18. Conformation-Odor Relationships in Norlabdane Oxides

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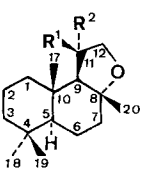
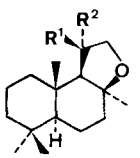
Conformational factors have been found responsible for the dramatic change in odor between (−)-deoxyambreinolide (**12**) and its (+)-epi derivative **13**. The presumably molecular event during the receptor interaction has been simulated by the diastereoisomeric 11-methyl-*ambrox* derivatives **3** and **5** as model compounds.

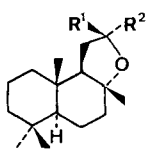
The sensory properties of ambergris odorants [1] and structurally related labdanoid derivatives [2] [3] greatly depend on their conformation, which has been defined in the 'triaxial rule' [2–4]. During our investigations, we discovered in the tricyclic ethers **12** and **13** a pair of diastereoisomers in which the 'triaxial rule' seemed to be perfectly fulfilled. While the ambergris tonality in the (−)-deoxyambreinolide (**12**) reached the highest perfection, its diastereoisomer **13** was odorless [1]. This drastic effect was the more



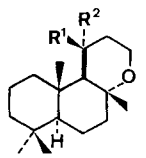
1 $R^1 = R^2 = H$
3 $R^1 = H$; $R^2 = CH_3$
5 $R^1 = CH_3$; $R^2 = H$
7 $R^1 = R^2 = CH_3$



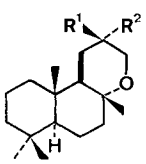
2 $R^1 = R^2 = H$
4 $R^1 = H$; $R^2 = CH_3$
6 $R^1 = CH_3$; $R^2 = H$



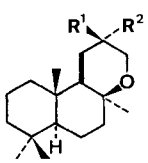
8 $R^1 = H$; $R^2 = CH_3$
9 $R^1 = CH_3$; $R^2 = H$



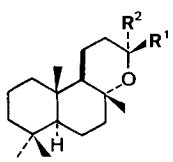
10 $R^1 = H$; $R^2 = CH_3$
11 $R^1 = CH_3$; $R^2 = H$



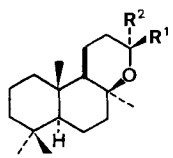
12 $R^1 = R^2 = H$
14 $R^1 = H$; $R^2 = CH_3$
16 $R^1 = CH_3$; $R^2 = H$
18 $R^1 = R^2 = CH_3$



13 $R^1 = R^2 = H$
15 $R^1 = H$; $R^2 = CH_3$
17 $R^1 = CH_3$; $R^2 = H$



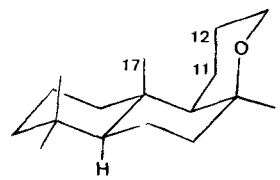
19 $R^1 = H$; $R^2 = CH_3$
21 $R^1 = CH_3$; $R^2 = H$



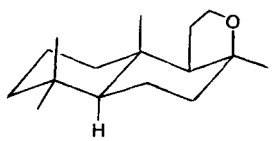
20 $R^1 = H$; $R^2 = CH_3$
22 $R^1 = CH_3$; $R^2 = H$

surprising as the lower homologs **1** and **2** showed qualitatively a similar odor, although (+)-*Isoambrox* (**2**) was a hundred times weaker than (−)-*Ambrox*® (**1**)[1]). An explanation for this discrepancy could simply be the fact that in ether **13** the molecular limit of odor perception in this series of odorants has been reached. Examination of molecular models, however, revealed that a striking difference in the conformation of the ether rings of **2** and **13** could be responsible for this phenomenon. Whereas the tetrahydropyran ring of **13** is clearly in a chair conformation (see **13a**) with the C(11)-C(12) bond parallel to the CH_3(17) group and thus in a 1,3-diaxial situation, the same bonds are at a marked angle in the tetrahydrofuran derivative **2** (see **2a**).

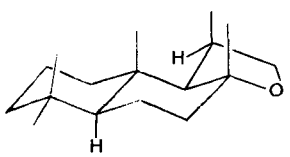
If this different odor effect indicated a stereochemical phenomenon during the receptor interaction, this process ought to be simulated by the introduction of a β-oriented CH_3 group at C(11) in *Ambrox*® (**1**). Indeed, conformation **5a** shows that the 11β-methyl-*ambrox* (**5**) simulates the spatial arrangement of the C(11)-C(12) bond in **13a**. The 11α-derivative **3a** does not reflect this situation. Tricyclic ether **5** is in fact an odorless compound, whereas diastereoisomer **3** has a distinct ambergris odor, the intensity of which lies between (−)-*Ambrox*® (**1**) [5] and (−)-deoxyambreinolide (**12**). As expected, the dimethyl derivative **7**, containing the two conformational features of **3** and **5**, is odorless.



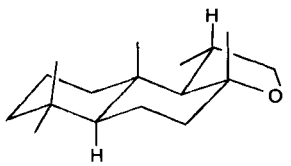
13a



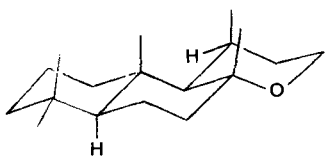
2a



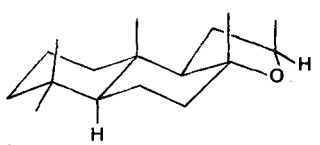
5a



3a



11a



9a

The methyl homologs **4** and **6** derived from (−)-*isoambrox* (**2**) show a similar sensory situation. Thus, the 11β-compound **6** is odorless, and the diastereoisomer **4** has an odor corresponding to the unsubstituted compound **2**. The same molecular situation as found in ethers **3a** and **5a** is created in **11** see (**11a**), formally obtained by introduction of an axial

[1]) Measured by comparison of their threshold concentration [5].

CH_3 group at C(11) of deoxyambreinolide. This is the reason why **11** is also odorless, while its diastereoisomer **10** has the diminished odor strength of (−)-deoxyambreinolide (**12**). Neither the ethers **14, 16,** and **18** CH_3-substituted at C(12) nor the diastereoisomers **15** and **17** possess any amber odor. A differentiation of the odor only occurs again when the CH_3 substituent is connected with the C-atom of the ether O-atom as shown in the diastereoisomeric pyranyl ethers **19–22** of oriental tobacco [6]. (+)-(13*S*)-8,13-Epoxy-15,16-dinorlabdane (**19**) possesses ambergris-like odor of medium strength [2], while the diastereoisomers **20–22** are odorless. The two trinorlabdane oxides **8** and **9** incarnate the typical odor in *Ambrox*® (**1**). The latter results show that the 1,3-diaxial position of the CH_3 groups adjacent to the ether O-atom in **9** (see **9a**) and **19** has no negative effect on the receptor interaction. The steric barrier for the approach of the tricyclic ether to the active site of the hypothetical receptor molecule arises from an axial OH_3 group at C(11). This shows the central role of the axial CH_3(17) group and gives an idea of how the ligand might approach the receptor molecule. In any event, these results encourage further investigation towards a molecular design for the ideal fit of a specific receptor interaction for ambergris odorants of the *Ambrox* type.

