Spirocyclic Ethers Related to *Ambrox*®: Synthesis and Structure-Odor Relationships

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Dedicated to Dr. *Günther Ohloff* on the occasion of his 80th birthday

The seven spirocyclic ethers **4**–**10**, related to the tricyclic odorant *Ambrox*® (**1**) and its diastereoisomers **2** and **3**, were synthesized. Their odoriferous activity/inactivity was correlated with the steric accessibility of the ether O-atom, calculated by computer-aided molecular modeling. The olfactory properties of the active compounds are discussed.

1. Introduction. – Several reviews [1] have highlighted the many facets of both the chemistry and the structure-odor relationships of the commercially important odorant (*Ambrox*®[1]) [2], its two diastereoisomers **2** [3] and **3** [4], and numerous analogues. In continuation of our studies [5] on analogues of **1**–**3**, we undertook to synthesize the racemic spirocyclic ethers **4**–**10**[2]) to evaluate their odor properties (*Fig. 1*).

Beforehand, we calculated the solvent-accessible surface area (probe radius = 1.4 Å) of the ether O-atom for all the envisaged compounds using the molecular-modeling software MacroModel [6][3]). The results of the calculations, given in *Fig. 1*, led us to a prediction of lack of ambergris-type odor activity for compound **10** and of more or less activity for compounds **4**–**9**, compound **7** being a borderline case.

2. Results and Discussion. – Racemic ketone **11** [7], with the *trans*-fused trimethyldecalin skeleton common to **1**–**3**, was the starting material for all the new compounds described hereafter.

For the synthesis of compound **4**, ketone **11** was treated with dibromomethane in the presence of Zn and $TiCl_4$ [8] to give alkene **12**, which was epoxidized with the alkaline hydrogen peroxide/benzonitrile system [9] in a selectivity of 99:1 to afford spiro-oxirane **4** (*Scheme 1*).

Alternatively, reaction of **11** with dimethyloxosulfonium methylide (= dimethylsulfoxonium methylide) in DMSO [10] gave selectively oxirane **5**

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[1]) *Ambrox*® is a registered trade name of *Firmenich SA*; systematic name of *Ambrox*®: (−)-(3a*R*,5a*S*,9a*S*,9b*R*)-dodecahydro-3a,6,6,9a-tetramethylnaphtho[2,1-*b*]furan.

[2]) Preliminary results for compounds **9** and **10** have been reported in [5c].

[3]) For compounds **9** and **10**, the values given in [5c] for the solvent-accessible surface area of the ether O-atom (9.2 Å for **9** and 0.7 Å for **10**) had been calculated at that time with the software MODEL (*W. C. Still*, University of Columbia, New York, 1985). In the present work, the calculations were performed with the software MacroModel [6].

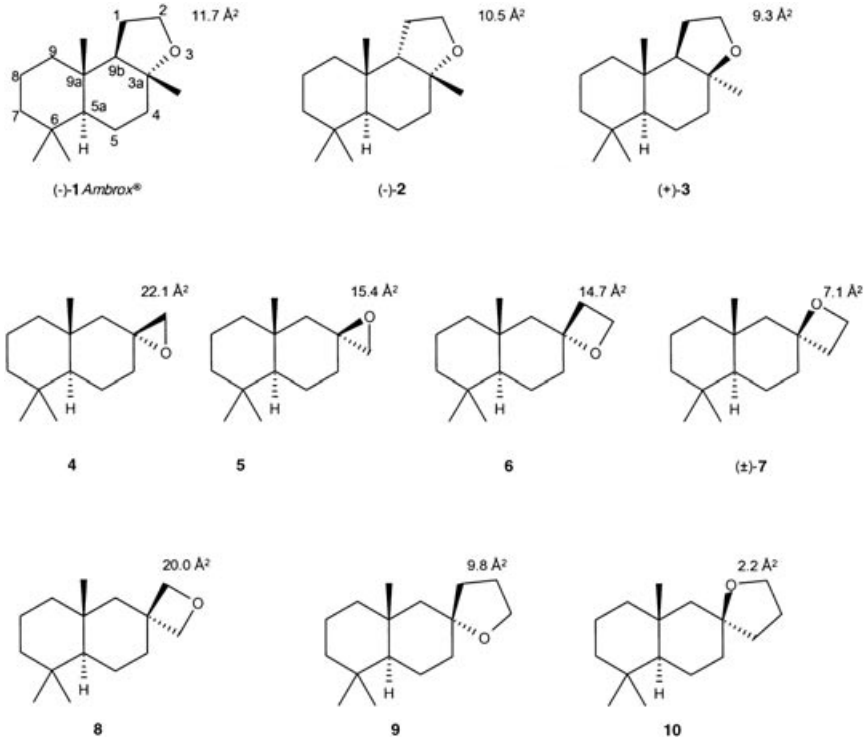

Fig. 1. *Solvent-accessible surface area of the O-atom of* Ambrox®, *of its diastereoisomers* **2** *and* **3**, *and of the synthesized spiro-ether analogs* **4**–**10**. Compounds **4**–**10** are racemates[4]).

(*Scheme 1*). When the same reaction was carried out under the conditions of *Okuma et al.* [11] (^{t}BuOH, 50–55°, 10 days), a double methylene-transfer reaction afforded spiro-oxetane **7**; in contrast, treatment of oxirane **4** under the same conditions gave no trace of spiro-oxetane **6**.

Oxirane **5** was rearranged in the presence of $BF_3 \cdot OEt_2$ to a 62:26 mixture of aldehydes **13** and **14**, which was equilibrated with K_2CO_3 in MeOH to afford a 98:2 mixture of the same aldehydes (*Scheme 1*). Reaction of either mixture with formaldehyde under alkaline conditions [12] gave diol **15**, which was cyclized to spiro-oxetane **8** by the method of *Picard et al.* [13].

For the synthesis of compound **6**, ketone **11** was subjected to the *Horner–Wadsworth–Emmons* reaction [14] to afford a 1:3 (*Z*)/(*E*) mixture of esters **16**, which was reduced with $LiAlH_4$ to give the corresponding mixture of unsaturated alcohols **17** (*Scheme 2*). Selective epoxidation of **17** afforded the corresponding mixture of *cis*/*trans*-oxiranes **18**, which was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate (*Vitride*®, *Red-Al*®) [15] to diol **19**; the latter was cyclized to the spiro-oxetane **6** under the same conditions as above for compound **8**.

