Internal Nucleophilic Termination in Acid-Mediated Polyene Cyclizations

Part 4[1])

Synthetic Access to Tetracyclic Didehydro and Tetradehydro Analogues of (±)-*Ambrox*®

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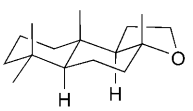
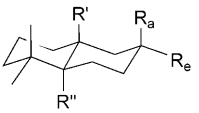
Dedicated to Dr. *Ferdinand Naef* on the occasion of his 65th birthday

Treatment of the unsaturated bicyclic homoallylic alcohols (*E*)- and (*Z*)-**5** and (*Z*)- and (*E*)-**10** and allenic alcohol **16** with an excess of $ClSO_3H$ in 2-nitropropane or CH_2Cl_2 at $-80°$ afforded, in moderate yields (*ca.* 30–70%), diastereoisomer mixtures of racemic tetracyclic ethers **12a**–**c** (*Table 1*) and **17a**,**b** (*Table 2*), respectively. These kinetically controlled stereospecific transformations are believed to proceed *via* concerted or nonconcerted pathways (see *Schemes 4* and *6*) and the results are fully consistent with our earlier work. Representing novel didehydro bridged analogues of known, olfactively active labdane tricyclic ethers, the organoleptic properties of **12a**–**c** and **17a**,**b** are briefly described, especially those of **12c** which, in the context of structure–activity studies, is a racemic didehydro analogue of the known ambergris odorant *Ambrox*®.

1. Introduction. – The relationship between the organoleptic properties of a compound and its chemical structure has been studied extensively [2]. The ambergris-type odor in particular, exemplified by the benchmark odorant *Ambrox*®[2]), has attracted special attention, and has been the subject of various theories, one of which is the empirical 'triaxial rule of odor sensation' [4]. Thus, a multi-point interaction between a dimethyl-*trans*-decalin skeleton and the complementary receptor site is considered to be associated with the axial orientation of the substituents R′, R″, and R_a, as shown in structure **A**. In this context, we reasoned that the tetracyclic ether **12c**, in which R′ and R_a are replaced by a C_2 ethanediyl bridge, would be an interesting test for this theory. Furthermore, we realized that, in analogy with our recent work on



Ambrox®



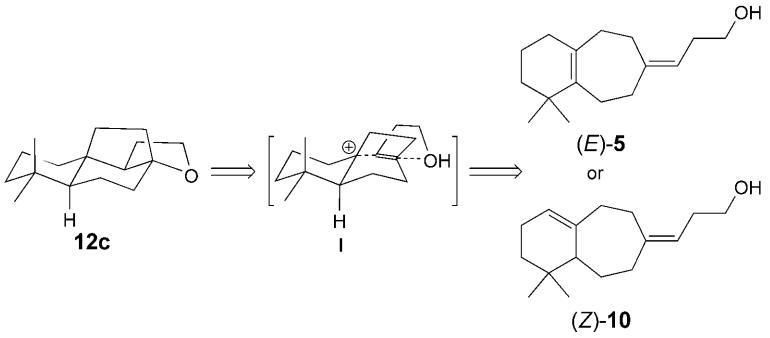
A

[1]) For Parts 1–3, see [1b], [1c], and [1d], resp.

[2]) *Ambrox*® (tradename of *Firmenich SA*) is a commercially important naturally occurring odorant; the racemate is also commercialized by *Firmenich SA* under the tradename of *Cetalox*® [3].

acid-mediated polyene cyclizations [1], **12c** would be accessible *via* cyclization of the cyclohexyl cation **I** by regioselective protonation of either one of the two homoallylic alcohols, (*E*)-**5** and (*Z*)-**10**, as shown in *Scheme 1*. We thus describe herein the synthesis of (*E*)-**5** and (*Z*)-**10**, and the outcome of their cyclizations. We also include results concerning the cyclizations of (*Z*)-**5** and (*E*)-**10**, as well as that of the dehydro analogue of (*E*)- and (*Z*)-**5**, allenic alcohol **16**.

Scheme 1



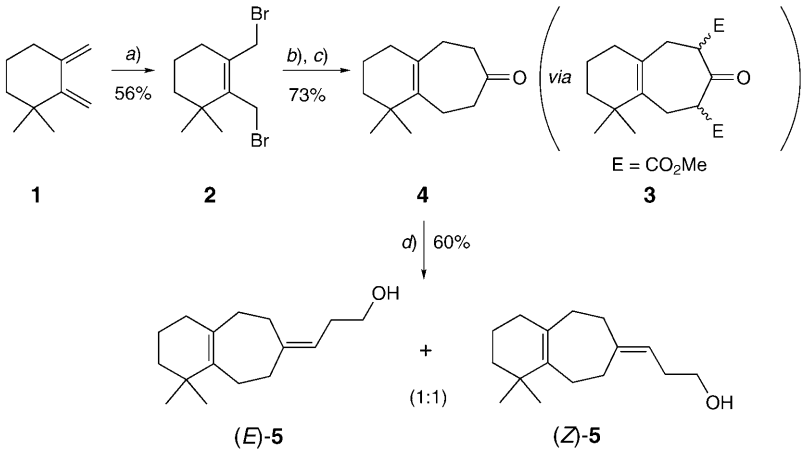
2. Results and Discussion. – 2.1. *Homoallylic Alcohols (*E*)- and (*Z*)-***5*** (see *Scheme 2*). Bromination of *δ*-pyronene (=1,1-dimethyl-2,3-bis(methylene)cyclohexane; **1**) [5] afforded dibromide **2** (56% yield), which was treated with dimethyl 3-oxoglutarate (=dimethyl 3-oxopentanedioate) under basic conditions to furnish, after bis-de(methoxycarbonylation) of the intermediate oxodicarboxylate **3**, cycloheptenone **4** in 73% yield (*Scheme 2*). A subsequent *Wittig* reaction with the ylid derived from (3-hydroxypropyl)triphenylphosphonium bromide [6] gave **5** (1:1 (*E*)/(*Z*) diastereoisomer mixture; 61% yield), which was chromatographed to afford pure samples of (*E*)- and (*Z*)-**5**.

2.2. *Homoallylic Alcohols (*E*)- and (*Z*)-***10***. Access to (*E*)- and (*Z*)-**10** was accomplished by the route described in *Scheme 3*. Accordingly, regioselective allylic oxidation of **6** ((*E*)/(*Z*) 1:1), the (*tert*-butyl)dimethylsilyl ether of **5**, was effected by using an excess of pyridinium dichromate (PDC) and *tert*-butyl hydroperoxide, to give **7** ((*E*)/(*Z*) 1:1) in low yield (32%); (*E*)- and (*Z*)-**7** were then separated by chromatography. Attempted formation of the corresponding tosylhydrazones (*E*)- and (*Z*)-**8**, was accompanied by concomitant hydrolysis of the silyl ether moiety, and thus directly afforded the alcohols (*E*)- and (*Z*)-**9** in 65% and 42%[3]) yield, respectively. Finally, hydride reduction with catecholborane (=1,3,2-benzodioxaborole) furnished (*E*)- and (*Z*)-**10** in 67 and 71% yield, respectively.

2.3. *Acid-Mediated Cyclization of (*E*)-***5***, (*Z*)-***5***, (*E*)-***10***, and (*Z*)-***10*** to Tetracyclic Ethers* **12a**–**c**. The acid-mediated cyclizations of (*E*)- and (*Z*)-**5** and of (*E*)- and (*Z*)-

[3]) As shown in *Scheme 3*, (*Z*)-**9** was accompanied by the non-hydrolyzed, intermediate silyl ether (*Z*)-**8** (29% yield), which was isolated, characterized, and then separately hydrolyzed under acidic conditions to (*Z*)-**9** (80% yield) (see *Exper. Part*).

Scheme 2



a) Br_2, CH_2Cl_2, 0°. *b*) Dimethyl 3-oxoglutarate, $NaHCO_3$, H_2O/CH_2Cl_2, r.t. *c*) NaCl, H_2O, DMSO, 128–135°. *d*) $[Ph_3P(CH_2)_3OH]^+Br^-$, BuLi (2 mol-equiv.), THF, −20° → r.t.

10 were effected by treatment of each substrate with an excess of chlorosulfuric acid ($ClSO_3H$; 4–6 mol-equiv.) in 2-nitropropane or CH_2Cl_2 at −80° during 30 min. Subsequent neutralization with aqueous Na_2CO_3 solution, extractive workup, and distillation *in vacuo* afforded mixtures of **11** and **12a–c** in 30–71% yield. The product distributions were determined by anal. GC (*Table 1*). Pure samples of each product were obtained by a combination of column chromatography and prep. GC, and were fully characterized spectroscopically. Structural attributions were determined by in-depth NMR experiments[4]).

