excess of **3b** at 25 °C, after 2 days 50% conversion of (-)-1 (GC monitoring) was achieved and (-)-2 was isolated in 30% yield.

The kinetic measurements were performed by following the procedure reported previously;[6b] the results are given in Table I.

Acknowledgment. This work was supported in part by the Deutsche Forschungsgemeinschaft (SFB No. 347 "Selective Reaktionen Metall-aktivierter Molekule"), the Fonds der Chemischen Industrie, the Spanish Dirección General de Investigación Científica y Técnica (PB87-0989), and the Italian Ministery for University and Scientific Research (MURST 40). We thank the A. von Humboldt Foundation (R.M. and M.E.G.-N.) and the Spanish Ministerio de Educación y Ciencia (R.M.) for postdoctoral fellowships. A generous gift of (*R*)-(-)-3-phenyl-1-butene was supplied by Prof. G. Wilke, Max-Planck-Institut für Kohleforschung (Mülheim, Germany), for which we are most grateful.

Registry No. (-)-1, 5787-29-1; (±)-1, 36383-15-0; (-)-2, 53777-08-5; **3a**, 115464-59-0.

Internal Nucleophilic Termination in Biomimetic Acid Mediated Polyene Cyclizations: Stereochemical and Mechanistic Implications. Synthesis of (±)-Ambrox and Its Diastereoisomers

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Treatment of 10 structurally related trienols and dienols **5–8** with an excess of fluorosulfonic acid in 2-nitropropane at -90 °C afforded, in 74–87% yield, diastereoisomeric mixtures of the odoriferous norlabdane oxides **9–15** ((-)-**9** (Ambrox) is a naturally occurring ambergris odorant). These transformations represent examples of efficient biomimetic acid-mediated cyclizations in which the hydroxyl group serves as the internal nucleophilic terminator. The stereochemical outcome of these kinetically controlled processes has been analysed in detail, and mechanistic hypotheses consistent with the results have been proposed. For the four acyclic trienols **5**, the major reaction pathway can be rationalized by a totally synchronous process involving three internal anti additions via chair or skew-boat conformations of the nascent cyclohexane rings. An alternative explanation postulates a nonsynchronous process in which ring closure to an intermediate cyclohexyl cation is followed by rapid cyclization, directed by a strong kinetic preference for equatorial C–C and C–O bond formation. In contrast, for the monocyclic dienols **6–8** only a nonsynchronous process, involving prior protonation of the cyclohexenyl bond, is fully consistent with the results. In the nonsynchronous processes, the orientation of the side chain vicinal to the cyclohexyl cation directs the stereochemical course of the cyclization. For the acyclic trienols, this factor is predetermined by the configuration of the C(7)=C(8) bond, whereas, for the monocyclic dienols, this orientation is determined by the stereoselective axial protonation of the cyclohexenyl bond in **6**, or by the distribution of cyclohexene and cyclohexane conformers in **7** and **8**, respectively. In the cases studied, it is clear that *conformational inversion of the six-membered ring is slower than cyclization* and thus ensures that an equatorial side chain leads to a trans A/B ring junction in the cyclization product, whereas an axial side chain affords a cis A/B ring junction.

Introduction

Despite extensive studies concerning the stereoselective construction of polycyclic systems via the nonenzymatic acid-catalyzed cyclization of polyenes,[1] the preparation of polycyclic ethers in which a hydroxyl group serves as an internal nucleophilic terminator has seldom been reported.[2,3] Our continued interest in stereocontrolled routes to naturally occurring drimanes[4] and norlabdanes[5] encouraged us to investigate the synthetic potential and stereospecificity of this biomimetic transformation. In this context we now present a detailed stereochemical analysis and mechanistic interpretation of the acid-mediated cyclizations of isomeric polyenols **5–8** to tricyclic ethers **9–15**,[6] compounds which have attracted considerable synthetic interest due to their special organoleptic properties.[7]

Results and Discussion

Stereochemically pure samples of homoallylic alcohols **5–8** were conveniently prepared, albeit in modest yield (21–23%), from ketones **1–4** using a Wittig reaction[8] fol-

(1) Caliezi, A.; Schinz, H. *Helv. Chim. Acta* **1949**, *32*, 2556; *Ibid.* **1950**, *33*, 1129; *Ibid.* **1952**, *35*, 1637. For a review see: Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1982; Vol. 3, Part B; p 390.

(2) (a) Sharpless, K. B. *J. Am. Chem. Soc.* **1970**, *86*, 6999. (b) Garst, M. E.; Cheung, Y.; Johnson, W. S. *Ibid.* **1979**, *95*, 4404. (c) Wolf, H.; Mätzel, U.; Brunke, E.-J.; Klein, E. *Tetrahedron Lett.* **1979**, 2339. (d) Vlad, P. F.; Ungar, N. D.; Perutskii, V. B. *Khim. Geterotsikl Soedin SSSR* **1990**, *26*, 896.

(3) For enzymatic cyclizations using squalene cyclase (including the transformation of (*E,E*)-**5** to **9**), see: Neumann, S.; Simon, H. *Biol. Chem. Hoppe-Seyler* **1986**, *367*, 723.

(4) Snowden, R. L.; Brauchli, R.; Wüst, M. *Helv. Chim. Acta* **1990**, *73*, 640.

(5) Escher, S.; Giersch, W.; Niclass, Y.; Bernardinelli, G.; Ohloff, G. *Helv. Chim. Acta* **1990**, *73*, 1935.

(6) All compounds synthesized in this work are racemic; for the individual syntheses and spectral characterization of **9–15**, see: Ohloff G.; Giersch, W.; Pickenhagen, W.; Furrer, A.; Frei, B. *Helv. Chim. Acta* **1985**, *68*, 2022 (for **9–11**) and ref 5 (for **12–15**).

(7) Ambrox ((-)-**9**, trade name of Firmenich SA) is a commercially important odorant naturally occurring in ambergris, see: Ohloff, G. In *Fragrance Chemistry*; Theimer, E. T., Ed.; Academic Press: New York, 1982; p 535. For syntheses of (-)-**9** and its racemate, see: Snowden, R. L.; Linder, S. M. *Tetrahedron Lett.* **1991**, *32*, 4119.

(8) Garst, M. E.; Tallman, E. A.; Bonfiglio, J. N.; Harcourt, D.; Ljungwe, E. B.; Tran. A. *Tetrahedron Lett.* **1986**, *27*, 4533.