Syntheses. – Of the twenty-two tricyclic ethers **1–22** sixteen (**3–11, 14–18,20,** and **22**) were unknown and have now been synthesized in a straightforward manner. The procedures have been adapted from the literature to readily available starting material, and the routes including all intermediates are described in the *Exper. Part.* The structures of all compounds are based on degradation products from (−)-sclareol [7] and (−)-ambrein [8] [9] and, therefore, belong to the same enantiomeric series. The synthesis of 12α- and 12β-methyl-*ambrox* (**8** and **9**, respectively) following *Scheme 3* (see *Exper. Part*) *via* stereospecific inversion at C(12) during mesylation of the corresponding diols **XIV** and **XV** is unusual, although an analogous transformation was previously found in the stereospecific preparation of the theaspirones [10].

Experimental Part

General. Prep. medium-pressure liquid chromatography was carried out on a *Jobin-Yvon Chromatospac 100.* All other instruments and anal. methods have been described in [1].

Tricyclic Oxides 3,5, and 7 from (+)-Sclareolide (I)[2]. – (+)-Sclareolide [7] (**I**; m.p. 124°, $[\alpha]_D^{20} = +48°$) was a product from *R.J. Reynolds* (USA). The mixture **II/III** could not be separated; therefore the diols **IV** and **V**, obtained pure by medium-pressure chromatography on silica gel in AcOEt, were reoxidized with Ag_2CO_3/*Celite*® [11]. (+)-*11α-Methyl-sclareolide* (= *Perhydro-1α,3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1-b]furan-2-one;* **II**). M.p. 131–132°, $[\alpha]_D^{20} = +2.63°$. IR: 1920, 1755, 1450. ^{1}H-NMR[3]): 0.84 (*s*, 3 H); 0.89 (*s*, 3 H); 0.97 (*s*, 3 H); 1.29 (*d*, *J* = 7, 3 H); 1.35 (*s*, 3 H); 1.61 (*d*, *J* = 14, 1 H); 2.62 (*dq*, *J* = 7, 14, 1 H). MS: 264 (0, M^+), 249 (2), 221 (4), 137 (5), 123 (10), 109 (10), 96 (14), 82 (100), 67 (20), 43 (22).

(+)-*11β-Methyl-sclareolide* (= *Perhydro-1β,3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1-b]furan-2-one*; **III**). M.p. 158.5–159.5°, $[\alpha]_D^{20} = +82.71°$. IR: 2920, 1755, 1460, 1390, 1010, 925. ^{1}H-NMR: 0.84 (*s*, 3 H); 0.87 (*s*, 3 H); 1.08 (*s*, 3 H); 1.44 (*d*, *J* = 8, 3 H); 1.54 (*s*, 3 H); 2.0 (*d*, *J* = 8, 1 H); 2.72 (*dq*, *J* = 8, 8, 1 H). MS: 264 (0, M^+), 249 (1), 191 (2), 164 (5), 149 (3), 135 (7), 123 (16), 109 (10), 95 (16), 82 (100), 67 (24), 55 (12), 41 (19).

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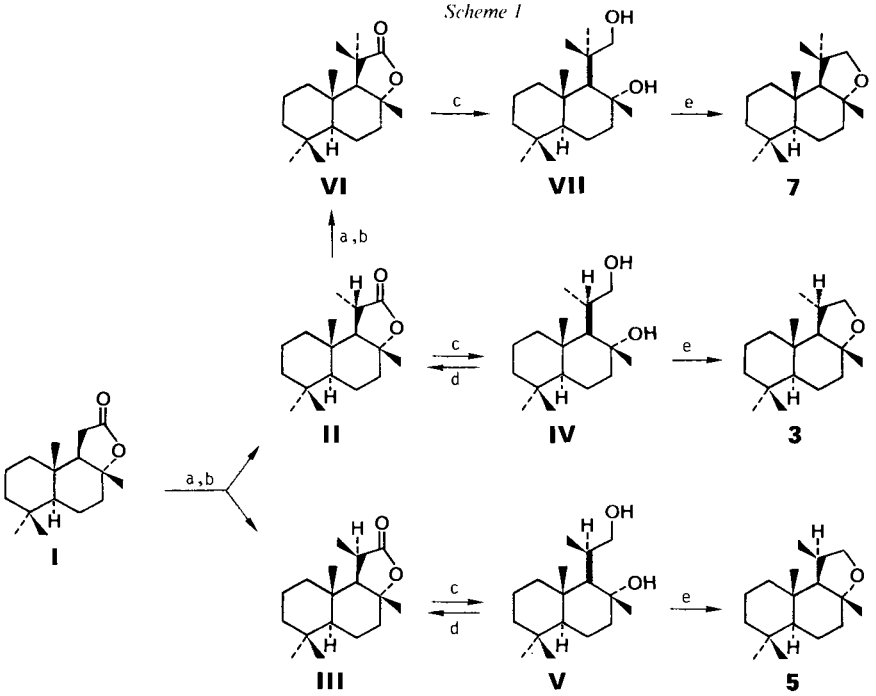
[2]) Roman numerals are used throughout for starting materials and intermediates not submitted to sensory evaluation.

[3]) The chemical shifts and the coupling constants were confirmed by decoupling techniques.

Scheme 1



a) $(i\text{-}Pr)_2NH$, BuLi, THF, 20°, 1 h; b) MeI, HMPT, 0°/30 min and 20°/30 min; c) $LiAlH_4$, Et_2O, 20°/1 h and reflux/1 h; d) Ag_2CO_3, *Celite*® [11], benzene, *Dean Stark* reflux, 1 h; e) TsCl/pyridine.

(−)-*Perhydro-1-((1S)-2-hydroxy-1-methylethyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**IV**). M.p. 144–145°, $[\alpha]_D^{20} = -9.25°$. IR: 3430, 3340, 3240, 2920, 1460, 1370, 1030. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.87 (*s*, 3 H); 0.95 (*s*, 3 H); 1.18 (*d*, *J* = 7, 3 H); 1.36 (*s*, 3 H); 2.18 (*m*, 1 H); 3.57 (*dd*, *J* = 7, 11, 1 H); 3.68 (*dd*, *J* = 4, 11, 1 H). MS: 268 (0, M^+), 250 (5), 235 (63), 191 (16), 177 (27), 163 (12), 149 (11), 137 (40), 123 (35), 109 (63), 95 (83), 81 (70), 69 (77), 55 (80), 43 (100).

(+)-*Perhydro-1-((1R)-2-hydroxy-1-methylethyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**V**). M.p. 130–131°, $[\alpha]_D^{20} = +11.66°$. IR: 3230, 1920, 1480, 1380, 1080. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.88 (*s*, 3 H); 0.93 (*s*, 3 H); 1.29 (*d*, *J* = 7, 3 H); 1.44 (*s*, 3 H); 1.46 (*d*, *J* = 1, 1 H); 2.22 (*m*, 1 H); 3.52 (*dd*, *J* = 3, 11, 1 H); 3.59 (*dd*, *J* = 4,11, 1 H). MS: 268 (0, M^+), 250 (8), 235 (17), 219 (5), 191 (17), 177 (32), 123 (38), 109 (73), 95 (87), 81 (65), 69 (94), 55 (67), 43 (100).

