Odoriferous Cyclic Ethers *via* Co-Halogenation Reaction: Facile Preparation of Nerol Oxide, *Florol*®, *Florol*® Methyl Ether, and *Pityol*® Methyl Ether

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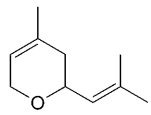
A series of odoriferous cyclic ethers, including nerol oxide (**1**), *Florol*® (**2**), *Florol* methyl ether (**3**), and *Pityol*® methyl ether (**4b**), were prepared by a versatile synthetic protocol based on co-halogenation with 1,3-dibromo-5,5-dimethylhydantoin (=1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione; DDH) as the key step. The methodology provides a facile access to important perfumery molecules from abundantly available monoterpene alcohols.

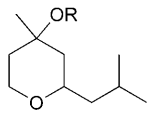
Introduction. – Monoterpene cyclic ethers with dihydropyran, tetrahydropyran, and tetrahydrofuran backbones are well-known for their fresh and stimulating fragrances. Some important members include rose oxides, nerol oxide, *Florol*®, *Clarycet*®, *Dermox*®, *Pityol*®, and *Rhubafuran*®[1]). Most of these compounds, particularly the tetrahydropyrans, possess a fresh floral fragrance coupled either with a dominant or a subdued ethereal fresh green note. Nerol oxide and rose oxides, with di- and tetrahydropyran frameworks, are the natural constituents of many aromatic plants. Rose oxides, for example, have been isolated from rose oil and also found in the essential oils of *Geranium bourbon* and *Eucalyptus citriodora* [1]. Similarly, nerol oxide was first isolated from Bulgarian rose oil and also detected in several *Pelargonium* species [2] and different grape varieties. *Pityol* has been identified as a pheromone [3] component of bark beetle, red pine cone beetle, and white pine cone beetle. Most commercial products such as *Florol*, *Clarycet*, *Dermox*, and *Rhubafuran* are non-natural, synthetic preparations being used in a large number of fragrances and formulations by the industry. So far, methyl ethers of neither *Pityol* nor *Florol* have been synthesized and evaluated.

In the present work, we describe a facile synthetic strategy based on co-halogenation [4] as a key step for the preparation of nerol oxide (**1**) and *Florol* (**2**), as well as *Florol* methyl ether (**3**) and *Pityol* methyl ether (**4b**). Earlier, we have developed and patented an efficient synthesis of racemic and non-racemic rose oxides from citronellol using the co-halogenation strategy [5]. The successful syntheses of these important perfumery compounds prompted us to investigate the general applicability of this strategy aimed at the preparation of cyclic ethers.

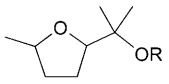
[1]) Most of these compounds are registered trade marks, but will not be marked as such in the following discussion.



Nerol oxide (**1**)



R = H *Florol* (**2**)
R = Me *Florol* methyl ether (**3**)

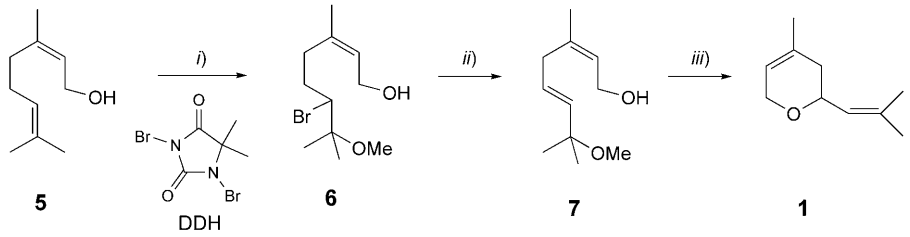


R = H *Pityol* (**4a**)
R = Me *Pityol* methyl ether (**4b**)

Results and Discussion. – 1. *Synthesis of Nerol Oxide.* There are only a few reported methods for the preparation of nerol oxide (=3,6-dihydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2*H*-pyran; **1**). The earliest methods were developed by *Ohloff* and co-workers [6–8], where natural nerol and (–)-(*R*)-linalool were used as starting materials for the preparation of racemic and optically active **1**, respectively. The method of *Tyman* and *Willis* [9] involves acid-catalyzed reaction of 3-methylbut-2-enol with 3-methylbut-3-enol. *Kitahara et al.* [10] reported the conversion of a natural monoterpene β-ketol to nerol oxide in 25% yield. A US patent [11] also disclosed the formation of **1** *via* photo-oxidation of nerol proper. In 1999, *Wust et al.* [12] reported an enantioselective total synthesis of (*S*)-nerol oxide ((*S*)-**1**) and of rose oxides from isoprene in a multi-step reaction sequence.

In the present work, nerol oxide was synthesized from nerol (**5**) by means of co-halogenation as the key step. The synthetic protocol is outlined in *Scheme 1*. In the first step, regioselective bromomethoxylation of **5** with 1,3-dibromo-5,5-dimethylhydantoin (=1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione; DDH) in MeOH was achieved at low temperature, affording the adduct **6** in 85% yield. Dehydrobromination of **6** was accomplished by exposure to KOH in MeOH to furnish the dienol **7** in high yield. Finally, rearrangement to nerol oxide (**1**) was effected with 10% HCl at 5–10° in 80% yield, the overall yield of **1**, thus, being *ca.* 61% (*Scheme 1*).