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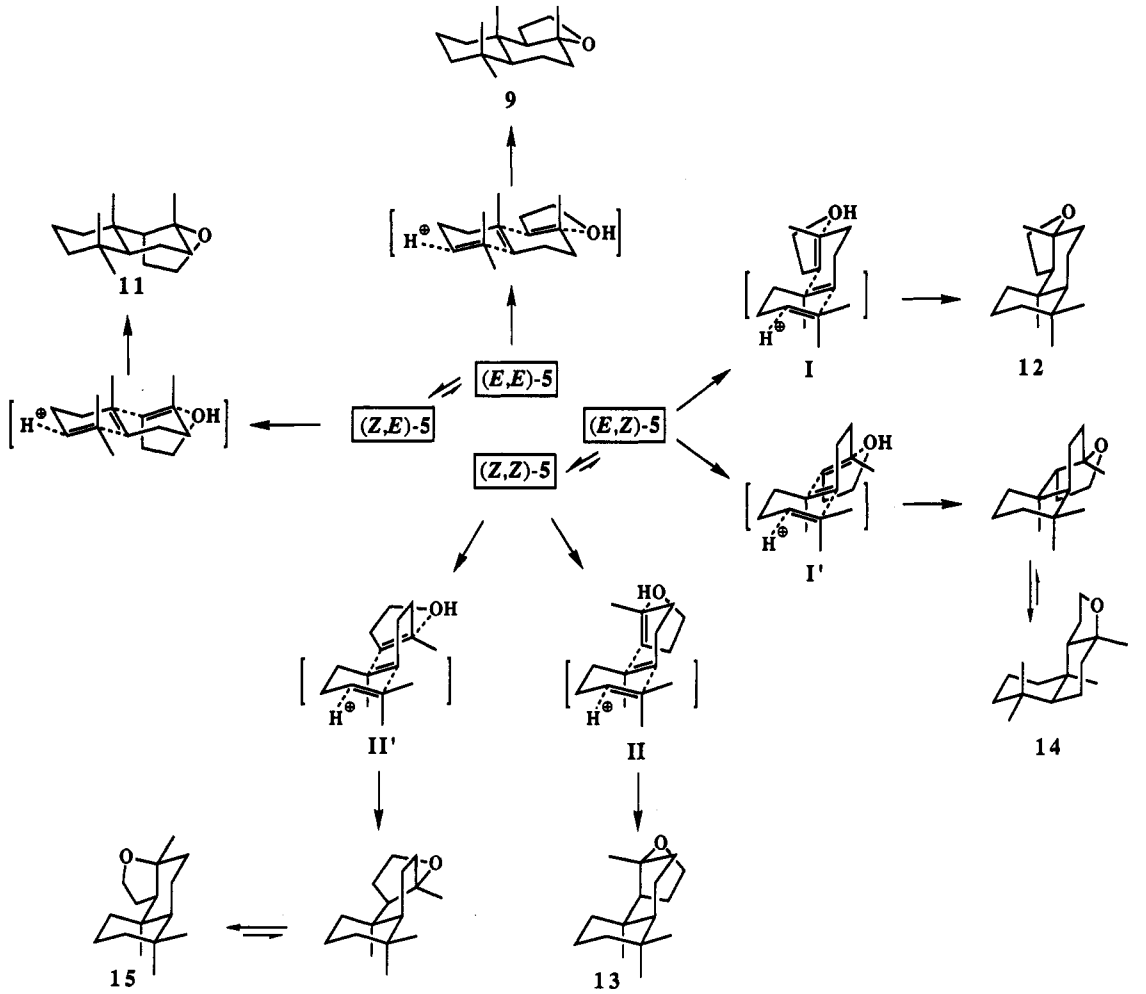
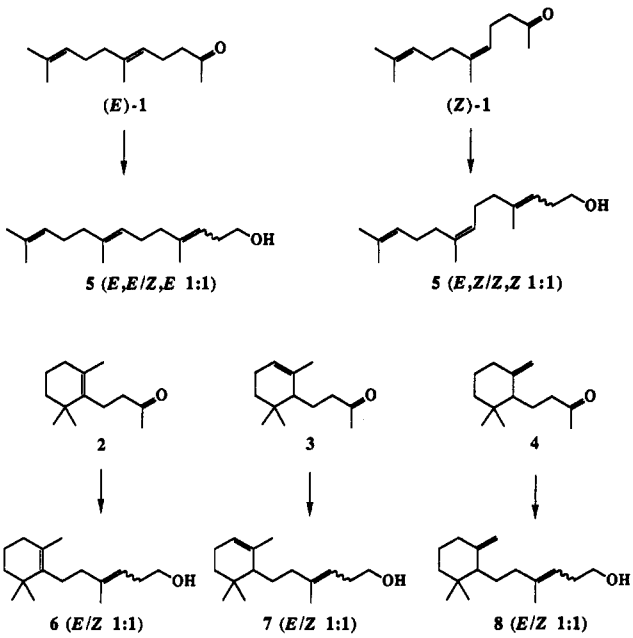


Figure 1. Acid-mediated cyclizations of (*E,E*)-, (*Z,E*)-, (*E,Z*)-, and (*Z,Z*)-**5**: synchronous pathway.

lowed by chromatographic separation of the resulting *E*/*Z* stereoisomeric mixtures (see Scheme I). Standard cyclization conditions then involved treatment of each alcohol with an excess of fluorosulfonic acid in 2-nitropropane at −90 °C[9] to afford, after workup (see Experimental Section), a mixture of **9**–**15** (yield 74–87%)[10] analyzed and identified by comparison with authentic samples[5,6] (see Table I, entries 1–10).

The stereospecific formation of **9** (40%), **11** (69%), **12** (46%), and **13** (57%) from acyclic trienols (*E,E*)-**5**, (*Z,E*)-**5**, (*E,Z*)-**5**, and (*Z,Z*)-**5**, respectively[11] (entries 1–4), may be rationalized by the Stork–Eschenmoser hypothesis,[12,13] which postulates synchronous internal anti additions via chairlike conformations of the nascent cyclohexane rings,

Scheme I. Preparation of Alcohols 5–8[a]



[a] Reaction conditions: $[Ph_3P(CH_2)_3OH]^+ Br^-$, *n*-BuLi (2 mol equiv), THF (yield 21–23%).

initiated by protonation at the terminal C(11)=C(12) bond (Figure 1). With respect to side products, the presence of **11** (35%), **12** (2%), and **14** (1%) (entry 1) indicates that

(9) These reaction conditions have been extensively used by Smit and Vlad in analogous acid-mediated cyclizations; see: Muntyan, G. E.; Kurbanov, M.; Smit, V. A.; Semenovskii, A. V.; Kucherov, V. F. *Izv. Akad. Nauk SSSR Ser. Khim.* **1973**, 633; Vlad, P. F.; Ungur, N. D.; Perutskii, V. B. *Khim. Prir. Soedin* **1986**, 793 and references cited therein. The use of other Bronsted or Lewis acids in a variety of solvents gave inferior results.

