158. Conformational Studies of Marine Polyhalogenated α-Chamigrenes Using Temperature-Dependent NMR Spectra

Inverted-Chair and Twist-Boat Cyclohexane Moieties in the Presence of an Axial Halogen Atom at C(8)[1])

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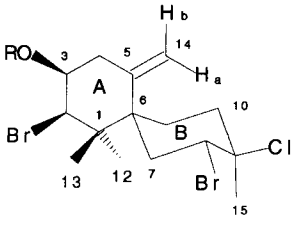
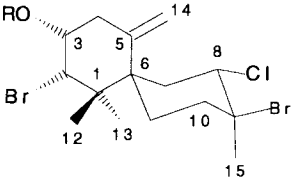
α-Chamigren-3-one (+)-**8** bearing an axial Cl-atom at C(8) exists as a largely dominant conformer with Me–C(5) at the envelope-shaped enone ring pointing away from Cl_{ax}–C(8) at the cyclohexane ring (= B) in the 'normal' chair conformation, as shown by ^{1}H-NMR. In contrast, the α-chamigren-3-ols (+)-**9** and (+)-**10**, obtained from hydride reduction of (+)-**8**, show a temperature-dependent equilibrium of conformers where the major conformers have ring B in the inverted-chair (and twist-boat for (+)-**9**) conformation to avoid repulsions between Me–C(5) and Cl_{ax}–C(8) (*Scheme 1*). This is in agreement with the conformation of the epoxidation product (+)-**12** of (+)-**9** where Me–C(5) is pushed away from Cl_{ax}–C(8) in a ring-B chair similar to that of (+)-**8** (*Scheme 2*). Introduction of a pseudoequatorial Br-atom at C(2) of (+)-**8**, as in enone (+)-**15** (*Scheme 3*), does not affect the conformation; but a pseudoaxial Br–C(2) experiences repulsive interactions with H_{eq}–C(7), as shown by the ^{1}H-NMR data of the isomeric enone (+)-**16** where the 'normal'-chair conformer *Cα*-**16** is in an equilibrium with the inverted chair conformer *ICβ*-**16** (*Scheme 3*). These results and the accompanying paper allow a unifying view on the conformational behavior of marine polyhalogenated α-chamigrenes. This view is supported by the acid-induced isomerization of α-chamigrene (+)-**9** (inverted chair) to β-chamigrene (+)-**17** ('normal' chair; *Scheme 4*), the driving force being the lesser space requirement of CH_2=C(5) than of Me–C(5). This explains why β-chamigrenes are so common in nature.

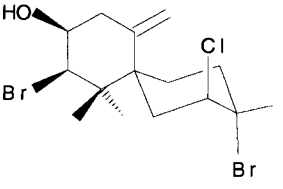
1. Introduction. – We recently reported on the conformational preferences of 8,9-dihalogenated marine β-chamigrenes that bear or not a further halogen atom at C(2)[1]) [1]. Included were rogiolol acetate ((+)-**1**), rogiolol ((–)-**2**), obtusol ((+)-**3**), and obtusol acetate ((–)-**4**), which undergo slow chair-chair inversion of ring A on the NMR time



(+)-**1** R = Ac
(–)-**2** R = H



(+)-**3** R = H
(–)-**4** R = Ac

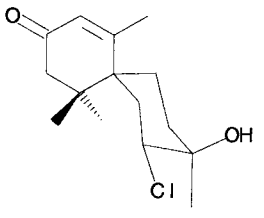


(+)-**5**

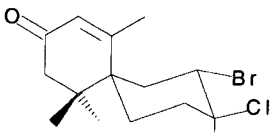
[1]) We use the chamigrene numbering for the structural formulae and spectroscopic data (see (+)-**1**); for IUPAC nomenclature and numbering for retrieval purposes, see *Exper. Part.*

scale, while ring B remains in the chair conformation. The picture was less clear for isoobtusol; structure (+)-**5** was proposed for it, representing either a locked conformer or a largely dominating fast-equilibrium conformer, in either case with ring A so flipped as to place CH_2=C(14) away from Cl_{ax}–C(8) at ring B in chair conformation [1].

We also showed that on treatment of the above β-chamigrenes with Zn/Et_2O/AcOH, easy elimination of BrCl from ring B occurs when Br is at the tertiary C-atom (C(9)), such as in (+)-**3**, (−)-**4**, and (+)-**5**, while in the case of (+)-**1** and (−)-**2**, ring B is inert, and only slow elimination of ROBr from ring A takes place [1].