Scheme 1



i) MeOH, 0–5°; 85%. *ii*) KOH, MeOH, reflux; 89%. *iii*) 10% aq. HCl; 80%.

It is interesting to note that when a natural mixture of geraniol/nerol 64:36 was subjected to the above co-halogenation with DDH at 10°, both geometric isomers[2]) gave the corresponding mono-adducts. However, only the (2*Z*)-isomer **7**, derived from nerol, could be cyclized to nerol oxide (22% yield).

2. *Synthesis of* Florol. *Florol* (=tetrahydro-4-methyl-2-(2-methylpropyl)-2*H*-pyran-4-ol; **2**) was developed by *Firmenich* as an exotic fragrance known for its fresh, soft, and natural floral note. Today, the compound is widely being used in the making of perfumes. *Florol* is used as a diastereoisomeric pair of racemates, and its exact method of preparation has not been disclosed by the firm [13]. All the previously reported syntheses of **2** [14] are low-yielding and involve complex reaction procedures. In 2004, *Abate et al.* [15] reported the first total synthesis of enantiomerically enriched *Florol* (**2**) by a biocatalytic route for the purpose of odor and threshold evaluations. This method, however, is only of academic interest.

Our co-halogenation strategy for the synthesis of **2** started from an easily available, natural mixture of geraniol/nerol. As described above for the preparation of **1**, reaction with DDH in MeOH gave the adduct **8**, which was immediately (without purification) subjected to oxymercuration–demercuration with $Hg(OAc)_2/NaBH_4$ at moderate temperature (*ca.* 18°) to avoid formation of side products. The resulting diol **9** was dehydrobrominated in the presence of base to afford **10**, which was cyclized to **11** obtained as a *syn*/*anti* 72:28 diastereoisomer mixture. The *syn*-**11** isomer was separated by column chromatography, the relative configuration being established by NOE experiments (20% enhancement of the signal for H–C(2) upon irradiation of the 4-Me group). Finally, hydrogenation on Pd/C afforded the racemic *syn*- and *anti*-diastereoisomers of *Florol* (**2**). The overall yield of **2** from geraniol/nerol was *ca.* 45%. The cyclization step with mineral acid (HCl) somewhat reduced the overall yield due to the formation of unwanted side products. However, no attempts were made to optimize this step.

3. *Synthesis of* Florol *Methyl Ether*. *Florol* methyl ether (=tetrahydro-4-methoxy-4-methyl-2-(2-methylpropyl)-2*H*-pyran; **3**) appeared to be an interesting target because it has not been used so far by the perfumery industry. An alternative route to its synthesis was envisaged in place of direct methylation of *Florol* (**2**). As shown in *Scheme 3*, we started from 3-methoxycitronellol (**12**), obtained as a by-product in 25–30% yield along with the major product geraniol/nerol upon reduction of citral/neral (**13**) with an excess of $NaBH_4$ in MeOH. Compound **12** was then converted to *syn*- and *anti*-**14** (60:40 diastereoisomer mixture) in almost 70% yield by co-halogenation (→ **15**), dehydrobromination (→ **16**), and cyclization (→ **14**). The cyclic compounds **14** already displayed a mild flowery note resembling that of *Florol*, but much weaker in intensity. Finally, hydrogenation of **14** over Pd/C resulted in the formation of both diastereoisomers of *Florol* methyl ether (**3**). The flowery note completely disappeared in the final product, and it became almost odorless. The *syn* and *anti* isomers of **3** were separated by column chromatography, and their structures and relative configurations were established on the basis of 1D- and 2D-NMR experiments.

4. *Synthesis of* Pityol *Methyl Ether*. Two enantiomers out of the four possible isomers of *Pityol* (=tetrahydro-2-(1-methoxy-1-methylethyl)-5-methylfuran; **4a**) are nat-