(10) In general, the conversion of substrate was total, and the yield refers to the weight of product obtained after Kugelrohr distillation. A substantial proportion of the missing yield is accounted for by uncharacterized, nonvolatile components (10–20% yield).

(11) After the completion of our work, Vlad and co-workers[2d] reported the stereospecific conversion of (*E,E*)-**5** to **9** (73% yield) under similar conditions, but using six times less solvent. A major discrepancy concerns the formation of **11**, which is not mentioned in the Russian work; it is thus likely that the concentration of FSO_3H in 2-nitropropane is a critical factor in the cyclization process.

(12) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068.

(13) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

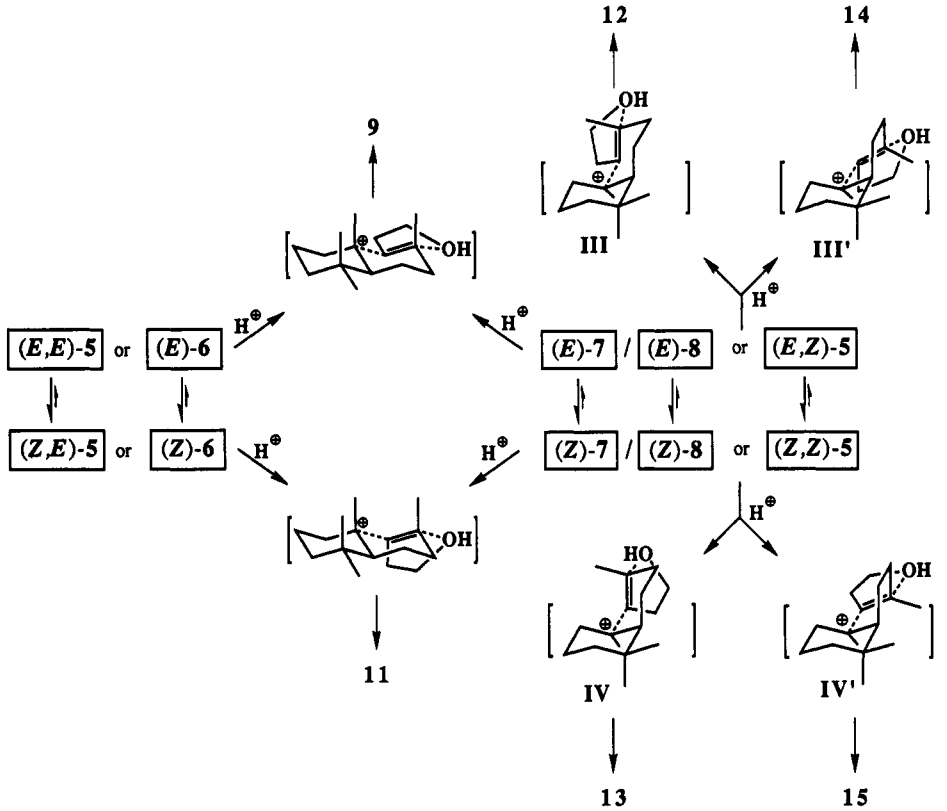


Figure 2. Acid-mediated cyclizations of (*E,E*)-, (*Z,E*)-, (*E,Z*)-, and (*Z,Z*)-**5**, (*E*)- and (*Z*)-**6**, (*E*)- and (*Z*)-**7**, and (*E*)- and (*Z*)-**8**: nonsynchronous pathway.

isomerization of (*E,E*)-**5** to (*Z,E*)-**5** is competitive with cyclization to **9** whereas isomerization to (*E,Z*)-**5** is a minor pathway.[14] In contrast, (*Z,E*)-**5** affords only a small amount (7%) of **13** (entry 2), implying that cyclization to **11** is considerably faster than isomerization to either (*Z,Z*)-**5** or (*E,E*)-**5**. Indeed, assuming that the cyclization transition states bear some structural resemblance to the final product, slower cyclization of (*E,E*)-**5** is consistent with the MM2 energies[15] of **9** and **11** (45.5 and 41.8 kcal/mol, respectively[16]), calculated using the MACROMODEL program.[17]

For the cyclizations of (*E,Z*)-**5** and (*Z,Z*)-**5** (entries 3 and 4), the formation of **14** (16%) and **15** (6%) respectively, is believed to result from transition states I′ and II′ in which the nascent B ring is in a skew-boat conformation. The observed ratios of **12**/**14** (2.8:1) and **13**/**15** (9.8:1) are thus a direct measure of the relative energies of the two competing transition states (viz. I/I′ and II/II′), which are again reflected in the MM2 energies of **12**–**15** (44.6, 43.1, 47.8 (48.9), and 45.0 (46.7) kcal/mol, respectively; the figures in brackets refer to the skew-boat conformers of **14** and **15**, see Figure 1). It is important to note that the only other explanation for the formation of **14** and **15** requires the intermediacy of monocyclic dienols **6** and **7** and subsequent cyclization via a putative trans-diaxial addition.[18] However, conclusive evidence against this alternative pathway is provided by the studies in which **6** and **7** are the cyclization substrates (see below). Once again, partial C=C bond isomerization accounts for the minor amounts of **9** (5%) and **11** (4%) found in entry 3, together with **11** (5%) and **12** (6%) found in entry 4.

It is important to note that these results may also be rationalized by a nonsynchronous process involving prior ring closure to a cyclohexyl cation whose conformational inversion[19] is slower than subsequent cyclization. This cyclization then involves internal anti additions which are controlled by a strong kinetic preference for equatorial C–C and C–O bond formation[20] (Figure 2). Indeed, this rationalization is strengthened by the striking similarity of the product distributions in entries 1–4 compared with entries **5**–**8**.[21]

(14) The exceptionally rapid isomerization of the C(3)=C(4) bond is worthy of comment. It is possible that this protonation–deprotonation process is accelerated by neighboring group participation of the protonated hydroxyl group. This hypothesis could then rationalize the retention of the positional integrity of the double bond and also explain why isomerization of the C(7)=C(8) bond in **5** is not competitive with cyclization. In contrast, as noted below in ref 21, rapid protonation–deprotonation of the cyclohexenyl bond in the monocyclic substrates **6**–**8** prior to cyclization cannot be discounted. It is also worth mentioning that, in all the experiments described in this work, we have no direct evidence (e.g., GC, NMR analysis) for the isomerization of the substrate.

