103. Internal Nucleophilic Termination in Acid-Mediated Polyene Cyclisations: Synthetic Access to Methyl Homologs of (±)-*Ambrox*® and Its Diastereoisomers

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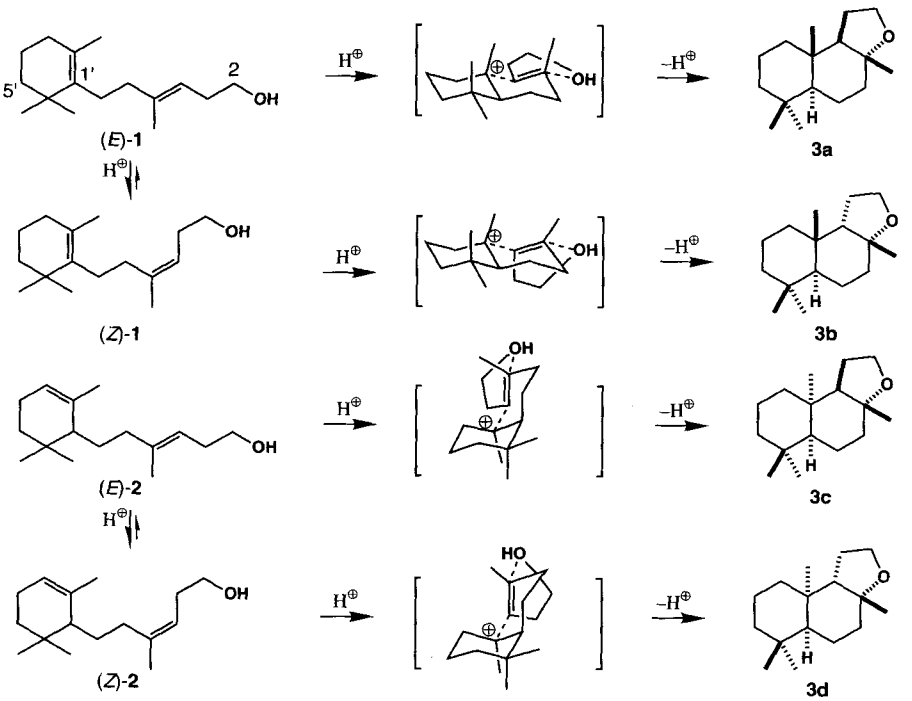
Treatment of ten monocyclic dienols **8–11** with an excess of fluorosulfonic acid in 2-nitropropane at −90° afforded diastereoisomeric mixtures of racemic tricyclic ethers **12–14** in 81–91% yield (see *Tables 1* and *2*). These transformations represent further examples of biomimetic acid-mediated cyclisations in which an OH group serves as the internal nucleophilic terminator. A non-synchronous process is postulated, and the examples described strongly re-inforce our working mechanistic hypothesis, whereby the stereochemical course of cyclisation is directed by the orientation of the side chain vicinal to the intermediate cyclohexyl cation (see *Schemes 4* and *5*). It is also demonstrated that the efficiency of this process is independent of the nature of the OH group, which may be primary, secondary, or tertiary. In addition, the organoleptic properties of **12–14**, Me homologs of known odorants such as *Ambrox*® ((−)-**3a**) and its diastereoisomers, are briefly discussed.

Introduction. – Recently, we described an efficient biomimetic access to organoleptically active tricyclic ethers, by treatment of appropriately substituted 6-(cyclohexenyl)hex-3-en-1-ols with an excess of fluorosulfonic acid in 2-nitropropane at −90° [1]. These kinetically controlled cyclisations[1]) were shown to proceed stereospecifically *via* protonation of the cyclohexenyl bond, followed by ring closure involving equatorial C–C bond formation with concomitant internal nucleophilic termination by *anti*-addition of the OH group across the C(3)=C(4) bond. For example, allowing for partial acid-catalysed isomerisation of the C(3)=C(4) bond, (*E*)- and (*Z*)-**1** selectively afford **3a** and **3b**, whereas (*E*)- and (*Z*)-**2** preferentially generate **3c** and **3d**, *via* a favoured chair conformation of the nascent cyclohexane ring (see *Scheme 1*). It was also established that conformational inversion of the six-membered ring is slower than ring closure, the orientation of the C(1′)-side chain vicinal to the cyclohexyl cation thus directing the stereochemical course of cyclisation. For **1**→**3a**/**3b**, this orientation is determined by stereoselective axial protonation of the tetrasubstituted cyclohexenyl bond, and ensures a *trans-A/B* ring junction; in contrast, the predominantly pseudoaxial orientation of the side chain in **2** results in the generation of **3c**/**3d** with a *cis-A/B* ring junction. In continuation of our studies, we now report the preparation and acid-mediated cyclisation of ten Me-substituted homologs of **1** and **2**. During this investigation, we planned to address two questions. Firstly, can the proposed mechanistic hypothesis predict the stereochemical outcome of cyclisation for substrates substituted at C(5′)? Secondly, is

[1]) For a review of acid-mediated cyclisations involving C–C bond formation, see [2].

Scheme 1. *Acid-Mediated Cyclisations of (*E*)- and (*Z*)-***1***, (*E*)- and (*Z*)-***2***: Major Reaction Pathways*



ring closure compatible with substitution at C(2), a situation in which internal termination is necessarily effected by a secondary or tertiary OH group? In addition, from a perfumistic viewpoint, it was of interest to discover the organoleptic properties of the racemic Me homologs[2]) of odorants such as **3a**[3]) and its C(9b)-epimer, **3b**[4]).

Results and Discussion. – Stereochemically pure samples of the ten alcohols, (*E*)- and (*Z*)-**8**, *cis*-**9**, *trans*-**9**, **10**, and **11**, were synthesised using standard methodology (see *Schemes 2* and *3*). Thus, pure samples of *β*-irone, *cis*-*α*-irone, and *trans*-*α*-irone, obtained by fractional distillation of a commercial mixture[5]), were catalytically monohydrogenated to ketones **4**, *cis*-**5**, and *trans*-**5**, respectively, in 80–90% yield. *Wittig* reaction using the ylide derived from (3-hydroxypropyl)triphenylphosphonium bromide [10] then afforded **8**, *cis*-**9**, and *trans*-**9** as 1:1 diastereoisomeric mixtures, in 40–50% yield. The known *β*,*γ*-unsaturated acid **6** ((*E*)/(*Z*) 2:1) [11] was treated with MeLi to give ketone **7** ((*E*)/(*Z*) 2:1, 66%); subsequent hydride reduction afforded **10** ((*E*)/(*Z*) 2:1, 94%),

