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A Formal Synthesis of (±)-*Ambrox*®

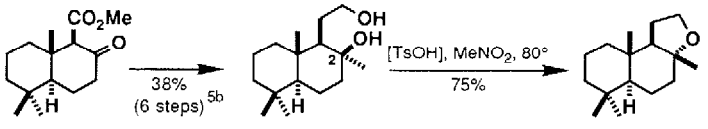
Roger L. Snowden* and Simon M. Linder

Firmenich SA, Research Laboratories, 1211 Geneva 8, Switzerland

Key Words ambergris, Ambrox, drimane, tetrahydrofuran, decalin

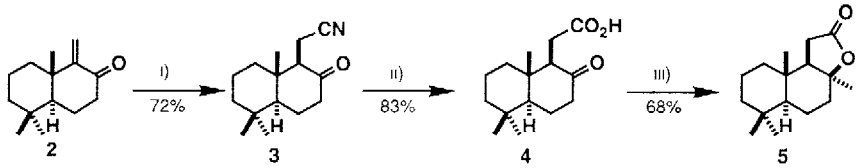
Abstract: Bicyclic diol **6**, a direct precursor of (±)-*Ambrox*® ((±)-**7**), has been synthesised in four steps (35% yield) from the known bicyclic enone **2**.

The unique organoleptic properties of ambergris have attracted considerable synthetic interest in its numerous odoriferous constituents [1] In particular, the norlabdane oxide ( )-**7** (*Ambrox*® [2]), the commercially most important constituent, is available by oxidative degradation of natural sclareol, either by classical oxidation methods [3] or *via* β-cleavage of an alkoxy radical [4] More recently, the limited availability of sclareol has led to efforts directed towards the synthesis of (±)-**7** [5], whose odour closely resembles that of the optically active material We now describe a formal synthesis of (±)-**7**, which involves an alternative access to the bicyclic diol **6**, the direct precursor of (±)-**7** in a recent approach starting from β-keto ester **1** [5b]



1 **6** **7**

Our synthetic route starts from the known bicyclic enone **2** [6] Using conditions described for a closely related system [7a], 1,4-addition of a C_1 moiety was effected with KCN and NH_4Cl in aqueous DMF, and stereoselectively furnished the more stable cyano ketone **3** (m p 82 - 83° [7]), with an equatorial cyanomethyl group, in 72% yield [8] Hydrolysis of the nitrile group with KOH in aqueous MeOH then gave keto acid **4** (m p 109-111° [9] 83%), whose subsequent treatment with MeLi (2 mol-equiv) resulted in stereoselective equatorial attack on the carbonyl group, to afford an intermediate hydroxy acid, immediately cyclised, under acid catalysis, to the *cis*-fused γ-lactone **5** (m.p 77 -



2 **3** **4** **5** **6**

i) KCN, NH_4Cl, DMF-H_2O, r.t ; ii) KOH, MeOH-H_2O, reflux, iii) MeLi, THF-Et_2O, -60° → r t then [TsOH], toluene, reflux, iv) $LiAlH_4$, Et_2O, r t

78° [10] 68%) Finally, reduction of **5** with $LiAlH_4$ in Et_2O furnished **6** (m p. 167-168° 85%), identical in all respects with an authentic sample [5b]

REFERENCES AND NOTES

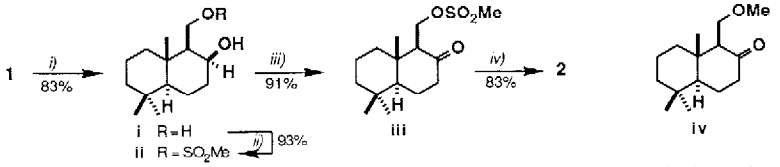
1. Ohloff, G. in *Fragrance Chemistry*, ed. E. T. Theimer, Academic Press, New York, **1982**, p. 535.
2. Tradename of *Firmenich SA*. All compounds described in this work are racemic; analytical data of **2** - **5**:

   2: ^{1}H-NMR: 0.84 (*m*, 1H); 0.92 (*s*, 3H); 0.96 (*s*, 3H); 1.01 (*s*, 3H); 1.01 (*s*, 3H); 1.23 (*m*, 1H); 1.30–2.20 (7H); 2.33 (*ddd*, *J*=16.5, 12.5, 8, 1H); 2.66 (*ddd*, *J*=16.5, 5.5, 2, 1H); 5.00 (*s*, 1H); 5.53 (s, 1H). ^{13}C-NMR: 204.1 (*s*); 159.1 (*s*); 113.5 (*t*); 50.5 (*d*); 41.9 (*t*); 40.9 (*t*); 40.6 (*s*); 37.6 (*t*); 33.8 (*s*); 33.3 (*q*); 22.0 (*q*); 21.4 (*q*); 20.7 (*t*); 18.8 (*t*). MS: 206 (24, $M^{+\cdot}$), 191 (42), 178 (57), 163 (96), 149 (61), 135 (78), 122 (100), 109 (93), 95 (66), 79 (70).