(−)-**6**



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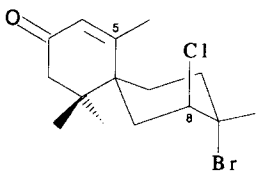


(+)-**8**

In the accompanying paper [2], it is shown that α-chamigrenes with equatorial halogen atoms at C(8) and C(9) undergo slow conformational flipping of ring A, while, in contrast with current views [3], no twist-boat conformations of ring B intervene. α-Chamigrenes possessing an axial bulky substituent at C(8) show such distinctive conformational behavior to warrant separate consideration. They are largely overlooked in the literature from the conformational viewpoint. The only exception is enone (−)-**6**, isolated from *Laurencia obtusa* collections of Jamaica [4], for which the inverted-chair conformation of ring B was proposed, based on its ^{1}H-NMR coupling pattern (J(8,7) = 12.5 and 4.7 Hz) and on a chemical correlation with an O-bridged chamigrane of established configuration; however, no dynamic phenomena were described [4].

Possibly, as discussed below, another α-chamigrene with an axial halogen atom at C(8) (and not equatorial as originally suggested with structure **7** [5]) is laurencenone D [5][2]).

This stimulated us to investigate in detail the conformational behavior of α-chamigrenes that bear a halogen atom at C(8). Although not available to us from natural sources, representative examples of this type of α-chamigrenes were obtained by chemical transformation of isoobtusol ((+)-**5**) which was left from our previous study [1]. Thus, we succeeded in determining the structural features of α-chamigrenes that cause ring B to adopt inverted-chair and twist-boat conformations.

2. Results and Discussion. – 2.1. *Conformational Analysis of α-Chamigrenones, α-Chamigrenols, and of Their Epoxides.* The α-chamigrenone (+)-**8**, obtained by treatment of isoobtusol ((+)-**5**) with KOH/MeOH, showed sharp ^{1}H- (see *Exper. Part*) and ^{13}C-NMR signals (*Table 1*) in $CDCl_3$ solution within a broad temperature range. Incipient

[2]) We already pointed out that the originally proposed structure **7** has to be revised to that of a diastereoisomer [6].

Table 1. *^{13}C-NMR Data* ($CDCl_3$) *for Some α-Chamigrenes Bearing an Axial Substituent at C(8)*[1])

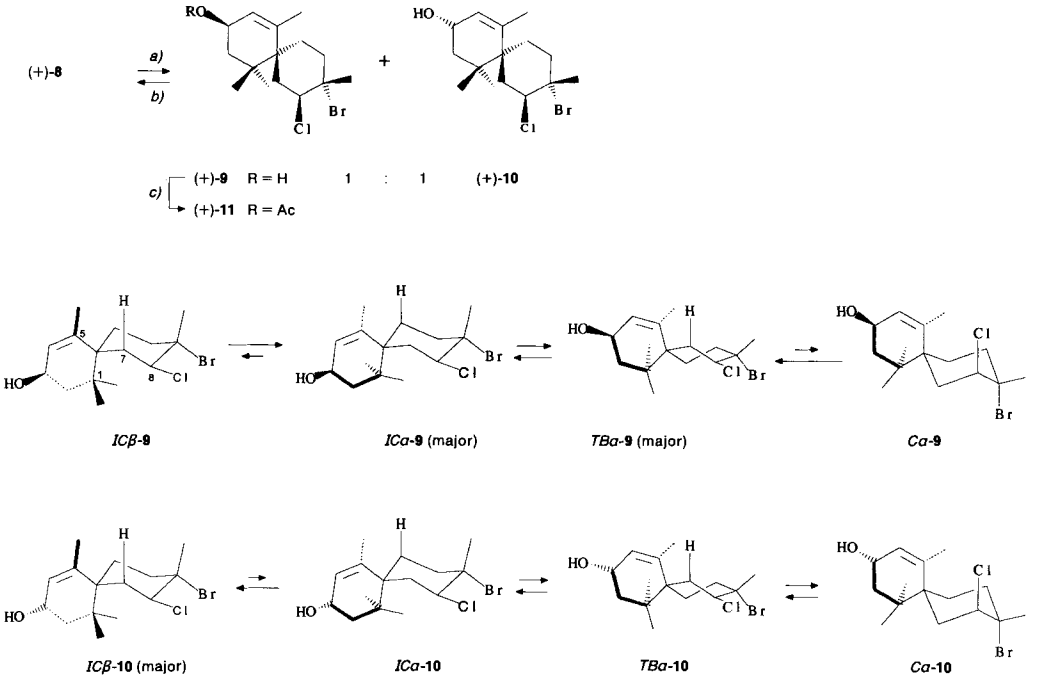
	(+)-**8**	(+)-**9**	(+)-**10**	(+)-**11**[a])	(+)-**12**	(+)-**13**	(+)-**15**	(+)-**16**	(+)-**18**
C(1)	42.20 (*s*)	39.02 (*s*)	37.87 (*s*)	38.67 (*s*)	37.76 (*s*)	38.66 (*s*)	44.68 (*s*)	45.60 (br. *s*)	40.69 (*s*)
C(2)	48.95 (*t*)	43.63 (*t*)	43.88 (*t*)	39.23 (*t*)	39.18 (*t*)	40.84 (*t*)	64.11 (*d*)	62.48 (br. *d*)	48.81 (*t*)
C(3)	not det.	65.43 (*d*)	64.92 (*s*)	68.56 (*d*)	64.97 (*d*)	65.74 (*s*)	190.10 (*s*)	not det.	201.52 (*s*)
C(4)	127.81 (*d*)	128.16 (*d*)	127.85 (*d*)	123.59 (*d*)	65.98 (*d*)	64.73 (*d*)	126.77 (*d*)	126.06 (*d*)	126.72 (*d*)
C(5)	not det.	141.54 (*s*)	141.71 (*s*)	144.05 (*s*)	65.54 (*s*)	67.40 (*s*)	170.65 (*s*)	not det.	174.87 (*s*)
C(6)	not det.	44.64 (*s*)	44.79 (*s*)	44.32 (*s*)	39.88 (*s*)	42.89 (*s*)	49.63 (*s*)	47.15 (br. *s*)	43.79 (*s*)
C(7)	39.44 (*t*)	38.66 (*t*)	36.84 (*t*)	38.48 (*t*)	31.80 (*t*)	37.75 (*t*)	40.01 (*t*)	39.32 (br. *t*)	30.57 (*t*)
C(8)	65.27 (*d*)	68.43 (*d*)	68.22 (*d*)	68.12 (*d*)	65.88 (*d*)	68.41 (*d*)	65.74 (*d*)	66.52 (*d*)	121.44 (*d*)
C(9)	68.39 (*s*)	68.60 (*s*)	68.76 (*s*)	68.50 (*s*)	69.83 (*s*)	68.03 (s)	68.00 (*s*)	66.85 (*s*)	134.21 (*s*)
C(10)	36.37 (*t*)	41.81 (*t*)	41.39 (*t*)	41.32 (*t*)	35.88 (*t*)	42.46 (*t*)	35.18 (*t*)	38.25 (br. *t*)	28.15 (*t*)
C(11)	25.88 (*t*)	24.72 (*t*)	26.17 (*t*)	24.73 (*t*)	25.67 (*t*)	25.56 (*t*)	25.40 (*t*)	not det.	27.87 (*t*)
C(12)	25.59 (*q*)	29.05 (*q*)	29.34 (*q*)	29.69 (*q*)	25.83 (*q*)	30.82 (*q*)	24.68 (*q*)	28.47 (*q*)	24.77 (*q*)
C(13)	24.05 (*q*)	24.22 (*q*)	25.68 (*q*)	24.37 (*q*)	23.35 (*q*)	25.95 (*q*)	19.03 (*q*)	23.38 (*q*)	23.84 (*q*)
C(14)	24.10 (*q*)	21.66 (*q*)	21.69 (*q*)	21.40 (*q*)	23.68 (*q*)	24.23 (*q*)	24.28 (*q*)	23.85 (*q*)	24.66 (*q*)
C(15)	31.57 (*q*)	27.17 (*q*)	27.00 (*q*)	27.52 (*q*)	32.60 (*q*)	24.04 (*q*)	32.66 (*q*)	26.82 (*q*)	23.31 (*q*)