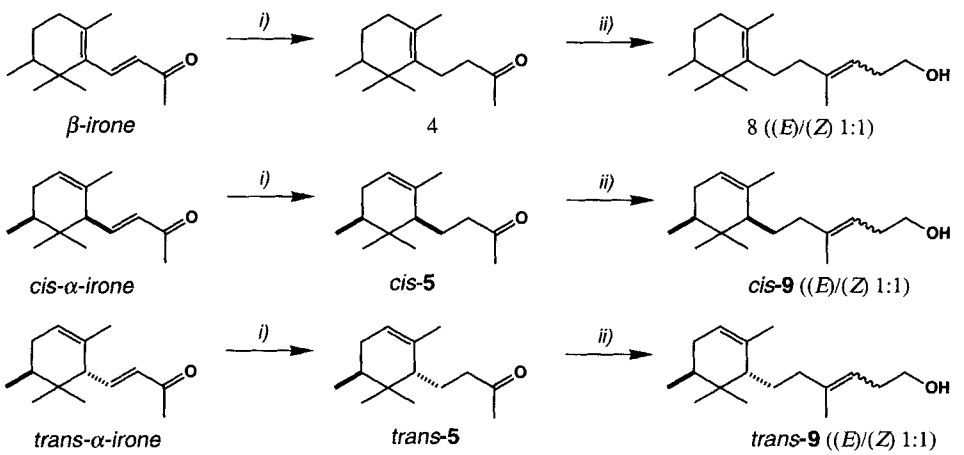
[2]) Both enantiomerically pure diastereoisomers of (–)-**13a** have been synthesised and reported to exhibit a 'typical *Ambrox*® odour', see [3]; (–)-**14a** has been described as odourless [4].

[3]) (–)-**3a** (*Ambrox*®: trade name of *Firmenich SA*) is a commercially important odourant naturally occurring in ambergris [5]; for recent syntheses of (–)-**3a** and (±)-**3a**, see [6] and [7], respectively.

[4]) (–)-**3b** is reported as exhibiting an odour strength unequalled by its diastereoisomers [8]; for a recent total synthesis, see [9].

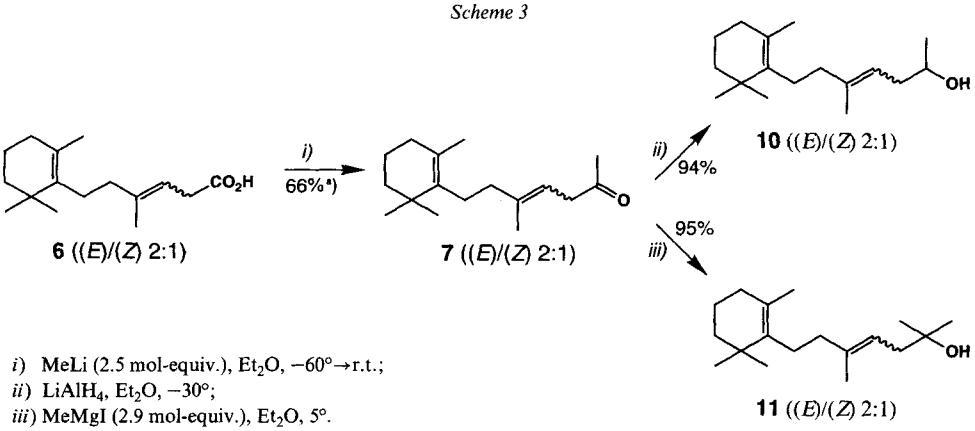
[5]) Purchased from *Givaudan-Roure*, see *Exper. Part* for analytical details.

Scheme 2



i) H_2, *Raney*-Ni, EtOH, r.t. (yield: 80–90%); *ii*) $[Ph_3P(CH_2)_3OH]^{\oplus}Br^{\ominus}$, BuLi (2 mol-equiv.), THF, r.t. (yield: 40–50%).

Scheme 3



i) MeLi (2.5 mol-equiv.), Et_2O, −60°→r.t.;
ii) $LiAlH_4$, Et_2O, −30°;
iii) MeMgI (2.9 mol-equiv.), Et_2O, 5°.

[a]) **11** ((*E*)/(*Z*) 2:1, 4%) also isolated, see *Exper.Part.*

whereas treatment with MeMgI furnished **11** ((*E*)/(*Z*) 2:1, 95%). Separation of the (*E*)/(*Z*)-diastereoisomeric mixtures **8**–**11** was readily effected by column chromatography.

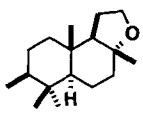
Standard cyclisation conditions involved treatment of each alcohol with a ten-fold excess of fluorosulfonic acid in 2-nitropropane at −90°. Subsequent neutralisation with aqueous $NaHCO_3$ solution, followed by an extractive workup, afforded mixtures of tricyclic ethers[6]) in 80–90% yield; the product distributions are presented in *Tables 1* and *2*. Structural identification of the products was effected either by preparative GC fol-

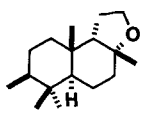
[6]) All chiral compounds synthesised in this work are racemic.

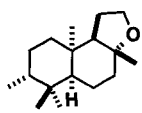
Table 1. *Acid-Mediated Cyclisations of* **8**, cis-**9**, *and* trans-**9**

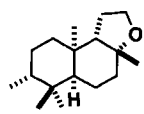
Entry	Substrate[a])	Product distribution (yield [%])[b])					
		12a	**12b**	**12c**	**12d**	**12e**	**12f**
1	(*E*)-**8**	48	35	–	–	–	3
2	(*Z*)-**8**	–	84	–	3	–	4
3	(*E*)-*cis*-**9**	48	39	–	–	–	2
4	(*Z*)-*cis*-**9**	2	77	–	3	–	4
5	(*E*)-*trans*-**9**	–	–	55	3	27	–
6	(*Z*)-*trans*-**9**	–	1	8	57	4	16

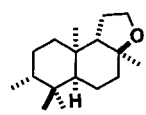
[a]) Reaction conditions: substrate (1 mmol), FSO_3H (10 mmol), 2-nitropropane (15 ml), –90°. [b]) GC Analysis of distilled product after workup.


12a


12b


12c


12d


12e

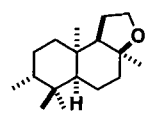
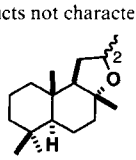
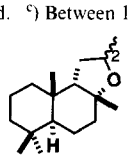

12f

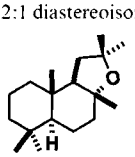
Table 2. *Acid-Mediated Cyclisations of* **10** *and* **11**

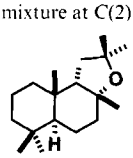
Entry	Substrate[a])	Product distribution (yield [%])[b])			
		13a[c])	**13b**[c])	**14a**	**14b**
1	(*E*)-**10**	55	26		
2	(*Z*)-**10**	–	82		
3	(*E*)-**11**			63	23
4	(*Z*)-**11**			–	85

[a]) Reaction conditions: see *Table 1*. [b]) GC Analysis of distilled product after workup; minor amounts (5–8%) of *cis*-decalin products not characterised. [c]) Between 1:1 and 2:1 diastereoisomeric mixture at C(2).