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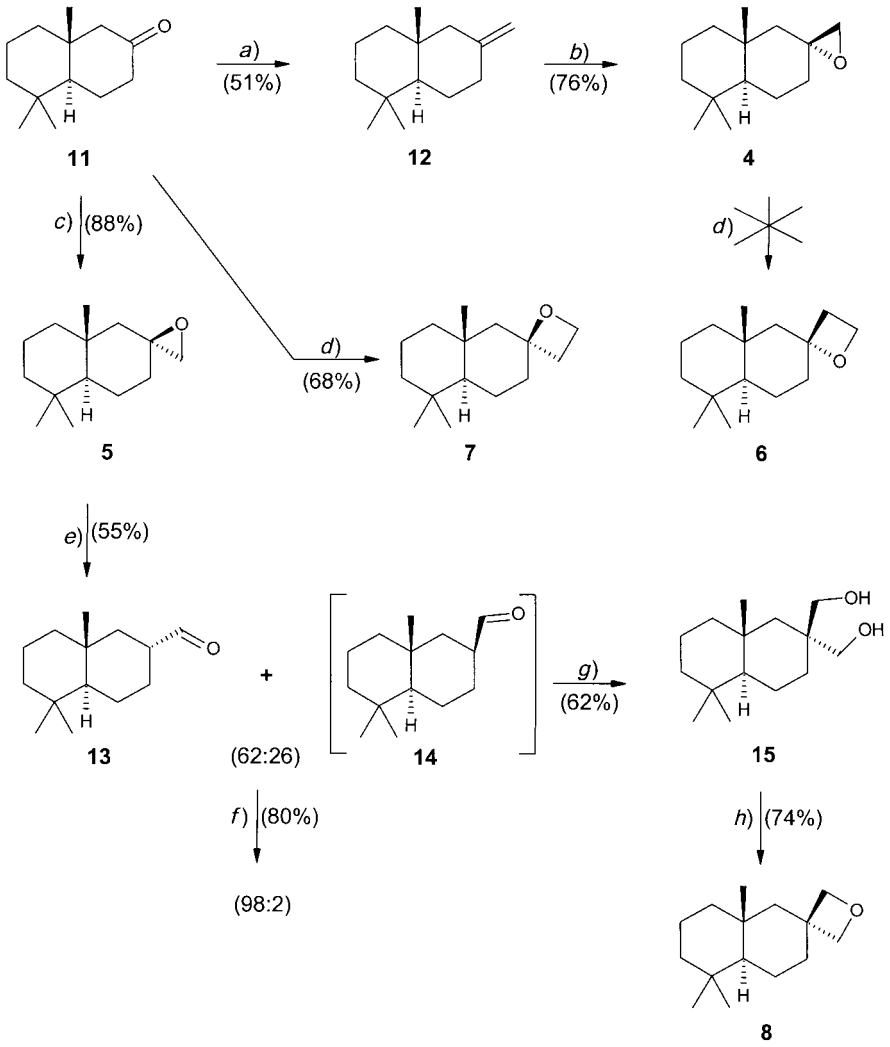
4) Only one enantiomer is depicted; all synthesized compounds are racemates.

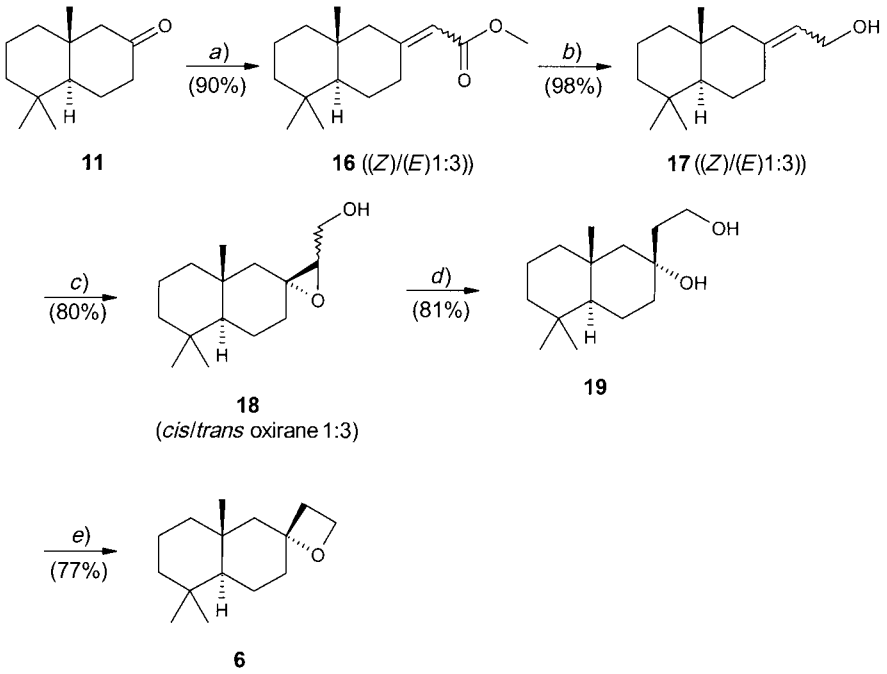
Scheme 1[4])



a) CH_2Br_2, Zn, $TiCl_4$, THF. *b*) 35% aq. H_2O_2 soln., PhCN, $KHCO_3$, MeOH. *c*) $Me_3SO^+I^-$, ^{t}BuOK, DMSO, r.t., 15 h. *d*) $Me_3SO^+I^-$, ^{t}BuOK, ^{t}BuOH, 50–55°, 10 d. *e*) $BF_3 \cdot OEt_2$, toluene, 0–10°, 0.5 h. *f*) K_2CO_3, MeOH, r.t., 1 h. *g*) 37% aq. CH_2O soln., KOH, ethylene glycol, 110–120°, 15 h. *h*) 1. BuLi, THF, 0°, 15 min.; 2. TsCl; 3. BuLi, 0° → 65°, 2 h.

Finally, for the synthesis of compounds **9** and **10**, ketone **11** was treated with the *Grignard* reagent prepared from 2-(2-bromoethyl)-1,3-dioxane and Mg [16] to give alcohol **20** (*Scheme 3*). Acidic hydrolysis of **20** afforded hemiacetal **21**, which was reduced with $LiAlH_4$ to diol **22**. Cyclization of **22** under acidic conditions gave a 42 : 58 mixture of spiro-tetrahydrofurans **9** and **10**, which was separated by column

Scheme 2[4])

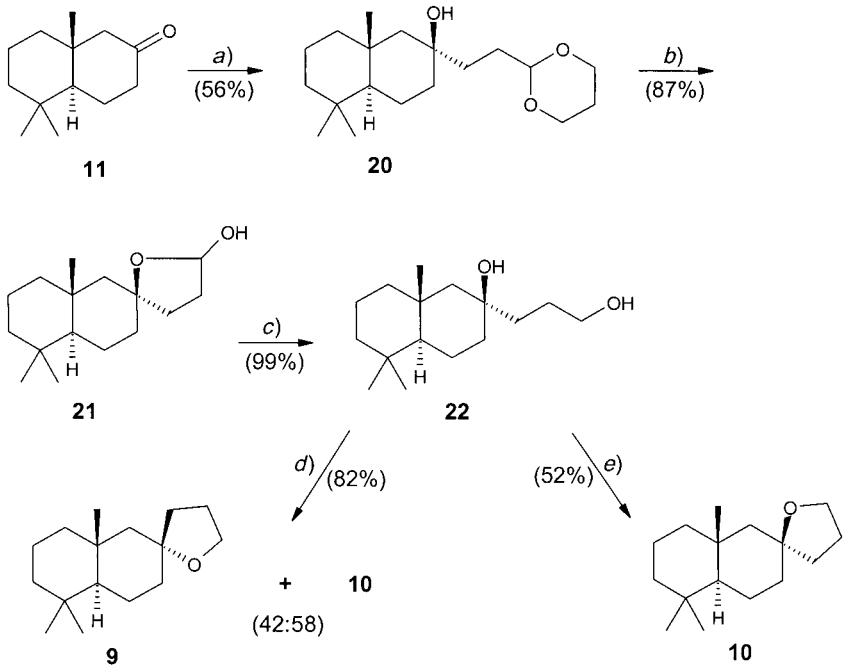


a) $(MeO)_2POCH_2COOMe$, NaOMe, pentane, r.t., 48 h. *b*) $LiAlH_4$, Et_2O, r.t., 2 h. *c*) *m*CPBA, Et_2O, 0–4°, 2 h. *d*) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, reflux, 15 h. *e*) 1. BuLi, THF, 0°, 15 min; 2. TsCl, r.t., 1 h; 3. BuLi, 60° → 65°, 2 h.

chromatography. In contrast, cyclization of diol **22** *via* the mono-*p*-toluenesulfonate in pyridine afforded exclusively spiro ether **10**.

