17. Structure and Synthesis of Novel C_{12} Terpenoids from Quince Fruit (*Cydonia oblonga* MILL.)

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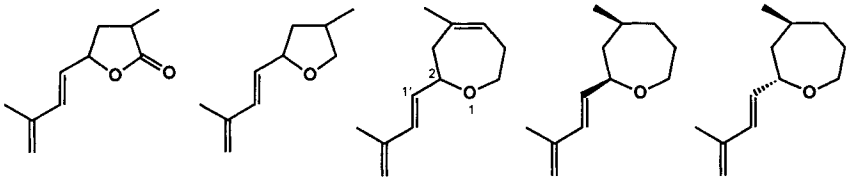
(19.XI.90)

The structure and synthesis of novel irregular C_{12} terpenoids isolated from quince fruit (*Cydonia oblonga* MILL.) are described: quince oxepine (= (*E*)-2,3,6,7-tetrahydro-4-methyl-2-(3-methylbuta-1,3-dienyl)oxepine; **3**) and the quince oxepanes as a 1:1 mixture of *cis*- and *trans*-isomers (= *cis*- and *trans*-(*E*)-4-methyl-2-(3-methylbuta-1,3-dienyl)oxepane; **4** and **5**, resp.). The absolute configurations of the natural compounds have not been determined due to the minute amounts available, but both relative and absolute configurations of synthetic **4** and **5** were established by chemial correlation with (*R*)-pulegone.

Introduction. – The ripe fruit of quince (*Cydonia oblonga* MILL.) imparts a powerful and characteristic flavor and is appreciated for preparing marmalade, candied fruit, sweets, and brandy. The volatile constituents have been extensively analyzed and investigated [1]. The list of compounds identified includes saturated and unsaturated esters and C_{13} constituents from carotene degradation. A series of C_{10} constituents of irregular isoprenoid structure attracted particular interest; the marmelo lactones (**1**) and marmelo oxides (**2**) [1c][2]. In the course of a recent, in-depth analysis of quince (fruit and brandy) [3], trace amounts of the related C_{12} ethers **3**–**5** have now been isolated. The major ether **3** was present to *ca.* 50 ppm in quince fruit, and the slightly less polar diastereoisomers **4** and **5** were detected by GC/MS besides **3** in quince brandy fractions [3][4].



1[a]) **2**[a]) **3** **4** **5**

[a]) Two diasteroisomers.

In this communication, we describe the structures and syntheses of these novel compounds **3**–**5** [4] which we propose to name quince oxepine (**3**) and *cis*- and *trans*-quince oxepane (**4** and **5**, resp.)[1]), in analogy to marmelo oxide.

Structures of 3–5. – The structures of **3**–**5** were established by spectroscopic means and confirmed by synthesis of the racemates (see below). The absolute configurations of the natural compounds could not be determined due to the minute amounts available.

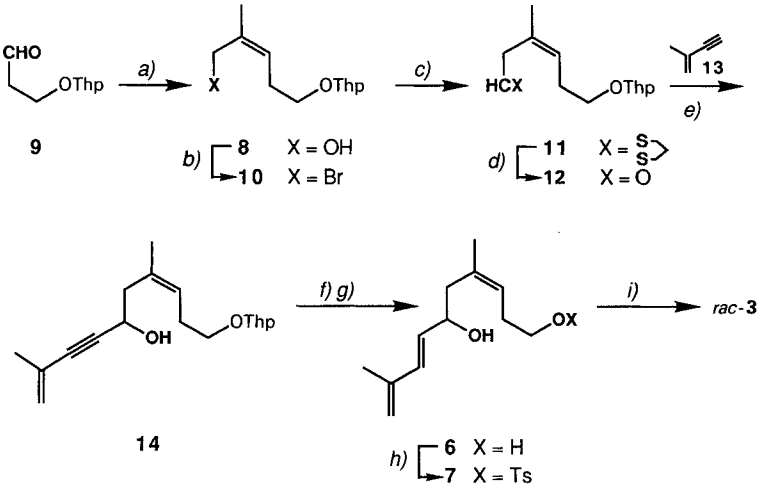
[1]) Presented, in part, at the *Weurman* symposium 1990 [5].

The high-resolution MS of **3** shows the molecular ion at *m/z* 178. The two most intense fragments are at *m/z* 67 ($C_5H_7^+$) and 82 ($C_6H_{10}^+$). Diagnostically useful fragments appear at *m/z* 163 ([*M* −15]$^+$), 135 ([*M* −43]$^+$), and 96 ($C_6H_8O^+$). The molecular formula $C_{12}H_{18}O$ is in good agreement with the MS fragmentation pattern and the ^{1}H-NMR integration curve. The ^{1}H-NMR spectrum clearly indicates the presence of a (*E*)-3-methylbuta-1,3-dienyl group attached to CH–O, in accordance with *m/z* 96. The second Me group (*s* at 1.76 ppm) is linked to a nonconjugated, triply substituted double bond. The signal of the olefinic proton is a broad *m* ($\Delta w_{1/2}$ = 14.5 Hz) at unusually low field (5.60 ppm). The remaining six protons belong to 3 CH_2 groups one of which is next to an O-atom (*ABX*$_2$ at 3.54 and *m* at 4.04 ppm). ^{1}H,^{1}H Decoupling experiments together with the apparent relationship with the oxides **2** then allowed the four moieties (C_5H_7–$CHOCH_2$, CH_3C=CH, and 2 CH_2) to be linked to the structure of the tetrahydrooxepine **3**.

The molecular weight of **4** and **5** is 180, and their MS are virtually identical. Besides *m/z* 165 ([*M* −15]$^+$) and 137 ([*M* −43]$^+$), the fragment at *m/z* 96 ($C_6H_8O^+$) and the base peak at *m/z* 69 ($C_5H_9^+$) strongly suggest that the isomers are structurally related to **3** and are, in fact, the oxepanes **4** and **5**.

Syntheses. – Diol **6** was chosen as the synthetic precursor of *rac*-**3** (*Scheme 1*). Its monotosylate **7** was expected to cyclize in an intramolecular S_N2 reaction and was assembled as follows: The allylic alcohol **8** was synthesized from the known aldehyde **9** [6] in 58% yield *via* a SCOOPY reaction [7]. Its conversion to the unstable allylic bromide **10** proceeded with PBr_3 (40%), whereas more subtle methods [8] [9] failed to produce any **10**, probably because of the sterically hindered reaction site ((*Z*)-double bond). Compound