(−)-*11α-Methyl*-ambrox (= *Perhydro-1α,3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1-b]furan*; **3**). After repeated chromatography on silica gel in hexane and prep. GC, pure **3** was obtained. $[\alpha]_D^{20} = -60.75°$. IR: 2900, 2850, 1460, 1375, 1130, 1020, 990, 930. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.88 (*s*, 3 H); 0.90 (*s*, 3 H); 1.08 (*d*, *J* = 6, 3 H); 1.11 (*d*, *J* = 10, 1 H); 1.15 (*s*, 3 H); 2.30 (*m*, 1 H); 3.29 (*dd*, *J* = 7, 9, 1 H); 4.07 (*dd*, *J* = 9, 9, 1 H); MS: 250 (1, M^+), 235 (100), 177 (5), 161 (3), 151 (5), 137 (38), 123 (10), 111 (63), 95 (27), 82 (36), 69 (29), 55 (29), 43 (36).

(+)-*11β-Methyl*-ambrox (= *Perhydro-1β, 3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphto-[2,1-b]furan*; **5**). After chromatography and sublimation, pure **5** was obtained. M.p. 58–59°, $[\alpha]_D^{20} = +46.51°$. IR: 2920, 1450, 1385, 1010, 985, 805. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.86 (*s*, 3 H); 1.03 (*s*, 3 H); 1.19 (*d*, *J* = 7, 3 H); 1.31 (*s*, 3 H); 1.44 (*d*, *J* = 9, 1 H); 2.49 (*m*, 1H); 3.50 (*dd*, *J* = 5, 9, 1 H); 4.16 (*dd*, *J* = 9, 9, 1 H). MS: 250, (18, M^+), 235 (45), 177 (4), 165 (7), 151 (45), 137 (34), 123 (27), 111 (67), 95 (53), 81 (52), 69 (53), 55 (55), 43 (100).

(+)-*11,11-Dimethyl-sclareolide* (= *Perhydro-1,1,3aβ,6,6,9aβ-hexamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphto[2,1-b]furan-2-one*; **VI**). After prep. TLC in hexane/AcOEt 4:1 and crystallization from hexane/ET_2O, **VI**

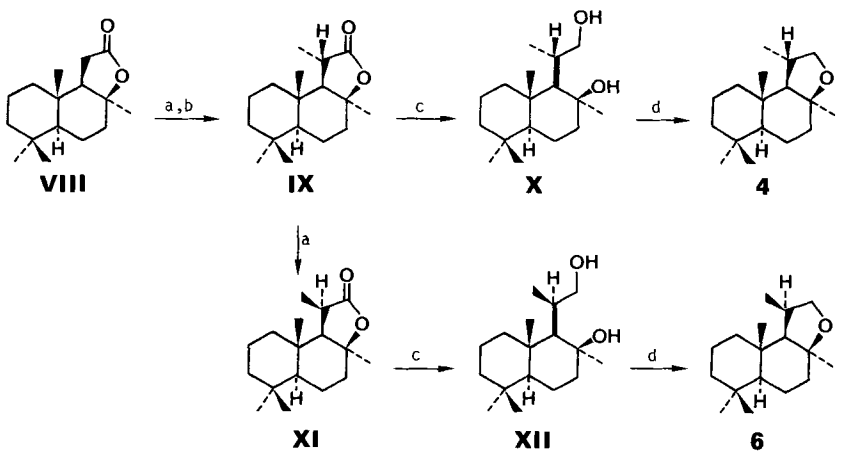
was obtained pure. M.p. 88–90°, $[\alpha]_D^{20} = +27°$ ($c = 1.1$, CH_2Cl_2). IR: 1760. ^{1}H-NMR: 0.83 (*s*, 6 H); 1.10 (*s*, 3 H); 1.37 (*s*, 6 H); 1.53 (*s*, 3 H). MS: 278 (0, M^+), 279 (2), 263 (10), 249 (6), 234 (48), 220 (19), 96 (100).

(–)-*Perhydro-1-(2-hydroxy-1,1-dimethylethyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphtol* (**VII**). After prep. TLC in hexane/AcOEt 1:1, **VII** was obtained pure. M.p. 141–142°, $[\alpha]_D^{20} = -7°$ ($c = 0.67$, CH_2Cl_2). IR (CH_2Cl_2): 3580, 3450. ^{1}H-NMR: 0.80 (*s*, 3 H); 0.86 (*s*, 3 H); 1.06 (*s*, 3 H); 1.08 (*s*, 3 H); 1.29 (*s*, 3 H); 1.44 (*s*, 3 H); 2.90 (*d*, $J = 11$, 1H); 4.0 (*d*, $J = 11$, 1H). MS: 282 (5, M^+), 264 (8), 249 (11), 234 (61), 211 (19), 177 (100).

11,11-Dimethyl-ambrox (= *Perhydro-1,1,3aβ,6,6,9aβ-hexamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan;* **7**). After prep. TLC in hexane/AcOEt 1:1 and crystallization from MeOH/H_2O, **7** was pure. M.p. 57–59°, $[\alpha]_D^{20} = 0°$ ($c = 0.62$, CH_2Cl_2). IR (CH_2Cl_2): 1380, 1010. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.86 (*s*, 3 H); 1.03 (*s*, 3 H); 1.22 (*s*, 3 H); 1.24 (*s*, 3 H); 1.32 (*s*, 3 H); 3.58 (*d*, $J = 9$, 1 H); 3.69 (*d*, $J = 9$, 1 H). MS: 264 (8, M^+), 249 (23), 177 (3), 165 (5), 137 (15), 125 (32), 108 (14), 96 (100), 81 (23), 69 (18), 55 (17), 43 (26).

Tricyclic Oxides 4 and 6 from (–)-Isosclareolide (VIII). – (–)-Isosclareolide (**VIII**) was prepared from (+)-sclareolide (**I**) following the known procedure [12] [13]. M.p. 92–93°, $[\alpha]_D^{20} = -32.7°$.

Scheme 2



a) $(i\text{-}Pr)_2NH$, BuLi, THF, 20°, 1 h; b) CH_3I, HMPT, 20°, 30 min; c) $LiAlH_4$, Et_2O, 20°, reflux, 1 h; d) TsCl/pyridine, 20°, 3.5 h; 80°, 1 h.