The observed results are explained by kinetically controlled cyclizations analogous to our previous work [1], and the mechanistic rationale is presented in *Scheme 4*. Accordingly, with (*E*)-**5** as substrate, a nonconcerted cyclization, *via* regioselective axial protonation of the tetrasubstituted cyclohexene C=C bond to the cyclohexyl cation **I**[5]), and subsequent ring closure involving *trans*-addition across the trisubstituted C=C bond with equatorial C–C and C–O bond formation, leads to **12c**. Alternatively, a concerted cyclization, comprising *trans*-additions across both of the two C=C bonds, gives **12a**. The anticipated by-product, tetrahydrofuran **11** (see *Table 1*), is formed *via* prior protonation of the trisubstituted C=C bond, followed by ring closure. Unexpectedly, our results show an unexplained solvent dependence: changing from 2-nitropropane to CH_2Cl_2 (*Table 1*, *Entries 1* and *2*) results in a higher yield (71% as opposed to 48%), an almost total suppression of **11**, and a reversal of selectivity in favor of

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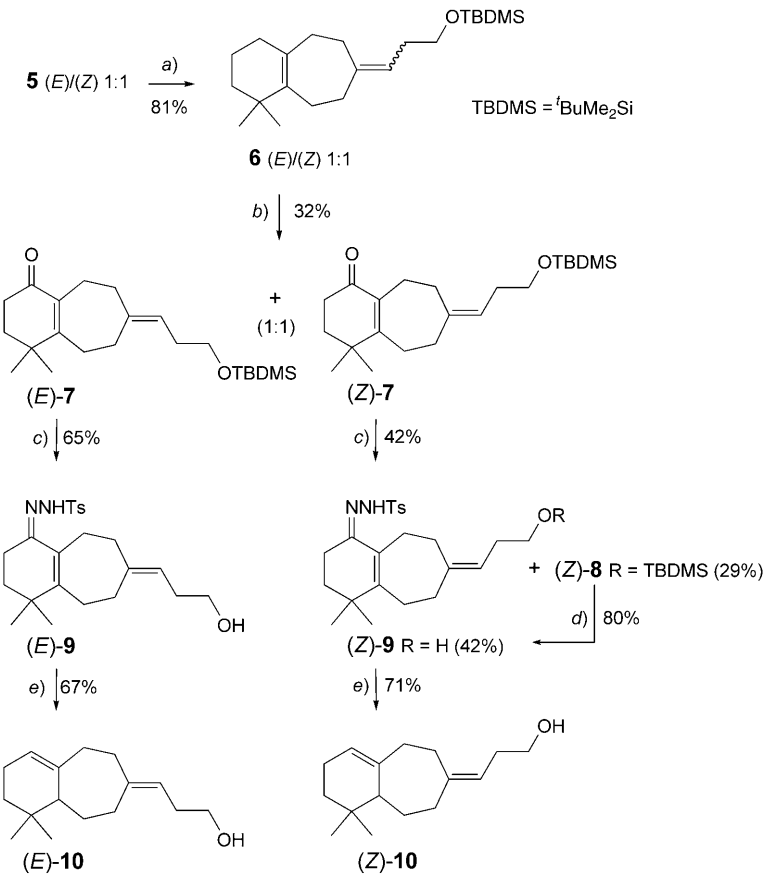
[4]) Structure determinations were greatly aided by comparison with the NMR spectra of analogous tricyclic ethers from earlier work [1][7].

[5]) The observed regioselectivity maximizes the hyperconjugative stabilization of **I** by the axial or pseudoaxial H-atoms at the adjacent C-atoms.

Scheme 3



a) NaH, THF, then *t*-$BuMe_2SiCl$, 52–54°. *b*) PDC (4.4 mol-equiv.), *t*-BuO_2H (3.1 mol-equiv.), toluene, r.t. *c*) $TsNHNH_2$, EtOH, reflux. *d*) AcOH, THF/H_2O, r.t. *e*) Catecholborane (2 mol-equiv.), $CHCl_3$, 5°, then $NaOAc \cdot 3\,H_2O$, reflux.

12c with respect to **12a** (3 : 1 *vs.* 0.8 : 1)[6]). In contrast, cyclization of (*Z*)-**10** with 2-nitropropane as solvent (*Table 1*, *Entry 5*) led to the highly selective formation of **12c**, with only small amounts of **12a** and **11**[7]) (**12c**/**12a**/**11** 91 : 5 : 4) as by-products. Despite the low yield (34%), this result nicely confirms the structure of **12c**, as cyclization is presumed to pass through **I** *via* a highly site-selective and regioselective protonation of the trisubstituted cyclohexene C=C bond.

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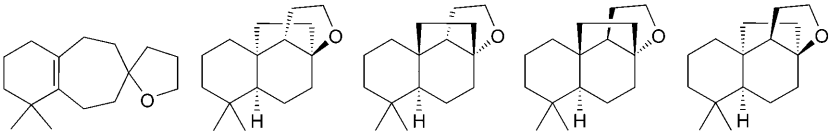
[6]) We have no explanation for this reversal in selectivity, though it is interesting to note that the observed selectivity in CH_2Cl_2 is reflected in the calculated MM2 energies of **12a** and **12c**: 48.7 and 46.7 kcal/mol, respectively.

[7]) The formation of **11** from (*Z*)-**10** necessarily involves isomerization of the trisubstituted cyclohexene C=C bond into the thermodynamically more favored tetrasubstituted position under the strongly acidic conditions.

Table 1. *Acid-Mediated Cyclizations of* (E)- *and* (Z)-**5**, *and* (Z)- *and* (E)-**10**



11 **12a** **12b** **12c** **12d**

Entry[a])	Substrate	Solvent	Product distribution[b])[c])					Yield [%][d])
			11	**12a**	**12b**	**12c**	**12d**	
1	(*E*)-**5**	*A*	30	40	–	30	–	48
2	(*E*)-**5**	*B*	2	24	–	74	–	71
3	(*Z*)-**5**	*A*	50	3	47	–	–	42
4	(*Z*)-**5**	*B*	2	1	97	–	–	52
5	(*Z*)-**10**	*A*	4	5	–	91	–	34
6	(*E*)-**10**	*A*	9	–	91	–	–	31

[a]) Reaction conditions: substrate (1 mol-equiv.), $ClSO_3H$ (4–6 mol-equiv.), solvent (2-nitropropane (*A*) or CH_2Cl_2 (*B*)), −80° (see *Exper. Part*). [b]) GC Analysis of crude product mixture: relative % of **11** and **12a**–**d**. [c]) Another tetracyclic ether, **i** (structure undetermined), was also detected (*ca.* 1–5%) in the cyclizations of (*E*)- and (*Z*)-**5** (*Entries 1–4*; see *Exper. Part* for spectral data). [d]) Refers to the yield of **11** and **12a**–**c** after chromatography and bulb-to-bulb distillation *in vacuo*.

Analogously, the acid-mediated cyclization of (*Z*)-**5** can theoretically occur *via* a nonconcerted pathway, involving the intermediacy of the cyclohexyl cation **II**, or a concerted pathway, to afford either **12b** or **12d**. In practice however, using once again 2-nitropropane or CH_2Cl_2 as solvent (*Table 1*, *Entries 3* and *4*), **12d** was not detected in the product mixtures[8]). In this case, it is logical to assume that the concerted pathway is strongly disfavored by important nonbonding interactions in the transition state[9]). As observed before (*vide supra*), CH_2Cl_2 as solvent gave a higher yield (52% *vs.* 42%), and once again only trace amounts of **11** (*ca.* 2%) were formed. As expected, cyclization of (*E*)-**10** in 2-nitropropane (*Table 1*, *Entry 6*) resulted in the highly selective formation of **12b**, whereas **11**[7]) (**12b**/**11** 91:9) was the only other compound detected in the product mixture (31% yield).

2.4. *Allenic Alcohol* **16** (see *Scheme 5*). By using known methodology [8], base-mediated 1,2-addition of prop-2-yn-1-ol to **4** afforded diol **13**, whose primary OH group was selectively acetylated to **14** and the tertiary OH group then protected, *via* acid-catalyzed addition of ethyl vinyl ether, to furnish **15**. Finally, treatment with $LiAlH_4$ resulted in deprotection of the primary OH group and internal hydride displacement of the *O*-(1-ethoxyethyl) group, affording **16** in 40% overall yield.

2.5. *Acid-Mediated Cyclization of* **16** *to Tetracyclic Ethers* **17a**,**b** *and* **18**. The acid-mediated cyclization of **16** was effected by treatment with an excess of $ClSO_3H$ (9 mol-equiv.) in either 2-nitropropane or CH_2Cl_2 at −80° during 1 h. Subsequent neutral-

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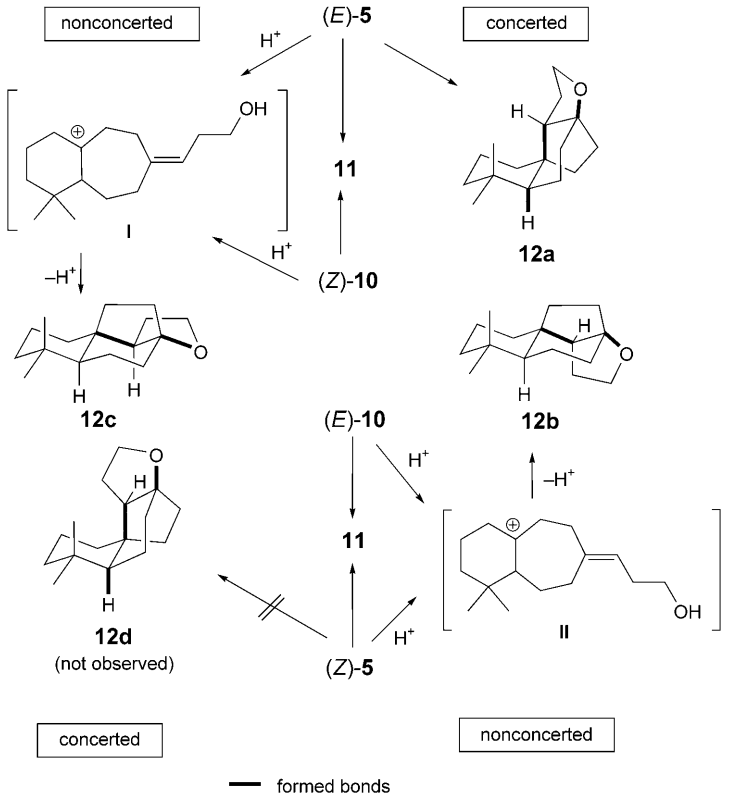
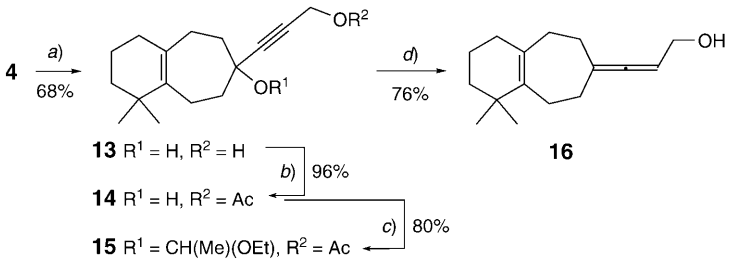
[8]) However, another tetracyclic ether, **i**, was detected (*ca.* 1–5%) in the product mixtures from the cyclizations of (*E*)- and (*Z*)-**5**. Unfortunately, though isolated and characterized (see *Exper. Part*), structure elucidation was not possible due to lack of material.