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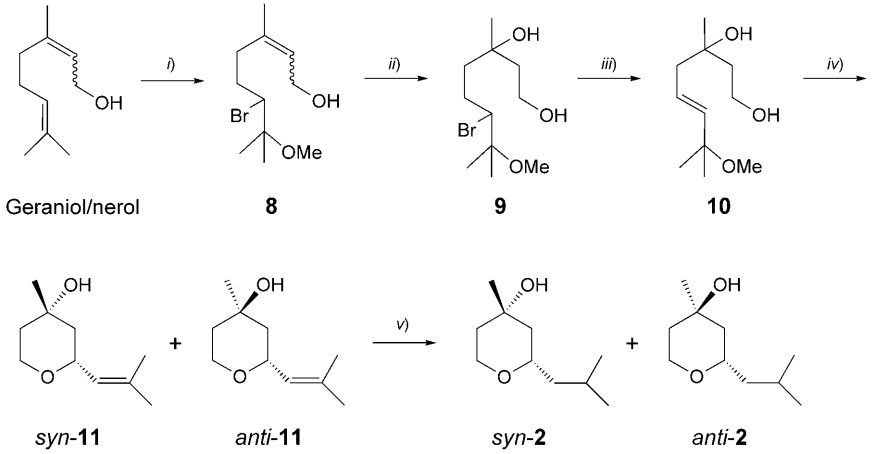
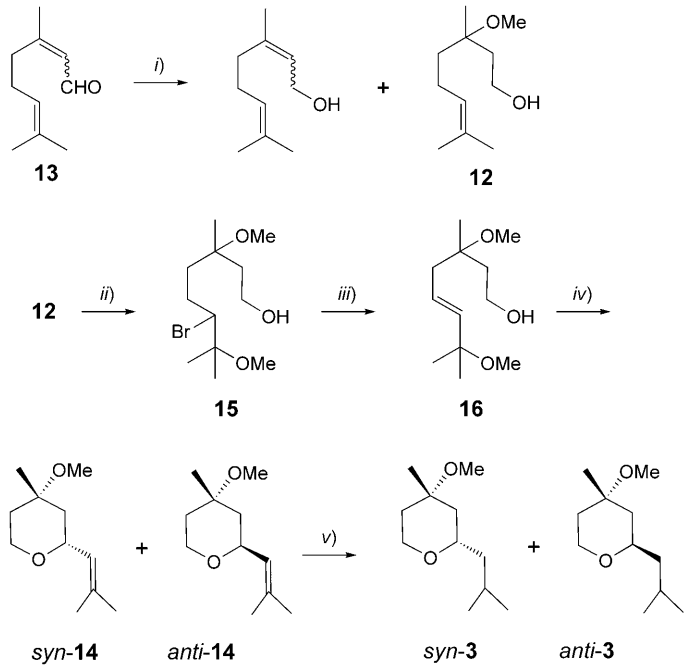
[2]) Geraniol is the (2*E*)-isomer of nerol (**5**).

Scheme 2



i) DDH, MeOH, 5–10°; 85%. *ii*) 1. $Hg(OAc)_2$,THF, H_2O; 2. $NaBH_4$, NaOH; 75%. *iii*) KOH, MeOH; 88%. *iv*) 5% aq. HCl; 82%. *v*) H_2, Pd/C; 97%.

Scheme 3

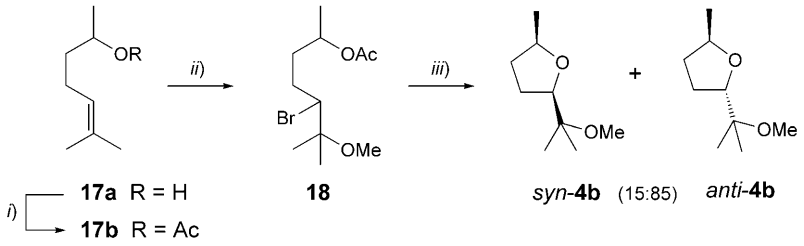


i) $NaBH_4$, MeOH; 25%. *ii*) DDH, MeOH, 5–10°; 92%. *iii*) KOH, MeOH, reflux; 89%. *iv*) 10% aq. HCl; 54% (*syn*), 38% (*anti*). *v*) H_2, Pd/C; quant.

urally occurring pheromones. The (2*R*,5*S*)-isomer serves as the male-specific attractant for the spruce bark beetle *Pityophthorus pityographus*, and the (2*R*,5*R*)-isomer was identified as the aggregation pheromone of the elm bark beetle *Pteleobius vittatus*. Due to its commercial importance, various syntheses of *Pityol* (**4a**) have been reported. Ruthenium(VII) oxide catalyzed cyclization was used to obtain predominantly the *anti*-isomer, as reported by *Tang* and *Kennedy* [16]. *Steinreiber et al.* [17] used racemic sulcatol as a raw material for the enantio- and diastereoconvergent synthesis of *Pityol* isomers, the key step being lipase-catalyzed ring closure of an oxirane derivative. *Ishihara et al.* [18] converted 2-methylhept-2-en-6-one to a mixture of **4a** and a tetrahydropyran isomer *via* ketal formation, followed by reduction. In a different approach, 3-hydroxybutanoate was used as a raw material for the synthesis of the non-racemic diastereoisomers of *Pityol* [19][20].

Our co-halogenation methodology could be successfully applied to the synthesis of *Pityol* methyl ether (**4b**), as outlined in *Scheme 4*. Racemic sulcatol (**17a**) was acetylated to **17b**, and the latter was subjected to bromomethoxylation to afford the intermediate **18**. In the next step, deacetylation and concomitant cyclization was effected with KOH in MeOH, which gave the target compound **4b** in *ca*. 70% yield. The ratio of *syn*- to *anti*-**4b** was 15 : 85 according to NMR and GC analyses. Both diastereoisomers were separated by column chromatography, and their structures were established by 1D- and 2D-NMR analyses.

Scheme 4



i) Ac_2O, CH_2Cl_2, DMAP cat.; quant. *ii*) DDH, MeOH, 5–10°; 85%. *iii*) KOH, MeOH, reflux; 82%.

In conclusion, co-halogenation has proved to be a very successful and versatile tool for the synthesis of odoriferous cyclic ethers such as nerol oxide, *Florol*, *Florol* methyl ether, and *Pityol* methyl ether. The overall yields of the final products were in all the syntheses either comparable or better than those reported in the literature.