(–)-*11a-Methyl-isosclareolide* (= *Perhydro-1α,3aα,6,6,9aβ-pentamethyl*-cis-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan-2-one;* **IX**). Yield of **IX** from **VIII**: only 50%. After prep. TLC in hexane/AcOEt 4:1 and crystallization from Et_2O, **IX** was obtained pure. M.p. 82–85°, $[\alpha]_D^{20} = -61°$ ($c = 1.02$, CH_2Cl_2). IR (CH_2Cl_2): 1760. ^{1}H-NMR: 0.86 (*s*, 3 H); 0.92 (*s*, 6 H); 1.37 (*d*, $J = 7$, 3 H); 1.44 (*s*, 3 H); 1.49 (*d*, $J = 5$, 1 H); 2.62 (*dq*, $J = 5, 7$, 1 H). MS: 264 (4, M^+), 249 (9), 221 (7), 177 (4), 136 (100), 121 (28), 108 (22), 95 (23), 81 (37), 69 (38), 55 (21), 43 (45).

(+)-*Perhydro-1-((1S)-2-hydroxy-1-methylethyl)-2α,5,5,8aβ-tetramethyl*-trans-*2β-napthol* (**X**). Crystallization from hexane/Et_2O gave pure **X**. M.p. 180–181°, $[\alpha]_D^{20} = +19°$ ($c = 1.14$, CH_2Cl_2). IR (CH_2Cl_2): 3600, 3450. MS: 268 (0, M^+), 250 (12), 235 (8), 220 (5), 195 (81), 177 (100).

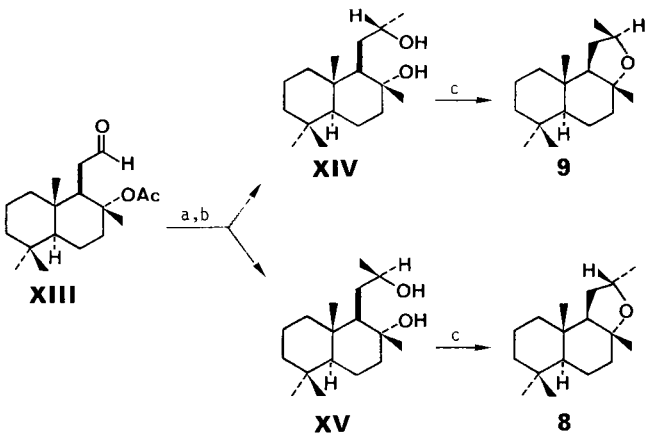
(–)-*11a-Methyl*-isoambrox (= *Perhydro-1α,3aα,6,6,9aβ-pentamethyl*-cis-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan;* **4**). Prep. TLC in hexane/AcOEt 1:1 and crystallization from MeOH/ET_2O gave pure **4**. M.p. 30–33°, $[\alpha]_D^{20} = -52°$ ($c = 1.05$, CH_2Cl_2). IR (CH_2Cl_2): 1370. ^{1}H-NMR: 0.85 (*s*, 3 H); 0.91 (*s*, 3 H); 0.92 (*s*, 3 H); 1.09 (*d*, $J = 7$, 3 H); 1.22 (*s*, 3 H); 2.21 (*m*, 1 H); 3.37 (*dd*, $J = 6, 9$, 1 H); 3.83 (*dd*, $J = 7, 9$, 1 H). MS: 250 (1, M^+), 235 (100), 177 (5), 151 (5), 137 (27), 95 (17), 81 (21), 69 (20), 55 (21), 43 (38).

Perhydro-1-((1R)-2-hydroxy-1-methylethyl)-2α,5,5,8aβ-tetramethyl-trans-*2β-naphthol* (**XII**). After isomerization of **IX** with $LiN(i\text{-}Pr)_2$ in THF at –78° for 1 h to a mixture **IX**/**XI** and subsequent $LiAlH_4$ reduction, **XII** was purified by repeated crystallization from hexane/Et_2O. M.p. 154–156°. MS: 268 (1, M^+), 250 (20), 235 (8), 195 (100), 177 (89).

(+)-*11β-Methyl*-isoambrox (= *Perhydro-1β,3aα,6,6,9aβ-pentamethyl*-cis-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan;* **6**). After bulb-to-bulb distillation, **6** was pure. $[\alpha]_D^{20} = +20°$ (*c* = 1.35, CH_2Cl_2). IR: 1360. ^{1}H-NMR: 0.87 (*s*, 6 H); 1.11 (*s*, 3 H); 1.14 (*s*, 3 H); 1.24 (*d*, *J* = 8, 3 H); 1.29 (*d*, *J* = 7, 1 H); 2.90 (*m*, 1 H); 3.39 (*dd*, *J* = 8, 11, 1 H); 3.81 (*dd*, *J* = 8, 10, 1 H). MS: 250 (0, *M*$^+$), 235 (100), 217 (5), 177 (5), 137 (27), 121 (6), 110 (51), 95 (17), 81 (17), 69 (13), 55 (11), 43 (13).

(–)-12α-Methyl-*ambrox* (8) and (–)-12β-Methyl-*ambrox* (9). – (+)-*Perhydro-1-((2*S*)-2-hydroxypropyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**XIV**) and (–)-*Perhydro-1-((2*R*)-hydroxypropyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**XV**). The two diols, obtained in equal amounts from (–)-acetoxyaldehyde **XIII** [14] [15], were separated by chromatography on silica gel in toluene containing increasing amounts of AcOEt and crystallized from pentane. **XIV**: M.p. 125°, $[\alpha]_D^{20} = +13.7°$. ^{1}H-NMR: 0.77 (*s*, 6 H); 0.85 (*s*, 3 H); 1.15 (*d*, *J* = 7, 3 H); 1.18 (*s*, 3 H); 4.05 (*m*, 1 H).

Scheme 3



a) MeLi, Et_2O, 10°, 1 h; b) $LiAlH_4$, Et_2O, 10°, 30 min; c) MsCl/pyridine, 0°, 1 h.

XV: M.p. 147°, $[\alpha]_D^{20} = -10.2°$. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.79 (*s*, 3 H); 0.87 (*s*, 3 H); 1.17 (*s*, 3 H); 1.19 (*d*, *J* = 7, 3 H), 4.30 (*m* 1 H).

