212. Significance of the Geminal Dimethyl Group in the Odor Principle of *Ambrox*® [1])

by **Günther Ohloff***, **Wolfgang Giersch**, **Wilhelm Pickenhagen**, **Anton Furrer**, and **Beatrice Frei**

Firmenich SA, Research Laboratories, CH–1211 Geneva 8

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The diastereoisomeric 18-nor- and 19-norambrox ((6α)- and (6β)-dodecahydro-3a,6,9a-trimethylnaphtho[2,1-*b*]furans resp.) as well as the corresponding 18,19-dinor-derivatives (dodecahydro-3a,9a-dimethylnaphtho[2,1-*b*]furans) have been synthesized and subjected to sensory evaluation. Threshold data and odor determination give an enlarged insight into the structure-activity relationship (SAR) in ambrox-type ambergris fragrances. As a general conclusion, the accumulation of axial CH_3 groups in the tricyclic ethers **1**–**12** leads to the strongest receptor affinity.

The release of ambergris scent is strongly related to structural elements of the labdane skeleton, ambrox (**1**)[1]) being the typical example. In the olfactory recognition process, which has been defined by the 'triaxial rule', the stereochemistry of the CH_3 groups at C(8) and C(10) in **1** plays an important role in the hydrophobic interaction with the hypothetical receptor site [1]. To assess the significance of the geminal CH_3 groups at C(4) for the specific ambergris odor sensation the diastereoisomeric tricyclic ethers **1**–**3** and the six nor-ethers **4**–**9**, belonging to the same enantiomeric series, were synthesized. The 18,19-dinor-ethers **10**–**12**, in racemic form, were also included in the investigation.

All compounds mentioned in the *Figure* had distinct odors of varying quality and strength. Surprisingly, (–)-9-epiambrox (**2**) possessed the strongest odor and the lowest threshold concentration of the total series (0.15 ppb). (–)-Ambrox (**1**) as well as the two 18-nor-derivatives **4** and **5** showed only a small qualitative deviation. Thus, the sensory result obtained from the racemate of **4** [2] [3] can be confirmed.

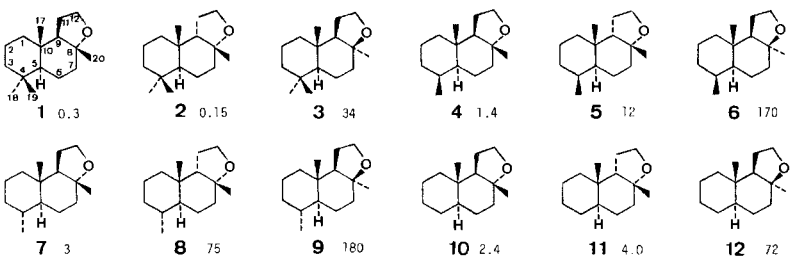
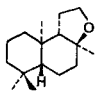


Figure. *The diastereoisomers of ambrox, 18-norambrox, 19-norambrox and 18,19-dinorambrox and their threshold concentrations in parts/10^9 (ppb) measured in water* [4]

[1]) *Ambrox*® is a registered trade name of *Firmenich SA*. Systematic name of ambrox: *[3a*R*-(3aα,5aβ,9aα,9bβ)]-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan.*