13a


13b

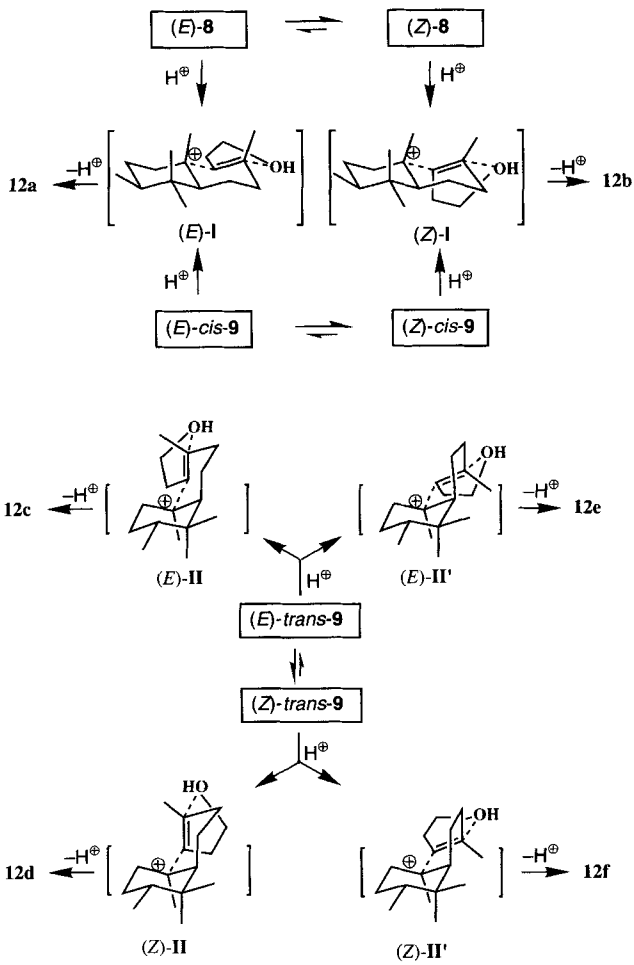

14a


14b

lowed by full spectral characterisation (*viz.* **12a–f**) or, where separation of diastereoisomers was not possible, GC/MS and NMR analysis of the mixtures, corroborated by comparison with authentic or closely analogous compounds was sufficient (*viz.* **13a,b** [3], **14a,b** [4]).

Cyclisation of (*E*)-**8** afforded two major products, **12a** (48%) and **12b** (35%), together with a minor amount of **12f** (3%; *Table 1, Entry 1*); in contrast, (*Z*)-**8** gave almost exclusively **12b** (84%) accompanied by **12d** (3%) and **12f** (4%; *Table 1, Entry 2*). In close analogy with the cyclisations of **1** and **2** (see *Scheme 1*), these results can be explained by a non-synchronous pathway involving stereoselective axial protonation of the tetrasubstituted cyclohexenyl bond to carbocations (*E*)- and (*Z*)-**I** in which the C(5′)–Me group

Scheme 4. *Acid-Mediated Cyclisations of (*E*)- and (*Z*)-***8***, (*E*)- and (*Z*)-*cis*-***9***, and (*E*)- and (*Z*)-trans-***9***

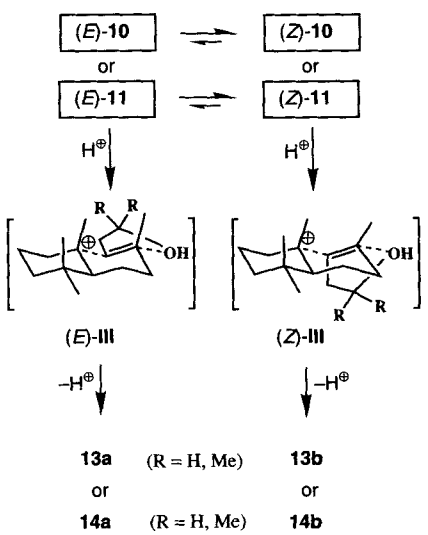


occupies an energetically favourable pseudoequatorial orientation, followed by cyclisation to products possessing a *trans-A/B* ring junction (see *Scheme 4*). Also analogously, cyclisation of (*E*)-**8** to **12a** completes with its isomerisation to (*Z*)-**8**, whose ring closure to **12b** is more rapid. Mechanistically, the cyclisations of (*E*)- and (*Z*)-*cis*-**9** (*Table 1, Entries 3* and *4*) are important, as they provide conclusive evidence that, when the cyclohexenyl bond is trisubstituted, the conformation of the substrate determines the stereochemical course of cyclisation. Because the *cis*-relationship of the C(1′)-side chain and the C(5′)–Me group forces these substituents into pseudoequatorial orientations, protonation is predicted to again lead to cyclohexyl cations, (*E*)- and (*Z*)-**I**, and thus the *same product distribution* which results from (*E*)- and (*Z*)-**8**, respectively. Within experimental error, this is indeed the case. Thus, cyclisation of (*E*)-*cis*-**9** afforded **12a** (48%) and **12b** (39%) as major products, with minor amounts of **12f** (2%); (*Z*)-*cis*-**9** gave a mixture

containing **12b** (77%) with small quantities of **12a** (2%), **12d** (3%), and **12f** (4%). For (*E*)- and (*Z*)-*trans*-**9**, the lowest-energy conformer has the C(1′)-side chain pseudoaxial with the C(5′)–Me group pseudoequatorial[7]), and thus their cyclisations mainly lead to products with a *cis-A/B* ring junction. Protonation of (*E*)-*trans*-**9** to carbocations (*E*)-**II** (chair conformation) or (*E*)-**II′** (skew-boat conformation)[8]), and subsequent cyclisation, furnished **12c** (55%) and **12e** (27%), respectively (*Table 1, Entry 5*). Similarly, the major products from the cyclisation of (*Z*)-*trans*-**9** were **12d** (57%) and **12f** (16%; *Table 1, Entry 6*), *via* carbocations (*Z*)-**II** (chair conformation) and (*Z*)-**II′** (skew-boat conformation)[7]), respectively (see *Scheme 4*).