Scheme 1



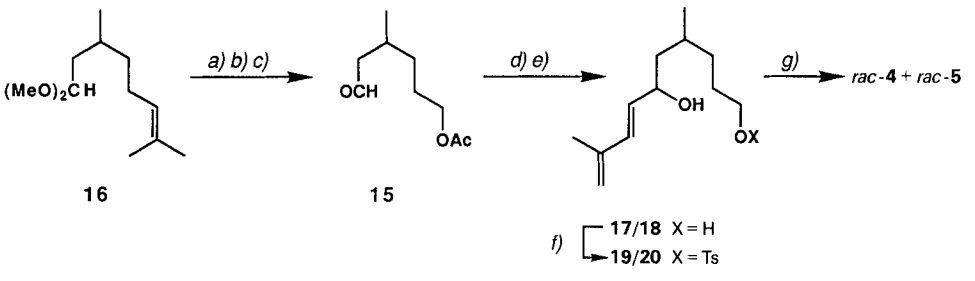
a) Ph_3P=CHMe, BuLi, CH_2O. *b)* PBr_3, Py, hexane, −5°. *c)* 2-Lithiodithiane. *d)* MeI, $CaCO_3$, MeCN/H_2O. *e)* BuLi, monoglyme, 0°. *f)* $LiAlH_4$, THF, reflux. *g)* 10% aq. HCl, MeOH. *h)* 1.1 equiv. of TsCl, Py, 0°. *i)* 3.0 equiv. of NaH, 1.0 equiv. of DMPU, monoglyme.

10 was submitted to a dithiane-mediated extension by one C-atom [10]. Hydrolysis of the intermediate dithiane **11** was done under conditions [11] known to preserve the (*Z*)-configuration of the β,γ-unsaturated aldehyde **12** (22% from **8**). Addition of the lithium derivative of acetylene **13** [12] to **12** gave the propargylic alcohol **14** in quantitative yield. Treatment of **14** with $LiAlH_4$ followed by acid hydrolysis of the tetrahydropyranyl protecting group afforded the target (3*Z*,7*E*)-decatrienol **6** in 60% yield. The structure of

6 was fully supported by the corresponding ^{1}H-NMR data[2]). When treated with excess NaH in monoglyme in the presence of *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU) [13], monotosylate **7** cyclized to tetrahydrooxepine *rac*-**3** in moderate yield (40%). Other methods to bring about cyclization of diol **6** (*Filtrol®*; TsOH; *N,N*-dimethylformamide diamyl acetal [14]) failed. MS, ^{1}H-NMR, and chromatographic data of synthetic *rac*-**3** coincided with those of the natural sample [3].

The synthetic scheme outlined above was also successfully applied to the preparation of the oxepanes *rac*-**4** and *rac*-**5** (*Scheme 2*). Thus, saturated aldehyde **15**, which was obtained from racemic citronellal dimethyl acetal (**16**) *via* standard transformations[2]), gave the diastereoisomeric (7*E*)-decadienols **17**/**18** in 57% yield. Under the conditions described above, the labile monotosylates **19**/**20** cyclized to a 1:1 mixture of the diastereoisomeric oxepanes *rac*-**4** and *rac*-**5** in 69% yield. The GC/MS data of the synthetic mixture were identical with those from the natural fraction. The isomers *rac*-**4** and *rac*-**5** were separated by prep. GC. Although their ^{1}H- and ^{13}C-NMR spectra differ in several respects (see below), it was impossible to derive the relative configurations from these data, and we decided to solve this problem by chemical correlation.

Scheme 2



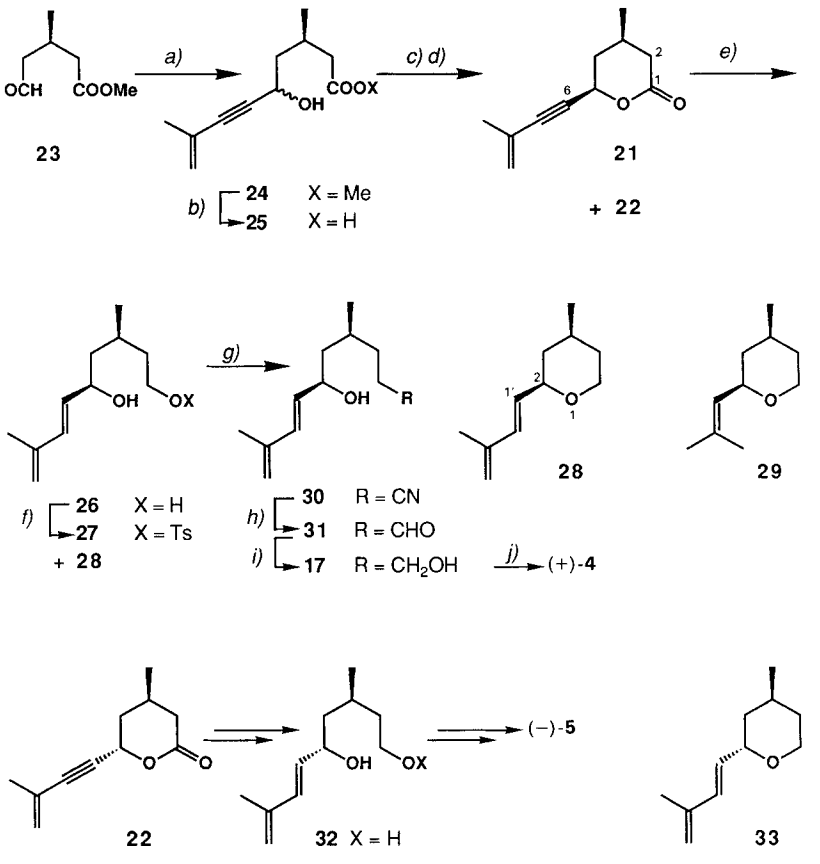
a) O_3, MeOH, then $NaBH_4$. *b)* Ac_2O, Py. *c) Amberlyst-15*, aq. acetone. *d)* **13**, BuLi, monoglyme, 0°. *e)* $LiAlH_4$, THF, reflux. *f)* 1.1 equiv. of TsCl, Py, 0°. *g)* 3.0 equiv. of NaH, 1.0 equiv. of DMPU, monoglyme.

Configurational Assignment of the Oxepanes 4 and 5. – The δ-lactones **21** and **22** with defined configuration seem to possess the required properties to function as precursors of **4** and **5**. Expected to be available in isomerically pure *cis*- and *trans*-form, respectively, there is no doubt that the relative configurations of **21** and **22** can be established unambiguously by NMR-spectroscopic methods. Hence, their stereochemical correlation with the oxepanes **4** and **5** by chemical transformation was planned as shown in *Scheme 3*. As the starting formyl ester **23** [15] was prepared from (*R*)-pulegone [16] [17], the absolute configurations of synthetic **4** and **5** will also be established.