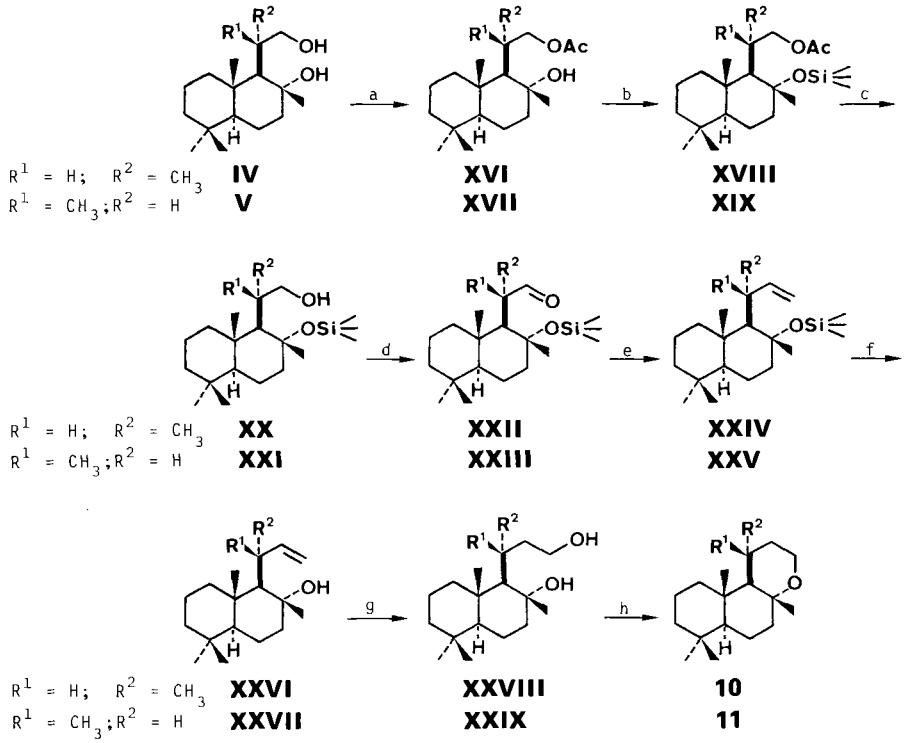
(–)-*12α-Methyl*-ambrox (= *Perhydro-2α,3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan;* **8**). Inversion at C(12) yielded pure **8**. M.p. 39° (from pentane), $[\alpha]_D^{20} = -11.5°$. IR: 1455, 1375, 1125, 1015. ^{1}H-NMR: 0.82 (*s*, 6 H); 0.87 (*s*, 3 H); 1.10 (*s*, 3 H); 1.18 (*d*, *J* = 6.5, 3 H); 4.21 (*ddq*, *J* = 8.5, 6.5, 2, 1 H). MS: 250 (2, *M*$^+$), 235 (100), 217 (5), 137 (17), 123 (5), 111 (17), 95 (10), 81 (12), 69 (11), 55 (12), 43 (20).

(–)-*12β-Methyl*-ambrox (= *Perhydro-2β,3aβ,6,6,9aβ-pentamethyl*-trans-*3a*-transoid-*9a,9b*-trans-*5a-naphtho[2,1*-b*]furan;* **9**). Pure **9** was obtained similarly. M.p. 61° (from pentane), $[\alpha]_D^{20} = -26°$. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.84 (*s*, 3 H); 0.86 (*s*, 3 H); 1.13 (*s*, 3 H); 1.28 (*d*, *J* = 6, 3 H): 4.07 (*tq*, *J* = 6, 6.5, 1 H). MS: 250 (3, *M*$^+$), 235 (100), 217 (5), 151 (7), 137 (14), 123 (3), 111 (16), 95 (8), 81 (9), 69 (9), 55 (11), 43 (22).

(–)-8α,13-Epoxy-11α-methyl-14,15,16-trinorlabdane (10) and (–)-8α,13-Epoxy-11β-methyl-14,15,16-trinorlabdane (11). – The two pure diols **IV** and **V** were treated in separate experiments following *Scheme 4*. The products **10** and **11** were chromatographed on silica gel.

(–)-*Perhydro-1α,4aβ,7,7,10aβ-pentamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6α-naphtho*[*2,1*-b]*pyran* (**10**). $[\alpha]_D^{20} = -6.9°$. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.88 (*s*, 6 H); 1.07 (*d*, *J* = 7, 3 H); 1.30 (*s*, 3 H); 3.54 (*m*, 1 H); 3.85 (*m*, 1 H). MS: 264 (2, *M*$^+$), 249 (100), 231 (2), 189 (3), 179 (4), 163 (11), 137 (33), 125 (51), 113 (26), 95 (33), 81 (28), 69 (34), 55 (35), 43 (38).

Scheme 4



a) $(Ac)_2O$/pyridine, b) $Me_3SiNHSiMe_3$/Me_3SiCl/pyridine [16]; c) $LiAlH_4$, Et_2O, reflux, 1 h; d) pyridinium dichromate, CH_2Cl_2, r.t., 18 h [17]; e) Ph_3PCH_3I, BuLi, Et_2O, reflux, 5 h [18]; f) EtOH, H_2O, HCl, r.t., 1 h; g) B_2H_6, THF; $NaOH/H_2O_2$ [19]; h) $POCl_3$, pyridine→r.t., 1 h.

(−)-*Perhydro-1β,4aβ,7,7,10aβ-pentamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1-b]pyran* (**11**). M.p. 60.5–62° (from pentane), $[\alpha]_D^{20} = -6.5°$. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.84 (*s*, 3 H); 0.98 (*s*, 3 H); 1.23 (*d*, *J* = 7, 3 H); 1.45 (*s*, 3 H); 3.61 (*m*, 1 H); 3.77 (*m*, 1 H). MS: 264 (4, M^+), 249 (88), 231 (2), 177 (10), 163 (17), 149 (8), 137 (65), 125 (100), 113 (74), 95 (61), 81 (62), 69 (63), 55 (64), 43 (77).

Diastereoisomeric 8α,13-Epoxy-12-methyl-14,15,16-trinorlabdanes 14 and 16, and 8α,13-Epoxy-12,12-dimethyl-14,15,16-trinorlabdane (18). – (+)-*12α-Methyl-ambreinolide* (= *Perhydro-2α,4aβ,7,7,10aβ-pentamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1-b]pyran-3-one*; **XXXII**) and (+)-*12,12-Dimethyl-ambreinolide* (= *Perhydro-2,2,4aβ,7,7,10aβ-hexamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1-b]pyran-3-one*; **XXXI**) from (+)-*Ambreinolide* (**XXX**) [9]. After prep. TLC in hexane/AcOEt 7:3 and crystallization from Et_2O **XXXI** and **XXXII** were obtained pure. **XXXI**: M.p. 139–140°, $[\alpha]_D^{20} = +30°$ (*c* = 1.02, CH_2Cl_2). ^{1}H-NMR: 0.83 (*s*, 6 H); 0.90 (*s*, 3 H); 1.30 (*s*, 6 H); 1.37 (*s*, 3 H). MS: 292 (0, M^+), 293 (1), 277 (9), 248 (27), 192 (100), 177 (92).

XXXII: M.p. 135–136°, $[\alpha]_D^{20} = +39°$ (*c* = 1.27, CH_2Cl_2). ^{1}H-NMR: 0.84 (*s*, 3 H); 0.87 (*s*, 3 H); 0.90 (*s*, 3 H); 1.27 (*d*, *J* = 7, 3 H); 1.40 (*s*, 3 H); 2.20 (*m*, 2 H); 2.70 (*m*, 1 H). MS: 278 (0, M^+), 279 (2), 263 (15), 234 (20), 219 (5), 192 (100), 177 (86).

Perhydro-1-((2S)-3-hydroxy-2-methylpropyl)-2β,5,5,8aβ-tetramethyl-trans-*2α-naphthol* (**XXXIV**). IR (CH_2Cl_2): 3600, 3420. ^{1}H-NMR: 0.82 (*s*, 6 H); 0.89 (*s*, 3 H); 0.92 (*d*, *J* = 7, 3 H); 1.13 (*s*, 3 H); 3.42 (br. *s*, 1 H); 3.50 (br. *s*, 1 H). MS: 282 (2, M^+), 267 (4), 264 (5), 249 (11), 195 (100), 177 (70).