   3: ^{1}H-NMR: 0.72 (*s*, 3H); 0.87 (*s*, 3H); 1.00 (*s*, 3H); 1.22–1.73 (8H); 2.10 (*m*, 1H); 2.23 (*dd*, *J*=16, 4, 1H); 2.38 (*ddd*, *J*=14, 14, 7, 1H); 2.56 (*m*, 1H); 2.58 (*dd*, *J*=7, 4, 1H); 2.72 (*dd*, *J*=16, 7 1H). ^{13}C-NMR: 208.1 (*s*); 120.0 (*s*); 60.6 (*d*); 53.7 (*d*); 42.2 (*s*); 41.6 (*t*); 41.4 (*t*); 39.4 (*t*); 33.7 (*s*); 33.4 (*q*); 23.4 (*t*); 21.7 (*q*); 18.7 (*t*); 14.1 (*q*); 11.0 (*t*). MS: 233 (12, $M^{+\cdot}$), 218 (17), 150 (24), 137 (100), 123 (77), 109 (31), 95 (50), 81 (65), 69 (95).

   4: ^{1}H-NMR (+D_2O): 0.74 (*s*, 3H); 0.87 (*s*, 3H); 0.99 (*s*, 3H); 1.25 (*m*, 2H); 1.40-1.75 (6H); 2.07 (*m*, 1H); 2.26 (*m*, 1H); 2.39 (*m*, 1H); 2.48 (*m*, 1H); 2.74 (*m*, 2H). ^{13}C-NMR: 210.6 (*s*), 179.2 (*s*); 59.7 (*d*); 53.9 (*d*); 41.9 (*t*); 41.5 (*t*); 41.5 (*s*); 39.2 (*t*); 33.7 (*s*); 33.5 (*q*); 27.6 (*t*); 23.5 (*t*); 21.7 (*q*); 18.9 (*t*); 14.9 (*q*). MS: 252 (5, $M^{+\cdot}$), 234 (15), 219 (38), 137 (62), 109 (61), 95 (64), 81 (85), 69 (76), 55 (100).

   5: ^{1}H-NMR: 0.87 (*s*, 3H); 0.91 (*s*, 3H); 0.92 (*s*, 3H); 1.16 (*m*, 1H); 1.32 (*s*, 3H); 1.35-1.65 (9H); 1.76 (*d*, *J*=7, 1H); 2.31 (*m*, 1H); 2.38 (*d*, *J*=18, 1H); 2.73 (*dd*, *J*=18, 7, 1H). ^{13}C-NMR: 177.8 (*s*); 85.7 (*s*); 54.7 (*d*); 51.5 (*d*); 41.7 (*t*); 40.8 (*t*); 36.0 (*s*); 35.1 (*t*); 33.6 (*q*); 32.9 (*s*); 32.4 (*t*); 30.0 (*q*); 22.2 (*q*); 18.3 (*t*); 18.0 (*t*); 14.6 (*q*). MS: 250 (1, $M^{+\cdot}$), 235 (14), 136 (100), 121 (43), 109 (24), 95 (29), 81 (55), 69 (46).
3. I. C. Coste-Manière, J. P. Zahra, B. Waegell, *Tetrahedron Lett.* **1988**, *29*, 1017 and ref. cited therein.
4. a) R. Decorzant, C. Vial, F. Näf, G. Whitesides, *Tetrahedron* **1987**, *43*, 1871; b) P. A. Christenson, *ibid.* **1988**, *44*, 1925.
5. a) T. Kawanobe, K. Kogami, M. Matsui, *Agric. Biol. Chem.* **1986** *50*, 1475; b) G. Büchi, H. Wüest, *Helv. Chim. Acta* **1989**, *72*, 996; c) P. F. Vlad, N. D. Ungur, V. B. Perutskii, *Khim. Geterotsikl. Soedin. Sb.* **1990**, *26*, 896.
6. For example, *cf.* E. Romann, A. J. Frey, P. A. Stadler, A. Eschenmoser, *Helv. Chim. Acta* **1957**, *40*, 1900; in our hands,



i) $LiAlH_4$, Et_2O, r.t.; *ii*) $MeSO_2Cl$, pyridine, 0°; *iii*) PCC, NaOAc, CH_2Cl_2, r.t.; *iv*) DBN, toluene, r.t.