Thus, addition of the lithium derivative of acetylene **13** to **23** afforded the diastereoisomeric hydroxy esters **24** which lactonized directly or after basic hydrolysis to the corresponding hydroxy acids **25**. The diastereoisomeric δ-lactones **21** and **22** could be separated conveniently by chromatography on silica gel. Their ^{13}C-NMR data (^{1}H,^{13}C-correlated) clearly showed that the less polar lactone is the *trans*-isomer **22** (3*R*,5*S*) with the acetylenic side chain in axial and the secondary Me group in equatorial position,

[2]) See *Exper. Part.*

Scheme 3



a) **13**, BuLi, monoglyme, 0°. *b)* KOH, aq. EtOH, reflux, then H^+. *c)* Δ. *d)* MPLC on silica gel. *e)* $LiAlH_4$, THF, reflux. *f)* 1.1 equiv. of TsCl, Py, 0°. *g)* NaCN, DMSO. *h)* DIBAH, C_6H_6. *i)* $LiAlH_4$. *j)* *Cf. Scheme 2.*

Table. *Selected ^{13}C- and ^1H-NMR Shifts* (ppm) *and Assignments for Compounds* **4**, **5**, **21**, **22**, **28**, **29**, *and* **33**

	C(1)	C(2)	C(3)	CH_3–C(3)	C(4)	C(5)	C(6)	H–C(5)
21	170.0	37.8	26.6	21.5	37.7	69.9	84.5	5.13
22	170.1	38.0	24.1	21.3	36.3	68.7	84.8	5.33

	C(2)	C(3)	C(4)	CH_3–C(4)	C(5)	C(6)	C(1′)	CH_3–C(4)
29	74.7	40.9	30.4	22.3	34.5	67.9	126.6	
28	77.8	40.9	30.3	22.2	34.4	68.1	130.7	0.95
33	72.5	37.9	25.0	19.4	32.7	62.4	130.5	1.06

	C(2)	C(3)	C(4)	CH_3–C(4)	C(5)	C(6)	C(7)	C(1′)	H–C(2)	H–C(4)	H–C(7)
4	78.2	45.4	33.6	23.9	35.0	29.0	67.3	131.7	4.08	> 2	3.78
5	77.7	43.1	29.9	23.2	36.1	30.6	69.5	131.9	4.20	1.95	3.53, 3.85

whereas the more polar *cis*-lactone **21** (3*R*,5*R*) has both ring substituents equatorial (see *Table*; *γ-gauche* effect on C(3) of **22**; $\delta(CH_3{-}C(3))$ of **21** = $\delta(CH{-}C(3))$ of **22**; $\delta(H_{ax}{-}C(5))$ of **21** < $\delta(H_{eq}{-}C(5))$ of **22**). Lactone **21** was reduced with $LiAlH_4$ to (3*S*,5*R*)-diol **26**. Tosylation yielded, not unexpectedly, the unstable monotosylate **27** as well as the (+)-(2*R*,4*S*)-tetrahydropyran **28**. The ^{13}C-NMR spectrum of **28** was very similar to that of *cis*-rose oxide (**29**) [18][3]) with respect to the relevant δ(C) (see *Table*). Homologation of **27** with NaCN in DMSO yielded hydroxynitrile **30**. This compound was reduced to (4*S*,6*R*)-diol **17** *via* aldehyde **31**. Finally, the conversion of diol **17** to (+)-**4** according to *Scheme 2* led to that diastereoisomer which corresponds to the more polar of the two natural isomers. Since the configuration of **21** is not affected during the transformation to (+)-**4** – the configurational integrity of each intermediate was confirmed analytically[2]) – it follows that the resulting *cis*-oxepane (+)-**4** has the (2*R*,4*S*)-configuration.

When lactone **22** was submitted to the same series of reactions, the less polar *trans*-oxepane (−)-**5** (2*S*,4*S*) was obtained. On monotosylation of diol **32**, the formation of some (+)-*trans*-tetrahydropyran **33** (2*S*,4*S*) was also observed; in contrast to **22**, its Me–C(4) is axial, whereas the methylbutadienyl side-chain is equatorial (see *Table*).

Discussion. – *Conformational Considerations.* The NMR data (*Table*) suggest that *trans*-oxepane **5** has the unsaturated side-chain in the axial position (*γ-gauche* effect on C(4); $\delta(H_{eq}{-}C(2))$ of **5** > $\delta(H_{ax}{-}C(2))$ of **4**; shielding effect on $H_{ax}{-}C(4)$ and $H_{ax}{-}C(7)$). This interpretation assumes that the oxepane ring has the same chair-boat conformation in **4** and **5**. The results of molecular modeling[4]), on the other hand, imply that both **4** and **5** possess low-energy conformations with the two substituents in the equatorial position, but with the oxepane in two different chair-boat conformations, and it is precisely the flexibility of the oxepane ring which made us hesitate to assign the relative configurations of **4** and **5** from the NMR data alone.

Biosynthesis. Intuitively, the compounds **3**–**5**, just as **1** and **2**, may be classified as 'irregular' isoprenoids, but nothing is known about their biosynthetic origin. It is worth mentioning that the C_{11} ethers **28** and **33** (*Scheme 3*) have *not* been traced in quince [3], suggesting that the pattern follows ($C_5 + C_5$) for **1** and **2**, and ($C_5 + C_{10} - C_3$) for **3**–**5**.

Odor Description. Quince oxepine *rac*-**3** has an odor related to rose oxide (**29**), but with more volume and tenacity. It has a natural fruity-quince character. A mixture of the quince oxepanes *rac*-**4** and *rac*-**5** was perceived as less strong and characteristic than *rac*-**3**, but also very similar to **29**. The *cis*-isomer *rac*-**4** was more green and floral than *rac*-**5** and had a pleasant, bitter character of hyacinth.

We are indebted to Mr. *W. Thommen* and Mr. *R. Brauchli* for the NMR measurements and Drs. *B. Maurer* and *V. Rautenstrauch* for stimulating discussions.

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[3]) The ^{13}C-NMR spectrum of **29** has only recently been recorded by *W. Thommen* and *R. Brauchli, Firmenich SA* (unpublished).

[4]) We thank Mr. *C. Vial, Firmenich SA*, for the calculations [19].

Experimental Part

General. If not stated otherwise, org. extracts were washed to neutral reaction with aq. H_2SO_4 and/or $NaHCO_3$ and NaCl soln., dried ($MgSO_4$), and evaporated. TLC: silica-gel plates. Medium-pressure chromatography (MPLC): prepacked *Lobar*® columns (*Merck*). Anal. GC: fused silica capillary columns (*Supelcowax*® *10*, 60 m × 0.25 mm; *SPB-1*, 60 m × 0.25 mm; *SPB-5*, 30 m × 0.25 mm). Prep. GC: 5% *SP-1000* (polyethylene glycol) on *Chromosorb G, AW-DMCS*, 100–120 mesh, 2 m × 3 mm; 4% *SOMB* (methyl silicone) on *Chromosorb G, AW-DMCS*, 80–100 mesh, 2.5 m × 3 mm. Optical rotation ($[\alpha]_D^{20}$): *Perkin-Elmer-241* polarimeter; $CHCl_3$ solns. IR: *Perkin-Elmer-720* spectrometer; $\tilde{\nu}$ in cm^{-1}. UV: *Uvikon-820* spectrophotometer; λ_{max} (ε) in nm. ^{1}H-NMR (360 MHz) and ^{13}C-NMR (90.5 MHz) spectra: *Bruker-AM-* and *-AMX-360* instrument; $CDCl_3$ solns.; δ in ppm rel. to TMS (= 0.0 ppm) as internal standard; *J* in Hz. MS: *Finnigan-MAT-4500* quadrupole instrument coupled with a capillary GC; electron energy *ca.* 70 eV; *m/z* in % of the most abundant peak.