The odor descriptions of the obtained spiro ethers **4**–**10** (*Table 1*) establish that the inactivity prediction for compound **10** is fully verified, whereas the odor of its diastereoisomer **9** is mainly woody; this result may be compared to the odor-quality alteration and odor-strength reduction observed for compound **3** relative to **1**, as reported by *Ohloff* and co-workers [3b][17]. In this respect, the critical arrangement of the 3a- and 9a-Me substituents in decalin-type ambergris odorants had been established [17], while the importance of the geometric position of the O-functionality relative to the axial 3a- and 9a-Me substituents in **1** was pointed out in an analysis of the superimposition of **1** with two non-decalin-type ambergris odorants [18]. Returning to *Table 1*, the only two compounds (*i.e.*, **4** and **8**) that evoke the ambergris descriptor, are those with the largest solvent-accessible surface area for the ether O-atom (see *Fig. 1*). However, compound **4** appears less active and with disturbing side notes, compared to the corresponding ring-opened analogue **23** [5b] (see *Fig. 2*), despite its larger solvent-accessible surface area of the ether O-atom, and the presence of a CH_2 substituent at the position corresponding to the 3a-Me substituent in **1**. Similarly, compound **6** is clearly less active and more offensive than the corresponding ring-opened analogues **24** and **25** [5b] (see *Fig. 3*).

Scheme 3[4])



a) 2-(2-Bromoethyl)-1,3-dioxane, Mg, THF/Et_2O, 25–35°, 20 h. *b*) 1.5N aq. HCl, THF, 80°, 5 h. *c*) $LiAlH_4$, Et_2O, r.t., 1 h. *d*) TsOH, $MeNO_2$, r.t., 16 h. *e*) TsCl, pyridine, r.t., 16 h.

Table 1. *Olfactory Properties of Spiro Ethers* **4**–**10**

Compound	Odor description
4	Woody, camphoraceous, amber, cresolic
5	Woody
6	Ionone residues, butter, rancid, burnt, dirty
7	Woody, camphoraceous, ink, residues, vitamins
8	Woody, amber, spicy, clove-buds
9	Woody
10	Weak, vague, difficult to describe

These results underline the inherent premise that the easily calculated steric accessibility of the functional group(s) in any bioactive compound is only one parameter among many. In the present case, other clues may reside in the increased rigidity of **4** and **6** (compared to **23**–**25**) and the different orientation of the heterocycle (as compared to **1** and **2**), causing a geometrically and/or sterically unfavorable position of the ether O-atom and/or of other atoms for an optimal interaction with the relevant sites on the receptor(s) for ambergris-type odorants, and possibly favoring competitive interactions with other receptors.

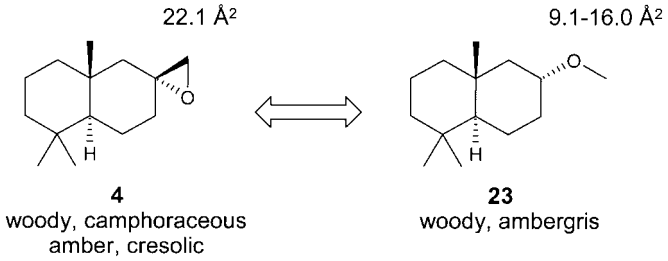


Fig. 2. *Comparison of* **4** *and* **23**[4])

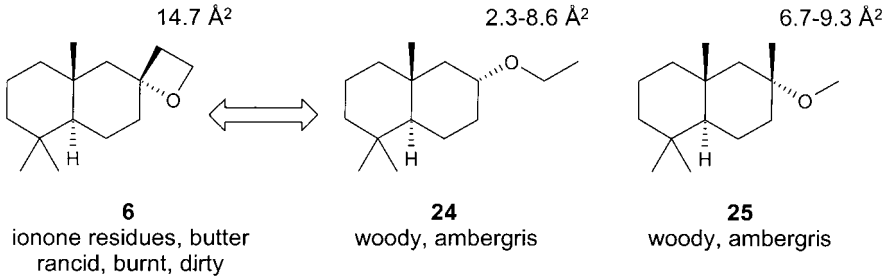


Fig. 3. *Comparison of* **6**, **24**, *and* **25**[4])

I wish to thank Dr. *F. Näf*, Corporate Vice President R&D Division, *Firmenich SA*, and Dr. *A. Boschung*, Senior Vice President R&D Division, for their support and interest in this work. I gratefully acknowledge the collaboration of Mrs. *A. Chollet*, Mr. *R. Pay*, Mr. *A. Sefrani*, and Mr. *S. Lamboley* for their experimental skill, of Mr. *W. Thommen* and Mr. *R. Brauchli* for NMR analysis, and of Dr. *P.-A. Blanc* for the evaluation of olfactory properties.

Experimental Part

General. All reactions were performed under N_2. GLC: *Hewlett-Packard-5890* instrument; flame-ionization detector coupled to a *Hewlett-Packard-3395* or *-3396A* integrator; capillary columns *Chrompack CP-Wax-52 CB* (10 m, 0.25 mm i.d.) and *CP-Sil-5 CB* (10 m, 0.25 mm i.d.). TLC: silica gel *60* (*Merck F-254*, layer thickness 0.25 mm). Prep. column chromatography (CC): silica gel *60* (*Merck*, 0.063–0.2 mm, 70–270 mesh, ASTM). Bulb-to-bulb distillation: *Büchi-GKR-50* or *-GRK-51* oven; b.p. correspond to the air temp. IR Spectra (liquid film): *Perkin-Elmer-297* or *-1600-FTIR* spectrometers; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra ($CDCl_3$): *Bruker AMX-360*, *DPX-400*, or *AV-500* spectrometers; δ in ppm downfield from $SiMe_4$, *J* in Hz. MS: *HP 5972* or *5973 MSD* (70 eV); *m*/*z* and intensities in % rel. to the base peak (100%).

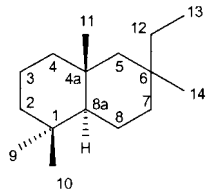
Computer-Aided Molecular Modeling. Calculations were carried out on a *Silicon-Graphics Iris-4D/35* computer system with the program MacroModel (versions 4.5 to 8.1) [6], by using the implemented MM2 energy minimization and Monte Carlo method.