Isoambrox (**3**) shows a considerable deviation from the model compound **1**, especially concerning its odor strength. Indeed, isoambrox (**3**) is more than a hundred times weaker and 18-norisoambrox (**6**) more than five hundred times weaker than ambrox (**1**), measured by their threshold values *(Figure)*. This result shows that an axial CH_3 group at C(8) is essential for the receptor event and confirms once more the 'triaxial rule' [1] [5] [6]. The amber note in 18-norisoambrox (**6**) is more clearly modified compared with its diastereoisomers **4** and **5** than the isoambrox (**3**) when compared with **1** and **2**. Ether **6** only possesses the woody note out of the complex odor profile of ambrox (**1**). No trace of any amber note can be perceived in 19-norisoambrox (**9**), whereas the ambrox note is still perceptible in the diastereoisomers **7** and **8**, although less pronounced than in the 18-nor-derivatives **4** and **5**. Surprisingly, the woody character of ambrox in the 18,19-dinor-compounds **10** and **11** has not completely disappeared, although it is masked, at the beginning, by a relatively complex odor. Thus ether **10** is dominated by a strong earthy odor reminiscent of a freshly plowed field[2]). In ether **11**, a striking spicy-woody and grapefruit-like odor is recognizable, accompanied by exotic flower scents[3]). Diastereoisomer **12** is musty with a tonality of rotten fruit, whereas the ambrox note disappears completely. A comparison of racemates **10–12** with the optically active ethers **1–3** seems permissible, since we only found rather small differences in the odors of (−)-ambrox (**1**) and (+)-ambrox (*ent*-**1**). (+)-Ambrox (*ent*-**1**) with its higher threshold value (2.4 ppb) and accentuated woody note lacks the strong and warm animal note of its enantiomer **1**. (+)-Ambrox has, therefore, been called 'poor man's ambrox' by our perfumers. The exotic, spicy undertone in (+)-ambrox (*ent*-**1**) disappears in its racemate, for which a threshold concentration of 0.5 ppb was measured[4]). Dinor ethers lacking substituents at C(4) and C(8) still possess amber-like odor properties with increasing complexity of their odor profile and decreasing intensity [3] [7]. Derivatives from that series have not been included in our experiments, because we found in (−)-20-norambrox and (+)-20-norisoambrox a considerable difference in their odor tonalities as well as a several hundred times intensity decrease in comparison with the reference substances **1** and **2**. Thus, no further results could be excepted for the theoretical aspect of the SAR study.



ent-**1** 2.4

The investigation shows a preference for axial CH_3 groups in the specific interaction with the hypothetical active site of the ambrox receptor. This striking effect of molecular structure in a biological response is remarkable. In fact, the sensory properties of the four compounds **1**, **2**, **4**, and **5** with an accumulation of three axial CH_3 groups show a qualitative resemblance, and exhibit the strongest receptor affinity. Among the nor-com-

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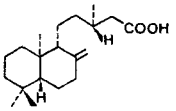
[2]) Reminiscent of the smell of the diastereoisomers of geosmin [N. N. Gerber, *Phytochem.* **1971**, *10*, 1985; **1972**, *11*, 385] but less aggressive.

[3]) The evaluation of odor strips of the two racemates **10** and **11** shows, after 12 h, an increase of the woody character, the loss of almost all other odor qualities. After the same time the odor of ether **12** was almost imperceptible.

[4]) A threshold concentration of 0.5 ppb for the racemate was calculated from the measured threshold values of **1** and *ent*-**1**.

pounds, ethers **4** and **12** show the greatest quality differences. The odor strength of ambrox (**1**) differs from the ether **6** by a factor of 570. The diastereoisomer **9**, with two equatorial CH_3 groups lacks any particular note of ambrox.

Syntheses. – The tricyclic ethers **1–3** were synthesized from the known diastereoisomeric sclareolides **I–III**, respectively, by literature procedures as described in the *Exper. Part.* Oxidative degradation of eperuic acid (**13**) leads to (+)-ambrox (*ent*-**1**), whereas the racemic ambrox [8] was synthesized from (*E,E*)-homofarnesic acid (**14**), (±)-scareolide [9]



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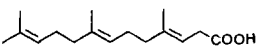

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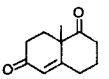

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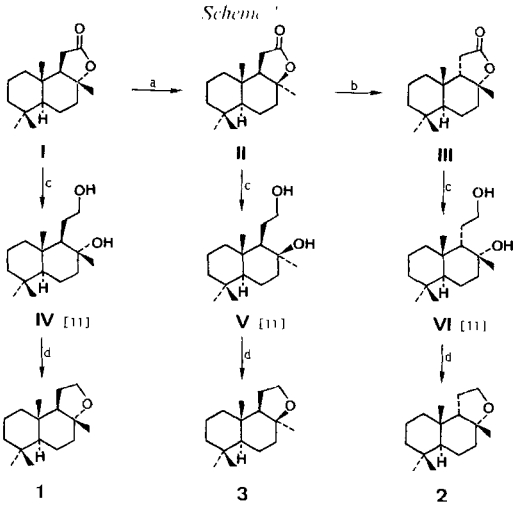
being the key intermediate. The common precursor for diastereoisomeric 18-nor- and 19-norambroxes **4–9** is podocarpic acid (**XI**) which was transformed into the norethers **4–9** using a multistep degradation. The synthesis of the racemic 18,19-dinorethers **10–12** were effected *via* a multistep sequence starting from the *Wieland-Miescher* ketone **15**.