1. *Oxepin* rac-**3**. 1.1. *(Z)-2-Methyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-2-en-1-ol* (**8**). The procedure was adapted from [7]. A mixture of ethyltriphenylphosphonium bromide (55.6 g, 150 mmol) and anh. THF (300 ml; freshly distilled from $LiAlH_4$) under Ar was cooled in an ice-water bath. BuLi in hexane (1.44N; 104 ml, 150 mmol) was introduced dropwise (→ deep red soln.), and the mixture was stirred at r.t. for 1 h and then cooled to −70°. Aldehyde **9** [6] (23.7 g, 150 mmol) in THF (71 ml) was added within 20 min such that the internal temp. remained < −60° (color fading). After 20 min at −70°, more BuLi (150 mmol) was introduced within 20 min. The now black soln. was warmed to −5°, and a soln. of formaldehyde in THF (*ca.* 0.7N; 450 ml, *ca.* 315 mmol; prepared immediately before use at −78° according to [7a]) was syphoned *via* a stainless steel capillary tube into the flask (→ decoloration, white precipitate). Stirring was continued at r.t. overnight. H_2O (74 ml) was added, and after 2 h, the orange soln. was concentrated to 200 ml, diluted with H_2O (350 ml), and worked up with Et_2O in the usual way. The crude product was distilled in a 12-cm *Vigreux* apparatus. At 60–90°/0.5 Torr, 20.3 g of *ca.* 80% pure **8** were obtained. This material was combined with 22.1 g derived from a parallel run and redistilled, yielding 35.01 g (58.3%) of **8** (b.p. 85–89°/0.5 Torr) that contained *ca.* 5% of what was assumed to be the corresponding (*E*)-isomer. An anal. sample of **8** was obtained by prep. GC (*SP-1000*). IR (liq.): 3400, 1205, 1140, 1125, 1080, 1040, 905, 880, 820. ^{1}H-NMR: 1.84 (*s*, CH_3–C(2)); 2.38 (*m*, 2 H–C(4)); 3.38, 3.51, 3.78, 3.84 (4*m*, 2 CH_2O); 4.03, 4.09 (*AB*, *J* = 8.3, 2 H–C(1)); 4.61 (*m*, CHO); 5.35 (*t*, *J* = 9.0, H–C(3)). MS: 200 (0, M^+), 85 (100), 43 (20), 67 (18), 57 (17), 101 (9), 116 (2), 170 (1).

1.2. *(Z)-1-Bromo-2-methyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-2-ene* (**10**). A soln. of **8** (8.00 g, 40 mmol) in hexane (400 ml) containing pyridine (4 ml) was treated dropwise at −7° with PBr_3 (4 ml, 42.4 mmol) in hexane (80 ml). After the addition (60 min), the mixture was stirred for another 30 min at −5°, then poured into ice water, and worked up with Et_2O in the usual way: 4.40 g (41.8%) of crude **10** that was used for the next step without purification. ^{1}H-NMR: 1.85 (*s*, CH_3–C(2)); 2.38 (*m*, 2 H–C(4)); 3.44, 3.55, 3.76, 3.85 (4*m*, 2 CH_2O); 4.00 (*s*, 2 H–C(1)); 4.60 (*m*, CHO); 5.44 (*t*, *J* = 7.6, H–C(3)).

1.3. *(Z)-2-{2-Methyl-5-[(tetrahydro-2*H*-pyran-2-yl)oxy]pent-2-enyl}-1,3-dithiane* (**11**). Following [10], a soln. of 1,3-dithiane (3.96 g, 33 mmol) in anh. THF (33 ml; freshly distilled from $LiAlH_4$) was treated with BuLi in hexane (1.45N; 23 ml, 33.3 mmol) under Ar at −20° and then cooled to −70°. Bromide **10** (8.70 g, 33 mmol) in THF (11 ml) was added dropwise such that the temp. remained < −45°. Then, the flask was stoppered and stored in the freezer (−20°) overnight. The mixture was then warmed to r.t. and worked up with Et_2O in the usual way. The crude mixture (12.8 g) was filtered through silica gel (100 g) eluting with hexane/AcOEt 8:2. As judged by TLC, the material obtained (8.50 g) contained, besides the desired **11**, several undefined components. The batch was combined with 8.00 g derived from a parallel run and submitted to MPLC (*Lobar C*, hexane/AcOEt 85:15): 12.85 g (65.5%) of TLC-pure **11**. IR (liq.): 1200, 1180, 1140, 1120, 1080, 1040, 990, 970, 910, 880, 820. ^{1}H-NMR: 1.78 (*s*, CH_3–C(2′)); 2.50 (*d*, *J* = 7.5, 2 H–C(1′)); 2.65 (*m*, 2 CH_2S); 3.41, 3.50, 3.73, 3.87 (4*m*, 2 CH_2O); 4.21 (*t*, *J* = 7.2, H–C(3′)). MS: 302 (1, M^+), 85 (100), 119 (53), 43 (20), 67 (15), 57 (14).

1.4. *(Z)-3-Methyl-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]hex-3-enal* (**12**). In analogy to [11]. To a vigorously stirred mixture of **11** (6.25 g, 20.7 mmol) and anh. $CaCO_3$ powder (8.28 g, 82.8 mmol) in H_2O/MeCN 1:4 (106 ml) was added dropwise and under Ar freshly distilled MeI (12.4 ml, 199 mmol). The mixture was stirred under Ar at r.t. overnight, extracted with Et_2O, and worked up in the usual way. The crude product was bulb-to-bulb distilled at 130–140°/0.5 Torr (oven temp.): 3.80 g (86.6%) of **12** which was immediately used for the next step. IR (liq.): 1715, 1210, 1140, 1130, 1080, 1040, 990, 910, 880, 820. ^{1}H-NMR: 1.78 (*s*, CH_3–C(3)); 3.12 (*m*, 2 H–C(2)); 3.40, 3.50, 3.75, 3.86 (4*m*, 2 CH_2O); 4.58 (*m*, CHO); 5.52 (*t*, *J* = 7.2, H–C(4)); 9.60 (*t*, *J* = 1.8, H–C(1)). MS: 212 (0, M^+), 85 (100), 67 (22), 55 (17), 41 (11), 101 (11), 93 (10), 110 (4), 128 (1), 183 (1).