Experimental Part

1. *General*. Reagents and solvents were of laboratory-routine (LR) grade. Nerol and citronellol (> 95%) were purchased from *Aldrich* (Mumbai), and racemic sulcatol (**17a**) was prepared from natural citral/neral by *retro*-aldol reaction in the presence of 5% NaOH, followed by hydro-distillation and purification (> 98%) by column chromatography (CC). Thin-layer chromatography (TLC) was performed on silica-gel-coated Al plates (*Merck*). GC Analyses were performed on a GC/MS *QP-2000* gas chromatograph. IR Spectra were recorded on a FT-IR *Bruker 270-30* spectrophotometer; in cm^{-1}. ^{1}H-NMR Spec-

tra were recorded on a *Bruker* 200-MHz spectrometer in $CDCl_3$; chemical shifts δ in ppm rel. to Me_4Si, *J* in Hz. Mass Spectra were recorded on a *Jeol MSD-300* or a *Bruker Esquire-3000* GC/MS apparatus; in *m*/*z* (rel. %).

2. *Synthesis of Racemic Nerol Oxide* (**1**). *(2Z)-6-Bromo-3,7-dimethyl-7-methoxyoct-2-en-1-ol* (**6**). In a flask fitted with a thermometer, a dropping funnel, and a gas inlet, 1,3-dibromo-5,5-dimethylhydantoin (DDH; 50.0 g, 0.174 mol) was added in small portions with vigorous stirring to a soln. of nerol (50.0 g, 0.324 mol) in anh. MeOH (150 ml) under N_2 atmosphere. The temp. during the addition of DDH was kept between 5 to 10°. When the reaction was complete, the mixture was poured in cold H_2O and extracted with AcOEt (3×50 ml). The combined org. layer was washed with 5% aq. Na_2CO_3 soln. (3×25 ml), and then washed neutral with H_2O (3×30 ml). The org. layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure to afford **6** (73.12 g, 85%). Colorless oil. IR (KBr): 3445, 2977, 1464, 1382, 1367, 1231, 1182, 1130, 1070, 861, 778, 746. ^{1}H-NMR: 1.27, 1.32 (2*s*, 2 Me); 1.74 (*s*, Me–C=); 1.75–1.81 (*m*, CH_2); 2.14 (*m*, CH_2–C=); 3.23 (*s*, MeO); 3.89 (*d*, *J*=11.6, CHBr); 4.19 (*d*, *J*=6.7, CH_2OH); 5.51 (*t*, *J*=6.0, HC=). ^{13}C-NMR: 20.9; 22.7; 23.1; 29.8; 31.1; 49.2; 58.4; 62.8; 76.1; 125.6; 137.3. MS: 265 (2, M^+), 185 (5), 170 (15), 153 (35), 139 (12), 135 (12), 123 (10), 109 (17), 85 (15), 73 (100), 79 (16).

*(2Z,5*E*)-3,7-Dimethyl-7-methoxyocta-2,5-dien-1-ol* (**7**). A soln. of crude **6** (70.0 g, 0.265 mol) in MeOH (200 ml) containing KOH (35.0 g) was heated at reflux for 9 h. Three quarters of the solvent were removed by distillation at reduced pressure. The remaining contents were poured into cold H_2O, and the mixture was extracted with $CHCl_3$ (4×50 ml). The org. layer was separated, washed neutral with H_2O (3×50 ml), dried ($CaCl_2$), and concentrated under reduced pressure to afford **7** (43.69 g, 89%). Pale-yellow oil. ^{1}H-NMR: 1.25, 1.27 (2*s*, 2 Me); 1.73 (*s*, Me); 2.41 (*d*, *J*=7.2, CH_2); 3.14 (*s*, MeO); 4.14 (*d*, *J*=6.6, CH_2OH); 5.47–5.55 (*m*, 3 CH). ^{13}C-NMR: 23.0; 25.3; 25.4; 34.6; 49.7; 58.3; 74.4; 124.6; 126.8; 136.2; 136.8. MS: 184 (4, M^+), 167 (6), 166 (35), 154 (43), 153 (5), 135 (100), 123 (23), 93 (2), 73 (7), 60 (5).

Nerol Oxide (**1**). To a soln. of crude **7** (40.0 g, 0.217 mol) in hexane (100 ml) was added 5% aq. HCl (15 ml) at 0°, and the mixture was stirred for 2 h. The org. layer was separated, extracted with 5% aq. $NaHCO_3$ soln. (3×20 ml), washed neutral with H_2O (3×30 ml), dried (Na_2SO_4), concentrated under reduced pressure, and purified by CC (SiO_2) to afford racemic **1** (26.47 g, 80%). Colorless oil. ^{1}H-NMR: 1.67, 1.70 (2*s*, 2 Me); 1.74 (*s*, Me); 2.11 (*m*, CH_2); 4.23 (*m*, OCH_2, OCH); 5.22 (*d*, *J*=7, HC=); 5.41 (*m*, HC=). ^{13}C-NMR: 19.6; 23.9; 26.9; 37.2; 66.8; 71.9; 120.9; 126.9; 133.1; 137.3. MS: 152 (3, M^+), 138 (21), 125 (100), 109 (4), 84 (7), 80 (14), 70 (9), 68 (16).