[9]) The MM2 energy of **12d** is 59.9 kcal/mol as compared to 53.3 kcal/mol for **12b**.

Scheme 4. *Acid-Mediated Cyclizations of* (E)- *and* (Z)-**5** *and of* (Z)- *and* (E)-**10**: *Mechanistic Rationale for the Formation of* **11** *and* **12a**–**c**



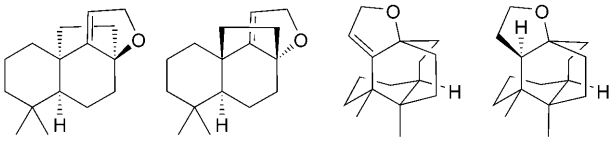
Scheme 5



a) Prop-2-yn-1-ol, KOH, THF, 40°. *b*) Ac_2O, Et_3N, cat. *N*,*N*-dimethylpyridin-4-amine (DMAP), CH_2Cl_2, r.t. *c*) Ethyl vinyl ether, cat. $TsOH \cdot H_2O$, toluene, 0°. *d*) $LiAlH_4$, THF, r.t.

ization with aqueous Na_2CO_3 solution, extractive workup, chromatography, and evaporation *in vacuo* afforded mixtures containing **17a**, **17b**, and **18** as major products (*ca.* 40% yield). The compositions of the mixtures were determined by anal. GC (*Table 2*). Pure samples of each component were obtained by chromatography and fully characterized spectroscopically. Structural attributions were established by NMR experi-

Table 2. *Acid-Mediated Cyclization of* **16**



17a **17b** **18** **19**

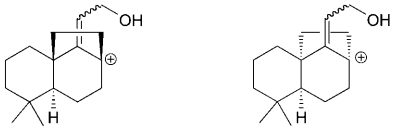
Entry[a])	Solvent	Product distribution[b])[c])			Yield [%][d])
		17a	**17b**	**18**[e])	
1	2-nitropropane	37	54	9	41
2	CH_2Cl_2	25	30	45	43

[a]) Reaction conditions: **16** (1 mol-equiv.), $ClSO_3H$ (9 mol-equiv.), solvent, $-80°$ (see *Exper. Part*). [b]) GC Analysis of crude product mixture: relative % of **17a**, **17b**, and **18**. [c]) Two other minor products, constitutional isomers of **17a**,**b** and **18**, but of unknown structures, were also detected (each *ca.* 5%). Catalytic hydrogenation (cat. 10% Pd/C, 1 bar H_2, cyclohexane, r.t.) of one of these compounds led stereoselectively to **i**, the tetracyclic ether of unknown structure which was formed in trace amounts during the acid-mediated cyclizations of (*E*)- and (*Z*)-**5** (see *Table 1*). [d]) Refers to the yield of **17a**,**b** and **18** confirmed by catalytic hydrogenation to **19** (see *Exper. Part*).

ments, and corroborated by catalytic hydrogenation of the crude product mixture to a mixture of **12a**, **12c**, and **19**, whose separation was again effected by chromatography. The purified compounds were then identified by GC and spectral comparison with authentic samples (for **12a** and **12c**), or by inspection of the NMR data (for **19**).

A mechanistic rationale for the observed results is presented in *Scheme 6*. A non-concerted pathway *via* regioselective protonation of the tetrasubstituted cyclohexene C=C bond of **16** to cyclohexyl cation **III** (presumed to be a 1:1 diastereoisomer mixture), followed by concerted ring closure[10]) *via trans*-addition across the allenyl C(3)=C(7′) bond leads to **17a** and **17b**[11]). Alternatively, **17a** could be the result of a direct concerted pathway from **16**, involving *trans*-additions across both the two C=C bonds. The formation of the relatively less strained **18**[12]) is thought to be thermodynamically driven by a successive 1,2-H and 1,2-methyl shift *via* cyclohexyl cations **IV**

[10]) It is important to note that, in contrast to previous work in which the ethane-1,2-diyl C_2 bridge is replaced by two axial Me groups [1d], the cyclization of **III** to **17a** and **17b** cannot involve the intermediacy of diastereoisomer mixtures of tricyclic allyl cations such as the hypothetical **VI** and **VI′**, due to obvious ring strain, and must proceed in a concerted manner. This means that only one of the two presumed diastereoisomers of **III** is able to undergo cyclization, and thus provides an explanation for the low yields.

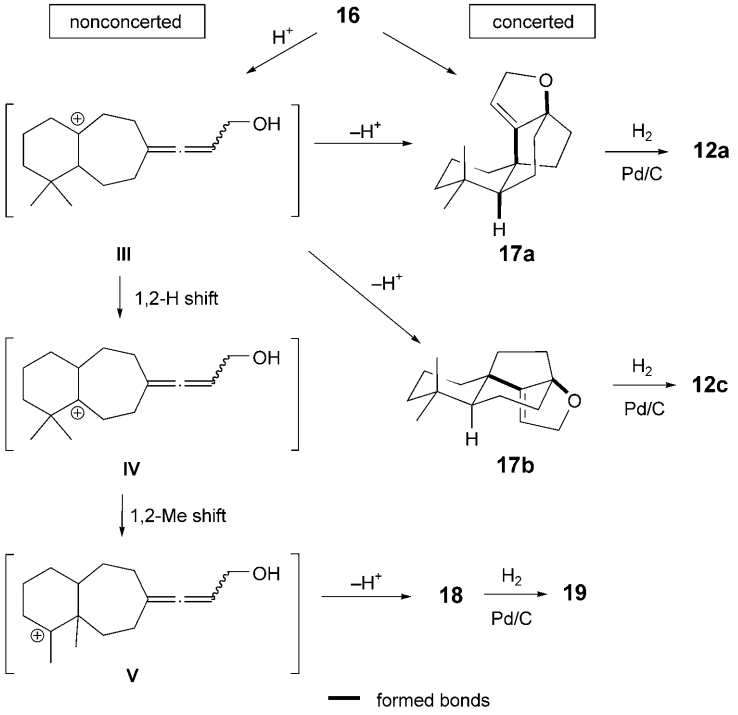


VI **VI'**

[11]) The MM2 energies of **17a** and **17b** are relatively close: 56.7 and 56.3 kcal/mol, respectively.

[12]) MM2 energy of **18**: 53.5 kcal/mol.

Scheme 6. *Acid-Mediated Cyclization of* **16**: *Mechanistic Rationale for the Formation of* **17a**,**b** *and* **18**



and **V** (diastereoisomer mixtures), and then stereoselective cyclization to **18**[13]). Catalytic hydrogenation of **17a**, **17b**, and **18** leads with complete stereoselection to **12a**, **12c**, and **19**, respectively. In the first case, β-face attack is favored[14]), whereas **17b** and **18** are hydrogenated exclusively from the α-face.

2.6. *Organoleptic Properties of* **12a**–**b** *and* **17a**–**b**. Due to the small amounts of compounds available, qualitative rather than quantitative odor evaluations were effected. Thus, in comparison with racemic *Ambrox*®, **12a** was perceived as amber and woody, whereas **12b** had woody, camphoraceous notes. In contrast, **12c** possessed a very powerful amber odor which was more tenacious than either of its two diastereoisomers. The dehydro analogues **17a** and **17b** also exhibited strong amber and woody notes but, especially here, the lack of sufficient material at our disposal rendered a precise organoleptic evaluation extremely difficult.

3. Conclusion. – Synthetic access to racemic tetracyclic didehydro and tetradehydro analogues of the labdane tricyclic ether *Ambrox*® was achieved, and their organoleptic

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[13]) Once again (*cf. Footnote 10*), only one of the two diastereoisomers of **V** is able to cyclize to **18**.

[14]) In the case of **17b**, when the ethane-1,2-diyl bridge is replaced by two axial Me groups, the hydrogenation stereoselectivity is completely reversed, and α-face attack is favored [1d]. This change in selectivity is attributed to subtle structural modifications engendered by the presence of the two fused five-membered rings in **17b**.

properties were evaluated. As well as providing further examples of *Brønsted* acid mediated polyene cyclizations in which the initiating group is an alkene and the terminating group is an alcohol, the described methodology demonstrates its ability to create multiple stereogenic centers with a high degree of stereoselectivity. Finally, the targeted tetracyclic ether **12c** was shown to represent another example of the 'triaxial rule' in possessing a strong ambergris-type odor similar to that exhibited by its dihydro tricyclic analogue, (±)-*Ambrox*®.