[a]) MeCO: 170.94 (*s*); 21.86 (*q*).

broadening could only be detected at a temperature as low as −60°, indicating the presence of a major conformer in which Me–C(5) at the envelope-shaped enone ring points away from Cl_{ax}–C(8) at the cyclohexane ring (ring B) in chair conformation. The structure of the major conformer is supported by positive NOE's between Me_{eq}–C(1) and both H_{ax}–C(7) and H_{ax}–C(11) (see *Exper. Part*).

DIBAL reduction of (+)-**8** gave the epimeric α-chamigren-3-ols (+)-**9** and (+)-**10**, and the former was acetylated affording (+)-**11** (*Scheme 1*). The structures of these products

Scheme 1



a) DIBAL, THF, r.t., 2 h; 64% overall yield. *b*) *Jones* reagent, Me_2CO, 30 min; 95% yield. *c*) Ac_2O/pyridine, r.t., 2 h; 100% yield.

are supported by ^{13}C-NMR (*Table 1*), ^{1}H-NMR, and MS data (*Table 2* and *Exper. Part*). Unexpectedly, the ^{1}H-NMR pattern of H–C(8) changed from that of an equatorial proton for (+)-**8** to that of an axial proton for both (+)-**9** and (+)-**10** (*Table 2*). This can be rationalized in terms of the ring-B inverted-chair conformers *IC*-**9** and *IC*-**10** (*Scheme 1*)[3]). Unambiguous support for the presence of conformers of type *IC*-**9** is given by positive NOE's among Me_{eq}–C(1), H_{ax}–C(8), H_{ax}–C(10), and H_{eq}–C(7), from one side, and among Me_{ax}–C(1), H_{ax}–C(3), and H_{eq}–C(11), from the other side (see *Exper. Part*).

[3]) The following abbreviations are used to distinguish individual conformers: *C* = chair, *IC* = inverted chair, *TB* = twist-boat (= skew); α and β refer to the position of *Me*–C(5) below and above, respectively, of the mean plane of the dihalogeno-substituted cyclohexane ring B.