3. *Synthesis of* Florol. *(*E*/*Z*)-6-Bromo-3,7-dimethyl-7-methoxyoct-2-en-1-ol* (**8**). Commercial geraniol/nerol (50.0 g, 0.324 mol) was converted to the title compound in analogy to the method described for nerol oxide (**1**). Yield of **8**: 73.12 g (85%). IR (KBr): 3445, 2977, 1464, 1382, 1367, 1231, 1182, 1130, 1070, 861, 778, 746. ^{1}H-NMR: 1.28, 1.33 (2*s*, 2 Me); 1.79 (*s*, Me); 1.74–1.81 (*m*, CH_2); 3.22 (*s*, MeO); 2.14 (*dt*, *J*=10.7, 5.5, CH_2C=); 3.42 (*t*, *J*=6.1, CHBr); 4.18 (*d*, *J*=5.9, CH_2OH); 5.48 (*t*, *J*=5.9, HC=). ^{13}C-NMR: 16.3; 19.9; 23.1; 29.8; 31.0; 49.2; 58.4; 62.8; 76.1; 122.6; 137.3. MS: 265 (M^+), 185 (5), 170 (15), 153 (35), 139 (12), 135 (12), 123 (10), 109 (17), 85 (15), 73 (100), 79 (16).

6-Bromo-3,7-dimethyl-7-methoxyoctane-1,3-diol (**9**). A soln. of isomeric **8** (5.3 g, 0.02 mol) in THF (100 ml) was added to a soln. of $Hg(OAc)_2$ (20 g, 0.062 mol) in THF/H_2O 1:1. The mixture was stirred for 2 h. After completion of the reaction (TLC control), 0.5M $NaBH_4$ (19 g, 0.05 mol) in 3M aq. NaOH soln. (100 ml) was added, and the mixture was stirred for 2 h. Workup included extraction with AcOEt (3×30 ml), washing with H_2O, and drying. After removal of the solvent, the crude product was purified by CC (SiO_2) to afford **9** (4.24 g, 75%). IR (KBr): 3384, 2974, 1464, 1382, 1368, 1248, 1183, 1130, 1069, 970, 932, 860, 780. ^{1}H-NMR: 1.19 (*s*, Me); 1.23, 1.26 (2*s*, 2 Me); 1.41–1.70 (*m*, $(CH_2)_2$); 1.86–2.04 (*m*, CH_2); 3.16 (*s*, MeO); 3.77–3.90 (*m*, CH_2OH, CHBr). ^{13}C-NMR: 21.4; 23.5; 26.5; 27.9; 41.2; 41.9; 49.7; 59.5; 64.9; 73.3; 125. MS: 283 (2, M^+), 265 (2), 253 (3), 219 (4), 195 (2), 183 (8), 165 (6), 153 (3), 139 (2), 107 (4), 85 (25), 73 (100), 45 (15).

*(5*E*)-3,7-Dimethyl-7-methoxyoct-5-ene-1,3-diol* (**10**). A soln. of crude **9** (2.83 g, 0.01 mol) and KOH (2.0 g) in MeOH (15 ml) was heated at reflux for 9 h. The solvent was removed by distillation at reduced pressure, bringing the total volume to one fourth. The remaining mixture was extracted with $CHCl_3$ (4×15 ml). The org. layer was washed neutral with H_2O (3×15 ml), dried ($CaCl_2$), and concentrated

to give a pale-yellow oily substance, which, after CC (SiO_2), gave **10** (1.77 g, 88%). Colorless liquid. IR (KBr): 3447, 2976, 1464, 1382, 1368, 1248, 1183, 1130, 1069, 970, 932, 860, 780. ^{1}H-NMR: 1.22–1.27 (3*s*, 3 Me); 1.67 (*m*, CH_2); 2.31(*d*, *J* = 6.2, CH_2–C=); 3.16 (*s*, MeO); 3.91 (*m*, CH_2OH); 5.58 (*m*, 2 HC=). ^{13}C-NMR: 25.2; 25.3; 26.2; 41.0; 45.2; 49.8; 59.1; 73.0; 74.3; 125.4; 139.3. MS: 202 (3, M^+), 185 (4), 144 (13), 103 (6), 85 (21), 73 (100), 69 (14).

*(2*RS*,4*RS*)- and (2*RS*,4*SR*)-3,4,5,6-Tetrahydro-4-methyl-2-(2-methylprop-1-en-1-yl)-2*H*-pyran-4-ol* (*anti*- and *syn*-**11**, resp.). To a cooled soln. of **10** (2.02 g, 0.01 mol) in hexane (100 ml) was added 5% aq. HCl (15 ml) at 0–5°, and the mixture was stirred for 2 h. The org. layer was separated, washed with 5% aq. $NaHCO_3$ soln. (3 × 20 ml) and H_2O (3 × 30 ml), dried, and concentrated under reduced pressure to give **11** (1.39 g, 82%; *anti/syn* 28 : 72). The diastereoisomer mixture was separated by CC (SiO_2; hexane/AcOEt 95 : 5).