Cyclisation of (*E*)-**10** afforded two main products, **13a** (55%) and **13b** (26%), whereas (*Z*)-**10** gave exclusively **13b** (82%; *Table 2, Entries 1* and *2*). It is worth noting that, not unexpectedly, both **13a** and **13b** are diastereoisomeric mixtures at C(2), the cyclisation proceeding with almost no stereochemical control at this centre[9]). Similarly, cyclisation of (*E*)-**11** afforded a mixture **14a**(63%)/**14b**(23%), whereas (*Z*)-**11** stereospecifically furnished **14b** (85%; *Table 2, Entries 3* and *4*). These results thus conclusively demonstrate that cyclisation proceeds efficiently, when the internal terminating group is either a secondary or a tertiary alcohol, and that the same non-synchronous process is operative (see *Scheme 5*). As observed previously (*vide supra*), it is

Scheme 5. *Acid-Mediated Cyclisations of* (E)- *and* (Z)-**10**, (E)- *and* (Z)-**11**



[7]) Strong evidence for this assumption is provided by MM2 molecular-mechanics calculations, ^{13}C-NMR data (see *Table 3*), and by analogy with known work [12].

[8]) Products derived from transition states having a skew-boat conformation of the nascent cyclohexane ring were also postulated in our previous work [1].

[9]) A slight stereochemical bias (*ca.* 1.2:1 diastereoisomeric mixtures) favours the transition state with a pseudo-equatorial Me group in the developing tetrahydrofuran ring (*i.e.* for **13a**, the diastereoisomer with an α-Me–C(2) group is preponderant, whereas for **13b** the favoured diastereoisomer has a β-Me–C(2) group; identification was effected by GC/MS and NMR comparison with authentic samples [3]).

again evident that the (*Z*)-isomers of **10** and **11** cyclise faster than the corresponding (*E*)-isomers, and that partial isomerisation of the C(4)=C(5) band in the substrate alcohol competes with the cyclisation process[10]).

A comparison of the olfactive properties of the six diastereoisomeric tricyclic ethers, **12a–f**, was possible due to their separation and isolation by preparative GC. In accordance with the organoleptic properties of their C(7)-demethylated analogues [8] [13], the two *trans-A/B* ring-junction isomers **12a,b** have strong amber, woody odours; in contrast, the four *cis-A/B* ring-junction isomers **12c–f** exhibited woody, resinous, perspiration notes with only weak amber undertones. Diastereoisomeric mixtures **13a,b** possessed typical amber, woody notes which are nonetheless weaker than the C(2)-demethylated analogues. The corresponding dimethylated homologs **14a** and **14b** were odourless.

Experimental Part

(with the collaboration of *O. Barbuzzi, H. Pamingle*, and *P. Sonnay*)

1. *General.* See [1].

2. *Materials.* A commercial mixture (*Givaudan-Roure*) of *(*E*)-4-(2',5',6',6'-tetramethylcyclohex-1'-enyl)but-3-en-2-one* (*β-irone*, 4%), *(*E*)-4-[(1'*RS*,5'*RS*)-2',5',6',6'-tetramethylcyclohex-2'-enyl]but-3-en-2-one* (cis-α-*irone*, 51%), and *(*E*)-4-[(1'*RS*,5'*SR*)-2',5',6',6'-tetramethylcyclohex-2'-enyl]but-3-en-2-one* (trans-α-*irone*,45%) was fractionally distilled *i.v.* to obtain anal. pure samples (distillation order: trans-α-*irone*, cis-α-*irone*, and *β-irone*).

3. *Preparation of Ketones* **4**, cis-**5**, *and* trans-**5**. *4-(2',5',6',6'-Tetramethylcyclohex-1'-enyl)butan-2-one* (**4**), *(1'*RS*,5'*RS*)-4-(2',5',6',6'-tetramethylcyclohex-2'-enyl)butan-2-one* (*cis*-**5**), and *(1'*RS*,5'*SR*)-4-(2',5',6',6'-tetramethylcyclohex-2'-enyl)butan-2-one* (*trans*-**5**) were prepared by catalytic monohydrogenation (*Raney*-Ni/EtOH) of *β-irone*, cis-α-*irone*, and trans-α-*irone*, respectively; purification (purity ≥ 99%) was effected by fractional distillation *i.v.*

Data of **4**: b.p. 88–92°/0.4 Torr; identical (t_R, MS) with an authentic sample [14]. ^{13}C-NMR: 208.9 (*s*); 136.3 (*s*); 127.5 (*s*); 44.7 (*t*); 39.4 (*d*); 38.3 (*s*); 31.7 (*t*); 29.7 (*q*); 27.3 (*t*); 26.7 (*q*); 22.7 (*t*); 21.6 (*q*); 19.9 (*q*); 16.6 (*q*).

Data of cis-**5**: b.p. 60–61°/0.02 Torr; identical (t_R, MS) with an authentic sample [14].

Data of trans-**5**: b.p. 52°/0.01 Torr; identical (t_R, MS) with an authentic sample [14].

4. *5-Methyl-7-(2',6',6'-trimethylcyclohex-1'-enyl)hept-4-en-2-one* (**7**; (*E*/*Z*) 2:1). MeLi (92 ml of a *ca.* 1.6M soln. in Et_2O; *Fluka*; 0.15 mol) was added dropwise within 1 h to a stirred soln. of *4-methyl-6-(2',6',6'-trimethylcyclohex-1'-enyl)hex-3-enoic acid* (**6**; (*E*)/(*Z*) 2:1 [11]; 12 g, 0.048 mol) in Et_2O (200 ml) at −60° under N_2. After 2 h at −60°, the mixture was allowed to attain r.t. during 2 h and stirred at r.t. for 18 h. The mixture was then poured cautiously into cold 10% aq. NH_4Cl soln. (300 ml) and saturated with NaCl. Separation of the org. phase and extraction of the aq. phase (Et_2O) afforded a combined org. phase which was successively washed with aq. 2N NaOH soln. and H_2O, dried (Na_2SO_4), and concentrated *i.v.* Chromatography (SiO_2 (360 g), toluene/AcOEt 9:1) followed by distillation *i.v.* afforded **7** ((*E*)/(*Z*) 2:1) as a pale yellow oil (7.8 g, 66%). TLC (toluene/AcOEt 9:1) R_f 0.47.

*Data of (*E*)-***7**: ^{1}H-NMR: 1.00 (*s*, 6 H); 1.42 (*m*, 2 H); 1.58 (*m*, 2 H); 1.60 (*s*, 3 H); 1.68 (*s*, 3 H); 1.91 (*t*, *J* = 7, 2 H); 2.08 (4 H); 2.15 (*s*, 3 H); 3.13 (*d*, *J* = 7, 2 H); 5.36 (br. *t*, *J* = 7, 1 H). MS: 248 (1, M^+), 190 (5), 137 (88), 95 (100), 81 (80), 43 (75).

*Data of (*Z*)-***7**: ^{1}H-NMR: 1.01 (*s*, 6 H); 1.42 (*m*, 2 H); 1.58 (*m*, 2 H); 1.64 (*s*, 3 H); 1.81 (*s*, 3 H); 1.92 (*t*, *J* = 7, 2 H); 2.04 (4 H); 2.15 (*s*, 3 H); 3.15 (*d*, *J* = 7, 2 H); 5.29 (br. *t*, *J* = 7, 1 H). MS: 248 (2, M^+), 190 (6), 137 (74), 95 (100), 81 (84), 43 (78).