*(4a*RS*,8a*SR*)-Decahydro-1,1,4a-trimethyl-6-methylenenaphthalene* (**12**). To a mixture of Zn powder (24.1 g, 0.369 mol) and dibromomethane (21.2 g, 0.122 mol) in THF (100 ml) at 25° was added 1M $TiCl_4$ in CH_2Cl_2 (90 ml, 0.09 mol). After 1 h, a soln. of **11** (15.8 g, 0.082 mol) in THF (60 ml) was added to the black slurry, and the mixture was stirred at r.t. for 15 h. The mixture was extracted with Et_2O, and the extracts were washed with H_2O and brine, dried (Na_2SO_4), and evaporated (16.5 g). Vacuum distillation (12-cm *Vigreux* column) gave **12** (8.08 g, 51%; purity 99%). Colorless oil. B.p. 92°/4.0 mbar. IR: 3080, 2930, 2850, 1655, 1460, 1390, 1380, 1370, 890, 880. ^1H-NMR: 0.80 (*s*, 3 H); 0.82 (*s*, 3 H); 0.87 (*s*, 3 H); 1.03–1.35 (*m*, 4 H); 1.41 (*m*, 3 H); 1.55–1.73

Table 2. *^{13}C-NMR Chemical Shifts* [ppm] *and Assignments for Compounds* **4**, **5**, **7**, **8**, **12**, **13**, *and* **15**[a]) (*Scheme 1*). Asterisks mark interchangeable signals.

	4	**5**	**7**	**8**	**12**	**13**	**15**
C(1)	33.1	33.0	33.0	32.9	33.1	33.0	33.1
C(2)	42.5	42.5	42.5	42.4	42.6*	42.4	42.4
C(3)	18.7	18.5	18.4	18.4	19.1	18.8	18.6
C(4)	42.1	42.1	42.3	41.8	42.1*	41.9	43.0
C(4a)	36.7	35.7	35.3	35.4	36.0	34.1	34.1
C(5)	51.8	50.8	56.2	52.9	53.9	44.4	48.7
C(6)	57.4	57.0	86.8	40.0	147.1	46.3	39.4
C(7)	34.9	34.6	40.2	38.0	36.0	27.0	31.6
C(8)	21.7	20.0	18.5	19.2	23.4	20.7	18.4
C(8a)	52.8	52.9	53.5	53.6	53.3	53.4	55.0
C(9)	33.3	33.3	33.3	33.2	33.1	33.0	33.0
C(10)	21.4	21.5	21.4	21.4	21.4	21.3	21.2
C(11)	19.9	19.7	20.0	19.3	19.1	19.3	20.8
C(12)	56.5	50.8	34.2	83.8 (α)	108.0	205.0	76.0 (α)
C(13)	–	–	64.3	–	–	–	–
C(14)	–	–		83.1 (β)	–	–	68.0 (β)

[a]) Arbitrary C-atom numbering:



(*m*, 2 H); 1.81 (br. *s*, 2 H); 2.0 (*m*, 1 H); 2.47 (*m*, 1 H); 4.53 (br. *s*, 1 H); 4.64 (br. *s*, 1 H). ^{13}C-NMR: *Table 2*. MS: 192 (32, M^+), 177 (58), 149 (13), 137 (65), 123 (60), 107 (38), 95 (67), 81 (70), 69 (52), 55 (50), 41 (100).

*(2*RS*,4a*SR*,8a*RS*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*)-2′-oxirane]* (**4**). To a soln. of **12** (5.52 g, 28.4 mmol) in MeOH (50 ml) at r.t. was added benzonitrile (3.66 g, 37.4 mmol), $KHCO_3$ (826 mg, 8.2 mmol), and 35% H_2O_2 soln. (4.4 ml, 45 mmol), and the mixture was stirred for 15 h at r.t. (GLC: only 50% conversion). The same amount of reagents was added and the mixture stirred for another 48 h at r.t. When no more starting material was detected, 10% aq. Na_2SO_3 soln. (70 ml) was added, followed by sat. aq. $NaHCO_3$ soln. and CH_3Cl_2. The org. phase was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Bulb-to-bulb distillation (oven temp. 120°/0.1 mbar) gave **4** (4.5 g, 76%; purity > 99%). Colorless oil. IR: 3050, 2940, 2850, 1465, 1395, 1370, 1160, 905, 840, 815, 740. ^{1}H-NMR: 0.83 (*s*, 3 H); 0.90 (*s*, 3 H); 0.98 (*m*, 2 H); 0.99 (*s*, 3 H); 1.18 (*m*, 2 H); 1.43 (*m*, 5 H); 1.56–1.91 (*m*, 4 H); 2.65 (*dd*, *J* = 5.0, 1.8, 1 H); 2.68 (*dd*, *J* = 5.0, 1.8, 1 H). ^{13}C-NMR: *Table 2*. MS: 208 (18, M^+), 193 (53), 175 (28), 161 (13), 152 (10), 147 (13), 137 (27), 123 (57), 109 (38), 123 (53), 91 (42), 81 (47), 69 (55), 55 (65), 41 (100).

*(2*RS*,4a*RS*,8a*SR*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*)-2′-oxirane]* (**5**). To a stirred suspension of trimethylsulfoxonium iodide (*Fluka purum*; 87.1 g, 388 mmol) in DMSO (50 ml) at r.t. was added **11** (50 g, 257 mmol) and then dropwise a hot soln. of KO^{t}Bu (*Fluka pract.*; 44.9 g, 388 mmol) in DMSO (350 ml). A slight exotherm (→ 30°) was observed. After 15 h at r.t., the mixture was poured on ice and extracted with Et_2O. The org. phase was washed with H_2O, sat. aq. $NaHCO_3$ soln. and brine (3×), dried (Na_2SO_4), and evaporated. The yellow oil (51.3 g) was subjected to vacuum distillation (10-cm *Vigreux* column): **5** (48.05 g, 88%; purity 99%). Colorless oil. B.p. 60–62°/0.1 mbar. IR: 2930, 2920, 1455, 1380, 1360, 1240, 940, 910, 800. ^{1}H-NMR: 0.86 (*s*, 3 H); 0.90 (*s*, 3 H); 0.95 (*dd*, *J* = 14, 2, 1 H); 0.98 (*dd*, *J* = 12, 3, 1 H); 1.07 (*m*, 1 H); 1.09 (*s*, 3 H); 1.20 (*m*, 1 H); 1.30–1.49 (*m*, 4 H); 1.51–1.70 (*m*, 3 H); 1.68 (br. *d*, *J* = 14, 1 H); 1.91 (*dt*, *J* = 5, 13, 1 H); 2.45 (*s*, 2 H). ^{13}C-NMR: *Table 2*. MS: 208 (12, M^+), 193 (100), 180 (20), 176 (17), 161 (40), 148 (13), 137 (20), 123 (32), 109 (36), 95 (48), 81 (52), 69 (60), 55 (67), 41 (95).