Experimental Part

General. M.p. are not corrected. Specific rotations were measured in $CHCl_3$ at 20° in ~ 1% soln. with a *Perkin-Elmer 141* polarimeter. Prep. column chromatography was performed on silica gel (*Merck 60*, under 230 mesh). GC was carried out on *a*) *Carlo Erba Fractovap 4200* using glass columns (ID = 3 mm) 3 m *Carbowax* (15%) or 3 m *SE 30* (15%) on *Chromosorb W*, 60–90 mesh; *b*) *Carlo Erba Fractovap 2900* using capillary columns (*Chrompack*): *a*) 10 m and 30 m *CP Wax 57 CP*; *b*) 10 m *CP Si 15 CB*; *c*) 60 m *UCON*. Recording of spectra was carried out on the following apparatus. IR: *Perkin-Elmer 297*; characteristic band positions are given in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker WH 360* and *Bruker HX 90*, resp.; measurements were run in $CDCl_3$ with TMS ($\delta = 0.00$ ppm) as internal standard. MS: *Finnigan 1020* (quadropole), using electrons of *ca.* 70 eV.

Preparation of the Diastereoisomers of Ambrox (1–3) [9] [10].

Scheme



Reagents: a) HCOOH (100%), conc. H_2SO_4/20°/4 h; b) like a) but 90°/5 h; c) $LiAlH_4$, Et_2O/reflux/1 h; d) $POCl_3$, pyridine/ − 20° → r.t./5 h.

Starting material, *sclareolide* (= *dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-b]furan-2-one;* **I**)[5]) (m.p. 124°, $[\alpha]_D^{20} = +48°$), was a product from *R.J. Reynolds* (USA). The final products were purified by prep. GC. (For a GC and ^{1}H-NMR comparison of all isomers see *Table 1* and *2*, resp.)

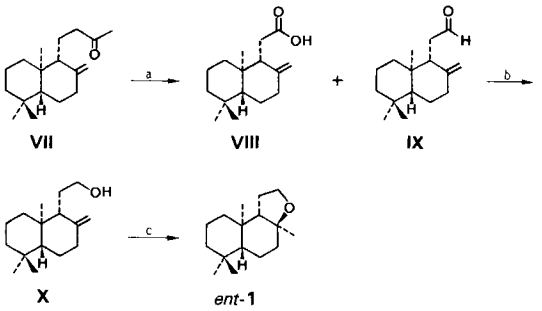
(−)-Ambrox (**1**). M.p. 77–77.5°, $[\alpha]_D^{20} = -24.7°$. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.84 (*s*, 3 H); 0.88 (*s*, 3 H); 1.0 (*s*, 3 H); 3.83 (*q*, *J* = 8, 1 H); 3.92 (*m*, 1 H). MS: 236 (2, M^+), 221 (100), 137 (36), 97 (34), 81 (15), 69 (17), 55 (15), 43 (24).

(−)-9-Epiambrox (**2**). $[\alpha]_D^{20} = -6.1$. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.90 (*s*, 3 H); 1.10 (*s*, 3 H); 1.38 (*s*, 3 H); 3.77 (*q*, *J* = 8.5, 1 H); 3.86 (*m*, 1 H). MS: 236 (18, M^+), 221 (68), 137 (100), 124 (12), 109 (20), 97 (29), 81 (27), 69 (28), 55 (26), 43 (47).

(+)-Isoambrox (**3**). M.p. 60–60.5°, $[\alpha]_D^{20} = +7.5°$. ^{1}H-NMR: 0.86 (*s*, 3 H); 0.89 (*s*, 3 H); 0.90 (*s*, 3 H); 1.06 (*s*, 3 H); 3.70 (*q*, *J* ≈ 8, 1 H); 3.78 (*m*, 1 H). MS: 236 (0, M^+), 221 (100), 137 (30), 97 (34), 81 (15), 69 (16), 55 (14), 43 (18).