Table 2. *Calculated Strain Energy* (kcal mol^{-1}), *Relative-% Population* (%), *J Values* (Hz), *and Torsional Angles* θ (°), *and Observed Values* J ($CDCl_3$) *for All Conformers Contributing to the* α-*Chamigrenols (+)-***9** *and (+)-***10** *and the* α-*Chamigrenone (+)-***16**

	ICβ-**9**	*IC*α-**9**	*TB*α-**9**	*C*α-**9**	Weighted average J^a) for **9**	Obs. *J* for (+)-**9**
Strain energy	23.72	22.78	22.95	23.64[b])		
Relative-% population x_i	9	46	31	11		
$J(10\beta,11\beta)(\theta)$	4.6 (52)	3.9 (56)	2.2 (66)	3.9 (66)	3.4	4.9
$J(10\beta,11\alpha)(\theta)$	3.4 (59)	4.5 (53)	13.0 (179)	12.3 (167)	8.1	7.0
$J(10\alpha,11\beta)(\theta)$	12.1 (165)	12.6 (170)	5.8 (46)	3.7 (57)	9.3	8.9
$J(10\alpha,11\alpha)(\theta)$	4.3 (54)	3.2 (60)	2.2 (66)	4.5 (53)	3.1	5.4
$J(8\alpha,7\beta)(\theta)$	12.8 (173)	12.4 (168)	13.0 (177)	2.7 (63)	11.6	11.5
$J(8\alpha,7\alpha)(\theta)$	2.8 (62)	3.9 (56)	1.8 (69)	5.4 (48)	3.9	4.9
	ICβ-**10**	*IC*α-**10**	*TB*α-**10**	*C*α-**10**	Weighted average J^a) for **10**	Obs. *J* for (+)-**10**
Strain energy	22.29	23.10	23.23	23.12[b])		
Relative-% population x_i	59	15	12	14		
$J(10\beta,11\beta)(\theta)$	4.8 (51)	3.7 (57)	2.2 (66)	3.9 (56)	4.2	5.2
$J(10\beta,11\alpha)(\theta)$	3.4 (59)	4.6 (52)	13.0 (179)	12.4 (168)	6.0	5.0
$J(10\alpha,11\beta)(\theta)$	12.0 (164)	12.7 (171)	5.8 (46)	3.7 (57)	10.2	10.6
$J(10\alpha,11\alpha)(\theta)$	4.5 (53)	3.0 (61)	2.2 (66)	4.3 (54)	4.0	5.7
$J(8\alpha.7\beta)(\theta)$	12.8 (173)	12.4 (168)	13.0 (177)	3.0 (61)	11.4	11.2
$J(8\alpha,7\alpha)(\theta)$	2.8 (62)	4.1 (55)	1.8 (69)	5.2 (49)	3.2	4.6
	TBβ-**16**	*ICβ*-**16**	*IC*α-**16**	*TB*α-**16**	*C*α-**16**	Weighted average J^a) for **16**	Obs. *J* for (+)-**16**
Strain energy	26.63	26.02	26.83	27.70	26.50[b])		
Relative-% population	17	47	12	3	21		
$J(10\beta,11\beta)(\theta)$	1.5 (71)	3.9 (56)	3.2 (60)	2.1 (67)	3.9 (56)	3.4	4.5
$J(10\beta,11\alpha)(\theta)$	13.0 (−176)	4.5 (53)	5.2 (49)	13.0 (179)	12.4 (168)	7.9	7.5
$J(10\alpha,11\beta)(\theta)$	6.0 (−43)	12.7 (171)	12.9 (174)	6.0 (45)	3.7 (57)	9.5	9.7
$J(10\alpha,11\alpha)(\theta)$	1.7 (70)	3.2 (60)	2.5 (64)	2.1 (67)	4.3 (54)	3.1	4.5
$J(8\alpha,7\beta)(\theta)$	13.0 (−177)	12.7 (172)	12.4 (168)	12.9 (176)	2.8 (62)	10.6	10.2
$J(8\alpha,7\alpha)(\theta)$	1.5 (71)	3.2 (60)	3.7 (57)	1.5 (71)	5.2 (49)	3.3	4.7

[a]) Calculated using *Eqn.* $^3J_w = \sum_i x_i J_i$.

[b]) This value was corrected by adding 2 kcal mol^{-1} to the molecular-mechanics-calculated [7b] value (see text).

Conformers of type *IC*-**10** are supported by similar evidence (see *Exper. Part*). For (+)-**9**, the coupling pattern of the protons at C(7) and C(8) is consistent with a cyclohexane chair, whereas the signals of the protons at C(10) and C(11), suggest a marked deviation from the chair conformation (see *Exper. Part*). For (+)-**10**, a similar but less marked deviation is observed (see *Exper. Part*).