(15) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

(16) For the sake of completeness, the MM2 energy of **10** (see ref 10) was calculated to be 43.0 kcal/mol.

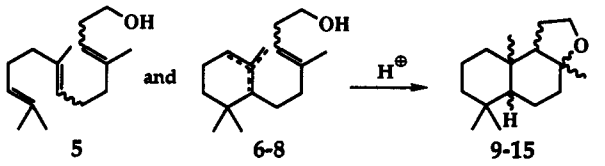
(17) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(18) This mechanistic hypothesis has often been proposed to explain the formation of *cis*-decalins from the cyclization of substituted cyclohexanols; for an example, see: Harding, K. E.; Lignon, R. C. *J. Org. Chem.* **1973**, *38*, 4345. In our particular system, quite apart from the fact that the formation of equatorial C–C bonds are energetically preferred (see ref 20), this transition state would be strongly disfavored by severe 1,3-diaxial nonbonding interactions with the axial C(6) methyl group in ring A.

(19) For a discussion concerning the relative rates of conformational inversion in six-membered rings and acid-mediated cyclizations, see: Johnson, W. S. *Trans. N.Y. Acad. Sci.* **1967**, *29*, 1001. For recent work which argues in favor of a nonsynchronous pathway for analogous biomimetic cyclizations, see: Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Am. Chem. Soc.* **1985**, *107*, 522; *J. Org. Chem.* **1986**, *51*, 806.

(20) For a discussion of this kinetic preference for the formation of equatorial C–C and C–O bonds, see: Harding, K. E. *Biorg. Chem.* **1973**, *2*, 248.

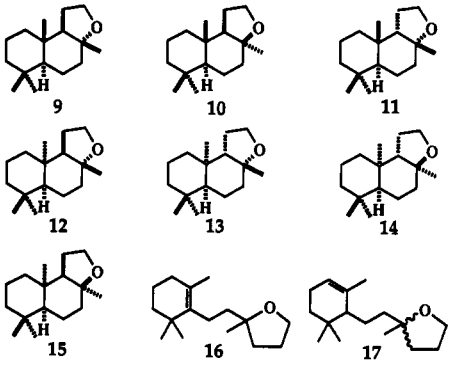
Table I. Acid-Mediated Cyclizations of 5–8



5 6-8 9-15

		product distribution (yield, %)[b]						
entry	substrate[a]	9	10[c]	11	12	13	14	15
1	(*E*,*E*)-5	40		35	2		1	
2	(*Z*,*E*)-5			69		7		
3	(*E*,*Z*)-5	5		4	46		16	
4	(*Z*,*Z*)-5			5	6	57		6
5	(*E*)-6	42		39	3		1	
6	(*Z*)-6	1		80	1	5		1
7	(*E*)-7	4		5	48		15	
8	(*Z*)-7			8	7	55		6
9	(*E*)-8	14		13	34		16	
10	(*Z*)-8			28	4	38		7

[a] Reaction conditions: substrate (100 mg), FSO_3H (400 mg), 2-nitropropane (10 mL), −90 °C. [b] GC analysis of distilled product after workup;[10] also detected and characterized (see Experimental Section) were minor amounts (1–2% yield) of **16** and **17** (ca. 10:1 mixture: entries 5, 6, 9, and 10; ca. 1:4 mixture, entries 7 and 8). [c] Tricyclic ether **10**, formed by acid-catalyzed epimerization of **9**, was detected in trace amounts (<0.5% yield) in entries 1 and 5.

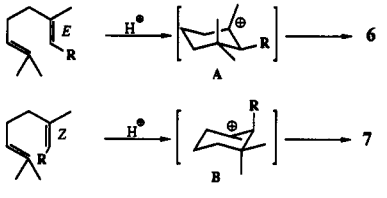


Monocyclic dienol (*E*)-**6** affords almost equal amounts of **9** (42%) and **11** (39%) together with **12** (3%) and **14** (1%) (entry 5); in contrast, (*Z*)-**6** gives almost exclusively **11** (80%) accompanied by **9** (1%), **12** (1%), **13** (5%), and **15** (1%) (entry 6). These results can be explained by a stepwise pathway involving stereoselective axial protonation[22] followed by a rapid cyclization which is identical to that described for the aforementioned nonsynchronous process (Figure 2). In analogy with entries 1 and 2, cyclization of (*E*)-**6** to **9** competes with its isomerization to (*Z*)-**6**, whose cyclization to **11** is rapid. The formation of side products is limited to small amounts of **12**–**15** (4–7%), presumably resulting from disfavored equatorial protonation of the cyclohexenyl bond.[23]

In contrast, the cyclizations of (*E*)-**7** and (*Z*)-**7** (entries 7 and 8) are rationalized by assuming that these substrates consist of ca. 95:5 mixtures of two cyclohexene half-chair conformers,[24] the side chain being either pseudoaxial (major conformer) or pseudoequatorial (minor conformer). Evidence for this assumption is provided by molecular mechanics calculations of a model system[25] and by analogy with known work.[26] Protonation of the trisubstituted cyclohexenyl bond[22] and subsequent cyclization via transition states III and IV, in which the nascent B ring adopts a chairlike conformation, then affords **12** (48%) and **13** (55%), respectively. Alternatively, cyclization via transition states III′ and IV′, with the B ring in a skew-boat conformation, accounts for the formation of **14** (15%) and **15** (6%). The presence of **9** and **11** (8–9%) may originate from the minor proportion of the substrate (ca. 5–10%) in which the side chain is pseudoequatorial, whereas partial C(3)=C(4) bond isomerization could explain the small amount of **12** (7%) observed in entry 8.[23]

The same arguments may be employed to rationalize the cyclizations of (*E*)-**8** and (*Z*)-**8** (entries 9 and 10). In the former case, **9** (14%) and **11** (13%) are formed in almost equal amounts, together with **12** (34%), and **14** (16%); in the latter case, **11** (28%) is accompanied by **12** (4%), **13** (38%), and **15** (7%). These product distributions indicate that, at the moment of cyclization, both substrates exist as ca. 2:1 mixtures of two cyclohexane chair conformers in which the side chain is axially orientated in the major conformer.[27] Gratifyingly, this conclusion is in qualitative agreement[28] with ^1H NMR studies[29] and molecular me-

(21) It has been pointed out by a reviewer that the results are also consistent with *rapid deprotonation of the intermediate cyclohexyl cation*. Accordingly, cyclohexenyl cation A, resulting from the two acyclic substrates with an *E*-configurated C(7)=C(8) bond (i.e., (*E*,*E*)- and (*Z*,*E*)-**5**), would predominantly generate **6** by axial deprotonation to give the most substituted double bond; in contrast, the two acyclic substrates with a *Z*-configurated C(7)=C(8) bond (i.e., (*E*,*Z*)- and (*Z*,*Z*)-**5**) selectively afford **7** because the cyclohexyl cation B cannot form **6** by axial deprotonation.