Preparation of (+)-Ambrox (*ent*-1).

Scheme 2



Reagents: a) O_2, *t*-BuOK, dry glyme (distilled over $LiAlH_4$); b) $LiAlH_4$, Et_2O/reflux/ 1 h; c) CH_3NO_2, TsOH/reflux/100°/1 h[6]).

4-(Decahydro-5,5,8a-trimethyl-2-methylene-1-naphthyl)-2-butanone (**VII**) was prepared from eperuic acid according to *Dey* and *Wolf* [12][7]).

(+)-Ambrox (ent-**1**). $[\alpha]_D^{20} = +21.7°$. NMR and MS are identical with those of (−)-ambrox (**1**).

Preparation of the Diastereoisomers of 18-Norambrox (= *(6α)-Dodecahydro-3a,6,9a-trimethylnaphtho[2,1-b]furans;* 4–6).

Podocarpic acid (1,2,3,4,4a,9,10,10a-octahydro-6-hydroxy-1,4a-dimethyl-1-phenanthrenecarboxylic acid; **XI**), a product from *Pfaltz and Bauer Inc.*, Stamford/Conn. USA ($[\alpha]_D^{20} = +140°$) was transformed to *(decahydro-5,8a-dimethyl-2-methylene-1-naphthyl)acetic acid* (**XX**) following [13] [14] and [15]. For the lactonisation step see [16].

The distribution of isomers found in the last step in %:

	4	**5**	**6**
XXI	15	13	72
XXII	1	7	92

The mixture of **4/5/6** was separated by chromatography on silica gel *(Merck 60)* with hexane/Et_2O 98:2 (pressure ~ 5 bar).

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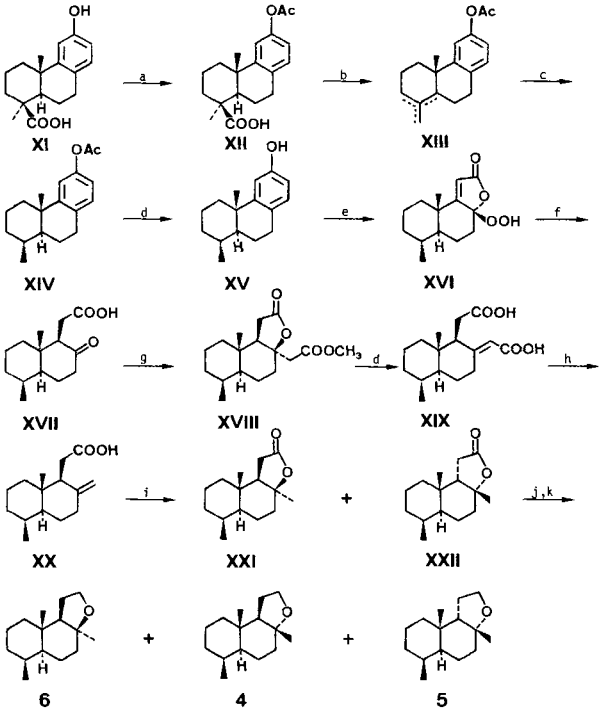
[5]) Roman numerals are used throughout for starting materials and intermediates not submitted to sensory evaluation.

[6]) We thank Dr. *Sina Escher (Firmenich SA)* for the communication of the conditions prior to publication.

[7]) The starting material was kindly supplied by Dr. *H.R. Wolf (F. Hoffmann-La Roche & Co*, Ltd., Basle).

Scheme 3



Reagents: a) $(Ac)_2O$, CH_3COONa/reflux/1 h [13]; b) Pb(OAc), toluene, pyridine/85°/2 h [13]; c) PtO_2, CH_3COOEt, H_2 [14]; d) NaOH, MeOH/reflux/3 h [14]; e) O_3, MeOH/ – 75° [14]; f) Pd/C 10%, EtOH, H_2 [14]; g) $BrCH_2COOMe$, toluene, Zn, trace I_2/80° [15]; h) quinoline, *Chromite* (*Geldner 22*)/230° [15]; i) HCOOH 100%, conc. H_2SO_4/80°/1 h→**XXI** (94%) and **XXII** (6%), 90 h→**XXI** (48%) and **XXII** (52%); j) $LiAlH_4$, Et_2O/reflux/1 h; k) TsOH/bulb-to-bulb distillation/0.01 Torr/130°.