The proposed conformational equilibria for (+)-**9** and (+)-**10** were analyzed by molecular-mechanics (MM) calculations [7]. The results could only be interpreted fully after a similar analysis of the conformational equilibria of enone (+)-**16** was performed (see below). In the case of (+)-**9**, the inverted chair *IC*α-**9** and the twist-boat *TB*α-**9** are

the most populated[3]) (*Scheme 1* and *Table 2*). In the case of (+)-**10**, there is a dominant ring-B inverted-chair conformer *ICβ*-**10** with Me–C(5) pointing toward H_{ax}–C(7). The conformers derived from ring-A flipping with Me–C(5) pointing toward H_{ax}–C(11) (*ICα*-**10**) or with ring B changed into either a twist-boat (*TBα*-**10**) or an inverted chair (*Cα*-**10**) are minor. The calculated energy barriers are low in both cases ($\Delta H^{\neq}$ 9–10 kcal mol^{-1}) for all motions, as expected for fast equilibrium processes, in agreement with ^{1}H-NMR line broadening becoming detectable only at temperatures as low as −60°.

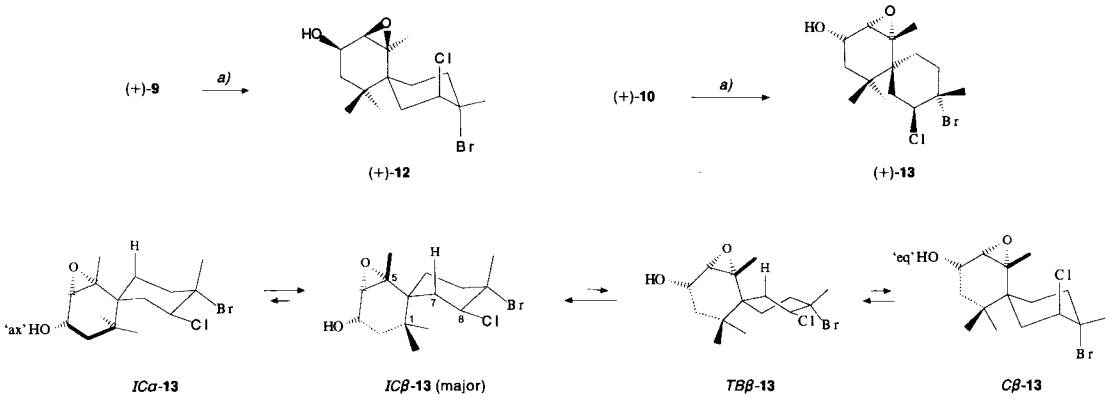
In *Table 2*, the observed *J* values for ring-B protons of (+)-**9** and (+)-**10** (α and β indicate protons below or above the mean plane of ring B), the corresponding torsional angles θ as evaluated from MM calculations [7b], and calculated *J* values (from modified *Karplus* relationships [8]), and the relative-% population of the various conformers are given. Agreement between the weighted averaged *J* and the observed *J* supports the validity of this type of analysis. As expected, this treatment is only meaningful when the conformers have largely different corresponding *J* values; under these conditions, the observed *J* values are well reproduced on the assumption of the equilibria depicted in *Scheme 1*. Acetate (+)-**11** showed *J* values similar to those of (+)-**9**, pointing to similar conformational equilibria.

The involvement of inverted-chair and twist-boat conformers in the equilibria of *Scheme 1* is not drastically determined by the nature of the solvent used ($CDCl_3$) as shown by the ^{1}H-NMR data of (+)-**9** in $(CD_3)_2SO$ (similar *J*'s, see *Exper. Part*). It must also be emphasized that the existence of both (+)-**9** and (+)-**10** in the conformations described in *Scheme 1* has a thermodynamic origin, since a mixture of them reverted to (+)-**8** on *Jones* oxidation.

The question then arises why reduction of chamigrenone (+)-**8** to the chamigrenols (+)-**9** and (+)-**10** determines both chair inversion and the intervention of twist-boat conformations of ring B. Repulsive interactions between Me–C(5) and Cl_{ax}–C(8) in conformer *Cα*-**9** and *Cα*-**10** are likely to be responsible for ring-B flipping to the other conformers. If this interpretation is correct, epoxidation of (+)-**9** from the side of the OH group, as expected for a peracid oxidation of an allylic alcohol [9], should drag Me–C(5) away from Cl_{ax}–C(8), allowing the normal-chair conformer to become populated. Conversely, epoxidation of (+)-**10** from the side of the OH group should place Me–C(5) just in the area of Cl_{ax}–C(8), forcing ring B to maintain the inverted-chair conformation. These prospects were nicely verified. Epoxidation of (+)-**9** gave (+)-**12**, where ring B is a 'normal' chair (*Scheme 2*), as shown by the typical ^{1}H-NMR pattern for H_{eq}–C(8) (see *Exper. Part*). Conversely, (+)-**10** gave (+)-**13**, which exists predominantly as the *ICβ*-**13** conformer, in equilibrium with the minor ring-A-flipped (*ICα*-**13**), ring-B twist-boat *TBβ*-**13**, and ring-B 'normal'-chair (*Cβ*-**13**) conformers (*Scheme 2*). This is supported by positive NOE's between Me_{eq}–C(1) and H_{ax}–C(8), from one side, and between Me–C(5) and H_{ax}–C(7), from the other side (see *Exper. Part*).