1.5. *(Z)-2,7-Dimethyl-10-[(tetrahydro-2*H*-pyran-2-yl)oxy]deca-1,7-dien-3-yn-5-ol* (**14**). To an Ar-flushed soln. of 2-methylbut-1-en-3-yne [12] (**13**; 11.58 g, 24 mmol) in monoglyme (60 ml; freshly distilled from $LiAlH_4$)

was introduced dropwise at −20° BuLi in hexane (1.6N; 13.8 ml, 22 mmol), followed after 45 min at −20° by a soln. of **12** (3.80 g, 17.9 mmol) in monoglyme (19 ml). The mixture was allowed to warm to 0° within 60 min. After further 30 min at r.t., it was hydrolyzed by addition of sat. aq. NH_4Cl soln. Usual workup with Et_2O produced 4.91 g (98.6%) of crude **14**, suitably pure for the next step. ^{1}H-NMR: 1.82 (*s*, CH_3–C(7)); 1.88 (*s*, CH_3–C(2)); 3.40, 3.50, 3.83 (3*m*, 2 CH_2O); 4.60 (*m*, 1 H–C(5), CHO); 5.21, 5.28 (2*s*, 2 H–C(1)); 5.40 (*t*, *J* = 7.6, H–C(8)).

1.6. *(3Z,7E)-4,9-Dimethyldeca-3,7,9-triene-1,6-diol* (**6**). To a suspension of $LiAlH_4$ (1.33 g, 35 mmol) in anh. THF (135 ml; freshly distilled from $LiAlH_4$) was added dropwise **14** (4.91 g, 35 mmol) in THF (67 ml). After being refluxed for 60 min, TLC showed complete absence of **14**. The mixture was cooled and hydrolyzed carefully with ice followed by sat. aq. NH_4Cl soln. Usual workup with Et_2O afforded 4.90 g (99.2%) of crude product which was dissolved in MeOH (39 ml) and treated with 10% aq. HCl soln. (10 ml) for 40 min. After workup with Et_2O, the residue (3.60 g) was purified by MPLC (*Lobar C*, hexane/AcOEt 1:1): 2.08 g (60.6%) of semi-crystalline **6**. UV (MeOH): 228 (16584). IR (liq.): 3300, 1610, 1120, 1060, 980, 890. ^{1}H-NMR: 1.80 (*s*, CH_3–C(4)); 1.85 (*s*, CH_3–C(9)); 3.59 (*ddd*, *J* = 10.4, 10.4, 4.3, 1 H–C(1)); 3.71 (*ddd*, *J* = 10.4, 5.4, 5.4, 1 H–C(1)); 4.35 (*m*, H–C(6)); 4.98 (*s*, 2 H–C(10)); 5.35 (*t*, *J* = 8.6, H–C(3)); 5.70 (*dd*, *J* = 14.4, 5.8, H–C(7)); 6.34, (*d*, *J* = 14.4, H–C(8)). MS: (0, M^+), 97 (100), 67 (33), 69 (23), 41 (19), 79 (16), 55 (13), 105 (5), 127 (4), 119 (3), 145 (2), 178 (1).

A by-product (300 mg) which was eluted before **6** had spectral data consistent with *(3Z,7E)-6-methoxy-4,9-dimethyldeca-3,7,9-trien-1-ol*. ^{1}H-NMR: 1.77 (*s*, CH_3–C(4)); 1.86 (*s*, CH_3–C(9)); 3.24 (*s*, CH_3O); 3.55 (*ddd*, *J* = 10.1, 10.1, 3.6, 1 H–C(1)); 3.65 (*ddd*, *J* = 10.1, 4.3, 4.3, 1 H–C(1)); 3.80 (*ddd*, *J* = 9.0, 9.0, 4.7, H–C(6)); 5.02 (br. *s*, 2 H–C(10)); 5.30 (*t*, *J* = 7.9, H–C(3)); 5.51 (*dd*, *J* = 16.2, 9.0, H–C(7)); 6.29 (*d*, *J* = 16.2, H–C(8)). MS: 210 (< 1, M^+), 111 (100), 79 (24), 81 (18), 77 (12), 112 (8), 67 (5), 53 (5), 41 (5).

1.7. *(E)-2,3,6,7-Tetrahydro-4-methyl-2-(3-methylbuta-1,3-dienyl)oxepin* (*rac*-**3**). To an ice-cold soln. of **6** (2.00 g, 10.2 mmol) in pyridine (22 ml) was added in small portions TsCl (2.13 g, 11.2 mmol) over 30 min. The mixture was stirred at 0° for 30 min, then stored overnight at 3°. Usual workup gave 2.85 g of crude product. TLC: 1 major (polar) and 1 minor spot. MPLC (*Lobar C*, hexane/AcOEt) yielded 2.20 g (61.6%) of unstable **7** (dec. in $CDCl_3$ soln.) and 220 mg of unidentified nonpolar by-product.

NaH dispersion (*ca.* 80%; 630 mg, *ca.* 21 mmol; freed from mineral oil by washing with 3 portions of anh. pentane) was suspended in monoglyme (30 ml; freshly distilled from $LiAlH_4$) and cooled to 0°. DMPU [13] (0.9 ml, 7.48 mmol) was added, followed by **7** (2.20 g, 6.28 mmol) in monoglyme (30 ml). The mixture was allowed to warm to r.t. and stirred overnight (TLC: complete conversion). Usual workup with Et_2O gave 1.14 g of crude *rac*-**3** which was purified by MPLC (*Lobar B*, hexane/Et_2O 95:5): 510 mg of TLC-pure *rac*-**3**. Evaporative distillation at 110–120°/11 Torr (oven temp.) yielded 450 mg (40.5%) of *rac*-**3**. Colorless oil. UV (MeOH): 228 (24865). IR (liq.): 1610, 1160, 1120, 1110, 1050, 970, 890. ^{1}H-NMR: 1.76 (*s*, CH_3–C(4)); 1.84 (*s*, CH_3–C(3′)); 3.54 (*ddd*, *J* = 12.0, 12.0, 1.0, 1 H–C(7)); 4.04 (*m*, 1 H–C(2), 1 H–C(7)); 4.98 (*s*, 2 H–C(4′)); 5.60 (br. *s*, $\Delta w_{1/2}$ = 14.5, H–C(5)); 5.69 (*dd*, *J* = 16.0, 6.5, H–C(1′)); 6.33 (*d*, *J* = 16.0, H–C(2′)). MS: 178 (2, M^+), 67 (100), 82 (40), 81 (12), 41 (9), 53 (9), 91 (6), 96 (6), 135 (4), 110 (3), 163 (3). GC, ^{1}H-NMR, MS: in full agreement with the ones of the natural product [3].