*(2*RS*,4a*RS*,8a*SR*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*),2′-oxetane]* (**7**). To a stirred soln. of trimethylsulfoxonium iodide (*Fluka* purum; 8.80 g, 40 mmol) in *t*BuOH (80 ml) was added a soln. of Ko*t*Bu (*Fluka pract.*; 4.48 g, 40 mmol) in *t*BuOH (50 ml), and the mixture was stirred at 50° (bath temp. 56°) for 0.5 h. A soln. of **11** (1.94 g, 10 mmol) in *t*BuOH (20 ml) was added, and the mixture was stirred at 50–55° (bath temp. 56–60°) for 10 days. The cooled mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. (2×), and evaporated. The residue was dissolved in Et_2O, the soln. washed with brine, dried (K_2CO_3), and evaporated, and the yellowish oil (2.3 g) subjected to bulb-to-bulb distillation (oven temp. 100°/0.2 mbar): **7** (1.52 g, 68%; purity >99%). Colorless oil. IR: 2918, 2900, 2868, 2838, 1456, 1424, 1383, 1223, 1128, 984, 957, 901, 826. ^{1}H-NMR: 0.81 (*s*, 3 H); 0.83 (*dd*, *J* = 10.6, 1 H); 0.86 (*s*, 3 H); 1.01 (*m*, 1 H); 1.02 (*s*, 3 H); 1.11 (br. *d*, *J* = 14, 1 H); 1.15 (*m*, 1 H); 1.30–1.59 (*m*, 6 H); 1.63 (*m*, 1 H); 1.95 (*dd*, *J* = 14, 3, 1 H); 2.24 (*ddd*, *J* = 20, 10, 8, 1 H); 2.29 (*ddd*, *J* = 20, 10, 8, 1 H); 2.41 (*m*, 1 H); 4.43 (*dd*, *J* = 10, 8, 2 H). ^{13}C-NMR: *Table 2*. MS: 222 (24, M^+), 207 (72), 194 (26), 177 (30), 161 (38), 137 (48), 123 (52), 109 (77), 95 (85), 81 (75), 69 (75), 55 (88), 41 (100).

*(2*RS*,4a*SR*,8a*RS*)-Decahydro-5,5,8a-trimethylnaphthalene-2-carboxaldehyde* (**13**). To a stirred soln. of **5** (4.5 g, 21.6 mmol) in toluene (50 ml) at 0-4° was added dropwise during 15 min $BF_3 \cdot OEt_2$ (*Fluka pract.*; 2.5 ml, 2.82 g, 20 mmol), and the mixture was stirred below 10° for 15 min. The mixture was poured into cold sat. aq. $NaHCO_3$ soln. and extracted with Et_2O; the org. phase washed with H_2O, dried (Na_2SO_4), and evaporated, and the yellowish oil (4.5 g) subjected to bulb-to-bulb distillation (oven temp. 150°/0.1 mbar): **13**/**14** 62:26 (2.84 g, 55%; purity 88%). To a stirred soln. of **13**/**14** (1.06 g, 4.5 mmol) in MeOH (10 ml) at r.t. was added K_2CO_3 (276 mg, 2 mmol), and the mixture was stirred at r.t. for 1 h. The mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and evaporated and the colorless oil (0.93 g) subjected to bulb-to-bulb distillation (oven temp. → 160°/0.2 mbar): **13**/**14** 91:3 (0.80 g, 80%; purity 93%) as a colorless oil. Further purification by CC (SiO_2 (60 g), toluene), followed by bulb-to-bulb distillation gave **13**/**14** 98:2 (0.66 g; purity >99%). IR: 2990, 2920, 2860, 2840, 2595, 1720, 1450, 1380, 1360, 985. ^{1}H-NMR: 0.80 (*s*, 3 H); 0.85 (*s*, 3 H); 0.88 (*dd*, *J* = 12, 3, 1 H); 0.96 (*s*, 3 H); 1.00–1.38 (*m*, 5); 1.43 (*m*, 3 H); 1.52 (*m*, 1 H); 1.62 (*m*, 1 H); 1.72 (*m*, 1 H); 2.03 (*m*, 1 H); 2.47 (*m*, 1 H); 9.55 (*d*, *J* = 2, 1 H). ^{13}C-NMR: *Table 2*. MS: 208 (42, M^+), 193 (28), 175 (31), 152 (26), 137 (32), 123 (74), 109 (54), 95 (82), 81 (70), 69 (80), 67 (69), 55 (79), 41 (100).

*(4a*RS*,8a*SR*)-Decahydro-5,5,8a-trimethylnaphthalene-2,2-dimethanol* (**15**). To a stirred mixture of **13**/**14** 80:14 (2.0 g, 9 mmol; purity 94%), ethylene glycol (15 ml), and 37% aq. formaldehyde (9 ml) at 0° was added 50% aq. KOH soln. (9 ml), and the mixture was heated to reflux (bath temp. 110–120°) for 15 h. The cooled mixture was extracted with CH_2Cl_2, the org. phase washed with sat. aq. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated, and the yellow solid (1.72 g) dissolved in hot CH_2Cl_2 (50 ml). After dilution with heptane (50 ml), the soln. was concentrated to *ca.* 50 ml and left at 0° for 1 h: **15** (1.40 g, 62%; purity 96%). Colorless crystals. M.p. 134–136°. IR ($CHCl_3$): 3590, 3400 (br.), 2980, 2920, 2830, 1450, 1380, 1360, 1030, 1015. ^{1}H-NMR: 0.79 (*s*, 3 H); 0.84 (*dd*, *J* = 12, 3, 1 H); 0.86 (*s*, 3 H); 0.88 (br. *d*, *J* = 14, 1 H); 1.02 (*s*, 3 H); 0.95–1.08 (*m*, 2 H); 1.12–1.72 (*m*, 9 H); 2.45 (br., 2 OH); 3.37 (*d*, *J* = 10, 1 H); 3.43 (*d*, *J* = 10, 1 H); 3.76 (*d*, *J* = 10, 1 H); 3.80 (*d*, *J* = 10, 1 H). ^{13}C-NMR: *Table 2*. MS: 222 (5), 209 (8), 191 (82), 177 (29), 135 (44), 123 (37), 113 (30), 109 (61), 95 (100), 81 (64), 69 (81), 55 (79), 41 (67).

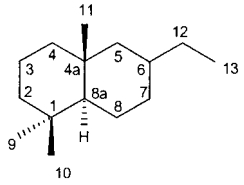
*(4a*RS*,8a*SR*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*),3′-oxetane]* (**8**). To a stirred soln. of **15** (0.8 g, 3.2 mmol, purity 96%) in THF (40 ml) at 0–4° was added dropwise 1.6M BuLi in hexane (*Fluka*; 2.4 ml, 3.8 mmol). After 15 min, a soln. of TsCl (720 mg, 3.8 mmol) in THF (5 ml) was added, and the mixture was stirred at r.t. for 1 h. The mixture was cooled again to 0–4°, and another portion of 1.6M *n*BuLi in hexane (2.4 ml, 3.8 mmol) was added dropwise. The mixture was heated to 60–65° for 2 h. The cooled mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried (K_2CO_3), and the yellowish oil (0.8 g) subjected to bulb-to-bulb distillation (oven temp. → 150°/0.2 mbar): **8** (0.54 g, 74%; purity 97%). Colorless oil. IR (neat): 2930, 2860, 1460, 1445, 1385, 1365, 990. ^{1}H-NMR: 0.77 (*s*, 6 H); 0.83 (*dd*, *J* = 12, 3, 1 H); 0.86 (*s*, 3 H); 1.09 (br. *d*, *J* = 14, 1 H); 0.97–1.48 (*m*, 7 H); 1.60 (*m*, 2 H); 1.77 (*dd*, *J* = 14, 2, 1 H); 2.45 (*m*, 1 H); 4.15 (*d*, *J* = 6, 1 H); 4.33 (*d*, *J* = 6, 1 H); 4.40 (*d*, *J* = 6, 1 H); 4.65 (*dd*, *J* = 6, 1 H). ^{13}C-NMR: *Table 2*. MS: 192 (65), 177 (73), 137 (100), 123 (73), 107 (42), 95 (76), 81 (76), 69 (55), 55 (53), 41 (85).