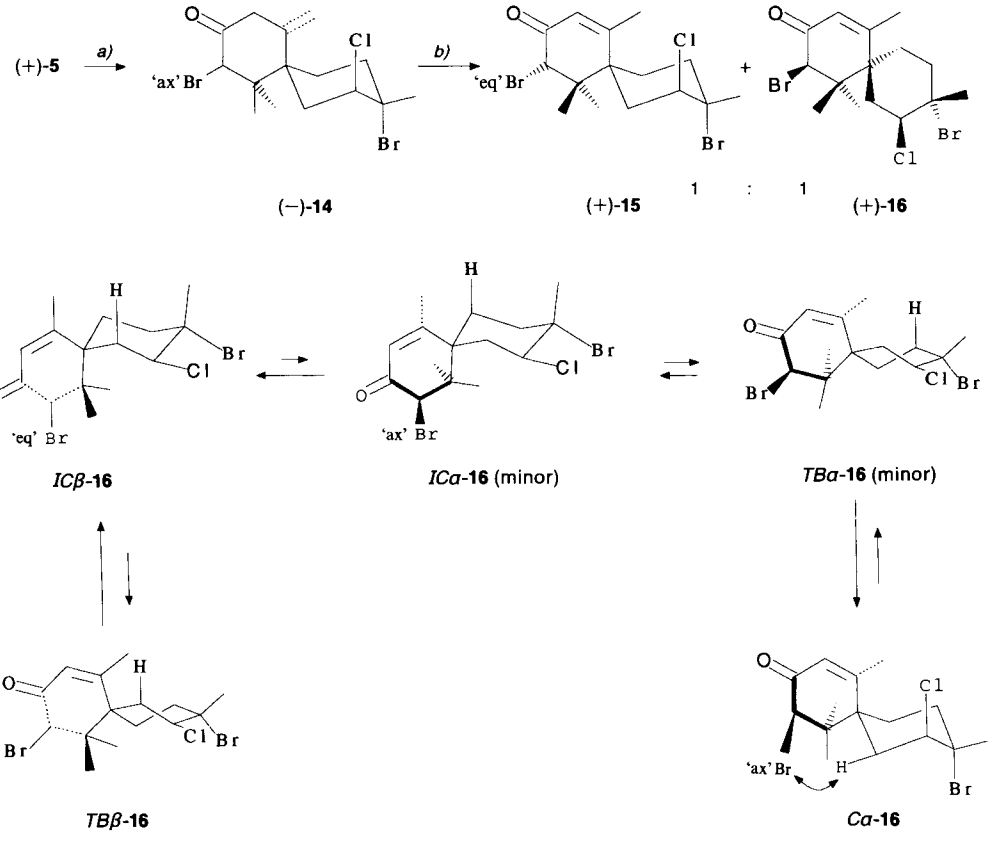
The above idea that repulsive interactions between Me–C(5) and an axial halogen substituent at C(8) are responsible for chair inversion of ring B was subjected to further experimental test. Although β-chamigrenes in general resist isomerization to the α-isomers [1] [2], acid isomerization accompanied by conjugation, such as from β- to α-chamigren-3-ones, can be carried out. Thus, acid treatment of (+)-**14** (obtained from (+)-**5** [1]) led to (+)-**16** and its C(2) epimer (+)-**15**, which were separated (*Scheme 3*). To minimize repulsive interactions between Me–C(5) and Cl_{ax}–C(8) on one side and between

Scheme 2



a) 3-$ClC_6H_4CO_3H/NaHCO_3$, r.t., 4 h; 80% yield.

Scheme 3



a) *Jones* reagent, Me_2CO, 30 min, 90% yield. *b*) TsOH, CCl_4, 55°, 2 h; 80% overall yield.

Br_{ax}–C(2) and H_{eq}–C(7) on the other side, (+)-**16** is expected to be in a ring-B inverted-chair conformation. An MM analysis of the type carried out above for (+)-**9**, (+)-**10**, and (+)-**13** revealed that for (+)-**16**, there are two main conformers (*Table 2*), a ring-B inverted chair in which Me–C(5) points toward H_{ax}–C(7), *ICβ*-, and a normal chair *Cα*-, in equilibrium with minor conformers deriving from either ring-A flipping in the inverted-chair conformation (*ICα*-**16**) or ring-B flipping to twist-boat (*TBα*-**16***TBα*)[3]). Moreover, the dominant conformer *ICβ*-**16** is in a side equilibrium with the minor twist-boat conformer *TBβ*-**16**. Enone (+)-**16** provided the most clear cut NMR and dynamic NMR spectra, being thus central in our conformational analysis. At room temperature, H–C(8) showed up in $CDCl_3$ as a *dd* (J = 9.1 and 4.7 Hz)[4]), which indeed can not be accounted for in terms of a ring-B inverted-chair only. At −70°, the ^{1}H-NMR spectrum revealed two conformers, in a 7:3 population ratio, with structures *ICβ*-**16** and *Cα*-**16**, respectively. The same proton in conformers *ICβ*-**16** and *Cα*-**16** was identified through cross saturation transfer experiments, whereas for each one of these two conformers, the protons were assigned *via* ^{1}H,^{1}H COSY 60 experiments at −70°. Dynamic ^{1}H-NMR analysis, in the −70 to +40° temperature range, was carried out by monitoring H–C(8) [1] [2] (*Table 3*).