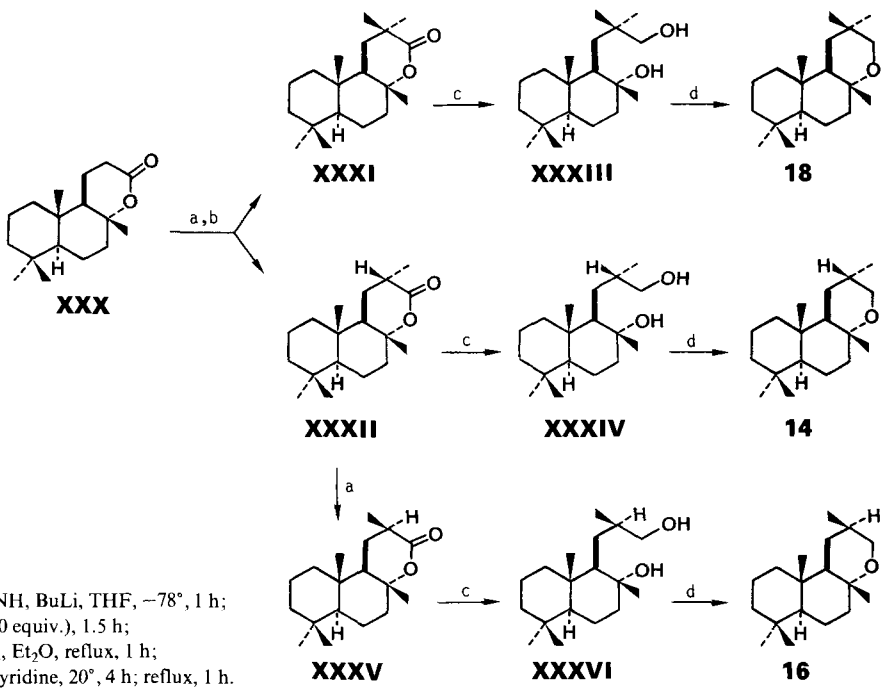
(+)-*Perhydro-2α,4aβ,7,7,10aβ-pentamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1-b]pyran* (**14**). M.p. 45° (from $MeOH/H_2O$), $[\alpha]_D^{20} = -17°$ (*c* = 0.95, CH_2Cl_2). IR (CH_2Cl_2): 1370, 1090. ^{1}H-NMR: 0.75 (*s*, 3 H);

Table. *^{13}C-NMR Chemical Shifts (δ in ppm) of* **1–22, I–V**,

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C(1)	39.9[a])	41.6[a])	40.6[a])	43.1	41.5	41.8[a])	41.6	40.0[a])	40.1[a])	39.2	38.9	39.0	41.5[a])	38.9
C(2)	18.5	18.6	18.5	18.3[a])	18.3	18.4[b])	18.4	18.5	18.5	18.9	18.5	18.6	18.6	18.6
C(3)	42.5	42.2[a])	42.4	42.2	42.4	42.0[a])	42.3	42.5	42.6	42.8	42.0	42.0[a])	41.9[a])	41.8[a])
C(4)	33.1	33.0	33.1	33.4	33.9	33.2	33.2	33.2	33.2	33.9	33.3	33.4	33.2	33.3
C(5)	57.4	57.3	57.3	48.9	58.5	53.2	58.8	57.4	57.2	56.4	57.7	56.5	55.3	56.7
C(6)	20.7	18.6	20.8	18.5[a])	20.7	18.6[b])	20.7	20.6	20.9	19.7	20.2	20.0	18.6[b])	20.0
C(7)	40.1[a])	35.7	40.0[a])	32.7	39.1	37.0	39.7	40.2[a])	40.6[a])	41.7	44.5	42.2[a])	42.8[a])	42.1[a])
C(8)	79.9	81.2	82.3	82.4	80.6	83.2	82.9	81.2	80.0	75.7	75.1	74.7	72.8	74.9
C(9)	60.2	52.6	66.2	67.7	61.7	60.0	67.5	59.0	61.6	63.4	58.8	57.9	50.3	50.7
C(10)	36.3	36.1	37.8	37.1	37.8	37.8	39.2[a])	36.1	36.3	40.0	37.9	36.9	38.7	36.4
C(11)	22.7	26.6	31.8	35.5	33.0	37.6	40.3[a])	29.9	31.1	29.1	26.3	18.2	17.8[b])	24.2
C(12)	65.0	64.7	73.3	72.2	73.3	71.6	80.9	71.7	74.9	41.9	37.0	27.7	21.6	29.0
C(13)	–	–	–	–	–	–	–	23.3	25.0	63.4	57.1	60.9	60.3	65.6
C(14)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
C(17)	15.1	14.9	16.1	16.6	16.8	16.2	16.4	15.0	15.7	16.1	17.1[a])	15.6	19.1	15.5
C(18)	33.6	33.7	33.8	33.0	33.9	33.8	34.0	33.6	33.6	33.9	33.5	33.4	34.2	33.3
C(19)	21.2	22.3	21.2	21.6	21.2	22.2	21.2	21.2	21.2	21.7[a])	21.4	21.4	22.3	21.4
C(20)	21.2	28.3	22.4	29.8	22.7	30.1	22.2	21.6	23.8	21.2[a])	23.1	20.0	25.9	19.6
CH_3---C(11)	–	–	20.0	20.7	–	–	25.7	–	–	24.7	–	–	–	–
CH_3►C(11)	–	–	–	–	18.8	14.3	34.0	–	–	–	17.3[a])	–	–	–
CH_3---C(12)	–	–	–	–	–	–	–	–	–	–	–	–	–	18.4
CH_3►C(12)	–	–	–	–	–	–	–	–	–	–	–	–	–	–

[a]) [b]) Values within any vertical column may be reversed.

Scheme 5



a) $(i\text{-Pr})_2NH$, BuLi, THF, −78°, 1 h;
b) MeI (10 equiv.), 1.5 h;
c) $LiAlH_4$, Et_2O, reflux, 1 h;
d) TsCl/pyridine, 20°, 4 h; reflux, 1 h.

VIII, IX, *and* **XXXII.** Labdane numbering; n.v. = not visible.