Also isolated was **11** ((*E*)/(*Z*) 2:1; 0.48 g, 4%). TLC (toluene/AcOEt 9:1): R_f 0.25. Identical (t_R, MS) with an authentic sample (*vide infra*).

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[10]) In our earlier work [1], we postulated that isomerisation of this double bond may be due to neighbouring group participation of the protonated homoallylic OH group.

5. *Preparation of (*E*)- and (*Z*)-***8***, (*E*)- and (*Z*)-cis-***9***, (*E*)- and (*Z*)-trans-***9***. (*E*)- and (*Z*)-4-methyl-6-(2′,5′,6′,6′-tetramethylcyclohex-1′-enyl)hex-3-en-1-ol* ((*E*)- and (*Z*)-**8**), *(*E*)- and (*Z*)-4-methyl-6-[(1′*RS*,5′*RS*)-2′,5′,6′,6′-tetramethylcyclohex-2′-enyl]hex-3-en-1-ol* ((*E*)- and (*Z*)-*cis*-**9**), and *(*E*)- and (*Z*)-4-methyl-6-[(1′*RS*,5′*SR*)-2′,5′,6′,6′-tetramethylcyclohex-2′-enyl]hex-3-en-1-ol* ((*E*)- and (*Z*)-*trans*-**9**) were prepared from **4**, *cis*-**5** and *trans*-**5**, respectively, using a standard *Wittig* procedure [10]. In each case, a *ca.* 1:1 (*E*/*Z*)-diastereoisomeric mixture of the product alcohol (2–3 g) was obtained (*ca.* 40–50% yield based on recovered, unreacted starting ketone). Chromatographic purification (SiO_2 (360 g), toluene/AcOEt 19:1; (*E*)-isomer more polar than (*Z*)-isomer) followed by *Kugelrohr* distillation (140–160°/0.02 Torr) afforded pure samples of each diastereoisomer (*ca.* 0.5–1 g, purity (GC) ≥ 99%).

*Data of (*E*)-***8***:* ^{1}H-NMR: 0.84 (*s*, 3 H); 0.88 (*d*, *J* = 6.5, 3 H); 1.02 (*s*, 3 H); 1.60 (*s*, 3 H); 1.68 (*s*, 3 H); 3.62 (*m*, 2 H); 5.17 (*m*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (2, M^+), 151 (36), 109 (46), 95 (100), 81 (39), 67 (28), 55 (27), 41 (28).

*Data of (*Z*)-***8***:* ^{1}H-NMR: 0.85 (*s*, 3 H); 0.88 (*d*, *J* = 6.5, 3 H); 1.14 (*s*, 3 H); 1.65 (*s*, 3 H); 1.78 (*s*, 3 H); 3.63 (*m*, 2 H); 5.11 (*m*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (1, M^+), 151 (51), 135 (10), 121 (12), 109 (57), 95 (100), 81 (40), 67 (31), 55 (23), 41 (29).

*Data of (*E*)-*cis-***9**: ^{1}H-NMR: 0.63 (*s*, 3 H); 0.84 (*d*, *J* = 7, 3 H); 0.89 (*s*, 3 H); 1.66 (*s*, 3 H); 1.70 (*s*, 3 H); 3.62 (*t*, *J* = 6, 2 H); 5.16 (*t*, *J* = 7, 1 H); 5.32 (*m*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (0, M^+), 150 (71), 135 (60), 121 (28), 107 (37), 95 (30), 81 (100), 69 (27), 55 (33), 41 (35).

*Data of (*Z*)-*cis-***9**: ^{1}H-NMR: 0.64 (*s*, 3 H); 0.84 (*d*, *J* = 7, 3 H); 0.92 (*s*, 3 H); 1.75 (br. *s*, 6 H); 3.62 (*t*, *J* = 6, 2 H); 5.12 (*t*, *J* = 7, 1 H); 5.33 (br. *s*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (0.5, M^+), 150 (49), 135 (30), 123 (20), 107 (26), 95 (30), 81 (100), 67 (20), 55 (27), 41 (28).

*Data of (*E*)-*trans-***9**: ^{1}H-NMR: 0.74 (*s*, 3 H); 0.81 (*d*, *J* = 7, 3 H); 0.91 (*s*, 3 H); 1.65 (*s*, 3 H); 1.67 (*s*, 3 H); 1.95 (*d*, *J* = 14, 1 H); 2.07 (*t*, *J* = 9, 2 H); 2.28 (*q*, *J* = 7, 2 H); 3.62 (br. *s*, 2 H); 5.13 (*t*, *J* = 7, 1 H); 5.22 (br. *s*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (1, M^+), 150 (37), 135 (39), 123 (58), 112 (33), 95 (54), 81 (100), 67 (31), 55 (38), 41 (38).

*Data of (*Z*)-*trans-***9**: ^{1}H-NMR: 0.75 (*s*, 3 H); 0.81 (*d*, *J* = 7, 3 H); 0.95 (*s*, 3 H); 1.69 (*s*, 3 H); 1.73 (*s*, 3 H); 3.62 (br. *s*, 2 H); 5.08 (*t*, *J* = 7, 1 H); 5.23 (br. *s*, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (2, M^+), 150 (19), 135 (23), 123 (68), 112 (28), 95 (49), 81 (100), 67 (24), 55 (32), 41 (32).

6. *(*E*)- and (*Z*)-5-Methyl-7-(2′,6′,6′-trimethylcyclohex-1′-enyl)hept-4-en-2-ol* ((*E*)- and (*Z*)-**10**). A soln. of **7** ((*E*)/(*Z*) 2:1 (*vide supra*); 6 g, 0.023 mol) in Et_2O (40 ml) was added dropwise, within 10 min, to a stirred slurry of $LiAlH_4$ (0.46 g, 0.012 mol) in Et_2O (20 ml) at −30° under N_2. After a further 15 min at −30°, H_2O (0.5 ml), 20% aq. NaOH soln. (0.5 ml), and H_2O (3 ml) were added dropwise successively. Filtration (*Hyflo*), concentration of the filtrate, and distillation *i.v.* afforded **13** ((*E*)/(*Z*) 2:1) as a colourless oil (5.4 g, 94%), b.p. 90–98°/0.02 Torr, which was purified by chromatography (SiO_2 (360 g), toluene/AcOEt 9:1) to furnish pure samples of (*E*)-**10** (2.2 g, more polar) and (*Z*)-**10** (2.0 g, less polar).