(–)-18-Norambrox (**4**). $[\alpha]_D^{20} = -8°$. ^{1}H-NMR: 0.84 (*s*, 3 H); 0.907 (*d*, *J* = 7.5, 3H); 1.09 (*s*, 3 H); 3.821 (*q*, *J* = 8, 1 H); 3.916 (*m*, 1 H). MS: 222 (1, M^+), 207 (100), 189 (6), 177 (2), 163 (5), 137 (10), 123 (77), 111 (17), 97 (40), 81 (35), 67 (23), 55 (27), 43 (42).

(+)-9-Epi-18-norambrox (**5**). $[\alpha]_D^{20} = +1.75°$. ^{1}H-NMR: 0.895 (*d*, *J* = 7.5, 3 H): 1.08 (*s*, 3 H); 1.38 (*s*, 3 H); 3.77 (*q*, *J* = 8.5, 1 H); 3.86 (*m*, 1 H). MS: 222 (23, M^+), 207 (57), 189 (10), 177 (5), 163 (27), 137 (46), 123 (100), 111 (64), 95 (52), 85 (64), 67 (37), 55 (46), 43 (98).

(+)-18-Norisoambrox (**6**). $[\alpha]_D^{20} = +33°$. ^{1}H-NMR: 0.89 (*s*, 3 H), 0.94 (*d*, *J* = 7.5, 3 H); 1.05 (*s*, 3 H); 3.75 (*q*, *J* = 10, 1 H); 3.85 (*m*, 1 H). MS: 222 (0, M^+), 107 (100), 189 (7), 177 (2), 163 (7), 123 (75), 107 (11), 97 (37), 81 (35), 67 (20), 55 (27), 43 (33).

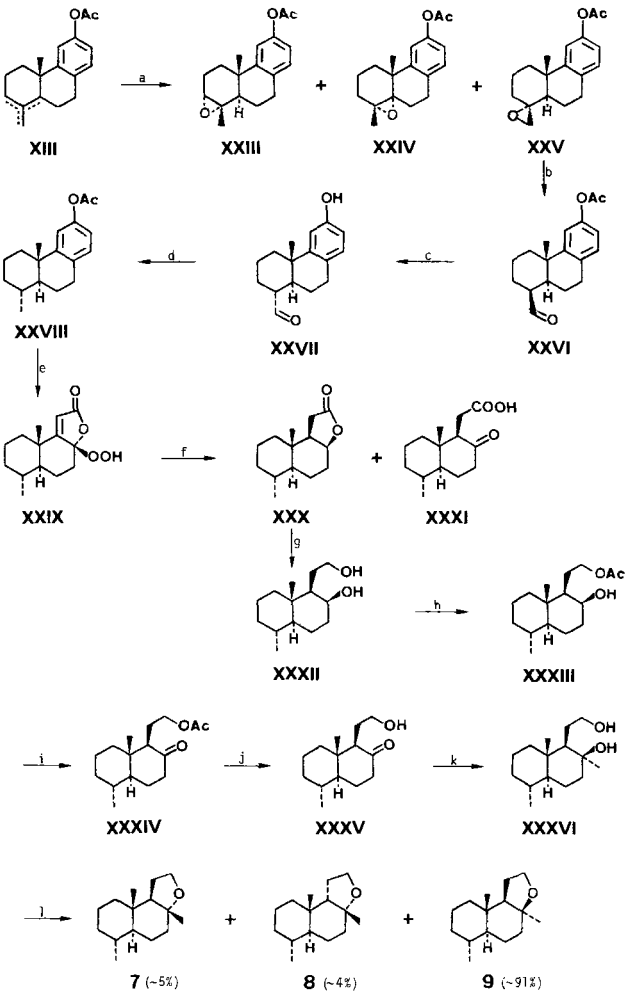
Preparation of the Diastereoisomers of 19-Norambrox (= *(6β)-Dodecahydro-3a,6,9a-trimethylnaphtho[2,1-b]furans;* **7–9**).