Experimental Part

General. See [1d].

1,2-Bis(bromomethyl)-3,3-dimethylcyclohex-1-ene (**2**). A soln. of Br_2 (4.4 g, 27.5 mmol) in CH_2Cl_2 (20 ml) was added dropwise during 30 min to a stirred soln. of 1,1-dimethyl-2,3-bis(methylene)cyclohexane (= δ-pyronene; **1**; 3.8 g, 26 mmol) in CH_2Cl_2 (35 ml) maintained at 0° under N_2. After a further 15 min at 0°, the pale-red soln. was allowed to attain 18° during 15 min, and then, after the addition of $NaHCO_3$ (100 mg), was evaporated at 5°/15 mbar. The resulting brown oil (8.4 g) was purified by CC (silica gel + 1% $NaHCO_3$, pentane) to afford, after evaporation at 25°/0.05 mbar, **2** (4.3 g, 56%). Pale-yellow oil. ^{1}H-NMR: 1.13 (*s*, 6 H); 1.49 (2 H); 1.65 (2 H); 2.22 (2 H); 4.08 (4 H). ^{13}C-NMR: 140.9 (*s*); 136.7 (*s*); 38.9 (*t*); 35.3 (*s*); 32.8 (*t*); 29.3 (*t*); 28.1 (*q*); 26.7 (*t*); 18.6 (*t*). MS: 296 (10, $M(^{79}Br^{81}Br)^+$), 217 (23), 215 (24), 135 (100), 121 (57), 107 (59), 93 (80).

*1,2,3,4,5,6,8,9-Octahydro-1,1-dimethyl-7*H*-benzocyclohepten-7-one* (**4**). A soln. of dimethyl 3-oxoglutarate (2.8 g, 7.9 mmol) and **2** (3.1 g, 10.6 mmol) in CH_2Cl_2 (50 ml) was added dropwise to a mechanically stirred mixture of $NaHCO_3$ (5 g, 59.5 mmol), H_2O (50 ml), and CH_2Cl_2 (10 ml) at r.t. under N_2. After 48 h, the mixture was extracted (Et_2O), and workup followed by evaporation afforded a pale-yellow viscous oil (3.4 g). CC (cyclohexane/AcOEt 85:15) furnished crude *dimethyl 2,3,4,5,6,7,8,9-octahydro-1,1-dimethyl-7-oxo-1*H*-benzocycloheptene-6,8-dicarboxylate* (**3**; 2.9 g; pale-yellow viscous oil). Without further purification[15]), a mixture of **3** (2.8 g), NaCl (0.65 g, 11.1 mmol), H_2O (0.6 g, 33.3 mmol), and DMSO (15 ml) was heated at 128–135° during 4.5 h. The cooled pale-brown mixture was then diluted with Et_2O (70 ml) and poured into 10% aq. NaCl soln. Extraction (Et_2O), workup, CC (cyclohexane/AcOEt 9:1), and bulb-to-bulb distillation *i.v.* afforded **4** (1.5 g, 73%). Pale-yellow oil. B.p. 130–140°/0.03 mbar. ^{1}H-NMR: 1.01 (*s*, 6 H); 1.45 (2 H); 1.60 (2 H); 2.02 (2 H); 2.18 (2 H); 2.27 (2 H); 2.41 (2 H); 2.45 (2 H). ^{13}C-NMR: 212.8 (*s*, C(7)); 140.1 (*s*, C(9a)); 132.8 (*s*, C(4a)); 44.0 (*t*, C(8)); 42.4 (*t*, C(6)); 39.2 (*t*, C(2)); 35.0 (*s*, C(1)); 32.5 (*t*, C(4)); 30.0 (*t*, C(5)); 27.7 (*q*, Me–C(1)); 23.4 (*t*, C(9)); 19.6 (*t*, C(3)). MS: 192 (36, M^+), 177 (100), 159 (20), 135 (24), 119 (27), 107 (43), 91 (49), 79 (45).

*3-(2,3,4,5,6,7,8,9-Octahydro-1,1-dimethyl-1*H*-benzocyclohepten-7-ylidene)propan-1-ol* (**5**; (*E*)/(*Z*) 1:1). At −20° 1.6M BuLi in hexane (50 ml, 0.08 mol) was added dropwise during 20 min to a stirred slurry of (3-hydroxypropyl)triphenylphosphonium bromide (18 g, 0.05 mol) in THF (130 ml) under N_2. The red-brown mixture was allowed to attain r.t. during 1 h and then stirred for 2 h. The orange mixture was cooled to −15°, (white precipitate), and a soln. of **4** (4 g, 0.02 mol) in THF (30 ml) was added dropwise during 15 min. The mixture was allowed to attain r.t. during 1 h, stirred at this temp. for 16 h, and then poured into sat. aq. NH_4Cl soln. Extraction (Et_2O), workup, and evaporation afforded an orange-brown viscous oil (7.7 g) which was triturated with Et_2O/pentane 7:3 (30 ml) at 5°. Filtration, and evaporation of the filtrate gave a brown oil (5.3 g). CC (cyclohexane/AcOEt 9:1) afforded unreacted **4** (0.4 g), and (*E*)/(*Z*)-**5** 1:1 (2.8 g, 60%). Pale-yellow oil. B.p. 160–170°/0.01 mbar. MPLC (*LiChroprep Si60*, 15–25 μm, cyclohexane/AcOEt 19:1) was used to isolate (*Z*)-**5** (1.1 g, less polar) and (*E*)-**5** (0.8 g, more polar).

*Data of (Z)-***5**: ^{1}H-NMR (after exchange with D_2O): 0.98 (*s*, 6 H); 1.90 (2 H); 1.56 (2 H); 1.95 (*dd*, *J* = 6, 6, 2 H); 2.03 (2 H); 2.06–2.20 (6 H); 2.29 (*dt*, *J* = 6, 6, 2 H); 3.61 (br. *t*, *J* = 6, 2 H); 5.08 (br. *t*, *J* = 7, 1 H). ^{13}C-NMR: 146.5 (*s*); 140.4 (*s*); 133.2 (*s*); 118.2 (*d*); 62.5 (*t*); 39.4 (*t*); 37.3 (*t*); 35.6 (*t*); 35.0 (*s*); 33.0 (*t*); 30.6 (*t*); 30.3 (*t*); 27.8 (*q*); 27.2 (*t*); 19.9 (*t*). MS: 234 (52, M^+), 219 (44), 175 (41), 145 (39), 119 (58), 105 (72), 91 (100), 79 (73).

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[15]) NMR Analysis indicated **3** to be a partially tautomerized (keto/enol *ca.* 5:1) *cis*/*trans*-diastereoisomer mixture.

*Data of (*E*)*-**5**: ^{1}H-NMR (after exchange with D_2O): 0.97 (*s*, 6 H); 1.90 (2 H); 1.57 (2 H); 1.94–2.02 (4 H); 2.10 (*s*, 4 H); 2.18 (2 H); 2.29 (*dt*, *J* = 6, 6, 2 H); 3.59 (br. *t*, *J* = 6, 2 H); 5.08 (br. *t*, *J* = 7, 1 H). ^{13}C-NMR: 146.4 (*s*); 140.6 (*s*); 133.2 (*s*); 118.4 (*d*); 62.5 (*t*); 39.4 (*t*); 38.8 (*t*); 34.8 (*s*); 34.1 (*t*); 33.0 (*t*); 30.6 (*t*); 28.6 (*t*); 28.3 (*t*); 27.8 (*q*); 19.9 (*t*). MS: 234 (49, M^+), 219 (46), 175 (38), 145 (39), 119 (55), 105 (71), 91 (100), 79 (72).

*7-{3-[[(*tert*-Butyl)dimethylsilyl]oxy}propylidene}-2,3,4,5,6,7,8,9-octahydro-1,1-dimethyl-1*H*-benzocycloheptene* (**6**;(*E*)/(*Z*) 1:1). A soln. of (*E*)/(*Z*)-**5** 1:1 (1 g, 4.3 mmol) in THF (3 ml) was added dropwise during 10 min to a stirred slurry of NaH (80% dispersion in oil; 0.2 g, 6.6 mmol) in THF (10 ml) at r.t. under N_2. The mixture was then heated at 52–54° during 1 h and cooled to 10° prior to the dropwise addition of a soln. of (*tert*-butyl)chlorodimethylsilane (1.1 g, 7.1 mmol) in THF (5 ml). After attaining r.t. during 15 min, the mixture was heated at 52–54° for 1 h, cooled to 10°, and poured into sat. aq. $NaHCO_3$ soln. Extraction (Et_2O), workup, CC (cyclohexane/AcOEt 92:8), and bulb-to bulb distillation *i.v.* afforded (*E*)/(*Z*)-**6** 1:1 (1.2 g, 81%). Colorless oil. B.p. 190–200°/0.1 mbar. ^{1}H-NMR: 0.06 (*s*, 6 H); 0.90 (*s*, 9 H); 0.97, 0.99 (2*s*, 6 H); 1.40 (2 H); 1.56 (2 H); 1.90–2.17 (10 H); 2.23 (*q*, *J* = 6, 2 H); 3.57, 3.58 (2*t*, *J* = 7, 2 H); 5.07 (*t*, *J* = 7, 1 H). ^{13}C-NMR: 144.8 (*s*); 140.7, 140.6 (2*s*); 133.4 (*s*); 118.8 (*d*); 63.6, 63.5 (2*t*); 39.6, 39.5 (2*t*); 38.9 (*t*); 37.4 (*t*); 35.7 (*t*); 35.1, 34.9 (2*s*); 34.4 (*t*); 33.2 (*t*); 31.1 (*t*); 30.3 (*t*); 28.8 (*t*); 28.5 (*t*); 27.9 (*q*); 27.4 (*t*); 26.1 (*q*); 20.0 (*t*); 18.5 (*s*); −5.1 (*q*). MS: 348 (< 0.5, M^+), 291 (77), 215 (24), 189 (62), 129 (75), 75 (100).