Table 3. *Experimental Thermodynamic and Kinetic Parameters for* (+)-**16** *and* (−)-**20**

	x_a/x_b	$\Delta H^{\neq}$ [a]) [kcal/mol]	$\Delta S^{\neq}$ [a]) [cal/mol K]	$\Delta G^{\neq}$ [a]) [kcal/mol]
(+)-**16**	*Table 2*	7.6 ± 0.2	−14.6 ± 1	12.0 ± 0.2
(−)-**20**	70:30	15.5 ± 0.5	− 1.3 ± 1	15.9 ± 0.2

[a]) Statistical relative errors are indicated for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, whereas errors in temperature and rate constants are reflected in the errors indicated for $\Delta G^{\neq}$.

Conformational barriers for (+)-**16**, drawn by DNMR5 simulations [11] (*Table 3*), are, as expected for a conjugated enone, higher than for the corresponding alcohols. Among the energy barriers for interconversion of the various conformers, evaluated from MM calculations through the driver angle option [7], the highest one is between the inverted chair *ICα*-**16** and the twist-boat *TBα*-**16** (*Fig.*), which is an obligatory step in the interconversion between the ^{1}H-NMR-detectable conformers *ICβ*-**16** and *Cα*-**16**.

2.2. *Isomerization of α- to β-Chamigrenes.* Previously [1] and in the accompanying paper [2], we reported on both the resistance of β-chamigrenes to isomerization into α-chamigrenes and a case of reverse isomerization. The α-to-β-chamigrene conversion (+)-**9**→(+)-**17**) is a further impressive case of an isomerization going against the rule of higher stability of the more substituted olefin (*Scheme 4*). In accordance with our ideas above, the driving force for this isomerization is the lesser steric requirement of CH_2=C(5) than of Me–C(5), the isomerization being also accompanied by reversion to the 'normal' chair. This isomerization is a further [2] indication of why β-chamigrenes are so common in nature. In fact, while natural α-chamigrenes are nearly as numerous as β-chamigrenes [3c], natural α-chamigrenes with a bulky axial substituent at C(8) (either

[4]) Coupling patterns in C_6D_6 (J = 10.2 and 4.7 Hz) and in CD_3OD (J = 10.4 and 4.7 Hz) indicated solvent-dependent conformational equilibria, as expected for conformers which differ largely in dipole moments.

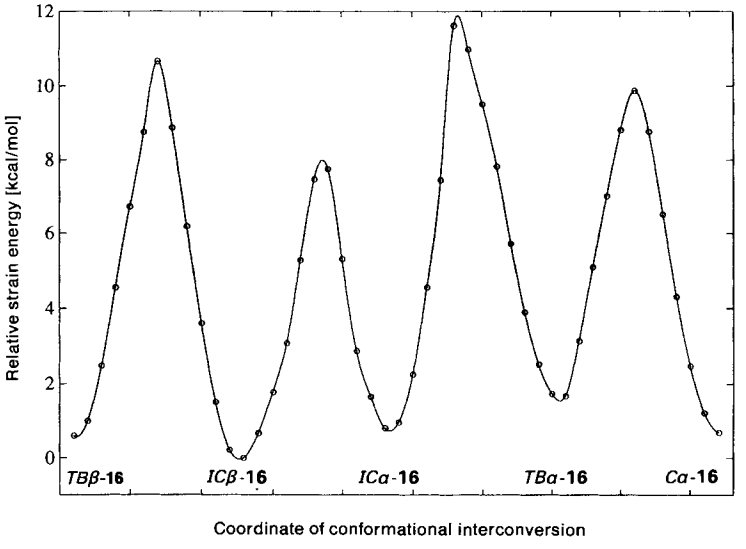
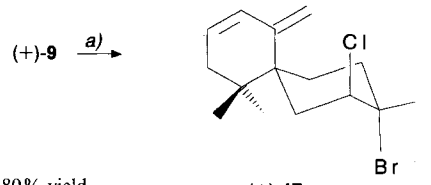


Figure. *Coordinate of conformational interconversion* vs. *relative strain energy for the various conformers of the α-chamigrenone* (+)-**16**. See *Scheme 3*.