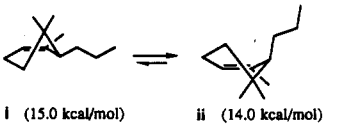
This mechanism could explain why differing amounts of **9** and **11** are formed from (*E*,*E*)-**5** under different cyclization conditions (see ref 11). Under higher acid concentrations, deprotonation reactions of A are less likely, and more cyclization to **9** is observed; when deprotonation to **6** occurs, there is then increased likelihood of isomerization of the C(3)=C(4) bond to form (*Z*)-**6**.

(22) Kinetically controlled axial protonation of a cyclohexenyl bond is stereoelectronically favored by hyperconjugative stabilization of the cyclohexyl cation by the developing C–H bond. For a general discussion of conformational analysis in cyclohexanes, see: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; Wiley: New York, 1969; p 36.

(23) As has been pointed out by a reviewer, these side products may also be a result of partial interconversion of **6** and **7** via a rapid protonation–deprotonation process.

(24) The activation energies for conformational inversion of cyclohexane and cyclohexene have been determined by ^1H NMR spectroscopy to be 10.3 and 5.4 kcal/mol, respectively; see: Anet, F. A. L.; Anet, R. In *Dynamic Nuclear Magnetic Resonance*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 543.

(25) For 6-propyl-1,5,5-trimethylcyclohex-1-ene, the calculated MM2 energies of the two half-chair conformers, i and ii, indicate that the latter conformer, in which the propyl side chain is pseudoaxial, is preferred; the energy difference of 1 kcal/mol corresponds to a ca. 95:5 conformer ratio (ii/i) at −90 °C.



i (15.0 kcal/mol) ii (14.0 kcal/mol)

(26) Ohloff, G.; Otto, E.; Rautenstrauch, V.; Snatzke, G. *Helv. Chim. Acta* **1973**, *56*, 1875.

(27) In light of the dichotomy of synchronous versus nonsynchronous pathways for the cyclizations of acyclic trienols **5**, we are grateful to a reviewer who has pointed out the possibility of a totally synchronous process (involving equatorial C–C and C–O bond formation) for the cyclizations of (*E*)- and (*Z*)-**8**.

(28) Any quantitative rationalization of the results would have to take into account the efficiency of the two cyclization pathways; in addition, if cyclization takes place at a temperature which is above the conformational coalescence temperature, more uncertainty is introduced by the temperature dependence of the conformer ratio.

chanics calculations of a model system.[30]

These results thus unambiguously demonstrate that the stereochemical courses of the cyclizations of the *E* and *Z* isomers of **6**, **7**, and **8** are controlled by the orientation of the side chain adjacent to the transient cyclohexyl cation, determined either by a stereoselective protonation (for (*E*)- and (*Z*)-**6**) or by the conformation of the six-membered ring (for (*E*)- and (*Z*)-**7**, (*E*)- and (*Z*)-**8**). It evidently follows that, as proposed above for the nonsynchronous cyclization of the acyclic trienols **5**, *conformational inversion is slower than cyclization*[19] and that an equatorial side chain affords **9–11** (trans A/B ring junction), whereas an axial side chain leads to **12–15** (cis A/B ring junction).

Conclusion

The present work conclusively demonstrates that biomimetic acid-mediated cyclizations which involve internal nucleophilic termination by a hydroxyl group can be preparatively efficient processes. In the 10 cases studied, the stereochemical outcomes of the cyclizations are consistent with a coherent mechanistic interpretation which encompasses fundamental stereoelectronic and conformational factors. Applications of these findings for the stereospecific syntheses of other polycyclic systems are under way.

Experimental Section

General Remarks. Thin-layer chromatography (TLC) was performed on 0.25-mm precoated $60F_{254}$ silica gel plates (Merck); R_f values were calculated using toluene/ethyl acetate (9:1) as eluent. Low-pressure column chromatography (LPLC) was carried out on silica gel 60, particle size 0.063–0.20 mm (Merck). Analytical GC: Supelco SPB1 capillary column, 30 m × 0.25 mm, carrier gas He. Kugelrohr distillation: bp correspond to the air temperature. IR spectra (liquid film): cm^{-1}. ^1H NMR (360 MHz) and ^{13}C NMR (90.5 MHz): in $CDCl_3$ solution unless stated otherwise; for description of ^1H NMR spectra small couplings are not reported; for ^{13}C NMR spectra multiplicities were determined from DEPT experiments. GC–MS: electron energy ca. 70 eV; fragment ions *m/e* in % of the most abundant peak.

Materials. THF was freshly distilled from $LiAlH_4$ under N_2; **(*E*)- and (*Z*)-geranyl acetone** ((*E*)- and (*Z*)-**1**), **α-ionone**, and **β-ionone** were purchased from Aldrich Chemical Co. and further purified (purity: ≥99%) by fractional distillation in vacuo. All other reagents and solvents were used as received.