*Data of (*E*)-***10***:* IR ($CHCl_3$): 3540, 3390 (br.), 1440, 1370, 1350, 1250, 1100, 1036, 922. ^{1}H-NMR: 1.00 (*s*, 6 H); 1.20 (*d*, *J* = 7, 3 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.61 (*s*, 3 H); 1.69 (*s*, 3 H); 1.91 (*t*, *J* = 7, 2 H); 2.07 (4 H); 2.18 (*m*, 2 H); 3.81 (*m*, 1 H); 5.20 (*t*, *J* = 7, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (1, M^+), 137 (97), 121 (19), 107 (15), 95 (100), 81 (81), 69 (25).

*Data of (*Z*)-***10***:* IR ($CHCl_3$): 3530, 3390 (br.), 1434, 1360, 1340, 1240, 1100, 1050, 1030, 920. ^{1}H-NMR: 1.02 (*s*, 6 H); 1.20 (*d*, *J* = 7, 3 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.65 (*s*, 3 H); 1.79 (*s*, 3 H); 1.92 (*t*, *J* = 7, 2 H); 1.96–2.12 (4 H); 2.18 (*m*, 2 H); 3.79 (*m*, 1 H); 5.14 (*t*, *J* = 7, 1 H). ^{13}C-NMR: see *Table 3*. MS: 250 (0, M^+), 137 (95), 121 (17), 107 (18), 95 (100), 81 (74), 69 (28).

7. *(*E*)- and (*Z*)-2,5-Dimethyl-7-(2′,6′,6′-trimethylcyclohex-1′-enyl)hept-4-en-2-ol* ((*E*)- and (*Z*)-**11**). A soln. of **7** ((*E*)/(*Z*) 2:1 (*vide supra*); 4.6 g, 0.018 mol) in Et_2O (50 ml) was added dropwise, within 20 min, to a stirred soln. of freshly prepared MeMgI (0.053 mol) in Et_2O (50 ml) at 5° under N_2. After a further 30 min at 5°, the mixture was poured into stirred cold 20% aq. NH_4Cl soln. (200 ml) and saturated with NaCl. Separation of the org. phase and extraction of the aq. phase (Et_2O) afforded a combined org. phase which was dried (anh. Na_2SO_4), filtered, and concentrated *i.v.* Distillation *i.v.* furnished **11** ((*E*)/(*Z*) 2:1) as a colourless oil (4.6 g, 95%), b.p. 110–115°/0.1 Torr, which was purified by chromatography (SiO_2 (360 g), toluene/AcOEt 19:1) to furnish pure samples of (*E*)-**11** (1.6 g) and (*Z*)-**11** (1.3 g).

*Data of (*E*)-***11***:* IR ($CHCl_3$): 3420 (br.), 1462, 1380, 1131, 900. ^{1}H-NMR: 1.00 (*s*, 6 H); 1.22 (*s*, 6 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.61 (*s*, 3 H); 1.68 (*s*, 3 H); 1.91 (*t*, *J* = 7, 2 H); 2.08 (4 H); 2.19 (*d*, *J* = 7, 2 H); 5.28 (*t*, *J* = 7, 1 H). ^{13}C-NMR: see *Table 3*. MS: 264 (0, M^+), 246 (4), 137 (100), 109 (77), 95 (88), 81 (59).

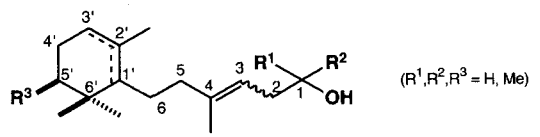

Table 3. *^{13}C-NMR Assignments* (δ [ppm]) *for* **8–11**

Compound	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	C(4)–*Me*	C(2′)–*Me*	C(1)–*Me* or C(5′)–*Me*	C(6)–*Me*$_\alpha$	C(6′)–*Me*$_\beta$
(*E*)-**8**	62.4	31.5	119.3	139.5	40.4	27.3	137.2	126.7	31.7	27.3	39.4	38.2	16.3	20.0	16.7	27.0	21.8
(*Z*)-**8**	62.7	31.6	120.2	139.7	32.8	27.7	137.2	127.0	31.7	27.3	39.4	38.2	23.5	20.1	16.7	27.1	21.9
(*E*)-*cis*-**9**	62.5	31.6	120.0	139.2	42.5	27.2	50.5	136.4	121.9	32.1	38.7	36.1	16.4	22.7	16.0	26.3	14.5
(*Z*)-*cis*-**9**	62.6	31.6	120.4	139.6	35.0	27.2	51.2	136.2	121.9	32.1	38.7	36.2	23.7	22.7	16.0	26.4	14.5
(*E*)-*trans*-**9**	62.5	31.6	119.7	139.3	41.3	30.1	51.7	137.4	120.1	32.7	31.8	35.4	16.3	23.5	15.4	25.6	21.4
(*Z*)-*trans*-**9**	62.7	31.6	120.0	139.8	33.7	29.9	52.2	137.2	120.0	32.6	31.9	35.4	23.6	23.5	15.4	25.6	21.4
(*E*)-**10**	68.0	38.0	119.4	139.8	40.5	28.0	137.1	127.1	32.8	19.6	39.9	35.0	16.4	19.8	22.8	28.7	28.7
(*Z*)-**10**	68.0	38.0	120.3	139.6	32.9	27.3	137.1	127.3	32.8	19.6	39.9	35.0	23.5	19.9	22.9	28.7	28.7
(*E*)-**11**	71.3	42.1	119.1	139.8	40.8	28.1	137.2	127.1	32.9	19.6	40.0	35.0	16.3	19.9	29.1	28.7	28.7
(*Z*)-**11**	70.9	42.1	119.7	139.7	32.9	27.3	137.1	127.3	32.7	19.6	40.0	35.0	23.6	19.9	29.2	28.7	28.7

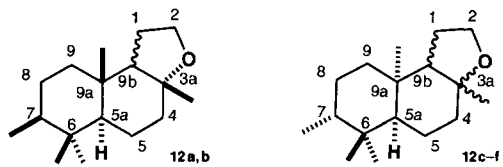

Table 4. *^{13}C-NMR Assignments* (δ [ppm]) *for* **12a–f**

Compound	C(1)	C(2)	C(3a)	C(4)	C(5)	C(5a)	C(6)	C(7)	C(8)	C(9)	C(9a)	C(9b)	C(3a)–*Me*	C(6)–*Me*$_\alpha$	C(6)–*Me*$_\beta$	C(7)–*Me*	C(9a)–*Me*
12a[a])	22.6	65.0	79.7	39.9	20.8	58.1	36.2[b])	42.8	27.3	39.8	36.4[b])	60.4	21.1	29.4	16.1	16.5	14.9
12b[a])	29.0	64.1	80.7	35.9	20.6	47.8	36.2[b])	43.0	27.4	38.6	36.4[b])	59.1	27.7	29.6	16.5	16.5	22.8
12c	24.3	64.4	78.9	38.8	23.4	55.4	36.9	36.5	28.2	27.6	38.1	58.5	20.7	26.4	31.0	16.1	29.5
12d	29.7	63.3	80.1	33.6	22.7	49.1	37.4	36.1	28.6	33.9	36.6	58.3	27.0	25.9	31.3	16.2	29.3
12e	23.7	65.2	80.4	36.9	21.0	54.2	34.9	38.2	26.6	37.6	36.2	48.8	24.4	27.3	30.8	16.0	24.4
12f	28.6	65.0	80.9	35.5	19.4	54.9	37.2	35.8	27.2	27.7	37.6	54.9	27.7	25.7	31.5	16.1	29.1

[a]) COSY, C,H correlation. [b]) Interchangeable.