15	16	17	18	19	20	21	22	I	II	III	IV	V	VIII	IX	XXXII
41.9[a])	39.0	42.5[a])	38.9	39.2	40.7[a])	39.2	41.5[a])	39.5[a])	40.0[a])	40.5[a])	40.2	39.8	40.9	42.7[a])	38.8
18.5	18.6	18.0[b])	18.6	18.6[a])	18.6[b])	18.6	18.6[b])	18.0	18.1	18.1	18.6	18.8	18.3[a])	18.2[b])	18.3
42.5[a])	42.1[a])	42.4[a])	42.1	42.2[b])	42.2	42.2	41.9[a])	42.2	42.0	42.2	42.0	41.9	41.8	42.0[a])	41.6[a])
33.2	33.4	33.2	33.4	33.3	33.4	33.3	33.2	33.1	33.3	33.1	33.5	33.6	33.0	33.6	33.0
55.3	56.5	57.9	56.7	56.5	53.4	56.6	55.4	56.7	56.6	57.9	57.0	56.8	54.8	48.0	55.9
18.5	19.9	18.7[b])	20.0	20.0	18.5[b])	20.2	18.7[b])	20.5	20.5	20.7	20.5	20.7	18.1[a])	17.9[b])	19.5
41.4[a])	41.8[a])	33.0	41.6	42.1[b])	40.4[a])	43.3	43.0	38.7[a])	38.8[a])	38.7[a])	46.0	47.7	36.1	31.5	41.4
72.5	n.v.	73.6	n.v.	74.8	73.1	74.9	73.3	86.1	83.8	86.5	74.6	73.4	85.5	84.8	83.6
50.9	57.3	48.3	52.5	57.4	52.4	53.1	49.6	59.1	65.1	59.9	62.4	62.1	51.5	63.7	52.6
38.4	n.v.	37.1	36.5	36.8	37.7	37.2	38.6	36.1	37.6	37.4	40.4	40.4	35.2	36.9	37.0
27.6	27.2	26.9	32.1	18.7[a])	16.7	15.4	18.8[b])	28.7	35.9	38.1	34.6	33.6	32.4	37.2	24.8
25.7	32.8	29.2	31.3	35.4	27.7	30.4	29.7	176.5	179.6	180.2	67.8	71.6	177.5	179.8	32.7
67.0	67.4	66.5	71.0	65.4	67.7	66.3	64.7	–	–	–	–	–	–	–	175.3
–	–	–	–	22.7	25.7	26.3	23.2	–	–	–	–	–	–	–	–
9.1[b])	15.6	21.0	15.5	15.6	15.9	15.3	19.3	15.0	16.1	17.0	16.4	16.2	14.7	16.8	14.5
34.2	33.4	32.7	33.4	33.5	33.5	33.5	34.3	33.1	33.3	33.5	33.8	33.6	33.4	32.7	33.3
22.4	21.4	21.4	21.3	21.4	21.9	21.5	22.4	21.5	20.9	20.9	21.7	21.4	22.2	21.2	21.4
35.9	19.9	29.0	19.5	20.8	34.2	23.5	26.7	20.9	22.6	25.0	25.2	26.4	30.0	31.8	22.5
	–		–	–		–	–		16.1	–	20.5	–	–	19.7	–
	–	–	–	–	–		–	–	–	14.2	–	17.8	–	–	–
18.8[b])	–	–	25.3	–	–	–	–	–	–	–	–	–	–	–	18,8
	17.6	16.6	28.1	–	–	–	–	–	–	–	–	–	–	–	–

0.81 (*s*, 3 H); 0.89 (*s*, 3 H); 1.11 (*d*, *J* = 7, 3 H); 1.25 (*s*, 3 H); 3.30 (*dd*, *J* = 12, 2, 1 H); 3.86 (*dd*, *J* = 12, 4, 1 H). MS: 264 (7, M^+), 249 (100), 177 (2).

(−)-*Perhydro-1-(3-hydroxy-2,2-dimethylpropyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**XXXIII**). M.p. 139–140° (from hexane/Et_2O), $[\alpha]_D^{20} = -13°$ (*c* = 1.05, CH_2Cl_2). ^{1}H-NMR: 0.78 (*s*, 3 H); 0.82 (*s*, 3 H); 0.88 (*s*, 3 H); 0.95 (*s*, 3 H); 1.23 (*s*, 3 H); 3.0 (*d*, *J* = 11, 1 H); 3.40 (*d*, *J* = 11, 1 H). MS: 296 (38, M^+), 278 (23), 266 (51), 263 (28), 249 (37), 192 (89), 177 (100).

(−)-*Perhydro-2,2,4aβ,7,7,10aβ-hexamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**18**). M.p. 110–112° (from MeOH/H_2O), $[\alpha]_D^{20} = -6°$ (*c* = 1.01, CH_2Cl_2). IR (CH_2Cl_2): 1370, 1070. ^{1}H-NMR: 0.72 (*s*, 3 H); 0.80 (*s*, 3 H); 0.83 (*s*, 3 H); 0.87 (*s*, 3 H); 1.03 (*s*, 3 H); 1.20 (*s*, 3 H); 3.12 (*d*, *J* = 12, 1 H); 3.41 (*d*, *J* = 12, 1 H). MS: 278 (12, M^+), 263 (100), 192 (5), 177 (13), 157 (19), 139 (19), 95 (27), 81 (24), 69 (36), 55 (36), 43 (77).

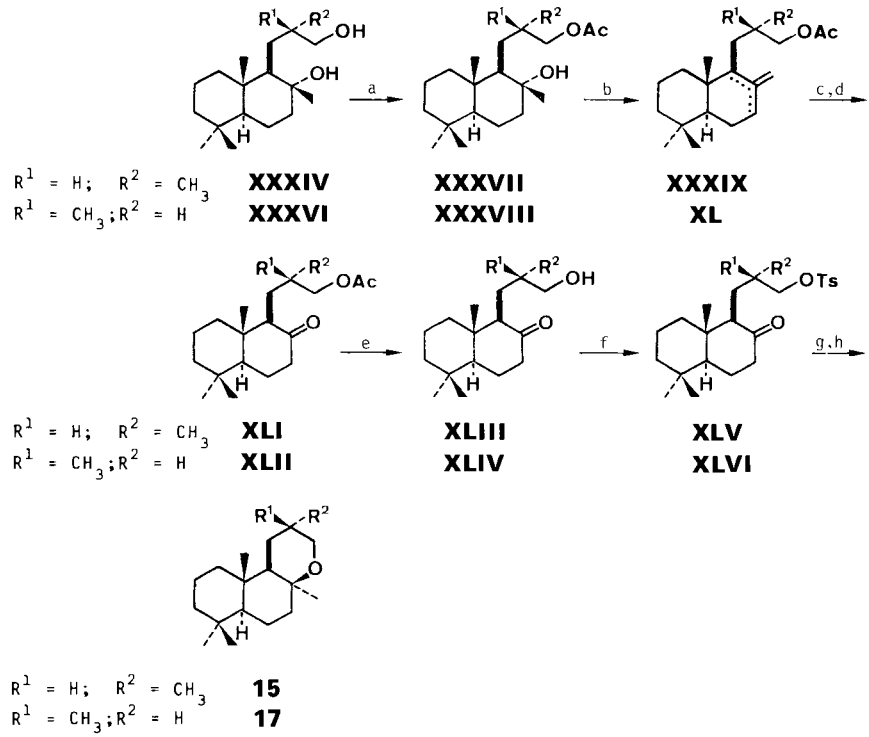
(−)-*Perhydro-1-((2*R*)-3-hydroxy-2-methylpropyl)-2β,5,5,8aβ-tetramethyl*-trans-*2α-naphthol* (**XXXVI**) via *12β-Methyl-ambreinolide* (**XXXV**). After isomerization, the mixture **XXXII/XXXV** was directly reduced to a mixture of diols, which were separated by prep. TLC in hexane/AcOEt 1:1. **XXXVI** had m.p. 133° (from hexane/Et_2O), $[\alpha]_D^{20} = -15°$ (*c* = 1.27, CH_2Cl_2). IR (CH_2Cl_2): 3590, 3450. ^{1}H-NMR: 0.80 (*s*, 6 H); 0.87 (*s*, 3 H); 0.91 (*d*, *J* = 7, 3 H); 1.16 (*s*, 3 H); 3.35 (*dd*, *J* = 11, 4, 1 H); 3.77 (*dd*, *J* = 11, 3, 1 H). MS: 282 (5, M^+); 267 (5), 264 (8), 249 (15), 195 (100), 177 (89).