Data of anti-**11**. IR (KBr): 3425, 2963, 1619, 1451, 1377, 1361, 1758, 1133, 1078, 1051, 1005, 926. ^{1}H-NMR: 1.42 (*s*, Me); 1.62 (*d*, *J* = 7.0, CH_2); 1.88–1.90 (2*s*, Me_2C); 1.70–1.86 (*m*, CH_2); 3.50 (*m*, OCH_2); 4.02 (*m*, OCH); 5.12 (*d*, *J* = 7.0, HC=).^{13}C-NMR: 18.5; 25.7; 31.8; 38.4; 44.7; 63.4; 67.9; 70.1; 125.7; 135.9. MS: 170 (100, M^+), 153 (20), 125 (8), 101 (2), 85 (3).

Data of syn-**11**. IR (KBr): 3425, 2963, 1619, 1451, 1377, 1361, 1758, 1133, 1078, 1051, 1005, 926. ^{1}H-NMR: 1.27 (*s*, Me); 1.62 (*d*, *J* = 7.0, CH_2); 1.76 (2*s*, Me_2C); 1.70–1.88 (*m*, CH_2); 3.84 (*dd*, *J* = 7.4 , 1.5, OCH_2); 4.38 (*dt*, *J* = 8.9, 3.4, OCH); 5.14 (*d*, *J* = 7.0, HC=). ^{13}C-NMR: 18.5; 23.3; 31.8; 38.5; 43.7; 64.4; 66.9; 70.1; 125.7; 135.9. MS: 170 (100, M^+), 153 (20), 125 (8), 101 (2), 85 (3).

Florol (= *(2*SR*,4*SR*)-3,4,5,6-Tetrahydro-4-methyl-2-(2-methylpropyl)-2*H*-pyran-4-ol*; *syn*-**2**). A soln. of *syn*-**11** (1.70 g, 0.01 mol) in MeOH (30 ml) was hydrogenated at 40 psi over 5% Pd/C (100 mg) to yield *Florol* (1.68 g, 97%). Colorless liquid. IR (KBr): 3430, 2963, 1451, 1377, 1361, 1133, 1078, 1051, 1000, 930. ^{1}H-NMR: 3.74–3.87 (*m*, H_{eq}–C(6), H–C(2)); 3.68 (*dd*, *J* = 11.6, 2.1, H_{ax}–C(6)); 1.67–2.08 (*m*, CH_2, CH); 1.41–1.60 (*m*, CH_2); 1.20–1.30 (*m*, CH_2); 1.26 (*s*, Me); 0.88 (*d*, *J* = 6.7, Me_2C). MS: 172 (5, M^+), 54 (25), 139 (20), 115 (58), 71 (100), 43 (75).

4. *Synthesis of Florol Methyl Ether* (**3**). *3-Methoxycitronellol* (=*3,7-Dimethyl-3-methoxyoct-6-en-1-ol*; **12**). To a soln. of citral (**13**; 150 g, 0.986 mol) in MeOH (500 ml) was slowly added $NaBH_4$ (9.65 g, 0.255 mol) at r.t. After completion of the reaction, the soln. was poured into cold H_2O and extracted with Et_2O (3 × 100 ml). The org. layer was separated, washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (SiO_2; hexane/AcOEt 10 : 1) to afford **12** (45.8 g, 25%). IR (KBr): 3395, 2969, 2931, 2826, 1671, 1453, 1376, 1343, 1115, 1077, 893, 834. ^{1}H-NMR: 1.23 (*s*, Me); 1.40–2.30 (*m*, $(CH_2)_3$); 1.63, 1.70 (2*s*, Me_2C=); 3.23 (*s*, MeO); 3.80 (*t*, *J* = 6.0, CH_2OH); 5.16 (*t*, *J* = 5.5, HC=). ^{13}C-NMR: 19.1; 23.7; 23.8; 27.1; 39.0; 40.7; 50.3; 60.9; 78.2; 124.5; 132.0. MS: 186 (M^+), 171, 154, 122, 120, 108, 102, 85, 69, 56.

6-Bromo-3,7-dimethoxy-3,7-dimethyloctan-1-ol (**15**). Prepared from **12** (11.1 g, 0.06 mol) in analogy to **6**. Yield: 16.3 g, 92%. IR (KBr): 3390, 2976, 1464, 1382, 1237, 1183, 1072, 966, 860. ^{1}H-NMR: 1.23 (*s*, Me); 1.30, 1.33 (2*s*, Me_2C); 3.26 (*s*, 2 MeO); 1.5–2.4 (*m*, $(CH_2)_3$); 3.53–4.10 (*m*, CH_2OH, CHBr). MS: 297 (M^+), 250, 216, 168, 153, 139, 125, 103, 97, 85, 73.

*(5*E*)-3,7-Dimethoxy-3,7-dimethyloct-5-en-1-ol* (**16**). A soln. of **15** (9.8 g, 0.033 mol) in MeOH (50 ml) containing KOH (5.1 g, 0.091 mol) was heated at reflux for 9 h. Usual workup and CC gave **16** (6.34 g, 89%). Pale-yellow oil. IR (KBr): 3447, 2976, 1650, 1463, 1380, 1074, 907. ^{1}H-NMR: 1.23 (*s*, Me); 1.26 (*s*, Me_2C); 1.50–1.70 (*m*, CH_2); 2.31 (*d*, *J* = 6.2, CH_2–C=); 3.16, 3.26 (2*s*, 2 MeO); 3.76 (*t*, *J* = 6, CH_2OH); 5.46–5.73 (*m*, 2 HC=). ^{13}C-NMR: 21.9; 24.3; 27.2; 36.7; 41.5; 49.4; 50.6; 61.1; 75.1; 75.7; 125.4; 139.2. MS: 217 ($[M+1]^+$), 185, 167, 144, 103, 97, 85, 73.