Preparation of Ketones 2–4. 4-(2′,6′,6′-Trimethylcyclohex-1′-enyl)butan-2-one (2), 4-(2′,6′,6′-trimethylcyclohex-2′-enyl)butan-2-one (3) and 4-(2′,2′-dimethyl-6′-methylidenecyclohexyl)butan-2-one (4) were prepared by catalytic (Raney-Ni/EtOH[31]) mono-hydrogenation of **β-ionone**, **α-ionone**, and **γ-ionone**,[32] respectively; purification (purity ≥99%) was effected by fractional distillation in vacuo, and the spectral data (IR, ^1H NMR, MS) of **2–4** are identical to those reported.[33,34] For completeness the ^{13}C NMR data are as follows: **2**: 208.7 (C), 136.1 (C), 127.8 (C), 44.5 (CH_2), 39.8 (CH_2), 35.0 (C), 32.8 (CH_2), 29.7 (CH_3), 28.4 (2 × CH_3), 22.3 (CH_2), 19.7 (CH_3), 19.5 (CH_2). **3**: 209.0 (C), 135.6 (C), 121.0 (CH), 48.6 (CH), 43.8 (CH_2), 32.6 (C), 31.5 (CH_2), 29.9 (CH_3), 27.6 (CH_3), 27.5 (CH_3), 24.4 (CH_2), 23.5 (CH_3), 23.0 (CH_2). **4**: 209.2 (C), 149.1 (C), 109.5 (CH_2), 53.5 (CH), 42.3 (CH_2), 35.8 (CH_2), 34.8 (C), 32.1 (CH_2), 30.0 (CH_3), 28.3 (CH_3), 26.5 (CH_3), 23.6 (CH_2), 20.4 (CH_2).

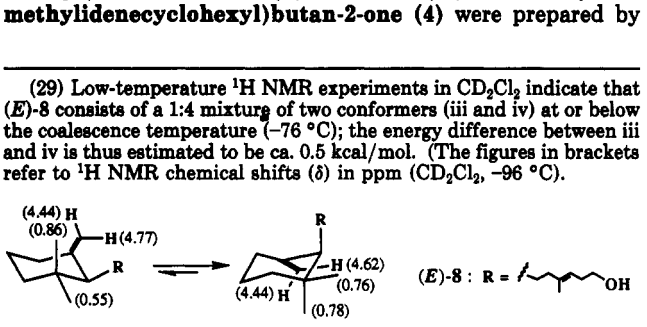
Preparation of Alcohols 5–8. General Procedure. *n*-BuLi (1.6 M in hexane (Fluka), 56 mL, 0.09 mol) was added dropwise during 30 min to a mechanically stirred slurry of (3-hydroxypropyl)triphenylphosphonium bromide[35] (20 g, 0.05 mol) in THF (70 mL) at −30 °C under N_2. The mixture was then allowed to attain 20 °C during 2 h and stirred at this temperature during a further 1 h. To this dark red mixture at −30 °C was then added dropwise, within 1 h, a solution of (*E*)-**1**, (*Z*)-**1**, **2**, **3**, or **4** (9.7 g, 0.05 mol) in THF (20 mL). The resultant orange-beige mixture was stirred for a further 1 h at −30 °C and 18 h at 20 °C and then poured into 10% aqueous NH_4Cl (200 mL). Saturation with NaCl, separation of the organic phase, and extraction of the aqueous phase with ether (4 × 100 mL) afforded a combined organic phase which was concentrated in vacuo. To the residual oil was added petroleum ether (bp 35–50 °C, 50 mL), and the resulting solution was dried (Na_2SO_4) and then filtered. Concentration and fractional distillation in vacuo of the filtrate afforded unreacted starting ketone (ca. 50% recovery) and a ca. 1:1 *E/Z* diastereoisomeric mixture of the product alcohol: 2.7–3.1 g (purity (GC) ca. 90%, yield 21–23%); bp (Kugelrohr distillation) 100–120 °C (0.02 mm). Purification by LPLC (silica gel (360 g), eluent toluene/ethyl acetate (95:5)) afforded pure samples (ca. 1 g, purity (GC) ≥99%) of (*E*,*E*)-**5**, (*Z*,*E*)-**5**, (*E*,*Z*)-**5**, (*Z*,*Z*)-**5**, (*E*)-**6**, (*Z*)-**6**, (*E*)-**7**, (*Z*)-**7**, (*E*)-**8**, and (*Z*)-**8**. Their chromatographic and spectral data are as follows:

(3*E*,7*E*)-4,8,12-Trimethyltrideca-3,7,11-trien-1-ol ((*E*,*E*)-5):[36] R_f 0.29; IR 3320 (broad), 2900, 1440, 1380, 1040, 876, 836; ^1H NMR (+D_2O) δ 1.60 (2s, 6 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.93–2.16 (8 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.60 (t, *J* = 7 Hz, 2 H), 5.09 (2t, *J* = 7 Hz, 2 H), 5.13 (t, *J* = 7 Hz, 1 H); ^{13}C NMR δ 138.6 (C), 135.3 (C), 131.2 (C), 124.5 (CH), 124.1 (CH), 120.0 (CH), 62.5 (CH_2), 39.9 (CH_2), 39.8 (CH_2), 31.6 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.2 (CH_3), 16.0 (CH_3); MS 236 (0, M^+), 167 (1), 123 (8), 107 (6), 93 (9), 81 (34), 69 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.82; H, 11.99.

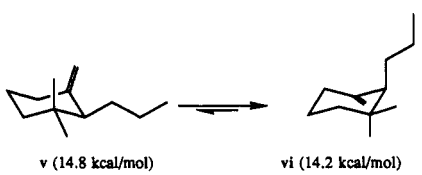
(3*Z*,7*E*)-4,8,12-Trimethyldeca-3,7,11-trien-1-ol ((*Z*,*E*)-5): R_f 0.33; IR 3320 (broad), 2900, 1440, 1378, 1040, 878, 836; ^1H NMR (+D_2O) δ 1.61 (2s, 6 H), 1.68 (s, 3 H), 1.73 (s, 3 H), 1.93–2.15 (8 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.60 (t, *J* = 7 Hz, 2 H), 5.10 (t, *J* = 7 Hz, 1 H), 5.14 (2t, *J* = 7 Hz, 2 H); ^{13}C NMR δ 138.7 (C), 135.5 (C), 131.3 (C), 124.5 (CH), 124.0 (CH), 120.9 (CH), 62.5 (CH_2), 39.8 (CH_2), 32.1 (CH_2), 31.5 (CH_2), 26.8 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 23.5 (CH_3), 17.7 (CH_3), 16.0 (CH_3); MS 236 (0, M^+), 167 (1), 123 (7), 107 (7), 93 (8), 81 (35), 69 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.90; H, 12.04.