*7-{3-[[(*tert*-Butyl)dimethylsilyl]oxy}propylidene}-2,3,4,5,6,7,8,9-octahydro-4,4-dimethyl-1*H*-benzocyclohepten-1-one* (**7**; (*E*)/(*Z*) 1:1). To a stirred soln. of (*E*)/(*Z*) **6** 1:1 (1.1 g, 3.15 mmol) in toluene (25 ml) containing *Celite*® (2 g) at 15° was added portionwise pyridinium dichromate (5.2 g, 13.8 mmol), and then dropwise 80% aq. *tert*-butyl hydroperoxide (1.25 ml, 9.9 mmol). After a further 22 h at r.t., the mixture was filtered through *Celite*® and the solid thoroughly washed with Et_2O. Evaporation of the filtrate afforded an orange oil (850 mg). Suspension of the filter cake in warm H_2O and further extraction (Et_2O), followed by workup and evaporation gave more orange oil (300 mg). CC (CH_2Cl_2) of the combined oils furnished unreacted (*E*)/(*Z*)-**6** 1:1 (200 mg; R_f (CH_2Cl_2) 0.70), (*E*)-**7** (180 mg, 16%), and (*Z*)-**7** (120 mg, 10%).

*Data of (*E*)*-**7**: Pale-yellow oil. R_f (CH_2Cl_2) 0.38. ^{1}H-NMR: 0.02 (*s*, 6 H); 0.86 (*s*, 9 H); 1.12 (*s*, 6 H); 1.79 (*dd*, *J* = 6, 6, 2 H); 2.02 (2 H); 2.15–2.50 (10 H); 3.54 (*t*, *J* = 7, 2 H); 5.09 (*t*, *J* = 7, 1 H). ^{13}C-NMR: 198.0 (*s*); 167.9 (*s*); 142.8 (*s*); 136.7 (*s*); 120.3 (*d*); 63.4 (*t*); 37.2 (*t*); 37.1 (*t*); 36.5 (*s*); 34.3 (*t*); 31.1 (*t*); 29.7 (*t*); 28.7 (*t*); 26.3 (*q*); 26.1 (*q*); 24.5 (*t*); 18.5 (*s*); −5.1 (*q*). MS: 362 (< 0.5, M^+), 347 (2), 305 (100), 181 (14), 73 (43).

*Data of (*Z*)*-**7**: Beige, semi-crystalline solid. R_f (CH_2Cl_2) 0.30. ^{1}H-NMR: 0.05 (*s*, 6 H); 0.89 (*s*, 9 H); 1.13 (*s*, 6 H); 1.80 (*m*, 2 H); 2.05–2.50 (12 H); 3.57 (*t*, *J* = 7, 2 H); 5.13 (*t*, *J* = 7, 1 H). ^{13}C-NMR: 197.9 (*s*); 168.0 (*s*); 142.7 (*s*); 136.7 (*s*); 120.7 (*d*); 63.4 (*t*); 37.2 (*t*); 37.1 (*t*); 36.5 (*s*); 34.3 (*t*); 31.0 (*t*); 30.7 (*t*); 28.6 (*t*); 26.3 (*q*); 26.1 (*q*); 23.4 (*t*); 18.5 (*s*); −5.1 (*q*). MS: 362 (< 0.5, M^+), 347 (2), 305 (100), 181 (9), 73 (38).

*(7*E*)-2,3,4,5,6,7,8,9-Octahydro-7-(3-hydroxypropylidene)-4,4-dimethyl-1*H*-benzocyclohepten-1-one Tosylhydrazone* ((*E*)-**9**). A stirred mixture of (*E*)-**7** (200 mg, 0.55 mmol) and tosylhydrazide (= 4-methylbenzenesulfonic acid hydrazide; 120 mg, 0.65 mmol) in EtOH (2 ml) was heated at reflux during 1 h, cooled to r.t., and then poured into 10% aq. NaCl soln. Extraction (Et_2O), workup, and recrystallization (Et_2O/pentane 1.5 :1) afforded (*E*)-**9** (150 mg, 65%). White crystals. M.p. 137–141°. ^{1}H-NMR (after exchange with D_2O): 1.02 (*s*, 6 H); 1.59 (br. *t*, *J* = 6, 2 H); 2.05 (2 H); 2.13–2.36 (7 H); 2.42 (*s*, 4 H); 2.54 (2 H); 3.60 (*t*, *J* = 6, 2 H); 5.09 (br. *t*, *J* = 7, 1 H); 7.29 (*d*, *J* = 7, 2 H); 7.86 (*d*, *J* = 7, 2 H). ^{13}C-NMR: 156.0 (*s*); 144.6 (*s*); 144.0 (*s*); 135.5 (*s*); 132.6 (*s*); 129.4 (*d*); 128.3 (*d*); 119.5 (*d*); 62.5 (*t*); 37.0 (*t*); 35.8 (*t*); 35.3 (*s*); 30.7 (*t*); 29.0 (*t*); 28.7 (*t*); 26.4 (2*q*); 25.7 (*t*); 21.7 (*q*); 21.3 (*t*). MS: 416 (< 0.5, M^+), 261 (4), 217 (5), 91(100).

*(7*Z*)-2,3,4,5,6,7,8,9-Octahydro-7-(3-hydroxypropylidene)-4,4-dimethyl-1*H*-benzocyclohepten-1-one Tosylhydrazone* ((*Z*)-**9**). As described for (*E*)-**9**, with (*Z*)-**7** (280 mg, 0.77 mmol), tosylhydrazide (170 mg, 0.91 mmol), and EtOH (3 ml) (75 min). After workup, CC (cyclohexane/AcOEt 4:1) furnished (7*Z*)-*7-{3-[[(*tert*-butyl)dimethylsilyl]oxy}propylidene}-2,3,4,5,6,7,8,9-octahydro-4,4-dimethyl-1*H*-benzocyclohepten-1-one Tosylhydrazone* ((*Z*)-**8**; 120 mg, 29%) and (*Z*)-**9** (135 mg, 42%).

*Data of (*Z*)*-**8**: White crystals (from pentane/Et_2O 4:1). R_f (cyclohexane/AcOEt 4:1) 0.50. M.p. 57–60°. ^{1}H-NMR: 0.04 (*s*, 6 H); 0.88 (*s*, 9 H); 0.97 (*s*, 6 H); 1.54 (br. *t*, *J* = 6, 2 H); 1.97–2.08 (4 H); 2.13–2.28 (5 H); 2.39 (*s*, 4 H); 2.47 (2 H); 3.52 (*t*, *J* = 6, 2 H); 5.06 (br. *t*, *J* = 7, 1 H); 7.28 (*d*, *J* = 7, 1 H); 7.85 (*d*, *J* = 7, 2 H). MS: 530 (< 0.5, M^+), 213 (18), 199 (29), 149 (39), 73 (100).

*Data of (*Z*)*-**9**: White crystals (from pentane/Et_2O 1.5:1). R_f (cyclohexane/AcOEt 4:1) 0.10. M.p. 145–149°. ^{1}H-NMR (after exchange with D_2O): 1.00 (*s*, 6 H); 1.58 (br. *t*, *J* = 6, 2 H); 2.05–2.35 (10 H); 2.43 (*s*, 4 H); 2.52 (2 H); 3.53 (*t*, *J* = 6, 2 H); 5.07 (br. *t*, *J* = 7, 1 H); 7.32 (*d*, *J* = 7, 2 H); 7.88 (*d*, *J* = 7, 2 H). ^{13}C-NMR: 144.0 (*s*); 135.3 (*s*); 129.4 (*d*); 128.3 (*d*); 120.2 (*d*); 62.5 (*t*); 37.1 (*t*); 35.6 (*t*); 35.1 (*s*); 30.6 (*t*); 29.2 (*t*); 27.9 (*t*); 26.3 (*q*); 24.2 (*t*); 21.6 (*q*); 21.2 (*t*). MS: 416 (1, M^+), 261 (9), 217 (10), 91 (100).

*Conversion of (*Z*)-***8*** to (*Z*)-***9***.* A mixture of (*Z*)-**8** (100 mg, 0.19 mmol), THF (2 ml), and 10% aq. AcOH soln. (1 ml) was stirred at r.t. during 2 h. Extraction (Et_2O), workup, and recrystallization (pentane/Et_2O 1.5:1) afforded (*Z*)-**9** (62 mg, 80%), identical to an authentic sample (*vide supra*).

