}$), 235 (6), 192 (19), 177 (76), 137 (32), 121 (35), 109 (90), 95 (92), 81 (86), 69 (97), 55 (87), 43 (100).

*Perhydro-1β-(2-hydroxyethyl)-2α,5,5,8aβ-tetramethyl-*trans*-naphthalen-2β-ol* (**9**). A soln. of 2.47 g (9.9 mmol) of **8** in 60 ml of MeOH was ozonized at −20 to −30°. It was then cooled to −60°, 1 g of $NaBH_4$ was added, and the stirred mixture was allowed to warm up to r.t. Most of the MeOH was evaporated, H_2O was added and the mixture extracted with Et_2O. Evaporation left a residue which was crystallized from AcOEt to afford 1.55 g (62%) of **9**. M.p. 168–170°. IR ($CHCl_3$): 3600, 3450. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.83 (*s*, 3 H); 0.87 (*s*, 3 H); 0.98 (*s*, 3 H); 1.14 (*s*, 3 H); 0.8–1.8 (*m*, 16 H); 3.57–3.66 (*m*, 2 H). ^{13}C-NMR: 73.0 (*s*); 65.0 (*t*); 55.9 (*d*); 54.7 (*d*); 42.3 (*t*); 42.0 (*t*); 39.4 (*t*); 38.8 (*s*); 33.4 (*q*); 33.3 (*s*); 30.7 (*q*); 28.7 (*t*); 21.7 (*q*); 18.3 (*t*); 18.2 (*t*); 15.1 (*q*). MS: 254 (1, $C_{16}H_{30}O_2^{+\cdot}$), 239 (3.4), 221 (17), 195 (32), 177 (62), 151 (38), 137 (32), 123 (41), 109 (100), 95 (85).

*Perhydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan* (= (±)-*Ambrox*; **10**). A stirred mixture of 640 mg (2.5 mmol) of **9**, 20 mg of TsOH, and 50 ml of nitromethane was heated at 80° (oil-bath temp.) for 75 min. It was diluted with Et_2O, washed with $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated. The remaining oil was chromatographed on silica gel. Hexane/AcOEt 98:2 eluted 446 mg (75%) of pure **10** which was sublimed. M.p. 83–84°. Identical in retention time, IR, ^{1}H-NMR, and MS with authentic *Ambrox*® ((−)-**10**). IR ($CHCl_3$): 1450, 1385, 995, 970. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.84 (*s*, 6 H); 0.88 (*s*, 3 H); 1.09 (*s*, 3 H); 0.93–2.00 (14 H); 3.85 (*dd*, J = 16, 7, 1 H); 3.95 (*m*, 1 H). ^{13}C-NMR: 79.9 (*s*); 65.0 (*t*); 60.2 (*d*); 57.3 (*d*); 42.5 (*t*); 40.0 (*t*); 39.8 (*t*); 36.2 (*s*); 33.6 (*q*); 33.1 (*s*); 22.6 (*t*); 21.2 (2 *q*); 20.7 (*t*); 18.4 (*t*); 15.1 (*q*). MS: 236 (2.2, $C_{16}H_{28}O^{+\cdot}$), 221 (100), 203 (6), 177 (7), 137 (47), 109 (18), 97 (64), 81 (30).

*Perhydro-1β-(3-hydroxypropyl)-2α,5,5,8aβ-tetramethyl-*trans*-napthalen-2β-ol* (**11**). To an ice-cold soln. of 2.42 g (9.7 mmol) of **8** in 50 ml of THF were added 9.7 ml (9.7 mmol) of 1M diborane/THF. The mixture was allowed to slowly warm up to r.t. overnight. It was cooled to 0°, then 1 ml of 5N NaOH and 5 ml of 30% H_2O_2 soln. were added. After 1 h of stirring at 20°, the mixture was poured into H_2O, extracted with Et_2O, dried (Na_2SO_4), and evaporated. Crystallization of the residue from AcOEt yielded 1.58 g (61%) of **11**. M.p. 147–148°. IR ($CHCl_3$): 3620. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.8 (*s*, 3 H); 0.85 (*s*, 3 H); 0.95 (*s*, 3 H); 1.1 (*s*, 3 H); 1.0–1.9 (*m*, 18 H); 3.6 (*t*, J = 7, 2 H). MS: 268 (2, $C_{17}H_{32}O_2^{+\cdot}$), 177 (22), 137 (17), 115 (58), 109 (95), 95 (76), 81 (80), 71 (100).

*Perhydro-4a,7,7,10a-tetramethylnaphtho[2,1-*b*]pyran* (**12**) was prepared from 1.80 g (6.7 mmol) of **11**, 50 mg of TsOH, and 100 ml of nitromethane (1 h at 80°) and worked up as described for **9** → **10**: 0.98 g (59%) of **12**, which was crystallized from MeOH. M.p. 74–75°. ^{1}H-NMR (60 MHz, $CDCl_3$): 0.76 (*s*, 3 H); 0.80 (*s*, 3 H); 0.87 (*s*, 3 H); 1.25 (*s*, 3 H); 0.8–1.9 (*m*, 16 H); 3.6 (*t*, J = 6, 2 H). ^{13}C-NMR (270 MHz, $CDCl_3$): 15.6, 18.1; 18.5; 19.9; 21.3; 27.6; 33.2; 33.3; 36.8; 38.9; 41.9, 42.0; 56.4; 57.8; 60.8; 74.6. Both spectra were identical with those reported in [9].

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