*Methyl [(4a*RS*,8a*SR*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalen-2(1*H*)-ylidene]acetate* ((*Z*)/(*E*) mixture; **16**). To a stirred mixture of 30% (*ca.* 5.4M) NaOMe in MeOH (*Fluka pract.*; 40 g, 216 mmol) and pentane (500 ml) at r.t. was added dropwise within 0.5 h methyl (dimethoxyphosphinyl)acetate (40.0 g, 220 mmol) (→ colorless precipitate). After 0.5 h, a soln. of **11** (38.8 g, 200 mmol) in pentane (250 ml) was added dropwise during 0.5 h. After 24 h, another portion of methyl (dimethoxyphosphinyl)acetate (40 g) and of 30% (*ca.* 5.4M) NaOMe in MeOH (40 g) was added, and stirring at r.t. was continued for 24 h. The mixture was then washed with brine (3×), dried (Na_2SO_4), and evaporated and the yellowish oil (49 g) subjected to bulb-to-bulb distillation (oven temp. → 160°/0.1 mbar): **16** (46.2 g, 90%; purity 97%; (*Z*)/(*E*) 1:3). Colorless oil. IR

Table 3. *^{13}C-NMR Chemical Shifts* [ppm] *and Assignments for Compounds* **6** *and* **16**–**19**[a]) (*Scheme 2*)

	6	(*E*)-**16** (major)	(*Z*)-**16** (minor)	(*E*)-**17** (major)	(*Z*)-**17** (minor)	*trans*-**18** (major)	*cis*-**18** (minor)	**19**
C(1)	32.9	33.2	33.2	33.1	33.1	33.0	33.0	33.0
C(2)	42.3	42.4	42.4	42.6	42.6	42.3	42.4	42.3
C(3)	18.3	19.0	19.1	19.1	19.2	18.6	18.7	18.6
C(4)	42.0	41.9	42.0	42.0	42.1	41.7	41.9	42.6
C(4a)	36.0	37.4	37.4	36.2	36.2	36.6	36.2	35.2
C(5)	56.4	56.1	47.3	55.4	47.1	53.4	47.1	57.2
C(6)	86.7	161.7	161.8	141.6	141.9	61.8	62.5	74.1
C(7)	40.6	30.2	38.5	29.3	37.7	30.4	36.8	41.7
C(8)	19.5	23.3	24.1	23.0	23.7	21.7	21.5	20.3
C(8a)	53.2	53.5	53.7	53.8	53.9	53.2	53.2	54.7
C(9)	33.3	33.2	33.1	33.2	33.2	33.2	33.3	33.2
C(10)	21.4	21.3	21.4	21.4	21.4	21.4	21.5	21.2
C(11)	19.9	19.3	18.6	19.2	19.2	19.6	19.6	20.7
C(12)	34.6	113.9	113.9	121.8	121.7	65.6	66.5	40.1
C(13)	65.3	167.0	167.2	58.4	58.5	61.1	61.7	60.0
MeO	–	50.8	50.7	–	–	–	–	

[a]) Arbitrary C-atom numbering:



((*Z*)/(*E*) mixture): 2980, 2930, 2830, 1715, 1650, 1430, 1375, 1255, 1210, 1200, 1155, 1040, 1025. ^{1}H-NMR: ((*E*)-**16** (major): 0.79 (*s*, 3 H); 0.82 (*s*, 3 H); 0.90 (*s*, 3 H); 3.68 (*s*, 3 H); 5.53 (br. *s*, 1 H); (*Z*)-**16** (minor): 0.79 (*s*, 3 H); 0.84 (*s*, 3 H); 0.88 (*s*, 3 H); 3.66 (*s*, 3 H); 5.66 (br. *s*, 1 H). ^{13}C-NMR: *Table 3*. MS ((*E*)-**16**): 250 (85, M^+), 235 (35), 219 (21), 176 (27), 137 (100), 123 (88), 114 (47), 95 (46), 81 (62), 69 (60), 55 (52), 41 (82).

*2-[(4a*RS*,8a*SR*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylnaphthalen-2(1*H*)-ylidene]ethanol* ((*Z*)/(*E*) mixture; **17**). To a stirred suspension of $LiAlH_4$ (1.52 g, 40 mmol) in Et_2O (50 ml) at r.t. was added dropwise a soln. of esters **16** (10.3 g, 40 mmol; purity 97%; (*Z*)/(*E*) 1:3) in Et_2O (50 ml), while maintaining the temp. below 30° (water bath). After 2 h at r.t., the mixture was cooled to 0–4°, acetone (*ca.* 3 ml) was added, then 1N aq. NaOH (7.5 ml), and the mixture was stirred to r.t. during 0.5 h. Na_2SO_4 was added, the solid filtered off, the filtrate evaporated, and the colorless syrup (9.5 g) subjected to bulb-to-bulb distillation (oven temp. → 175°/0.2 mbar): **17** (8.91 g, 98%; purity 98%; (*Z*)/(*E*) 1:3). Colorless syrup. IR ((*Z*)/(*E*) mixture): 3300 (br.), 2990, 2960, 2920, 2830, 1655, 1450, 1435, 1380, 1370, 1360, 1015, 995. ^{1}H-NMR: (*E*)-**17** (major): 0.78 (*s*, 3 H); 0.80 (*s*, 3 H); 0.87 (*s*, 3 H); 4.15 (br. *d*, *J* = 7, 2 H); 5.28 (br. *t*, *J* = 7, 1 H); (*Z*)-**17** (minor): 0.78 (*s*, 3 H); 0.80 (*s*, 3 H); 0.86 (*s*, 3 H); 4.10 (br. *d*, *J* = 7, 2 H); 5.45 (br. *t*, *J* = 7, 1 H). ^{13}C-NMR: *Table 3*. MS ((*E*)-**17**): 222 (31, M^+), 204 (48), 189 (45), 137 (99), 123 (53), 109 (47), 95 (73), 81 (80), 69 (70), 55 (71), 41 (100).

*(2*RS*,4a*SR*,8a*RS*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*),2′-oxirane]-3′-methanol* (**18**). To a stirred soln. of **17** (8.84 g, 39 mmol; purity 98%) in CH_2Cl_2 (90 ml) at 0–4° (ice-water bath) was added portionwise *m*-chloroperbenzoic acid (*m*CPBA; *Aldrich*; 50% purity; 13.8 g, 40 mmol), and the mixture was stirred at 0–4° for 2 h. The mixture was diluted with AcOEt, washed with 1N aq. NaOH (2×), sat. aq. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and evaporated and the yellowish syrup (9.6 g) subjected to bulb-to-bulb distillation (oven temp. → 200°/0.5 mbar): **18** (9.06 g, 80%; purity *ca.* 82%; 1:3 *cis*/*trans*-oxirane diastereoisomer mixture (not well resolved)). Colorless syrup. IR: 3410 (br.), 2930, 2830, 1450, 1380, 1360, 1030, 900, 800. ^{1}H-NMR: *trans*-**18** (major): 0.81 (*s*, 3 H); 0.89 (*s*, 3 H); 0.98 (*s*, 3 H); 2.68 (br. *s*, OH); 3.72 (*dd*, *J* = 12, 7, 1 H); 3.88 (*dd*, *J* = 12, 4, 1 H); *cis*-**18** (minor): 0.85 (*s*, 3 H); 0.89 (*s*, 3 H); 0.90 (*s*, 3 H); 2.68 (br. *s*, OH); 3.58

(*dd*, *J* = 12, 7, 1 H); 3.91 (*dd*, *J* = 12, 4, 1 H). ^{13}C-NMR: *Table 3*. MS (*trans*-**18**): 238 (0.5, M^+), 223 (59), 195 (48), 177 (48), 161 (32), 137 (34), 121 (30), 109 (50), 95 (59), 81 (64), 69 (62), 55 (69), 41 (100).