Data of (Z)-**11**: IR ($CHCl_3$): 3420 (br.), 1460, 1370, 1130. ^{1}H-NMR: 1.02 (*s*, 6 H); 1.22 (*s*, 6 H); 1.42 (*m*, 2 H); 1.57 (*m*, 2 H); 1.65 (*s*, 3 H); 1.80 (*s*, 3 H); 1.91 (*t*, *J* = 7, 2 H); 2.06 (4 H); 2.22 (*d*, *J* = 7, 2 H); 5.22 (*t*, *J* = 7, 2 H). ^{13}C-NMR: see *Table 3*. MS: 264 (0, M^+), 246 (4), 137 (100), 121 (21), 109 (69), 95 (97), 81 (75).

8. *Acid-Mediated Cyclisation of Alcohols* **8–11**. *Preparation of (3a*RS,*5a*SR,*7*SR,*9a*SR,*9b*RS*)-, (3a*RS,*5a*SR,*7*SR,*9a*SR,*9b*SR*)-, (3a*RS,*5a*SR,*7*RS,*9a*RS,*9b*RS*)-, (3a*RS,*5a*SR,*7*RS,*9a*RS,*9b*SR*)-, (3a*RS,*5a*RS,*7*SR,*9a*SR, *9b*RS*)-, and (3a*RS,*5a*RS,*7*SR,*9a*SR,*9b*SR*)-Perhydro-3a,6,6,7,9a-pentamethylnaphtho[2,1-*b*]furan* (**12a–f**), *(2*RS/SR,*3a*RS,*5a*SR,*9a*SR,*9b*RS*)- and (2*RS/SR,*3a*RS,*5a*SR,*9a*SR,*9b*SR*)-Perhydro-2,3a,6,6,9a-pentamethylnaphtho[2,1-*b*]furan* (**13a,b**), *(3a*RS,*5a*SR,*9a*SR,*9b*RS*)- and (3a*RS,*5a*SR,*9a*SR,*9b*SR*)-Perhydro-2,2,3a,6,6,9a-hexamethylnaphtho[2,1-*b*]furan* (**14a,b**). A soln. of the alcohol (1 mmol) in 2-nitropropane (5 ml) was added dropwise, within 10 min to a stirred mixture of FSO_3H (*Bayer*, 10 mmol) and 2-nitropropane (10 ml) at −90° (cooling bath: liquid N_2/MeOH) under N_2. After the addition, the mixture was poured, with stirring, into sat. aq. $NaHCO_3$ soln. (50 ml) at 0–5° and extracted with Et_2O. The combined org. phase was washed with sat. aq. NaCl soln. and dried (anh. Na_2SO_4). Filtration, concentration, and *Kugelrohr* distillation *i.v.* (120–140°/0.04 Torr) afforded the product mixture whose distribution of tricyclic ethers **12a–f**, **13a,b**, and **14a,b** is presented in *Tables 1* and *2*. Prep. GC allowed the isolation of stereochemically pure samples of **12a–f** whose structures were assigned by comparison (GC/MS and NMR) with analogous compounds [8] [13][11]). For **13a,b** and **14a,b**, the unseparated diastereoisomeric mixtures were analysed by comparison with authentic samples [3] or analogues [4].

Data of **12a**: ^{1}H-NMR: 0.67 (*s*, 3 H); 0.81 (*s*, 3 H); 0.85 (*d*, *J* = 7, 3 H); 0.90 (*s*, 3 H); 1.09 (*s*, 3 H); 3.86 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (2, M^+), 235 (100), 151 (33), 137 (42), 109 (20), 97 (47), 81 (13), 67 (14), 55 (16), 43 (21).

Data of **12b**: ^{1}H-NMR: 0.66 (*s*, 3 H); 0.84 (*d*, *J* = 7, 3 H); 0.91 (*s*, 3 H); 1.07 (*s*, 3 H); 1.37 (*s*, 3 H); 3.81 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (7, M^+), 235 (47), 151 (100), 137 (53), 123 (17), 109 (22), 95 (27), 81 (17), 67 (17), 55 (17), 43 (25).

Data of **12c**: ^{1}H-NMR: 0.81 (*d*, *J* = 7, 3 H); 0.93 (*s*, 3 H); 1.04 (*s*, 3 H); 1.14 (*s*, 3 H); 1.15 (*s*, 2 H); 3.85 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (1, M^+), 235 (88), 151 (22), 137 (21), 121 (25), 109 (29), 97 (100), 81 (26), 67 (30), 55 (42), 43 (42).

Data of **12d**: ^{1}H-NMR: 0.79 (*d*, *J* = 7, 3 H); 0.92 (*s*, 3 H); 0.98 (*s*, 3 H); 1.09 (*s*, 3 H); 1.35 (*s*, 3 H); 3.76 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (3, M^+), 235 (100), 151 (27), 137 (28), 123 (31), 109 (31), 97 (89), 81 (42), 67 (37), 55 (50), 43 (76).

Data of **12e**: ^{1}H-NMR: 0.84 (*d*, *J* = 7, 3 H); 0.97 (*s*, 3 H); 0.98 (*s*, 3 H); 1.05 (*s*, 3 H); 1.14 (*s*, 3 H); 3.85 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (3, M^+), 235 (100), 151 (29), 137 (25), 123 (30), 109 (30), 97 (77), 83 (36), 67 (33), 55 (52), 43 (55).

Data of **12f**: ^{1}H-NMR: 0.76 (*d*, *J* = 7, 3 H); 0.94 (*s*, 3 H); 0.98 (*s*, 3 H); 1.02 (*s*, 3 H); 1.06 (*s*, 3 H); 3.77 (*m*, 2 H). ^{13}C-NMR: see *Table 4*. MS: 250 (0, M^+), 235 (89), 151 (17), 135 (14), 121 (21), 109 (26), 97 (100), 81 (41), 69 (34), 55 (43), 43 (47).

Data of **13a**: see [3].