2. *Oxepanes* rac-**4** *and* rac-**5**. 2.1. *4-Methyl-6-oxohexyl Acetate* (**15**). A soln. of citronellal dimethyl acetal (**16**; 55.5 g, 275 mmol; prepared from *rac*-citronellal according to [20]) in MeOH (550 ml), was treated at −75° with a stream of ozone for 3.5 h (4.5 g O_3/h, 328 mmol). The excess of ozone was flushed off with Ar. The soln. was allowed to warm to 0° and treated with a soln. of $NaBH_4$ (5.22 g, 137.5 mmol) in MeOH/H_2O 1:1 (154 ml). After 2 h, it was concentrated at reduced pressure. Usual workup with Et_2O yielded 60.2 g (100%) of *ca.* 85% pure *6,6-dimethoxy-4-methylhexan-1-ol* which was used for the next step. An anal. sample was obtained by prep. GC (*SOMB*). ^{1}H-NMR: 0.93 (*d*, *J* = 6.1, CH_3–C(4)); 3.31 (2*s*, 2 CH_3O); 3.63 (*t*, *J* = 6.1, 2 H–C(1)); 4.67 (*t*, *J* = 6.1, H–C(6)). MS: 176 (0, M^+), 75 (100), 85 (22), 61 (18), 69 (17), 41 (12), 55 (12), 95 (8), 113 (7), 145 (3).

The crude alcohol was acetylated in Ac_2O/Py 1:2 (225 ml) at r.t. overnight. Workup with Et_2O and distillation of the crude product through a 12-cm *Vigreux* column afforded 49.8 g of *ca.* 90% pure *6,6-dimethoxy-4-methylhexyl acetate* at 120–125°/11 Torr (overall yield from **16**, *ca.* 74.8%). An anal. sample was obtained by prep. GC (*SOMB*). ^{1}H-NMR: 0.93 (*d*, *J* = 6.5, CH_3–C(4)); 2.05 (*s*, CH_3COO); 3.32 (*s*, 2 CH_3O); 4.05 (*t*, *J* = 7.2, 2 H–C(1)); 4.46 (*t*, *J* = 6.1, 1 H–C(6)). MS: 216 (0, M^+), 75 (100), 85 (39), 43 (16), 95 (13), 55 (10), 113 (4), 126 (4),187 (1).

To a soln. of the above acetal (47.9 g, *ca.* 200 mmol) in acetone (880 ml) was added H_2O (13.2 ml) and *Amberlyst-15* (8.8 g; *cf.* [21]). After stirring for 2 h, GC analysis (*SOMB*) indicated 30% of residual acetal. A second batch of *Amberlyst* (4.4 g) and H_2O (6.6 ml) was added followed by a third batch after another 2 h. When the conversion of the acetal was complete (5.5 h total), the suspension was filtered and concentrated to remove the bulk of the acetone. The residue was diluted with Et_2O, dried ($MgSO_4$) and concentrated. The crude product was distilled through a 12-cm *Vigreux* column: 31.4 g (83%) of *ca.* 90% pure **15**, b.p. 115–120°/11 Torr. For spectroscopic purposes, a sample was purified by prep. GC (*SOMB*). IR (liq.): 1730, 1250, 1050. ^{1}H-NMR: 0.98 (*d*,

J = 6.5, CH_3–C(4)); 2.05 (*s*, CH_3COO); 4.06 (*t*, J = 5.8, 2 H–C(1)); 9.77 (*t*, J = 1.0, H–C(6)). MS: 172 (0, $M^{+\cdot}$), 43 (100), 69 (88), 68 (61), 61 (57), 55 (28), 56 (25), 84 (15), 97 (15), 129 (9).

2.2. *(E)-4,9-Dimethyldeca-7,9-diene-1,6-diol* (**17**/**18**). As described in *1.5* and *1.6*, from **13** (14.4 g, 218 mmol), BuLi in hexane (1.6N; 121 ml, 197 mmol), and **15** (30.96 g, *ca.* 90% pure, *ca.* 160 mmol). Without purification, the crude propargylic alcohol (47.9 g) was reduced with $LiAlH_4$ (11.0 g, 289 mmol) in THF (1700 ml). The crude material (35.0 g) was filtered through silica gel (250 g, hexane/AcOEt 1:1): **17**/**18** (20.5 g, *ca.* 93% pure by GC on *SOMB*, 57% yield; ratio 1:1 (*SPB*-1)). For anal. purposes, a sample was purified by prep. GC (*SOMB*) whereby the diastereoisomers were not separated. UV (MeOH): 228 (21780). IR (liq.): 3350, 3080, 1620, 980, 900. ^{1}H-NMR, MS: see *3.4* and *3.6*.

2.3. cis- *and* trans-*(E)-4-Methyl-2-(3-methylbuta-1,3-dienyl)oxepane* (*rac*-**4** and *rac*-**5**, resp.). As described in *1.7*, with **17**/**18** (10.0 g, *ca.* 50 mmol). Usual workup with Et_2O and MPLC (*Lobar C*, hexane/AcOEt 7:3) of the crude product (13.3 g) afforded 8.52 g (*ca.* 48%) of unstable **19**/**20** which were immediately cyclized and 1.65 g of an unidentified nonpolar by-product. The residue obtained after cyclization (5.1 g) was subjected to MPLC (*Lobar C*, hexane/Et_2O 9:1) to give 3.0 g (69%) of > 98% pure *rac*-**4**/*rac*-**5** 1:1 which were distilled at 111–112°/11 Torr as a colorless liquid. For spectroscopic purposes and for olfactory evaluation, *rac*-**4**/*rac*-**5** were separated by repetitive prep. GC (*SP-1000*). Cap. GC (*Supelcowax® 10*) and MS data of *rac*-**4** and *rac*-**5** were in full agreement with the data from the natural samples [3].

trans-*Diastereoisomer* rac-**5**. Less polar (GC). UV (MeOH): 228 (25527). IR (liq.): 3090, 1615, 980, 900. ^{1}H-NMR: 0.98 (*d*, J = 6.8, CH_3–C(4)); 1.84 (*s*, CH_3–C(3′)); 1.95 (*m*, H–C(4)); 3.53 (*m*, 1 H–C(7)); 3.85 (*m*, 1 H–C(7)); 4.21 (*ddd*, J = 6.1, 6.1, 6.1, H–C(2)); 4.95 (*s*, 2 H–C(4′)); 5.68 (*dd*, J = 15.1, 6.1, H–C(1′)); 6.29 (*d*, J = 15.1, H–C(2′)). ^{13}C-NMR: *Table*. MS: 180 (30, $M^{+\cdot}$), 69 (100), 41 (100), 165 (78), 55 (75), 81 (61), 96 (57), 11 (44), 137 (17), 121 (21), 151 (5).

cis-*Diastereoisomer* rac-**4**. More polar (GC). UV (MeOH): 228 (27964). IR (liq.): 3090, 1615, 980, 900. ^{1}H-NMR: 0.97 (*d*, J = 6.5, CH_3–C(4)); 1.84 (*s*, CH_3–C(3′)); 3.78 (*m*, 2 H–C(7)); 4.08 (*ddd*, J = 10.8, 6.1, 2.1, H–C(2)); 4.95 (*s*, 2 H–C(4′)); 5.67 (*dd*, J = 16.2, 6.1, H–C(1′)); 6.28 (*d*, J = 16.2, H–C(2′)). ^{13}C-NMR: *Table*. MS: 180 (33, $M^{+\cdot}$), 69 (100), 41 (100), 55 (82), 165 (80), 81 (63), 96 (60), 111 (43), 137 (15), 123 (12), 151 (5).