The mixture **7**/**8**/**9** was also purified by chromatography as before.

19-Norambrox (**7**). ^{1}H-NMR: 0.76 (*s*, 3 H); 0.83 (*d*, *J* = 6, 3 H); 1.09 (*s*, 3 H); 3.828 (*q*, *J* = 8, 1 H); 3.9 (*m*, 1 H). MS: 222 (0, M^+), 207 (100), 189 (8), 177 (1), 163 (9), 123 (23), 109 (8), 97 (21), 81 (22), 67 (15), 55 (16), 43 (22).

9-Epi-19-norambrox (**8**). ^{1}H-NMR: 0.835 (*d*, *J* = 6, 3 H); 1.0 (*s*, 3 H); 1.37 (*s*, 3 H); 3.766 (*q*, *J* = 8.5, 1 H); 3.85 (*m*, 1 H). MS: 222 (20, M^+), 207 (100), 189 (12), 177 (3), 163 (21), 137 (21), 123 (33), 111 (27), 95 (22), 81 (26), 67 (21), 55 (23), 43 (43).

Scheme 4

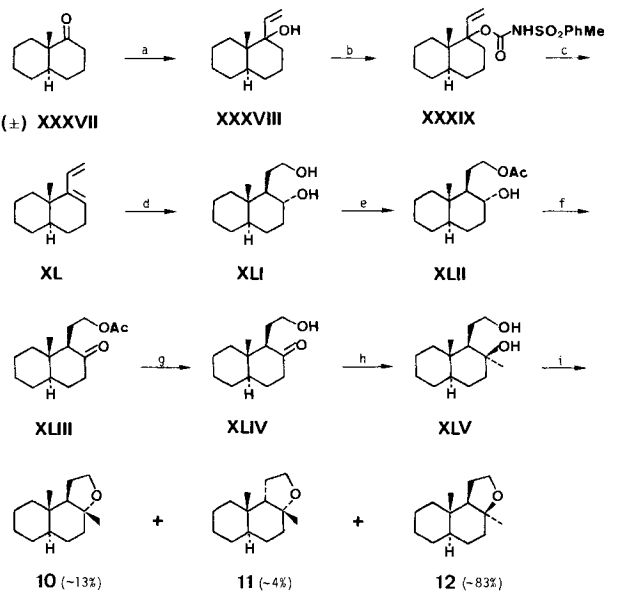


Reagents: a) *m*-Cl-PhCOOOH, CH_2Cl_2/r.t./12 h [14]; b) $BF_3 \cdot Et_2O$, toluene/20°/1 h (cooling with ice is necessary) [14]; c) dil. HCl [14]; d) hydrazine hydrate, diethylene glycol/reflux 1 h; KOH→220°/4 h [14]; e) O_3, MeOH/ – 70°, then Ph_3P→r.t. [14]; f) If **XXIX** is hydrogenated [14] over Pd/C no reaction occurs. With PtO_2/EtOH **XXX** was the main product with **XXXI** (traces); g) $LiAlH_4$, Et_2O/reflux/1 h; h) $(Ac)_2O$, pyridine/r.t./24 h; i) PDC, CH_2Cl_2 [17]; j) KOH, EtOH/reflux/1 h; k) excess MeMgI, Et_2O/reflux/1 h; l) TsOH/bulb-to-bulb distillation/0.01 Torr/130°.

(–)-19-Norisoambrox (**9**). $[\alpha]_D^{20} = -5.2°$. ^{1}H-NMR: 0.845 (*s*, 3 H); 0.855 (*d*, *J* = 6, 3 H); 1.1 (*s*, 3 H); 3.734 (*q*, *J* = 8, 1 H); 3.788 (*m*, 1 H). MS: 222 (0, M^+), 207 (100), 189 (5), 177 (1), 163 (8), 147 (3), 133 (4), 123 (22), 107 (5), 97 (19), 81 (18), 67 (12), 55 (13), 43 (18).