*(3*E*)-3-(1,2,3,5,6,8,9,9a-Octahydro-1,1-dimethyl-7*H*-benzocyclohepten-7-ylidene)propan-1-ol* ((*E*)-**10**). Catecholborane (60 mg, 0.5 mmol) was added to a stirred soln. of (*E*)-**9** (100 mg, 0.24 mmol) in $CHCl_3$ (2 ml) at 2° under N_2. After 2 h at 5°, $NaOAc \cdot 3H_2O$ (200 mg, 1.47 mmol) was added portionwise, and the mixture was allowed to attain r.t. prior to refluxing during 1 h. Then 1N HCl (100 mg) was added to the cooled mixture, and stirring was continued at r.t. during 15 min. Extraction (Et_2O), workup, CC (cyclohexane/AcOEt 4:1), and evaporation afforded (*E*)-**10** (37 mg, 67%). Colorless oil. ^{1}H-NMR (after exchange with D_2O): 0.84 (*s*, 3 H); 0.88 (*s*, 3 H); 1.10–1.22 (2 H); 1.39 (*t*, *J* = 6, 1 H); 1.43 (*t*, *J* = 6, 1 H); 1.65 (1 H); 1.84 (*m*, 1 H); 1.94–2.42 (9 H); 3.62 (2 H); 5.09 (br. *t*, *J* = 7, 1 H); 5.32 (1 H). ^{13}C-NMR: 144.4 (*s*); 140.4 (*s*); 120.9 (*d*); 119.9 (*d*); 62.3 (*t*); 49.3 (*d*); 38.2 (*t*); 38.0 (*t*); 32.3 (*s*); 31.6 (*t*); 31.1 (*t*); 29.6 (*t*); 29.0 (*t*); 27.4 (*q*); 26.2 (*q*); 23.2 (*t*). MS: 234 (100, M^+), 219 (57), 175 (80), 119 (78), 105 (72), 91 (87).

*(3*Z*)-3-(1,2,3,5,6,8,9,9a-Octahydro-1,1-dimethyl-7*H*-benzocyclohepten-7-ylidene)propan-1-ol* ((*Z*)-**10**). As described for (*E*)-**10**, with (*Z*)-**9** (95 mg, 0.23 mmol): (*Z*)-**10** (38 mg, 71%). Colorless oil. ^{1}H-NMR (after exchange with D_2O): 0.85 (*s*, 3 H); 0.88 (*s*, 3 H); 1.04–1.18 (2 H); 1.39 (2 H); 1.65 (1 H); 1.92 (*m*, 1 H); 1.92–2.38 (9 H); 3.60 (2 H); 5.15 (br. *t*, *J* = 7, 1 H); 5.32 (1 H). ^{13}C-NMR: 144.8 (*s*); 141.1 (*s*); 120.6 (*d*); 120.2 (*d*); 62.3 (*t*); 49.4 (*d*); 37.4 (*t*); 35.8 (*t*); 32.2 (*s*); 31.7 (*t*); 31.5 (*t*); 31.1 (*t*); 30.0 (*t*); 27.3 (*q*); 26.7 (*q*); 23.2 (*t*). MS: 234 (100, M^+), 219 (60), 175 (80), 119 (79), 105 (74), 91 (92).

Acid-Mediated Cyclization ($ClSO_3H$/2-nitropropane) *of (*E*)-***5***. 1,2,3,4,4′,5,5′,6,8,9-Decahydro-1,1-dimethylspiro[7*H*-benzocycloheptene-7,2′(3′*H*)-furan]* (**11**)*, and (1*RS*,6*RS*,9*SR*,13*RS*)- and (1RS,6*SR*,9*SR*,13*RS*)-5,5-Dimethyl-10-oxatetracyclo[7.4.2.0^{1,6}.0^{9,13}]pentadecane*[16]) (=(*1*RS*,4*SR*,9*SR*,10*SR*)- and (*1*RS*,4*RS*,9*SR*,10*SR*)-5,5-Dimethyl-13-oxatetracyclo[7.4.2.0^{1,10}.0^{4,9}]pentadecane,* resp., or *(3a*RS*,5a*SR*,9a*SR*,9b*SR*)- and (3a*RS*,5a*RS*,9a*SR*,9b*SR*)-Octahydro-6,6-dimethyl-2*H*,4*H*-3a,9a-ethanonaphtho[2,1-*b*]furan*, resp.; **12a** and **12c**, resp.). A soln. of (E)-**5** (0.77 g, 3.29 mmol) in 2-nitropropane (12 ml) was added dropwise during 10 min to a mechanically stirred soln. of $ClSO_3H$ (0.9 ml, 13.4 mmol) in 2-nitropropane (12 ml) at −80° under N_2. After 20 min at −80°, sat. aq. Na_2CO_3 soln. (22 ml) was added dropwise to the orange-brown mixture (temp. rise to *ca.* −15°), which was then allowed to attain 10° during 30 min prior to extraction (Et_2O). Workup and GC analysis of the crude product showed the presence of five components, in ascending order of retention times: **4** (1%), **11** (27%), **12a** (37%), **20c** (28%), and **i** (7%, undetermined structure). MPLC (*LiChroprep Si60*, 15–25 μm, cyclohexane/AcOEt 19:1) and bulb-to-bulb distillation at 130–140°/0.01 mbar enabled the isolation of **11** (110 mg, 14%), **12a** (160 mg, 20%), **12c** (110 mg, 14%), and **i** (4 mg, 5%), all as colorless oils.

Data of **11**: ^{1}H-NMR: 1.96 (*s*, 6 H); 1.35–2.00 (16 H); 2.23 (2 H); 3.82 (*t*, *J* = 6.5, 2 H). ^{13}C-NMR: 140.8 (*s*); 133.5 (*s*); 85.5 (*s*); 66.5 (*t*); 39.4 (*t*); 38.9 (*t*), 37.5 (*t*); 34.8 (*s*); 32.9 (*s*); 32.9 (*t*); 30.1 (*t*); 27.8 (*q*); 27.6 (*q*); 25.7 (*t*); 23.3 (*t*); 20.0 (*t*). MS: 234 (81, M^+), 219 (44), 175 (42), 105 (70), 97 (100).

Data of **12a**: ^{1}H-NMR: 0.91 (*s*, 3 H); 0.98 (*s*, 3 H); 1.08–1.90 (17 H); 2.01 (*dd*, *J* = 11, 8, 1 H); 3.92 (*m*, 1 H); 4.07 (*m*, 1 H). ^{13}C-NMR: 90.9 (*s*, C(9)); 67.3 (*t*, C(11)); 52.6 (*d*, C(6)); 50.2 (*d*, C(13)); 46.9 (*s*, C(1)); 42.0 (*t*, C(4)); 37.5 (*t*, C(14)); 36.3 (*t*, C(8)); 36.0 (*t*, C(2)); 34.8 (*s*, C(5)); 34.4 (*q*, Me_α-C(5)); 31.0 (*t*, C(15)); 26.2 (*t*, C(12)); 24.0 (*q*, Me_β-C(5)); 20.9 (*t*, C(7)); 20.8 (*t*, C(3)). MS: 234 (3, M^+), 205 (100), 163 (10), 96 (26).

Data of **12c**: ^{1}H-NMR: 0.88 (*s*, 3 H); 0.92 (*s*, 3 H); 1.00–2.00 (18 H); 3.92 (*dd*, *J* = 18, 6.5, 1 H); 4.09 (*m*, 1 H). ^{13}C-NMR: 89.6 (*s*, C(9)); 67.9 (*t*, C(11)); 61.9 (*d*, C(13)); 53.2 (*d*, C(6)); 45.7 (*s*, C(1)); 42.5 (*t*, C(4)); 36.4 (*t*, C(8)); 36.3 (*t*, C(2)); 33.4 (*q*, Me_α-C(5)); 33.4 (*t*, C(15)); 33.4 (*s*, C(5)); 29.3 (*t*, C(14)); 25.9 (*t*, C(12)); 21.5 (*q*, Me_β-C(5)); 21.5 (*t*, C(7)); 19.6 (*t*, C(3)). MS: 234 (31, M^+), 219 (11), 135 (25), 97 (100).

Data of **i**: ^{1}H-NMR: 0.95 (*s*, 3H); 0.96 (*s*, 3 H); 1.00–2.00 (17 H); 2.07 (*m*, 1 H); 3.66 (*m*, 1 H); 3.86 (*m*, 1 H). ^{13}C-NMR: 83.2 (*s*); 66.5 (*t*); 54.7 (*d*); 48.8 (*s*); 43.0 (*t*); 41.7 (*d*); 37.0 (*t*); 36.3 (*s*); 35.6 (*t*); 30.1 (*t*); 29.4 (*t*); 29.0 (*t*); 26.4 (*q*); 26.1 (*t*); 25.6 (*t*); 23.0 (*q*). MS: 234 (5, M^+), 219 (11), 124 (100), 109 (6).

Acid-Mediated Cyclization ($ClSO_3H/CH_2Cl_2$) *of (*E*)-***5***.* As described in the foregoing experiment (*vide supra*), except that 2-nitropropane was replaced by CH_2Cl_2. Workup and GC analysis of the crude product showed the presence of **11** (2%), **12a** (23%), **12c** (73%), and **i** (2%), whose bulb-to-bulb distillation at 130–140°/0.01 mbar afforded a colorless oil (560 mg, 73%).

Acid-Mediated Cyclization ($ClSO_3H$*/2-nitropropane) of (*Z*)-***5***. (1*RS*,6*SR*,9*SR*,13*SR*)-5,5-Dimethyl-10-oxatetracyclo[7.4.2.0^{1,6}.0^{9,13}]pentadecane*[16]) (=(*1*RS*,4*RS*,3*SR*,10*RS*)-5,5-Dimethyl-13-oxatetracyclo[7.4.2.0^{1,10}.0^{4,9}]-pentadecane* or *(3a*RS*,5a*RS*,9a*SR*,9b*RS*)-Octahydro-6,6-dimethyl(-2*H*,4*H*-3a,9a-ethanonaphtho[2,1-*b*]furan*;

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[16]) Systematic names of **12a–c** and **17a**,**b** are given in parentheses.