3. *Relative and Absolute Configuration of the Oxepanes* **4** *and* **5**. 3.1. *(+)-(3R,5R)- and (+)-(3R,5S)-3,8-Dimethylnon-8-en-6-yn-5-olide* (**21** and **22**, resp.). Aldehyde **23** [15] (from (+)-(*R*)-pulegone ($[\alpha]_D^{20}$ = +22.7 (*c* = 1.10)) according to [16] [17]; $[\alpha]_D^{20}$ = –2.5 (*c* = 1.18); 13.50 g, 94 mmol) was treated with the Li salt of **13** (derived from 7.50 g (114 mmol) of **13** and BuLi in hexane (2.42N; 39 ml, 94 mmol)) as described in *1.5*. Upon usual workup, 6.52 g of neutral and 10.50 g of acidic products were obtained. The acidic part was distilled in a 6-cm *Vigreux* apparatus to give 7.93 g of **21**/**22** 65:35 at 115–121°/2 Torr. The neutral part (**24**) was heated to reflux in the presence of KOH (7.0 g) in EtOH/H_2O 2:1 (22.5 ml) for 4 h. After workup with Et_2O, the crude acids **25** (4.50 g) were bulb-to-bulb distilled at 130°/2 Torr to give 3.14 g of **21**/**22** 32:68 (*SOMB*). Overall yield of **21**/**22**: 11.07 g (66%). Lactones **21** and **22** were readily separated by MPLC (*Lobar C*, hexane/AcOEt 8:2). The *trans*-isomer **22** was eluted before the *cis*-isomer **21** (silica gel, polar and apolar GC columns).

Lactone **22**: $[\alpha]_D^{20}$ = +59.2 (*c* = 1.25). UV (MeOH): 220 (12221), 229 (10114). IR (liq.): 2320, 1740, 1610, 1210, 1160, 1080, 1060, 1020, 980, 900, 800. ^{1}H-NMR (^{1}H,^{13}C-correlated): 1.09 (*d*, J = 6.5, CH_3–C(3)); 1.74 (*m*, H–C(3)); 1.88 (*s*, CH_3–C(8)); 2.05 (*m*, 1 H–C(4)); 2.11 (*ddd*, J = 9.0, 9.0, 9.0, 1 H–C(2)); 2.45 (*m*, H–C(3)); 2.77 (*ddd*, J = 9.0, 7.2, 1.0, 1 H–C(2)); 5.28, 5.33 (2*m*, 2 H–C(9), 1 H–C(5)). ^{13}C-NMR: *Table*. MS: 178 (3, $M^{+\cdot}$), 91 (100), 92 (65), 56 (56), 69 (33), 108 (30), 135 (25), 79 (21), 163 (4).

Lactone **21**: $[\alpha]_D^{20}$ = +27.0 (*c* = 1.11). UV (MeOH): 220 (12863), 228 (10747). IR (liq.): 2320, 1740, 1605, 1220, 1150, 1100, 1060, 1040, 980, 900, 810. ^{1}H-NMR (^{1}H,^{13}C-correlated): 1.08 (*d*, J = 6.5, CH_3–C(3)); 1.65 (*m*, 1 H–C(4)); 1.89 (*s*, CH_3–C(9)); 2.0–2.2 (*m*, 1 H–C(2), 1 H–C(3), 1 H–C(4)); 2.68 (*m*, 1 H–C(2)); 5.13 (*dd*, J = 10.8, 3.6, H–C(5)); 5.29, 5.35 (2*s*, 2 H–C(9)). ^{13}C-NMR: *Table*. MS: 178 (4, $M^{+\cdot}$), 91 (100), 92 (65), 56 (61), 135 (41), 69 (41), 108 (33), 77 (20), 41 (14), 121 (10), 163 (4).

3.2. *(3S,5R,E)-3,8-Dimethylnona-6,8-diene-1,5-diol* (**26**). To a soln. of **21** (2.20 g, 12.3 mmol; > 95% *cis*) in THF (110 ml) was added in portions $LiAlH_4$ (1.10 g, 29 mmol). The mixture was refluxed for 2 h, cooled, and hydrolyzed with H_2O. The precipitate was filtered and the filtrate worked up in the usual way to afford 2.30 g (100%) of **26**. Cap. GC (*SPB-1*): **26** is eluted after the (3*S*,5*S*)-isomer. **26**: ^{1}H-NMR: 0.91 (*d*, J = 6.8, CH_3–C(3)); 1.84 (*s*, CH_3–C(8)); 3.70 (*m*, 2 H–C(1)); 4.28 (*m*, H–C(5)); 4.98 (*s*, 2 H–C(9)); 5.68 (*dd*, J = 15.8, 7.2, H–C(6)); 6.32 (*d*, J = 15.8, H–C(7)). MS: 184 (< 1, $M^{+\cdot}$), 97 (100), 69 (98), 55 (43), 41 (37), 115 (32), 151 (22), 166 (8).

3.3. *Homologation of Diol* **26**. A soln. of **26** (2.30 g, 12.3 mmol) in pyridine (44 ml) was cooled in an ice-bath, and TsCl (2.50 g, 13.1 mmol) was added in portions. The mixture was stirred at 0° for 30 min, then abandoned in the refrigerator overnight. Workup with Et_2O gave 2.20 g of crude product which was immediately subjected to MPLC (*Lobar C*, hexane/Et_2O 1:1). Besides **28** (350 mg), 1.50 g of **27** were obtained which were immediately

redissolved in DMSO (*p.a.*, 37.5 ml) and stirred in the presence of NaCN (375 mg, 7.6 mmol) at r.t. overnight. After workup, 730 mg (30.7%) of **30** were obtained. Cap. GC (*SPB-1*): **30** is eluted after the (4*S*,6*S*)-isomer.

*(4*S*,6*R,E*)-6-Hydroxy-4,9-dimethyldeca-7,9-dienenitrile* (**30**). ^{1}H-NMR: 0.99 (*d*, *J* = 6.5, CH_3–C(4)); 1.85 (*s*, CH_3–C(9)); 2.37 (*m*, 2 H–C(2)); 4.28 (*m*, H–C(6)); 5.00 (*s*, 2 H–C(10)); 5.66 (*dd*, *J* = 15.1, 6.5, H–C(7)); 6.32 (*d*, *J* = 15.1, H–C(8)). MS: 193 (8, M^+), 97 (100), 96 (88), 124 (68), 69 (60), 41 (50), 55 (38), 79 (18).