*(2*RS*,4*SR*)- and (2*SR*,4*SR*)-3,4,5,6-Tetrahydro-4-methoxy-4-methyl-2-(2-methylprop-1-en-1-yl)-2*H*-pyran* (*syn*- and *anti*-**14**, resp.). To a soln. of **16** (5.86 g, 0.027 mol) in hexane (50 ml) was added 20% aq. HCl (3 ml) at 0–5°. The mixture was stirred vigorously for 15 min. The org. layer was separated, washed neutral with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The diastereoisomeric mixture was separated by CC (SiO_2; hexane/AcOEt 20 : 1) to afford *syn*-**14** (2.7 g, 54%) and *anti*-**14** (1.9 g, 38%).

Data of syn-**14**. IR (KBr): 2968, 2939, 1677, 1460, 1376, 1256, 1175, 1081, 1001, 912, 821, 728. ^{1}H-NMR: 1.14 (*s*, Me); 1.27 (*dd*, *J* = 11.4, 2.5, H_{ax}–C(3)); 1.47 (*dd*, *J* = 8.6, 5.5, H_{eq}–C(3)); 1.65–1.91 (*m*,

CH_2); 1.70 (*s*, Me_2C=); 3.20 (*s*, MeO); 3.76 (*dd*, *J* = 7.4, 1.5, OCH_2); 4.30 (*m*, OCH); 5.12 (*d*, *J* = 8.0, HC=). ^{13}C-NMR: 18.4; 24.9; 25.7; 35.3; 41.6; 48.7; 63.2; 69.8; 71.4; 125.9; 135.6. MS: 184 (4, M^+), 170 (10), 169 (10), 153 (35), 145 (11), 137 (36), 133 (23), 123 (14), 108 (18), 104 (100), 98 (44), 92 (19), 80 (51).

Data of anti-**14**. IR (KBr): 2971, 2936, 1450, 1401,1376, 1250, 1172, 1092, 1049, 896, 867, 835, 801. ^{1}H-NMR: 1.32 (*s*, Me); 1.43–1.81 (*m*, 2 CH_2); 1.68, 1.72 (2*s*, Me_2C=); 3.24 (*s*, MeO); 3.50 (*dd*, *J* = 13.0, 3.5, OCH_2); 4.02–4.09 (*m*, OCH); 5.18 (*d*, *J* = 7, HC=). ^{13}C-NMR: 18.4; 20.5; 25.7; 36.7; 42.8; 48.1; 65.0; 71.9; 72.1; 125.7; 135.8. MS: 184 (4, M^+), 170 (10), 169 (10), 153 (35), 145 (11), 137 (36), 133 (23), 123 (14), 108 (18), 104 (100), 98 (44), 92 (19), 80 (51).

Florol Methyl Ether (= *(2*SR,*4*SR*))-3,4,5,6-Tetrahydro-4-methoxy-4-methyl-2-(2-methylpropyl)-2*H*-pyran*; *syn*- and *anti*-**3** resp.). *syn*-**14** or *anti*-**14** (2.0 g, 0.011 mol) were subjected separately to hydrogenation at 40 psi in MeOH (30 ml) in the presence of 5% Pd/C (100 mg) to yield 1.98 g (98%) of the corresponding product **3**.

Data of syn-**3**. IR (KBr): 2954, 2869, 1489, 1464, 1430, 1381, 1369,1306, 1277, 1251, 1176, 1144, 1085, 1039, 912, 865, 835. ^{1}H-NMR: 0.89 (*d*, *J* = 6.1, Me_2C); 1.07–1.22 (*m*, CH_2); 1.51–1.68 (*m*, CH_2); 1.79–1.88 (*m*, CH_2, CH); 3.23 (*s*, MeO); 3.56–3.77 (*m*, OCH_2, OCH). ^{13}C-NMR: 22.4; 23.4; 24.4; 25.1; 35.4; 42.4; 45.6; 48.7; 63.5; 70.7; 71.5. MS: 186 (2, M^+), 171 (5), 155 (2), 139 (17), 112 (31), 109 (1), 101 (10), 98 (1), 83 (4), 81 (2), 69 (100), 67 (5).

Data of anti-**3**. IR (KBr): 2955, 2869, 1467, 1375, 1347, 1250, 1173, 1141, 1089, 1037, 982, 905, 868, 814, 800, 733, 631. ^{1}H-NMR: 0.90 (*d*, *J* = 6.6, Me_2C); 1.07–1.23 (*m*, CH_2); 1.29 (*s*, Me); 1.33–1.55 (*m*, CH_2); 1.68–1.77 (*m*, CH_2, CH); 3.18 (*s*, MeO); 3.32–3.49 (*m*, OCH_2); 3.96 (*dt*, *J* = 11.6, 4.7, OCH). ^{13}C-NMR: 18.4; 20.5; 25.4; 36.7; 42.8; 48.1; 64.4; 72.1; 72.6; 125; 135.8. MS: 186 (2, M^+), 171 (5), 155 (2), 139 (17), 112 (31), 109 (1), 101 (10), 98 (1), 83 (4), 81 (2), 69 (100), 67 (5).