12b). A soln. of (*Z*)-**5** (1 g, 4.27 mmol) in 2-nitropropane (15 ml) was added dropwise during 10 min to a mechanically stirred soln. of $ClSO_3H$ (1.2 ml, 18 mmol) in 2-nitropropane (15 ml) at $-80°$ under N_2. Following the same procedure as for the cyclization of (*E*)-**5** (*vide supra*), GC analysis of the crude product showed the presence of **4** (8%), **11** (45%), **12a** (3%), **12b** (42%), and **i** (2%). MPLC (cyclohexane/AcOEt 19:1) and bulb-to-bulb distillation at 130–140°/0.01 mbar enabled the isolation of **4** (50 mg, 6%) and **11** (220 mg, 22%), both identical to authentic samples (*vide supra*), and **12b** (190 mg, 19%).

Colorless oil. ^{1}H-NMR: 0.88 (*s*, 3 H); 0.90 (*s*, 3 H); 1.00–2.00 (17 H); 2.32 (*m*, 1 H); 4.35 (2 H). ^{13}C-NMR: 89.6 (*s*, C(9)); 74.0 (*t*, C(11)); 60.9 (*d*, C(13)); 43.5 (*d*, C(6)); 42.5 (*t*, C(4)); 39.5 (*t*, C(2)); 39.2 (*s*, C(1)); 38.7 (*t*, C(15)); 33.0 (*s*, C(5)); 32.7 (*q*, Me_α-C(5)); 31.0 (*t*, C(14)); 30.6 (*t*, C(8)); 21.7 (*q*, Me_β-C(5)); 21.5 (*t*, C(7)); 20.4 (*t*, C(12)); 19.9 (*t*, C(3)). MS: 234 (35, M^+), 219 (13), 205 (79), 149 (51), 96 (100).

Acid-Mediated Cyclization ($ClSO_3H/CH_2Cl_2$) *of (*Z*)-***5***.* As described in the foregoing experiment (*vide supra*), except that 2-nitropropane was replaced by CH_2Cl_2. Workup and GC analysis of the crude product showed the presence of **11** (2%), **12a** (1%), **12b** (95%) and **i** (2%), whose bulb-to-bulb distillation at 130–140°/0.01 mbar afforded a colorless oil (530 mg, 53%).

Acid-Mediated Cyclization ($ClSO_3H$/2-nitropropane) *of (*Z*)-***10***.* A soln. of (*Z*)-**10** (35 mg, 0.15 mmol) in 2-nitropropane (1 ml) was added dropwise during 5 min to a mechanically stirred soln. of $ClSO_3H$ (0.06 ml, 0.9 mmol) in 2-nitropropane (2 ml) at $-80°$ under N_2. After 25 min at $-80°$, sat. aq. Na_2CO_3 soln. (2 ml) was added dropwise to the orange mixture (temp. rise to *ca.* $-15°$). Extraction (Et_2O), workup, and evaporation afforded a viscous oil (25 mg), shown by GC analysis to contain three major products: **11** (4%), **12a** (5%), and **12b** (91%). Subsequent CC (cyclohexane/AcOEt 19:1) and bulb-to-bulb distillation at 180–190°/0.01 mbar afforded **12b** (11 mg, 31%), identical to an authentic sample (*vide supra*).

Acid-Mediated Cyclization ($ClSO_3H$/2-nitropropane) *of (*E*)-***10***.* As described in the foregoing experiment (*vide supra*), (*E*)-**10** (35 mg, 0.15 mmol) was converted to a crude product mixture, shown by GC analysis to contain two major products: **11** (9%) and **12b** (91%). The latter compound was isolated (10 mg, 28%) and shown to be identical to authentic material.

*2,3,4,5,6,7,8,9-Octahydro-7-(3-hydroxyprop-1-ynyl)-1,1-dimethyl-1*H*-benzocyclohepten-7-ol* (**13**). A soln. of **4** (3 g, 15.1 mmol) in prop-2-yn-1-ol (5.1 g, 91 mmol) was added dropwise during 10 min to a stirred slurry of powdered KOH (6 g, 90 mmol) in THF (30 ml) at 40° under N_2. The mixture was then refluxed during 2.5 h, cooled, and poured into cold sat. aq. NH_4Cl soln. Extraction (Et_2O), workup, CC (cyclohexane/AcOEt 7:3), and recrystallization (pentane/Et_2O 95:5) afforded **13** (2.5 g, 68%). White crystals. M.p. 80–81°. ^{1}H-NMR (after exchange with D_2O): 0.95 (*s*, 3 H); 0.97 (*s*, 3 H); 1.39 (2 H); 1.42–1.60 (4 H); 1.80–2.30 (8 H); 4.30 (*s*, 2 H). ^{13}C-NMR: 140.8 (*s*); 133.6 (*s*); 89.9 (*s*); 82.1 (*s*); 72.2 (*s*); 50.7 (*t*); 40.7 (*t*); 39.3 (2*t*); 34.8 (*s*); 33.0 (*t*); 29.5 (*t*); 27.7 (*q*); 27.6 (*q*); 22.8 (*t*); 19.9 (*t*). MS: 248 (2, M^+), 215 (31), 187 (57), 105 (60), 91 (100).

*3-(2,3,4,5,6,7,8,9-Octahydro-7-hydroxy-1,1-dimethyl-1*H*-benzocyclohepten-7-yl)propy-2-nyl Acetate* (=*7-[3-(Acetyloxy)prop-1-ynyl)-2,3,4,5,6,7,8,9-octahydro-1,1-dimethyl-1*H*-benzocyclohepten-7-ol*; **14**). Et_3N (2.7 ml, 19.1 mmol) was added dropwise during 5 min to a stirred soln. of **13** (3.6 g, 14.5 mmol) and Ac_2O (1.7 ml, 17.9 mmol) in CH_2Cl_2 (10 ml) at 2°. After a further 2 h at 5°, GC analysis showed 94% conversion. Addition of DMAP (2 mg) and stirring during a further 30 min completed the reaction. The mixture was poured into cold 5% aq. HCl soln. and extracted (Et_2O). Workup, CC (cyclohexane/AcOEt 4:1), and evaporation afforded **14** (4.05 g, 96%). Pale-yellow oil. ^{1}H-NMR (after exchange with D_2O): 0.96 (2*s*, 6 H); 1.39 (2 H); 1.54 (4 H); 1.80–2.30 (8 H); 2.10 (*s*, 3 H); 4.72 (*s*, 2 H). ^{13}C-NMR: 170.4 (*s*); 140.8 (*s*); 133.6 (*s*); 91.0 (*s*); 77.7 (*s*); 72.1 (*s*); 52.4 (*t*); 40.7 (*t*); 39.3 (*t*); 39.2 (*t*); 34.8 (*s*); 33.0 (*t*); 29.4 (*t*); 27.7 (*q*); 27.6 (*q*); 22.7 (*t*); 20.8 (*q*); 19.9 (*t*). MS: 290 (< 0.5, M^+), 220 (31), 205 (33), 187 (35), 91 (41), 43 (100).

*3-[7-(1-Ethoxyethoxy)-2,3,4,5,6,7,8,9-octahydro-1,1-dimethyl-1*H*-benzocyclohepten-7-yl]prop-2-ynyl Acetate* (**15**; 1:1 diastereoisomer mixture). A soln. of ethyl vinyl ether (2.4 g, 34.6 mmol) in toluene (5 ml) was added dropwise during 10 min to a stirred soln. of **14** (3.9 g, 13.4 mmol) in toluene (15 ml) containing TsOH·H_2O (20 mg) at $-15°$ under N_2. After a further 2 h at $-10°$ and 2 h at 0°, the mixture was poured into sat. aq. $NaHCO_3$ soln. Extraction (Et_2O), workup, CC (cyclohexane/AcOEt 93:7) and evaporation afforded **15** (3.9 g, 80%). Pale-yellow oil. ^{1}H-NMR: 0.96 (*s*, 6 H); 1.19 (2*t*, *J*=6, 3 H); 1.33 (2*d*, *J*=7, 3 H); 1.39 (2 H); 1.54 (2 H); 1.50–2.30 (10 H); 2.09 (*s*, 3 H); 3.50 (*m*, 1 H); 3.69 (*m*, 1 H); 4.74 (*s*, 2 H); 5.17 (*q*, *J*=6, 1 H). ^{13}C-NMR: 170.2 (2*s*); 140.9, 140.6 (2*s*); 133.6, 133.3 (2*s*); 96.1 (2*d*); 60.8, 60.7 (2*t*); 52.3 (2*t*); 39.6, 39.4 (2*t*); 39.3 (2*t*); 38.2, 38.0 (2*t*); 34.8 (2*s*); 32.9 (2*t*); 29.3, 29.1 (2*t*); 27.6 (4*q*); 22.5 (2*q*); 22.3 (2*t*); 20.7 (2*q*); 19.9 (2*t*); 15.3 (2*q*). MS: 362 (< 0.5, M^+), 272 (2), 187 (10), 73 (100).