*(2*RS*,4a*SR*,8a*RS*)-Decahydro-2-hydroxy-5,5,8a-trimethylnaphthalene-2-ethanol* (**19**). To a stirred soln. of **18** (9.0 g, 31 mmol; purity 82%) in THF (100 ml) at r.t. was added dropwise 70% (3.5M) $NaAlH_2(OCH_2CH_2OMe)_2$ in toluene (*Fluka pract.*; 20 ml, 70 mmol), and the mixture was heated to reflux (65°) for 3 h. Another portion of reducing agent (20 ml, 70 mmol) was added at r.t. and reflux continued for 15 h. The cooled mixture was diluted with Et_2O and AcOEt, washed successively with 5% aq. HCl soln., H_2O, and sat. aq. $NaHCO_3$ soln., dried (Na_2SO_4), and evaporated and the solid (9 g) crystallized from Et_2O (50 ml) at 0°: **19** (6.85 g, 81%; purity 90%). Two further recrystallizations from AcOEt gave anal. pure **19**. M.p. 162–3°. IR ($CHCl_3$): 3320 (br.), 2920, 2830, 1440, 1375, 1360, 1060, 1005, 845. ^{1}H-NMR: 0.77 (*s*, 3 H); 0.87 (*s*, 3 H); 0.94 (*s*, 3 H); 0.95 (*dd*, *J* = 12, 3, 1 H); 1.00–1.25 (*m*, 3 H); 1.25 (br. *d*, *J* = 13, 1 H); 1.40 (*m*, 4 H); 1.63 (*m*, 2 H); 1.78 (*dd*, *J* = 13, 3, 1 H); 1.92 (*m*, 2 H); 2.06 (*m*, 1 H); 2.36 (br. *s*, OH); 2.90 (br. *s*, OH); 3.89 (br. *t*, *J* = 4, 2 H). ^{13}C-NMR: *Table 3*. MS: 240 (3, M^+), 222 (3), 207 (3), 195 (22), 177 (12), 137 (18), 109 (12), 101 (100), 95 (17), 83 (27), 69 (24), 55 (20), 41 (15).

*(2*RS*,4a*SR*,8a*RS*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethylspiro[naphthalene-2(1*H*),2′-oxetane]* (**6**). To a stirred soln. of **19** (1.3 g, 5.4 mmol, purity 99%) in THF (50 ml) at 0–4° (ice-water bath) was added dropwise 1.6M BuLi in hexane (*Fluka*; 4 ml, 6.4 mmol). After 15 min, a soln. of TsCl (1.14 g, 6 mmol) in THF (10 ml) was added, and the mixture was stirred to r.t. for 1 h. The mixture was cooled again to 0–4°, 1.6M BuLi in hexane (4 ml, 6.4 mmol) was added, and the mixture was heated to 60–65° for 1 h. The cooled mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and H_2O, dried (K_2CO_3), and evaporated and the yellowish oil (1.3 g) subjected to bulb-to-bulb distillation (oven temp. → 150°/0.2 mbar): **6** (1.0 g, 77%; purity 92%). Colorless oil. IR: 2920, 2870, 2840, 1455, 1440, 1375, 1360, 1220, 1060, 965, 920. ^{1}H-NMR: 0.78 (*s*, 3 H); 0.88 (*s*, 3 H); 0.89 (overlapped *dd*, 1 H); 0.90 (*s*, 3 H); 1.02–1.28 (*m*, 3 H); 1.24 (br. *d*, *J* = 12, 1 H); 1.40 (*m*, 4 H); 1.61 (*m*, 2 H); 1.89 (*dd*, *J* = 12, 2, 1 H); 2.37 (*m*, 2 H); 2.63 (*m*, 1 H); 4.43 (*dt*, *J* = 8, 6, 1 H); 4.53 (*dt*, *J* = 8, 7, 1 H). ^{13}C-NMR: *Table 3*. MS: 222 (10, M^+), 207 (13), 194 (10), 179 (18), 161 (15), 137 (49), 123 (34), 109 (47), 95 (67), 83 (75), 69 (53), 55 (73), 41 (100).

*(2*RS*,4a*SR*,8a*RS*)-2-[2-(1,3-Dioxan-2-yl)ethyl]decahydro-5,5,8a-trimethylnaphthalen-2-ol* (**20**). To stirred Mg turnings (5.0 g, 208 mmol) at 30° was added dropwise during 1.5 h a soln. of 2-(2-bromoethyl)-1,3-dioxane (*Fluka*; 40.0 g, 205 mmol) in THF (150 ml). A soln. of ketone **11** (20.0 g, 103 mmol) in Et_2O was added dropwise at r.t., and the mixture was stirred at r.t. for 20 h. The mixture was poured on ice-cold sat. aq. NH_4Cl soln. and extracted with Et_2O; the extracts were washed with H_2O (4×), dried (Na_2SO_4), and evaporated to a syrup, which solidified on standing (32 g; purity 96%). Two crystallizations from petroleum ether (30–50°) at −30° afforded **20** (17.8 g, 56%; purity > 99%). M.p. 62–64°. IR (solid): 3476, 3347 (br.), 2988, 2923, 2862, 2838, 1455, 1406, 1383, 1264, 1116, 1037, 952, 937, 926, 846, 838. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.83 (*dd*, *J* = 12, 3, 1 H); 0.86 (*s*, 3 H); 0.95 (*m*, 1 H); 1.12 (*s*, 3 H); 1.05–1.58 (*m*, 12 H); 1.58–1.84 (*m*, 4 H); 1.84 (br. *s*, OH); 2.07 (*m*, 1 H); 3.76 (*td*, *J* = 11, 2, 2 H); 4.10 (*dd*, *J* = 11, 5, 2 H); 4.53 (*t*, *J* = 4.5, 1 H). ^{13}C-NMR: *Table 4*. MS: 310 (7), 292 (3), 234 (31), 201 (29), 194 (30), 177 (66), 171 (63), 116 (80), 109 (44), 100 (79), 95 (59), 87 (100), 81 (49), 69 (46), 58 (52), 55 (40), 41 (45).

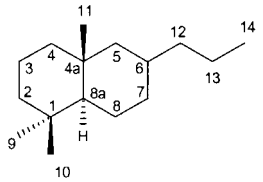
*(2*RS*,4′a*SR*,8′a*RS*)-Decahydro-5′,5′,8′a-trimethylspiro[furan-2(3*H*),2′(1′*H*)-naphthalen]-5-ol* (**21**). To a stirred soln. of **20** (3.0 g, 8.5 mmol; purity 88%) in THF (50 ml) was added 1.5N aq. HCl (50 ml), and the mixture was heated under reflux for 1 h. The cooled mixture was extracted with Et_2O, and the extracts were washed with H_2O, sat. aq. $NaHCO_3$ soln. and brine, dried (K_2CO_3), and evaporated at r.t.: **21** (2.5 g, 87%; purity 75%) as a solid. Crystallization from pentane at −30° afforded an anal. sample (M.p. 86.5–87°) which, by NMR, was as a *ca.* 1:1 diastereoisomer mixture (unresolved by GC). IR (solid): 3269 (br.), 2915, 2864, 2837, 1460, 1440, 1383, 1262, 1168, 1096, 1056, 995, 961, 846. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.87 (*s*, 3 H); 1.05, 1.10 (2*s*, 3 H); 0.85–2.05 (*m*, 16 H); 2.58, 3.00 (2 br. *s*, OH); 5.50 (br. *t*, 1 H). ^{13}C-NMR: *Table 4*. MS: 252 (7, M^+), 234 (53), 219 (22), 201 (15), 190 (16), 177 (100), 137 (27), 123 (30), 113 (53), 109 (45), 97 (58), 81 (63), 69 (41), 55 (37), 41 (44).