(3*E*,7*Z*)-4,8,12-Trimethyltrideca-3,7,11-trien-1-ol ((*E*,*Z*)-5): R_f 0.26; IR 3320 (broad), 2900, 1440, 1378, 1040, 878, 836; ^1H NMR (+D_2O) δ 1.61 (s, 3 H), 1.64 (s, 3 H), 1.69 (2s, 6 H), 2.00–2.14 (8 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.60 (t, *J* = 7 Hz, 2 H), 5.05–5.17 (3 H); ^{13}C NMR δ 138.7 (C), 135.5 (C), 131.5 (C), 124.9 (CH), 124.4 (CH), 120.0 (CH), 62.5 (CH_2), 40.1 (CH_2), 32.1 (CH_2), 31.6 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 25.7 (CH_3), 23.4 (CH_3), 17.6 (CH_3), 16.2 (CH_3); MS 236 (0, M^+), 167 (1), 123 (7), 107 (9), 95 (14), 81 (77), 69 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.87; H, 11.96.

(29) Low-temperature ^1H NMR experiments in CD_2Cl_2 indicate that (*E*)-**8** consists of a 1:4 mixture of two conformers (iii and iv) at or below the coalescence temperature (−76 °C); the energy difference between iii and iv is thus estimated to be ca. 0.5 kcal/mol. (The figures in brackets refer to ^1H NMR chemical shifts (δ) in ppm (CD_2Cl_2, −96 °C).



(30) The calculated MM2 energies of the two chair conformers of 1,1-dimethyl-2-propyl-3-methylidenecyclohexane, v and vi, indicate that vi (axial propyl group) is 0.6 kcal/mol more stable than v.



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(3*Z*,7*Z*)-4,8,12-Trimethyltrideca-3,7,11-trien-1-ol ((*Z*,*Z*)-5): R_f 0.31; IR 3320 (broad), 2900, 1440, 1378, 1040, 878, 834; ^{1}H NMR (+D_2O) δ 1.61 (s, 3 H), 1.69 (2s, 6 H), 1.73 (s, 3 H), 2.00–2.10 (8 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.60 (t, *J* = 7 Hz, 2 H), 5.06–5.18 (3 H); ^{13}C NMR δ 138.7 (C), 135.6 (C), 131.6 (C), 124.9 (CH), 124.4 (CH), 120.9 (CH), 62.7 (CH_2), 32.4 (CH_2), 32.0 (CH_2), 31.5 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 25.7 (CH_3), 23.6 (CH_3), 23.4 (CH_3), 17.6 (CH_3); MS 236 (0, M^+), 167 (1), 123 (6), 107 (8), 95 (15), 81 (79), 69 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.92; H, 11.85.

(*E*)-4-Methyl-6-(2′,6′,6′-trimethyl-1′-cyclohexenyl)hex-3-en-1-ol ((*E*)-6):[8] R_f 0.25; IR 3310 (broad), 1462, 1378, 1356, 1200, 1040, 870; ^{1}H NMR (+D_2O) δ 1.00 (s, 6 H), 1.41 (m, 2 H), 1.58 (m, 2 H), 1.61 (s, 3 H), 1.70 (s, 3 H), 1.91 (t, *J* = 6.5 Hz, 2 H), 2.06 (4 H), 2.30 (dt, *J* = 7, 7 Hz, 2 H), 3.63 (t, *J* = 7 Hz, 2 H), 5.16 (t, *J* = 7 Hz, 1 H); ^{13}C NMR 139.8 (C), 137.0 (C), 127.1 (C), 119.2 (CH), 62.5 (CH_2), 40.4 (CH_2), 39.9 (CH_2), 35.0 (C), 32.8 (CH_2), 31.5 (CH_2), 28.6 (2 × CH_3), 27.9 (CH_2), 19.8 (CH_3), 19.6 (CH_2), 16.3 (CH_3); MS 236 (2, M^+), 137 (77), 121 (11), 107 (15), 95 (100), 81 (83), 69 (32), 55 (35). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.90; H, 12.04.

(*Z*)-4-Methyl-6-(2′,6′,6′-trimethyl-1′-cyclohexenyl)hex-3-en-1-ol ((*Z*)-6):[8] R_f 0.31; IR 3320 (broad), 1470, 1442, 1370, 1358, 1200, 1040, 870, 824; ^{1}H NMR (+D_2O) δ 1.02 (s, 6 H), 1.22 (m, 2 H), 1.37 (m, 2 H), 1.64 (s, 3 H), 1.78 (s, 3 H), 1.91 (t, *J* = 6 Hz, 2 H), 2.06 (m, 4 H), 2.31 (dt, *J* = 7, 7 Hz, 2 H), 3.63 (t, *J* = 6 Hz, 2 H), 5.11 (t, *J* = 7 Hz, 1 H); ^{13}C NMR δ 139.6 (C), 137.0 (C), 127.3 (C), 120.2 (CH), 62.7 (CH_2), 39.9 (CH_2), 35.0 (C), 32.8 (2 × CH_2), 31.5 (CH_2), 28.7 (2 × CH_3), 27.4 (CH_2), 23.5 (CH_3), 19.9 (CH_3), 19.6 (CH_2); MS 236 (2, M^+), 137 (100), 121 (9), 107 (12), 95 (81), 81 (51), 69 (19). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.86; H, 11.90.

(*E*)-4-Methyl-6-(2′,6′,6′-trimethyl-2′-cyclohexenyl)hex-3-en-1-ol ((*E*)-7): R_f 0.29; IR 3300 (broad), 2900, 1440, 1380, 1360, 1040, 812; ^{1}H NMR (+D_2O) δ 0.87 (s, 3 H), 0.92 (s, 3 H), 1.12 (m, 1 H), 1.30–1.65 (4 H), 1.65 (s, 3 H), 1.68 (s, 3 H), 1.96 (m, 2 H), 2.05 (m, 2 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.61 (t, *J* = 7 Hz, 2 H), 5.13 (t, *J* = 7 Hz, 1 H), 5.28 (m, 1 H); ^{13}C NMR δ 139.6 (C), 136.8 (C), 120.1 (CH), 119.7 (CH), 62.6 (CH_2), 49.2 (CH), 40.7 (CH_2), 32.7 (C), 31.7 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 27.6 (CH_3), 27.5 (CH_3), 23.5 (CH_3), 23.1 (CH_2), 16.3 (CH_3); MS 236 (2, M^+), 136 (74), 121 (56), 109 (41), 95 (26), 81 (100), 69 (26), 55 (31), 41 (64). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.97; H, 12.07.