*3-(1,2,3,4,5,6,8,9-Octahydro-1,1-dimethyl-7*H*-benzocyclohepten-7-ylidene)prop-2-en-1-ol* (**16**). A soln. of **15** (3.4 g, 9.1 mmol) in THF (20 ml) was added dropwise during 20 min to a stirred slurry of $LiAlH_4$ (0.42 g, 10.7 mmol) in THF (15 ml) at 18–20° under N_2. After a further 30 min at r.t., the mixture was cooled to 5° prior

to the successive addition of H_2O (0.4 ml), 15% aq. NaOH soln. (0.4 ml), Et_2O (10 ml), and H_2O (1.2 ml). Stirring was continued for 30 min and then followed by filtration through *Hyflo*. Concentration of the filtrate afforded a yellow oil (2.4 g) which was purified by CC (cyclohexane/AcOEt 85 :15) and bulb-to-bulb distillation under high vacuum: **16** (1.6 g, 76%). Colorless oil. B.p. 180–190°/0.01 mbar. ^{1}H-NMR (after exchange with D_2O): 0.97 (*s*, 6 H); 1.40 (2 H); 1.57 (2 H); 1.98 (*t*, *J* = 6, 2 H); 2.05–2.25 (8 H); 4.07 (*d*, *J* = 6, 2 H); 5.18 (br. *t*, *J* = 6, 1 H). ^{13}C-NMR: 199.3 (*s*); 140.7 (*s*); 133.6 (*s*); 109.6 (*s*); 89.0 (*d*); 61.1 (*t*); 39.4 (*t*); 34.9 (*t*); 34.8 (*t*); 34.8 (*s*); 33.0 (*t*); 32.9 (*t*); 31.5 (*t*); 28.0 (*t*); 27.8 (*q*); 19.9 (*t*). MS: 232 (12, M^+); 204 (72), 189 (81), 145 (66), 105 (63), 91 (100).

Acid-Mediated Cyclization ($ClSO_3H$/2-nitropropane or CH_2Cl_2) *of* **16**. *(1*RS,*6*RS,*9*SR*)- and (1*RS,*6*SR,*9*SR*)-5,5-Dimethyl-10-oxatetracyclo[7.4.2.0^{1,6}.0^{9,13}]pentadec-12-ene*[16]) (= *(1*RS,*4*SR,*9*SR*)- and (1*RS,*4*RS,*9*SR*)-5,5-Dimethyl-13-oxatetracyclo[7.4.2.0^{1,10}.0^{4,9}]pentadec-10-ene* or *(3a*RS,*5a*SR,*9a*SR*)- and (3a*RS,*5a*RS,*9a*SR*)-5,5a,6,7,8,9-Hexahydro-6,6-dimethyl-2*H,*4*H-*3a,9a-ethanonaphtho[2,1-*b*]furan*; **17a** and **17b**, resp.), *and (1*RS,*6*RS,*10*RS,*11*SR*)-6,11-Dimethyl-2-oxatetracyclo[8.3.2.0^{1,5}.0^{6,11}]pentadec-4-ene* (= *(3a*RS,*5a*SR,*6*RS,*9a*RS*)-4,5,5a,6,7,8,9,9a-Octahydro-5a,9a-dimethyl-2*H-*3a,6-ethanonaphtho[2,1-*b*]furan*; **18**). A soln. of **16** (150 mg, 0.65 mmol) in 2-nitropropane (5 ml) was added dropwise during 10 min to a mechanically stirred soln. of $ClSO_3H$ (0.4 ml, 6 mmol) in 2-nitropropane (5 ml) at −80° under N_2. After 1 h at −80°, sat. aq. Na_2CO_3 soln. (10 ml) was added dropwise to the yellow mixture (temp. rise to *ca.* −10°), followed by Et_2O (10 ml), and the mixture was allowed to attain 10° during 30 min prior to extraction (Et_2O). Workup, filtration (silica gel, cyclohexane/AcOEt 19 :1), and evaporation afforded a yellow oil (70 mg), shown by GC analysis to contain three major products: **17a** (37%; 15% yield), **17b** (54%; 22% yield), and **18** (9%; 4% yield), subsequently separated by prep. GC. Colorless oils. B.p. 130–140°/0.1 mbar (bulb-to-bulb distillation).

Data of **17a**: ^{1}H-NMR: 0.88 (*s*, 3 H); 0.91 (*s*, 3 H); 1.10–2.00 (15 H); 4.78 (*dd*, *J* = 12, 2, 1 H); 4.88 (*dd*, *J* = 12, 1.5, 1 H); 5.22 (*m*, 1 H). ^{13}C-NMR: 153.1 (*s*, C(13)); 107.5 (*d*, C(12)); 96.1 (*s*, C(9)); 79.0 (*t*, C(11)); 52.8 (*d*, C(6)); 42.8 (*t*, C(4)); 42.5 (*s*, C(1)); 40.5 (*t*); 36.6 (*t*); 35.5 (*t*); 35.2 (*s*, C(5)); 32.8 (*q*, Me_α-C(5)); 31.6 (*t*); 22.6 (*q*, Me_β-C(5)); 20.9 (*t*, C(3)); 20.4 (*t*, C(7)). MS: 232 (80, M^+), 204 (100), 189 (25), 136 (62), 91 (61).

Data of **17b**: ^{1}H-NMR: 0.88 (*s*, 3 H); 0.95 (*s*, 3 H); 1.10–1.85 (11 H); 1.96 (br. *dd*, *J* = 12, 5, 2 H); 2.23 (*m*, 2 H); 4.81 (*dd*, *J* = 12, 2, 1 H); 4.89 (*d*, *J* = 12, 1 H); 4.99 (br. *s*, 1 H). ^{13}C-NMR: 157.9 (*s*, C(13)); 104.3 (*d*, C(12)); 95.3 (*s*, C(9)); 79.6 (*t*, C(11)); 51.4 (*d*, C(6)); 42.2 (*t*, C(4)); 41.6 (*s*, C(1)); 37.7 (*t*, C(8)); 34.8 (*t*, C(2)); 33.7 (*t*, C(14)); 33.5 (*s*, C(5)); 32.9 (*q*, Me_α-C(5)); 32.8 (*t*, C(15)); 21.6 (*q*, Me_β-C(5)); 21.4 (*t*, C(7)); 19.4 (*t*, C(3)). MS: 232 (99, M^+), 203 (71), 135 (75), 91 (80), 41 (100).

Data of **18**: ^{1}H-NMR: 0.95 (*s*, 3 H); 1.10 (*s*, 3 H); 1.38–1.85 (12 H); 2.00–2.10 (3 H); 4.55 (*dd*, *J* = 12, 2, 1 H); 4.68 (br. *d*, *J* = 12, 1 H); 5.36 (br. *s*, 1 H). ^{13}C-NMR: 155.4 (*s*, C(5)); 115.5 (*d*, C(4)); 88.6 (*s*, C(1)); 73.6 (*t*, C(3)); 44.0 (*d*, C(10)); 39.5 (*t*, C(13)); 38.5 (*s*, C(6)); 38.0 (*s*, C(11)); 37.6 (*t*, C(7)); 32.2 (*t*, C(14)); 31.2 (*t*, C(12)); 30.7 (*t*, C(9)); 29.7 (*t*, C(15)); 29.1 (*q*, Me-C(6)); 25.7 (*q*, Me-C(11)); 22.4 (*t*, C(8)). MS: 232 (100, M^+), 217 (22), 203 (33), 189 (34), 175 (22), 161 (39), 149 (35), 133 (38), 109 (68).

Repetition of the above procedure, replacing 2-nitropropane by CH_2Cl_2, afforded a yellow oil (65 mg), shown by GC and NMR analysis to contain **17a** (25%; 11% yield), **17b** (30%; 13% yield), and **18** (45%, 19% yield).

Catalytic Hydrogenation of **17a**, **17b**, *and* **18**: *(1*RS,*5*SR,*6*SR,*10*RS,*11*SR*)-6,11-Dimethyl-2-oxatetracyclo[8.3.2.0^{1,5}.0^{6,11}]pentadecane* (= *(3a*RS,*5a*SR,*6*RS,*9a*SR,*9b*SR*)-Decahydro-5a,9a-dimethyl-2*H-*3a,6-ethanonaphtho[2,1-*b*]furan*; **19**). A stirred soln. of **17a** (26%), **17b** (24%), and **18** (50%) (95 mg, 0.41 mmol) in cyclohexane (25 ml) containing 10% Pd/C (30 mg) was hydrogenated (1 bar H_2) at r.t. during 5 h. A further quantity of 10% Pd/C (30 mg) was then added, and hydrogenation was continued for a total of 27 h. Filtration (*Celite*®), evaporation, and bulb-to-bulb distillation at 130–140°/0.1 mbar afforded a colorless oil (90 mg), shown by GC analysis to consist of unreacted **17a** (3%), **12a** (23%), **12c** (23%), and **19** (49%). The identities of **17a**, **12a**, and **12c** were confirmed by GC and NMR comparison with authentic samples (*vide supra*). A sample of **19** (13 mg) was isolated by extensive CC purification (cyclohexane/AcOEt 19 :1 and CH_2Cl_2): Colorless oil.

^{1}H-NMR: 0.92 (*s*, 3 H); 0.93 (*s*, 3 H); 1.23 (*m*, 1 H); 1.36–2.00 (16 H); 2.08 (*m*, 1 H); 3.71 (*m*, 1 H); 3.86 (*dd*, *J* = 10, 9, 1 H). ^{13}C-NMR: 82.3 (*s*, C(1)); 65.4 (*t*, C(3)); 51.2 (*d*, C(5)); 44.5 (*d*, C(10)); 40.4 (*t*, C(13)); 38.2 (*t*, C(7)); 37.0 (*s*, C(11)); 34.3 (*s*, C(6)); 31.9 (*t*, C(12)); 30.3 (*t*, C(4)); 29.7 (*t*, C(9)); 29.1 (*t*, C(15)); 28.0 (*t*, C(14)); 26.6 (*q*, Me-C(11)); 24.4 (*q*, Me-C(6)); 20.1 (*t*, C(8)). MS: 234 (16, M^+), 219 (100), 150 (65), 135 (17), 109 (25).

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