Preparation of the Diastereoisomers of (±)-18,19-Dinorambrox (*Dodecahydro-3a,9a-dimethylnaphtho[2,1-b]furans;* **10–12**). – The racemic ketone **XXXVII** (*decahydro-8a-methyl-1-naphthalenone*) was prepared from racemic *Wieland-Miescher* ketone (3,4,8,8a-tetrahydro-8a-methyl-1,6(2*H*,7*H*)naphthalenedione; **15**) [18] in a multistep sequence [5]:

Scheme 5



Reagents: a) CH_2=CHMgI, THF/reflux/1 h [19]; *p*-toluenesulfonyl isocyanate, toluene/r.t./18 h [19]; c) distillation/0.01 Torr/180° bath temp. [19]; d) B_2H_6, THF; NaOH, H_2O_2 [20]; e) Ac_2O, pyridine/r.t. /18 h; f) PDC, CH_2Cl_2 [17]; g) KOH, EtOH/reflux/1 h; h) excess MeMgI, Et_2O/reflux/1 h; i) TsOH/bulb-to-bulb distillation/0.01 Torr/130°.

The mixture **10**/**11**/**12** was purified by chromatography like before.

(±)-18,19-Dinorambrox (**10**). ^{1}H-NMR: 0.755 (*s*, 3 H); 1.09 (*s*, 3 H); 3.835 (*q*, *J* = 7.5, 1 H); 3.92 (*m*, 1 H). MS: 208 (2, M^+), 193 (100), 175 (11), 149 (9), 137 (9), 109 (39), 97 (14), 81 (12), 67 (18), 55 (12), 43 (16).

(±)-9-Epi-18,19-dinorambrox (**11**). ^{1}H-NMR: 1.0 (*s*, 3 H); 1.39 (*s*, 3 H); 3.78 (*q*, *J* = 8.5, 1 H); 3.87 (*m*, 1 H). MS: 208 (18, M^+), 193 (100), 175 (13), 149 (49), 137 (67), 124 (48), 109 (52), 81 (27), 67 (30), 55 (22), 43 (45).

(±)-18,19-Dinorisoambrox (**12**). ^{1}H-NMR: 0.82 (*s*, 3 H); 1.065 (*s*, 3 H); 3.74 (*q*, *J* = 7, 1 H); 3.81 (*m*, 1 H). MS: 208 (0, M^+), 207 (2), 193 (100), 175 (12), 149 (11), 109 (33), 97 (12), 67 (15), 55 (11), 43 (13).

Table 1. *Comparative GC-Retention Times for Compounds* **1**–**12**

Compound	t_R [sec]	GC conditions
1	770	30 m *Carb*, 90°–190°, 10°/min
2	710	30 m *Carb*, 90°–190°, 10°/min
3	670	30 m *Carb*, 90°–190°, 10°/min
4	890	60 m *UCON*, 140°–180°, 3°/min
5	851	60 m *UCON*, 140°–180°, 3°/min
6	785	60 m *UCON*, 140°–180°, 3°/min
7	730	30 m *Carb*, 100°–200°, 5°/min
8	670	30 m *Carb*, 100°–200°, 5°/min
9	570	30 m *Carb*, 100°–200°, 5°/min
10	910	30 m *Carb*, 100°–200°, 3°/min
11	850	30 m *Carb*, 100°–200°, 3°/min
12	740	30 m *Carb*, 100°–200°, 3°/min

Table 2. *Chemical Shifts of the CH_3 and the H–C(12) Signals in the ^{1}H-NMR Spectra of Compounds* **1**–**12**

Compounds	C(17)H_3	C(18)H_3	C(19)H_3	C(20)H_3	H–C(12)	H–C(12)
1	0.84	0.83	0.88	1.02	3.83	3.92
4	0.84	–	0.907 (d)	1.09	3.821	3.916
7	0.76	0.83 (d)	–	1.09	3.828	3.9
10	0.755	–	–	1.09	3.835	3.92
2	0.90	0.83	1.10	1.38	3.77	3.86
5	1.08	–	0.895 (d)	1.38	3.77	3.86
8	1.0	0.835 (d)	–	1.37	3.766	3.85
11	1.0	–	–	1.39	3.78	3.87
3	0.90	0.86	0.89	1.06	3.70	3.78
6	0.89	–	0.94 (d)	1.05	3.75	3.85
9	0.845	0.855 (d)	–	1.1	3.734	3.788
12	0.82	–	–	1.065	3.74	3.81

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