5. *Synthesis of Pityol Methyl Ether* (**4**). *1,5-Dimethylhex-4-en-1-yl Acetate* (**17b**). To a soln. of racemic sulcatol (**17a**; 6.4 g, 0.05 mol) in anh. CH_2Cl_2 was added Ac_2O (6 g, 0.06 mol) and a cat. amount of DMAP (5 mg). The mixture was kept overnight at r.t., poured in ice-cold H_2O, and extracted with CH_2Cl_2. The org. layer was washed with H_2O, dried, and evaporated to afford **17b** (8.45 g, quant.). The anal. data of **17b** were identical to those reported in the literature [21].

4-Bromo-5-methoxy-1,5-dimethylhexyl Acetate (**18**). A soln. of crude **17b** (6.8 g, 0.04 mol) in anh. MeOH (60 ml) was placed in a flask fitted with a thermometer, a dropping funnel, and a gas inlet. Then, 1,3-dibromo-5,5-dimethylhydantion (DDH; 6.5 g, 0.022 mol) was slowly added under N_2 atmosphere with vigorous stirring, the temp. being kept between 5 to 10°. When the reaction was completed, the mixture was poured into cold H_2O and extracted with AcOEt (3 × 25 ml). The combined org. layer was washed with 5% aq. Na_2CO_3 soln. (3 × 15 ml) and H_2O (3 × 15 ml), dried (Na_2SO_4), and concentrated under reduced pressure to afford **18** (9.55 g, 85%). Colorless oil. IR (KBr): 2979, 1736, 1462, 1370-, 1243, 1182, 1133, 1070, 1022, 958, 852, 778, 748. ^{1}H-NMR: 1.20 (*d*, *J* = 6.5, Me); 1.27, 1.32 (2*s*, Me_2C); 1.57–1.72 (*m*, 2 CH_2); 2.03 (*s*, Ac); 3.22 (*s*, MeO); 3.93 (*t*, *J* = 7.8, CHBr); 4.88–4.95 (*m*, OCH). ^{13}C-NMR: 14.2; 19.9; 21.3; 21.4; 23.5; 29.5; 35.2; 49.7; 70.8; 76.8; 77.3; 170.7. MS: 282 (80), 226 (3), 200 (82), 186 (100), 166 (5), 131 (6), 118 (2).

Pityol Methyl Ether (= *(2*RS,*5*RS*)- and (2*SR,*5*RS*)-2,3,4,5-Tetrahydro-2-methyl-5-(1-methoxy-1-methylethyl)furan*; *syn*- and *anti*-**4** resp.). A soln. of **18** (5.64 g, 0.02 mol) in MeOH (20 ml) containing KOH (4.0 g, 0.071 mol) was heated at reflux for 9 h. The solvent was partly removed by distillation at reduced pressure to bring the total volume to one fourth. The reaction contents were then poured into cold H_2O and extracted with $CHCl_3$. The org. layer was washed neutral with H_2O (3 × 20 ml), dried ($CaCl_2$), and concentrated under reduced pressure. The residue was subjected to CC (SiO_2; hexane/AcOEt 98 : 3) to afford **4** (2.59 g, 82%). A *syn*/*anti* ratio of 15 : 85 was determined on the basis of ^{1}H- and ^{13}C-NMR analyses.

Data of syn-**4**. IR (KBr): 2973, 1461, 1381, 1367, 1293, 1230, 1181, 1130, 1070, 1021, 997, 867, 836. ^{1}H-NMR: 1.10 (*d*, *J* = 5.0, Me); 1.20, 1.30 (2*s*, Me_2C); 1.71–2.20 (*m*, 2 CH_2); 3.15 (*s*, MeO); 3.81–3.85 (*m*, OCH); 3.98 (*dd*, *J* = 10.9, 1.6, OCH). ^{13}C-NMR: 21.2; 22.8; 25.7; 29.2; 37.8; 49.6; 64.1; 66.8; 67.3; 76.5. MS: 158 (5, M^+), 143 (27), 126 (4), 113 (90), 111 (70), 100 (70), 99 (88), 82 (7), 73 (4), 67 (9), 56 (6), 47 (100).

Data of anti-**4**. IR (KBr): 2973, 1461, 1381, 1367, 1293, 1230, 1181, 1130, 1070, 1021, 997, 867, 836. ^{1}H-NMR: 1.20 (*d*, *J* = 6.2, Me); 1.29, 1.33 (2*s*, Me_2C); 1.71–2.20 (*m*, 2 CH_2); 3.23 (*s*, MeO); 3.81–3.85 (*m*, OCH); 3.98 (*dd*, *J* = 10.9, 1.6, OCH). ^{13}C-NMR: 21.4; 23.6; 25.8; 30.1; 38.4; 50.2; 64.7; 67.8; 77.1. MS: 158 (5, M^+), 143 (27), 126 (4), 113 (90), 111 (70), 100 (70), 99 (88), 82 (7), 73 (4), 67 (9), 56 (6), 47 (100).

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