(*Z*)-4-Methyl-6-(2′,6′,6′-trimethyl-2′-cyclohexenyl)-hex-3-en-1-ol ((*Z*)-7): R_f 0.35; IR 3320 (broad), 2900, 1442, 1380, 1360, 1042, 760; ^{1}H NMR (+D_2O) δ 0.88 (s, 3 H), 0.96 (s, 3 H), 1.14 (m, 1 H), 1.30–1.60 (4 H), 1.71 (s 3 H), 1.74 (s, 3 H), 1.96 (m, 2 H), 2.07 (m, 2 H), 2.28 (dt, *J* = 7, 7 Hz, 2 H), 3.62 (t, *J* = 7 Hz, 2 H), 5.09 (t, *J* = 7 Hz, 1 H), 5.31 (m, 1 H); MS 236 (2, M^+), 136 (38), 121 (31), 109 (42), 95 (21), 81 (100), 69 (25), 55 (21), 41 (62). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.99; H, 12.01.

(*E*)-4-Methyl-6-(2′,2′-dimethyl-6′-methylidenecyclohexyl)hex-3-en-1-ol ((*E*)-8): R_f 0.31; IR 3300 (broad), 2900, 1640, 1440, 1380, 1360, 1042, 884, 630; ^{1}H NMR (+D_2O) δ 0.84 (s, 3 H), 0.92 (s, 3 H), 1.21 (m, 1 H), 1.35–1.85 (7 H), 1.64 (s, 3 H), 1.92–2.12 (3 H), 2.29 (dt, *J* = 7, 7 Hz, 2 H), 3.62 (t, *J* = 7 Hz, 2 H), 4.54 (s, 1 H), 4.76 (s, 1 H), 5.12 (t, *J* = 7 Hz, 1 H); ^{13}C NMR δ 149.4 (C), 139.4 (C), 119.6 (CH), 108.9 (CH_2), 62.6 (CH_2), 53.8 (CH), 38.5 (CH_2), 36.5 (CH_2), 34.9 (C), 32.6 (CH_2), 31.6 (CH_2), 28.5 (CH_3), 26.2 (CH_3), 24.9 (CH_2), 23.8 (CH_2), 16.3 (CH_3); MS 236 (2, M^+), 221 (25), 177 (25), 121 (26), 109 (61), 95 (38), 81 (84), 69 (61), 55 (41), 41 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.00; H, 12.02.

(*Z*)-4-Methyl-6-(2′,2′-dimethyl-6′-methylidenecyclohexyl)hex-3-en-1-ol ((*Z*)-8): R_f 0.37; IR 3300 (broad), 2900, 1640, 1440, 1380, 1362, 1040, 884, 630; ^{1}H NMR (+D_2O) δ 0.83 (s, 3 H), 0.92 (s, 3 H), 1.22 (m, 1 H), 1.34–1.70 (6 H), 1.73 (s, 3 H), 1.80–2.15 (4 H), 2.25 (m, 2 H), 3.60 (t, *J* = 7 Hz, 2 H), 4.58 (s, 1 H), 4.79 (s, 1 H), 5.11 (t, *J* = 7, 1 H); MS 236 (2, M^+), 221 (25), 177 (27), 121 (29), 109 (70), 95 (42), 81 (90), 69 (60), 55 (47), 41 (100). Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.01; H, 12.00.

Acid-Mediated Cyclization of Alcohols 5–8. General Procedure. A solution of the alcohol (100 mg, 0.42 mmol) in 2-nitropropane (Fluka, 5 mL) was added dropwise during 5 min to a mechanically stirred mixture of FSO_3H (Bayer, 400 mg, 4.0 mmol) and 2-nitropropane (5 mL) at −90 °C (cooling bath, liquid nitrogen/methanol)[37] under N_2. After the addition the mixture was poured, with stirring, into saturated aqueous $NaHCO_3$ (20 mL) at 0–5 °C and extracted with ether (3 × 10 mL). The combined organic phase was then washed with saturated aqueous NaCl and dried (Na_2SO_4). Filtration, concentration and Kugelrohr distillation in vacuo (150 °C (0.05 mm)) afforded the product mixture whose distribution of tricyclic ethers **9–15** (R_f 0.46) is presented in Table I. Rigorous identification of **9–15** was effected by GC coinjection of the distilled cyclization product mixtures with authentic samples of the pure diastereoisomers[6] (GC column temp 150–230 °C (15 °C/min)). Under these conditions the GC peaks are clearly baseline separated (retention times (min) **9** (8.15), **10** (7.18), **11** (7.59), **12** (8.45), **13** (7.75), **14** (7.70), **15** (7.34)). In addition, this analysis was corroborated by inspection of the ^{1}H NMR spectra of the product mixtures. In entries 5–10 minor amounts (1–2% yield) of **2-methyl-2-[2′-(2″,6″,6″-trimethylcyclohex-1″-enyl)ethyl]tetrahydrofuran (16) and 2-methyl-2-[2′-(2″,6″,6″-trimethylcyclohex-2″-enyl)ethyl]tetrahydrofuran** (17, 1:1 diastereoisomeric mixture), were detected by GC (retention times (min) 5.68 and 5.46, respectively) and isolated by LPLC (eluent toluene/ethyl acetate (95:5)): R_f 0.63; bp (Kugelrohr distillation) 120 °C (0.02 mm); IR 2920, 1440, 1360, 1342, 1030. Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 80.92; H, 12.08.

Data of 16: ^{1}H NMR δ 0.99 (s, 6 H), 1.22 (s, 3 H), 1.35–2.15 (14 H), 1.60 (s, 3 H), 3.83 (m, 2 H); ^{13}C NMR δ 137.1 (C), 126.6 (C), 82.8 (C), 67.1 (CH_2), 41.4 (CH_2), 40.0 (CH_2), 36.8 (CH_2), 35.2 (C), 32.9 (CH_2), 28.7 (2 × CH_3), 26.2 (CH_2), 25.4 (CH_3), 23.5 (CH_2), 19.7 (CH_3), 19.6 (CH_2); MS 236 (1, M^+), 177 (5), 136 (21), 121 (29), 107 (19), 93 (19), 85 (100).

Data of 17: ^{1}H NMR δ 0.86 (s, 3 H), 0.93 (s, 3 H), 1.17 (s, 3 H), 5.29 (m, 1 H); MS (diastereoisomer A) 236 (<0.5, M^+), 177 (1), 136 (70), 121 (57), 107 (26), 93 (32), 85 (100); MS (diastereoisomer B) 236 (0.5, M^+), 177 (0.5), 136 (62), 121 (52), 107 (20), 93 (36), 85 (100).

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