*(+)-(2*R,*4*S,E*)-Tetrahydro-4-methyl-2-(3-methylbuta-1,3-dienyl)-2*H*-pyran* (**28**). An anal. sample was collected by prep. GC (*SOMB*). Cap. GC (*SPB-1*): **28** precedes (2*S*,4*S*)-isomer **33**. **28**: $[\alpha]_D^{20}$ = +44.3 (*c* = 0.70). IR (liq.): 3090, 1610, 1100, 980, 890. ^{1}H-NMR (^{1}H,^{13}C-correlated): 0.95 (*d*, *J* = 6.1, CH_3–C(4)); 1.83 (*s*, CH_3–C(3′)); 3.38 (*ddd*, *J* = 11.8, 11.8, 1.8, H_{ax}–C(6)); 3.85 (*ddd*, *J* = 11.8, 5.5, < 1, H_{eq}–C(6)); 4.04 (*ddd*, 10.8, 5.8, < 1, H_{ax}–C(1)); 5.65 (*dd*, *J* = 15.8, 5.8, H–C(2′)); 6.32 (*d*, *J* = 15.8, H–C(3′)). MS: 166 (18, M^+), 151 (100), 81 (81), 97 (80), 55 (79), 69 (65), 41 (33), 123 (16), 137 (14).

3.4. *(4*S*,6*R,E*)-4,9-Dimethyldeca-7,9-diene-1,6-diol* (**17**). A soln. of **30** (700 mg, 3.6 mmol) in anh. hexane/toluene 6:1 (42 ml) was cooled to −60°. Diisopropylaluminium hydride (DIBAH; *Aldrich;* 1.5N in toluene; 5 ml, 7.5 mmol) was added dropwise *via* syringe. The mixture was stirred at −60° for 30 min, then allowed to warm to r.t. within 45 min, left for further 30 min, and quenched with sat. aq. NH_4Cl soln. (40 ml). The mixture was vigorously stirred for 40 min and then treated in the usual way to give 750 mg (100%) of **31**. MS: 196 (0, M^+), 93 (100), 91 (95), 79 (80), 77 (73), 119 (65), 41 (47), 105 (43), 134 (26), 163 (17) 178 (12).

Aldehyde **31** in anh. Et_2O (30 ml) was reduced with $LiAlH_4$ (140 mg, 3.7 mmol) at r.t. for 1 h. After workup, the crude **17** (600 mg) was purified by MPLC (*Lobar B*, hexane/AcOEt 1:1): 250 mg (35%) of **17**. Cap. GC (*SPB-1* and *SPB-5*): **17** is eluted after **18**. **17**: ^{1}H-NMR: 0.95 (*d*, *J* = 6.5, CH_3–C(4)); 1.85 (*s*, CH_3–C(10)); 3.63 (*t*, *J* = 6.5, 2 H–C(1)); 4.28 (*m*, H–C(6)); 4.99 (*s*, 2 H–C(10)); 5.66 (*dd*, *J* = 15.1, 7.2, H–C(7)); 6.31 (*d*, *J* = 15.1, H–C(8)). MS: 198 (< 1, M^+), 69 (100), 97 (85), 55 (76), 83 (61), 41 (50), 111 (21), 129 (18), 180 (3).

3.5. *(+)-(2*R,*4*S*)-Oxepane (+)*-**4**. As described in *1.7*, 150 mg (0.75 mmol) of (4*S*,6*R*)-**17** were converted to 80 mg of (+)-**4** and purified by prep. GC (*SP-1000*). $[\alpha]_D^{20}$ = +11.4 (*c* = 0.35). MS, ^{1}H-NMR: identical with those of *rac*-**4** (see *2.3*). Cap. GC (*Supelcowax®10, SPB-1*): **4** is eluted after **5**.

3.6. *(−)-(2*S,*4*S*)-Oxepane (−)*-**5**. Lactone **22** (2.83 g, 15.9 mmol) was converted to (−)-**5** (111 mg, 3.8% overall yield) as described for lactone **21**. $[\alpha]_D^{20}$ = −6.5 (*c* = 0.77). MS, ^{1}H-NMR: identical with those of *rac*-**5** (see *2.3*).

*(3*S,*5*S,E*)-3,8-Dimethylnona-6,8-diene-1,5-diol* (**32**). ^{1}H-NMR: 0.95 (*d*, *J* = 6.5, CH_3–C(3)); 1.85 (*s*, CH_3–C(8)); 3.71 (*m*, 2 H–C(1)); 4.31 (*ddd*, *J* = 6.5, 6.5, 6.5, H–C(5)); 4.99 (*m*, 2 H–C(9)); 5.65 (*dd*, *J* = 15.5, 6.5, H–C(6)); 6.32 (*d*, *J* = 15.5, H–C(7)). MS: 184 (< 1, M^+), 97 (100), 69 (87), 55 (42), 41 (37), 115 (36), 151 (25), 166 (5).

*(4*S,*6*S,E*)-6-Hydroxy-4,9-dimethyldeca-6,8-dienenitrile*. ^{1}H-NMR: 0.96 (*d*, *J* = 6.5, CH_3–C(4)); 1.85 (*s*, CH_3–C(9)); 2.36 (*m*, 2 H–C(2)); 4.27 (*m*, H–C(6)); 5.00 (*s*, 2 H–C(10)); 5.62 (*dd*, *J* = 15.1, 7.2, H–C(7)); 6.32 (*d*, *J* = 15.1, H–C(8)). MS: 193 (12, M^+), 97 (100), 96 (89), 124 (68), 69 (57), 41 (54), 55 (35), 79 (20).

*(+)-(2*S,*4*S,E*)-Tetrahydro-4-methyl-2-(3-methylbuta-1,3-dienyl)-2*H*-pyran* (**33**). $[\alpha]_D^{20}$ = +26.1 (*c* = 0.46). ^{1}H-NMR (^{1}H,^{13}C-correlated): 1.06 (*d*, *J* = 6.5, CH_3–C(4)); 1.85 (*s*, CH_3–C(3′)); 2.00 (*m*, H–C(4)); 3.75 (*m*, 2 H–C(6)); 4.27 (*m*, $\Delta w_{1/2}$ = 15.8, H–C(2)); 4.97 (*s*, 2 H–C(4′)); 5.69 (*dd*, *J* = 15.0, 5.4, H–C(2′)); 6.31 (*d*, *J* = 15.0, H–C(3′)).

*(4*S,*6*S,E*)-4,9-Dimethyldeca-7,9-diene-1,6-diol* (**18**). ^{1}H-NMR: 0.93 (*d*, *J* = 7.2, CH_3–C(4)); 1.85 (*s*, CH_3–C(9)); 3.63 (*t*, *J* = 6.5, 2 H–C(1)); 4.28 (*ddd*, *J* = 7.2, 7.2, 7.2, H–C(6)); 4.99 (*s*, 2 H–C(10)); 5.62 (*dd*, *J* = 15.1, 7.2, 2 H–C(6)); 6.31 (*d*, *J* = 15.1, H–C(7)). MS: 198 (1, M^+), 69 (100), 55 (85), 97 (85), 41 (58), 83 (56), 111 (22), 129 (20), 165 (4), 180 (3).

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