the reported conditions for the final elimination step of **iii** to **2**, employing MeONa in MeOH/benzene 1:1 at r.t., afforded **2** (80%) contaminated with methoxy ketone **iv** (15%), resulting from 1,4-addition of MeOH to **2**. An alternative procedure, which avoids the formation of **iv**, involves treatment of **iii** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN: 1.5 mol-equiv.) in toluene at r.t. to give **2** in 83% yield. For NMR data ($CDCl_3$) of **i**-**iv**:

   i: ^{1}H-NMR ($DMSO_{d6}$ + D_2O): 0.81 (*s*, 3H); 0.85 (*s*, 3H); 0.93 (*s*, 3H); 0.80–0.95 (2H); 0.98 (*m*, 1H); 1.13 (*m*, 1H); 1.30–1.60 (6H); 1.70 (br. *d*, *J*=12, 1H); 1.81 (*m*, 1H); 3.52 (*m*, 2H); 3.98 (*m*, 1H). ^{13}C-NMR: 68.7 (*d*); 61.0 (*t*); 56.0 (*d*); 55.6 (*d*); 42.1 (*t*); 39.8 (*t*); 37.4 (*s*); 35.5 (*t*); 33.8 (*q*); 33.3 (*s*); 21.8 (*q*); 18.3 (*t*); 17.2 (*t*); 17.1 (*q*).

   ii: ^{1}H-NMR (+D_2O): 0.86 (*s*, 3H); 0.89 (*s*, 3H); 1.03 (*s*, 3H); 0.89 (*m*, 1H); 1.07 (*m*, 1H); 1.17 (*m*, 1H); 1.35–1.66 (8H); 1.69 (*m*, 1H); 1.96 (*m*, 1H); 3.03 (*s*, 3H); 4.10 (br. *s*, 1H); 4.37 (*dd*, *J*=10, 4, 1H); 4.51 (*dd*, *J*=10, 10, 1H). ^{13}C-NMR 68.4 (*t*); 65.9 (*d*); 55.6 (*d*); 53.1 (*d*); 41.8 (*t*); 39.8 (*t*); 37.2 (*q*), 37.2 (*s*), ; 35.0 (*t*); 33.7 (*q*); 33.3 (*s*); 21.8 (*q*); 18.2 (*t*); 16.9 (*t*); 16.7 (*q*).

   iii: ^{1}H-NMR: 0.77 (*s*, 3H); 0.86 (*s*, 3H); 0.99 (*s*, 3H); 1.15–1.80 (8H); 2.11 (*m*, 1H); 2.37 (*m*, 1H); 2.50 (*m*, 1H); 2.56 (*m*, 1H); 3.07 (*s*, 3H); 4.24 (*dd*, *J*=11, 3.5, 1H); 4.57 (*dd*, *J*=11, 10, 1H). ^{13}C-NMR: 208.8 (*s*); 65.0 (*t*); 62.4 (*d*); 53.9 (*d*); 42.1 (*s*); 42.0 (*t*); 41.7 (*t*); 39.3 (*t*); 37.1 (*q*); 33.7 (*s*); 33.5 (*q*); 23.8 (*t*); 21.7 (*q*); 18.8 (*t*); 15.6 (*q*).

   iv: ^{1}H-NMR: 0.74 (*s*, 3H); 0.86 (*s*, 3H); 0.97 (*s*, 3H); 1.20–1.75 (7H); 1.77 (br. *d*, *J* = 14, 1H); 2.06 (*m*, 1H); 2.36 (*m*, 2H); 2.45 (*m*, 1H); 3.32 (*s*, 3H); 3.35 (*dd*, *J* = 9, 4, 1H); 3.81 (*dd*, *J* = 9, 8, 1H). ^{13}C-NMR: 210.5 (*s*); 66.6 (*t*); 64.0 (*d*); 58.8 (*q*); 54.1 (*d*); 42.3 (*t*); 42.0 (*t*); 42.0 (*s*); 39.3 (*t*); 33.7 (*s*); 33.5 (*q*); 24.0 (*t*); 21.7 (*q*); 19.0 (*t*); 15.4 (*q*).
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8. Using a different synthetic approach, the preparations of (–)-**3** and (+)-**3** have recently been reported; their respective conversions to (–)-**7** and (+)-**7** *via* the enantiomers of the C(2)-epimer of **6** have also been described. See: K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1990**, 361.
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