(+)-*Perhydro-2β,4aβ,7,7,10aβ-pentamethyl*-trans-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**16**) was purified by prep. TLC in hexane/AcOEt 4:1. M.p. 65–68°, $[\alpha]_D^{20} = +7°$ (*c* = 0.67, CH_2Cl_2). IR (CCl_4): 1370, 1090. ^{1}H-NMR: 0.74 (*s*, 3 H); 0.80 (*s*, 3 H); 0.87 (*s*, 3 H); 0.82 (*d*, *J* = 6.5, 3 H); 1.22 (*s*, 3 H); 3.24 (*dd*, *J* = 11.5, 11.5, 1 H); 3.54 (*dd*, *J* = 11.5, 5, 1 H). MS: 264 (2, M^+), 248 (100), 177 (20), 125 (30), 109 (76), 95 (29), 81 (40), 69 (63), 55 (63), 43 (89).

Diastereoisomeric 8β,13-Epoxy-12-methyl-14,15,16-trinorlabdanes 15 and 17. – The pure diols **XXXIV** and **XXXVI** were treated in separate operations following *Scheme 6*, and **15** and **17** were crystallized from MeOH/H_2O.

(−)-*Perhydro-2α,4aα,7,7,10aβ-pentamethyl*-cis-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**15**). M.p. 49–51°, $[\alpha]_D^{20} = -31°$ (*c* = 0.19, CH_2Cl_2). IR: 1360, 1090. ^{1}H-NMR: 0.74 (*d*, *J* = 7, 3 H); 0.88 (*s*, 6 H); 1.16 (*s*, 3 H);

Scheme 6



a) $(Ac)_2O$/pyridine, 20°, 12 h; b) MsCl/pyridine, 0°, 48 h; c) O_3, CH_2Cl_2/pyridine 10:1, −78°; d) H_2O_2 30%, 20°, 12 h; e) NH_3, MeOH, 0°, 48 h; f) TsCl, pyridine, 0°, 12 h; g) MeLi, Et_2O, reflux, 2 h; h) HCl 10%.

1.21 (*s*, 3 H); 3.35 (*dd*, *J* = 12, 12, 1 H); 3.60 (*dd*, *J* = 6, 12, 1 H). MS: 264 (1, M^+), 249 (100), 231 (3), 177 (4), 149 (4), 137 (22), 125 (37), 112 (13), 95 (16), 81 (20), 69 (21), 55 (22), 43 (37).

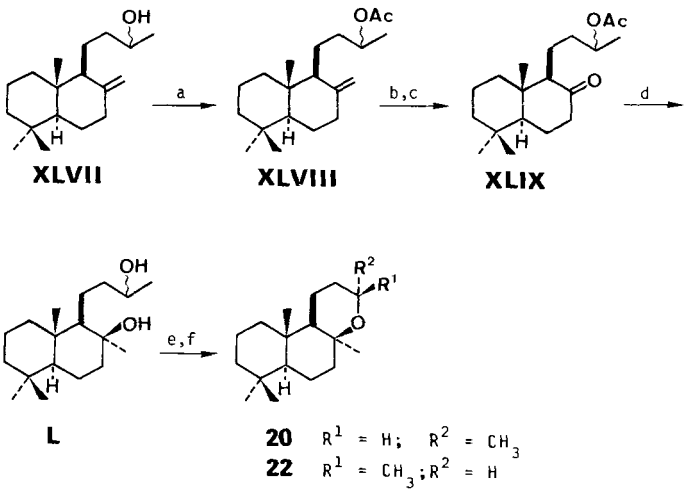
(−)-*Perhydro-2β,4aα,7,7,10aβ-pentamethyl*-cis-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**17**). $[\alpha]_D^{20}$ = −9° (*c* = 1.29, CH_2Cl_2). IR: 1370, 1140. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.91 (*s*, 6 H); 0.93 (*d*, *J* = 7, 3 H); 1.26 (*s*, 3 H); 3.17 (*dd*, *J* = 6, 11, 1 H); 3.93 (*dd*, *J* = 6, 11, 1 H). MS: 264 (0, M^+), 249 (100), 231 (3), 177 (4), 161 (3), 149 (4), 137 (25), 125 (45), 112 (13), 95 (21), 81 (26), 69 (29), 55 (32), 43 (55).

Diastereoisomeric 8β,13-Epoxy-15,16-dinorlabdanes 20 and 22. – The alcool **XLVII** [20] was transformed following *Scheme 7 via* the diastereoisomeric diols **L** to the ethers **20** and **22**, which were separated by chromatography in toluene/AcOEt 95:5.

(−)-*Perhydro-3α,4aα,7,7,10aβ-pentamethyl*-cis-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**20**). M.p. 93°, $[\alpha]_D^{20}$ = −19.74°. ^{1}H-NMR: 0.85 (*s*, 3 H); 0.86 (*s*, 3 H); 0.99 (*s*, 3 H); 1.16 (*d*, *J* = 6, 3 H); 1.26 (*s*, 3 H); 3.92 (*m*, 1 H). MS: 264 (1, M^+), 249 (100), 231 (13), 175 (4), 161 (3), 149 (6), 137 (27), 125 (27), 109 (13), 95 (17), 81 (18), 69 (18), 55 (18), 43 (29).

(+)-*Perhydro-3β,4aα,7,7,10aβ-pentamethyl*-cis-*4a*-transoid-*10a,10b*-trans-*6a-naphtho[2,1*-b*]pyran* (**22**). M.p. 94°, $[\alpha]_D^{20}$ = +3.69°. ^{1}H-NMR: 0.87 (*s*, 6 H); 1.14 (*s*, 3 H); 1.11 (*d*, *J* = 6, 3 H); 1.23 (*s*, 3 H); 3.90 (*m*, 1 H). MS: 264 (0, M^+), 249 (100), 231 (10), 175 (3), 149 (5), 137 (21), 125 (23), 113 (10), 95 (13), 81 (13), 69 (13), 55 (15), 43 (27).

Scheme 7



a) $(Ac)_2O$/pyridine, 20°/12h, 50°/1 h; b) O_3, MeOH, −30°; c) Me_2S, −10°/1 h, 0°/1 h, 20°/1 h; d) MeMgI, ET_2O, 20°, 15 h; e) MsCl/pyridine, 20°, 20 h; f) toluene/pyridine 1:1, reflux, 15 h.

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