*(2*RS*,4a*SR*,8a*RS*)-Decahydro-2-hydroxy-5,5,8a-trimethylnaphthalene-2-propanol* (**22**). To a stirred suspension of $LiAlH_4$ (180 mg, 4.7 mmol) in Et_2O (25 ml) at 0° was added a soln. of **21** (1.2 g, 3.5 mmol; purity 75%) in Et_2O (10 ml), and the mixture was stirred at r.t. for 15 h. The mixture was cooled to 0°, hydrolyzed with 1N aq. NaOH (0.9 ml), stirred at r.t. for 0.5 h, dried (Na_2SO_4), filtered, and evaporated. The obtained solid (1.1 g, purity 80%) was crystallized from Et_2O at −30°: **22** (0.46 g, 51%; purity > 99%). Colorless crystals. M.p. 141–142°. IR (solid): 3288 (*br.*), 2919, 2897, 2864, 2838, 1454, 1439, 1382, 1364, 1357, 1053, 1038, 954, 922, 834. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.83 (overlapping *dd*, 1 H); 0.87 (*s*, 3 H); 0.97 (*m*, 1 H); 1.12 (*s*, 3 H); 1.10–1.57

Table 4. *^{13}C-NMR Chemical Shifts* [ppm] *and Assignments for Compounds* **9**, **10**, **20**–**22**[a]) (*Scheme 3*). Asterisks mark interchangeable signals.

	9	**10**	**20**	**21**	**22**
C(1)	33.0	33.0	33.0	33.0	33.0
C(2)	42.4	42.6	42.4	42.5*	42.4
C(3)	18.7	18.6	18.4	18.5	18.3
C(4)	42.4	42.8	42.6	42.6*	42.5
C(4a)	35.3	32.2	34.6	35.0/35.3	34.6
C(5)	56.4	54.0	55.5	55.4/56.8	55.5
C(6)	82.8	92.3	71.9	84.5/84.6	72.4
C(7)	39.2	38.7	39.6	40.0/41.1	39.6
C(8)	20.9	19.5	18.4	19.1/19.5	18.3
C(8a)	54.2	54.5	54.5	54.2	54.5
C(9)	33.3	33.3	33.2	33.3	33.2
C(10)	21.4	24.4	21.3	21.4	21.3
C(11)	20.4	20.3	21.0	21.1/21.4	21.0
C(12)	36.2	39.7	39.4	37.4/37.5	42.6
C(13)	26.7	24.8	29.0	32.4/32.8	26.4
C(14)	65.3	66.7	102.7	99.0/99.1	63.5
$OCH_2CH_2CH_2O$	–	–	66.9	–	–
$OCH_2CH_2CH_2O$	–	–	25.7	–	–

[a]) Arbitrary C-atom numbering:



(*m*, 11 H); 1.67 (*m*, 3 H); 1.82 (*m*, 1 H); 2.08 (br., 2 OH); 3.64 (*t*, *J* = 5.5, 2 H). ^{13}C-NMR: *Table 4*. MS: 254 (1, M^+), 236 (8), 221 (8), 195 (100), 177 (62), 137 (36), 115 (25), 97 (42), 95 (27), 81 (22), 69 (27), 55 (21), 41 (18).

*(2*RS*,4′a*RS*,8′a*SR*)-Decahydro-5′,5′,8′a-trimethylspiro[furan-2(3*H*),2′(1′*H*)-naphthalene]* (**9**) *and (2*RS*,4′a*SR*,8′a*RS*)-Decahydro-5′,5′,8′a-trimethylspiro[furan-2(3*H*),2′(1′*H*)-naphthalene]* (**10**). To a stirred suspension of **22** (3 g, 11.8 mmol) in nitromethane (150 ml) was added TsOH (0.71 g, 3.7 mmol), and the mixture was stirred at r.t. for 16 h. The mixture was diluted with Et_2O, washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4) and evaporated: oily mixture[5]) of **9**/**10** 42 : 58 (2.8 g; purity > 99%). CC (silica gel (300 g), CH_2Cl_2) afforded **10** (1.16 g, 42%) in the first fraction. IR: 2950, 2850, 1465, 1450, 1395, 1390, 1375, 1365, 1330, 1180, 1130, 1100, 1055, 1025, 975, 935. ^{1}H-NMR: 0.82 (*s*, 3 H); 0.86 (*s*, 3 H); 0.86 (overlapping *dd*, 1 H); 0.98 (*m*, 1 H); 1.08 (*s*, 3 H); 1.05–1.60 (*m*, 11 H); 1.65 (*m*, 1 H); 1.83 (*m*, 3 H); 3.82 (*t*, *J* = 7, 2 H). ^{13}C-NMR: *Table 4*. MS: 236 (20, M^+), 221 (3), 137 (11), 119 (18), 105 (25), 97 (100), 85 (20), 71 (40), 57 (75), 43 (73), 41 (46).

The second fraction (1.12 g, 40%) was bulb-to-bulb distilled (oven temp. → 120°/0.1 mbar): **9**. IR: 2950–2830 (br.), 1455, 1440, 1375, 1360, 1045, 1010, 960, 940, 920, 880, 835, 710. ^{1}H-NMR: 0.79 (*s*, 3 H); 0.87 (*s*, 3 H); 0.94 (overlapping *dd*, 1 H); 0.95 (*s*, 3 H); 1.08 (*m*, 1 H); 1.10–1.55 (*m*, 8 H); 1.64 (*m*, 3 H); 1.78 (*m*, 1 H); 1.91 (*m*, 3 H); 3.68 (*dt*, *J* = 14, 7, 1 H); 3.79 (*dt*, *J* = 14, 6, 1 H). ^{13}C-NMR: *Table 4*. MS: 236 (4, M^+), 221 (2), 137 (8), 124 (5), 109 (5), 97 (100), 81 (9), 67 (6), 55 (15), 41 (9).

Selective Synthesis of **10** *from* **22**. To a stirred soln. of **22** (238 mg, 1.1 mmol; purity 95%) in pyridine (5 ml) at 0° was added TsCl (190 mg, 1.0 mmol), and the mixture was stirred at r.t. for 16 h. The mixture was diluted

[5]) Compound **10** was eluted before **9** on GC (*Sil* and *Carb*) as well as CC (SiO_2).

with Et_2O and H_2O, the org. phase washed with H_2O, 10% aq. HCl soln., H_2O, and sat. aq. $NaHCO_3$ soln. dried (Na_2SO_4), and evaporated and the yellowish oil (197 mg) subjected to CC (SiO_2, toluene): **10** (135 mg, 52%; purity >99%).

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