Data of **13b** (unseparated 1.2:1 diastereoisomeric mixture at C(2)): *Major Isomer:* ^{1}H-NMR: 0.81 (*s*, 3 H); 0.89 (*s*, 3 H); 1.09 (*s*, 3 H); 1.16 (*d*, *J* = 7, 3 H); 1.37 (*s*, 3 H); 4.11 (*m*, 1 H). MS: 250 (6, M^+), 235 (85), 151 (30), 137 (100), 111 (57), 95 (58), 81 (60), 43 (98). *Minor Isomer:* ^{1}H-NMR: 0.81 (*s*, 3 H); 0.89 (*s*, 3 H); 1.09 (*s*, 3 H); 1,26 (*d*, *J* = 7, 3 H); 1.37 (*s*, 3 H); 4.04 (*m*, 1 H). MS: 250 (8, M^+), 235 (46), 151 (46), 137 (95), 109 (52), 95 (48), 81 (58), 43 (100).

Data of **14a** [4]: ^{1}H-NMR: 0.83 (*s*, 3 H); 0.85 (*s*, 3 H); 0.87 (*s*, 3 H); 1.16 (*s*, 3 H); 1.19 (*s*, 3 H); 1.35 (*s*, 3 H). ^{13}C-NMR: 81.3 (*s*); 79.1 (*s*); 60.4 (*d*); 57.3 (*d*); 42.6 (*t*); 41.1 (*t*); 40.1 (*t*); 36.1 (*s*); 36.0 (*t*); 33.6 (*q*); 33.1 (*s*); 30.8

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[11]) The preferred conformation of *cis*-fused *A*/*B* ring diastereoisomers **12c–f** is indicated by their NMR data and molecular-mechanics calculations using the MACROMODEL program [15]. In analogy to the previously studied C(7)-demethylated tricyclic ethers [13], we believe that the chair/chair conformation, in which the Me–C(7) group is equatorial and the Me–C(9a) group is axial in ring *A*, is preferred for **12c**, **12d**, and **12f**. For **12e**, however, the equatorial Me–C(7) group indicated by the NMR data implies a chair/skew-boat conformation for rings *A* and *B*, in which the Me–C(9a) group is axial to the ring *A*. In the alternative chair/chair conformation, the Me–C(7) group is axial and the Me–C(9a) group equatorial. It is gratifying to note that calculations indeed favour the former conformation, albeit by only 0.3 kcal/mol. For the C(7)-demethylated analogue of **12e** [13], the NMR data show that this preference is reversed, again in agreement with calculations which, in this case, estimate the chair/chair conformation to be 1.1 kcal/mol lower in energy than the chair/skew-boat conformation.

(*q*); 24.0 (*q*); 21.1 (*q*); 20.8 (*t*); 18.5 (*t*); 15.5 (*q*). MS: 264 (0.5, M^{+}), 249 (58), 191 (35), 137 (33), 109 (53), 95 (52), 43 (100).

Data of **14b**: ^{1}H-NMR: 0.81 (*s*, 3 H); 0.90 (*s*, 3 H); 1.10 (*s*, 3 H); 1.17 (*s*, 3 H); 1.32 (*s*, 3 H); 1.36 (*s*, 3 H). ^{13}C-NMR: 81.6 (*s*); 77.5 (*s*); 59.1 (*d*); 47.3 (*d*); 42.4 (*t*); 41.7 (*t*); 39.0 (*t*); 38.9 (*t*); 35.9 (*s*); 33.6 (*q*); 33.0 (*s*); 31.2 (*q*); 30.8 (*q*); 29.5 (*q*); 23.0 (*q*); 21.9 (*q*); 20.7 (*t*); 18.6 (*t*). MS: 264 (1, M^{+}), 249 (52), 191 (62), 137 (42), 109 (53), 95 (44). 43 (100).

REFERENCES

[1] R. L. Snowden, J.-C. Eichenberger, S. M. Linder, P. Sonnay, C. Vial. K. H. Schulte-Elte, *J. Org. Chem.* **1992,** *57,* 955.

[2] P. A. Bartlett, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, New York, 1982, Vol. 3, Part B, p. 390.

[3] G. Ohloff, C. Vial, E. Demole, P. Enggist, W. Giersch, E. Jégou, A. J. Caruso, J. Polonsky, E. Lederer, *Helv. Chim. Acta* **1986,** *69,* 163.

[4] I. B. Bersuker, A. S. Dimoglo, M. Yu. Gorbachov, M. N. Kaltsa, P. F. Vlad, *Nouv. J. Chem.* **1985,** *9,* 211.

[5] G. Ohloff, in 'Fragrance Chemistry', Ed. E. T. Theimer, Academic Press, New York, 1982, p. 535.

[6] a) M. I. Farbood, B. J. Willis, P. A. Christenson, South African Patent ZA 8584306, 1985; b) S. Neumann, H. Simon, *Biol. Chem. Hoppe-Seyler* **1986,** *367,* 723; c) R. Decorzant, C. Vial, F. Näf, G. Whitesides, *Tetrahedron* **1987,** *43,* 1871; d) H. Koyama, Y. Kaku, M. Ohno, *Tetrahedron Lett.* **1987,** *28,* 2863; e) P. A. Christenson, *Tetrahedron* **1988,** *44,* 1925; f) K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1990,** 361; g) H. Kosugi, K. Hoshino, H. Uda, *J. Chem. Soc., Chem. Commun.* **1991,** 1173.

[7] a) T. Kawanobe, K. Kogami, M. Matsui, *Agric. Biol. Chem.* **1986,** *56,* 1475; b) G. Büchi, H. Wüest, *Helv. Chim. Acta* **1989,** *72,* 996; c) P. F. Vlad, N. D. Ungur, V. B. Perutskii, *Khim. Geterotsikl. Soedin. Sb* **1990,** *26,* 896; d) R. L. Snowden, S. M. Linder, *Tetrahedron Lett.* **1991,** *32,* 4119.

[8] G. Ohloff, W. Giersch, W. Pickenhagen, A. Furrer, B. Frei, *Helv. Chim. Acta* **1985,** *68,* 2022.

[9] R. E. Maleczka Jr., L. A. Paquette, *J. Org. Chem.* **1991,** *56,* 6538.

[10] M. E. Garst, E. A. Tallman, J. N. Bonfiglio, D. Harcourt, E. B. Ljungwe, A. Tran, *Tetrahedron Lett.* **1986,** *27,* 4533.

[11] A. Saito, H. Matsushita, Y. Tsujino, H. Kaneko, *Chem. Lett.* **1981,** 757.

[12] G. Ohloff, E. Otto, V. Rautenstrauch, G. Snatzke, *Helv. Chim. Acta* **1973,** *56,* 1875.

[13] S. Escher, W. Giersch, Y. Niclass, G. Bernardinelli, G. Ohloff, *Helv. Chim. Acta* **1990,** *73,* 1935.

[14] B. Maurer, A. Hauser, J.-C. Froidevaux, *Helv. Chim. Acta* **1989,** *72,* 1400.

[15] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caulfield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990,** *11,* 440.