Scheme 4



a) TsOH, CCl_4, 40°, 20 min; 80% yield. (+)-**17**

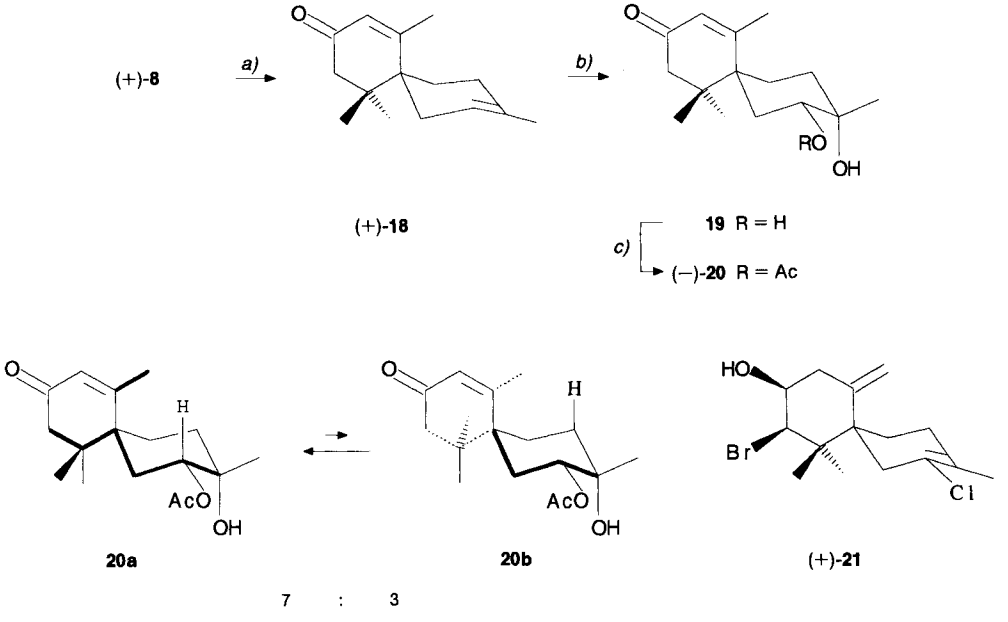
as such or in a different conformation) are limited, to our knowledge, to enones (−)-**6** [4] and (+)-**8** [5].

2.3. *Explanations for Puzzling Reports on Chamigrenes.* Puzzling results in the literature of α-chamigrenes can be rationalized in conformity to the above views, such as for laurencenone D [5]. Being enantiomeric to a product of transformation of rogiolol ((−)-**2**), which has different NMR data [6], laurencenone D can not have structure **7**. A *trans*-diaxial relationship between the halogen atoms at ring B is also ruled out for laurencenone D by comparison with compound (+)-**8**, where ring B takes the 'normal'-chair conformation. We suggest that the 'normal'-chair/inverted-chair equilibrium originally described for laurencenone D [5] can be rationalized by assuming that the halogen atoms at C(8) and C(9) are *cis*-related[5]), so as to have an axial halogen atom at C(8) in the

[5]) The facile 1,2-elimination of the halogen atoms in laurencenone D by $Zn/Et_2O/AcOH$ [5] is also compatible with their *cis*-relationship. However, the present meager knowledge on halogen eliminations by $Zn/Et_2O/AcOH$ does not allows to rule out that, like with rogiolol ((+)-**3**) and rogiolol acetate ((−)-**4**), it is the position of the Br-atom at the quaternary C-atom that dictates a higher reactivity [1] [6]. This is why we are uncommitted about the relative position of the halogen atoms at C(8) and C(9).

'normal'-chair conformation. The reported *J* values for laurencenone D [5] are consistent with this hypothesis. As laurencenone D is no more available[6]), we turned our attention to semisynthetic analogues to prove this point. But only compound **19** with the uninteresting *cis*-arrangement OH_{ax}–C(9)/OH_{eq}–C(8) could be easily obtained, by dehalogenation of (+)-**8** *via* (+)-**18** (*Scheme 5*). Acetylation gave (−)-**20**. It was immediately clear that (−)-**20** is of the type of the 'wrong' *cis*-diastereoisomer: ring B appeared as the 'normal' chair (see **20a**) according to the data in *Table 3* and the *Exper. Part.* No 'normal'-chair/inverted-chair slow equilibration as with laurencenone D [5] was observed with (−)-**20**.

Scheme 5



a) Zn/Et_2O/AcOH, r.t., 2 h; 60% yield. *b*) OsO_4, pyridine, r.t., 4 h. *c*) Ac_2O, pyridine, r.t., 6 h; 10% (rel. to (+)-**18**).

Therefore, unless we are dealing with conformational preferences that depend drastically on the nature of the substituents, the *cis*-arrangement of the substituents at ring B of (−)-**20** does not reproduce the configuration of laurencenone D. For the reasons given in *Footnote 5*, the alternative *cis*-disposition X_{eq}–C(9)/X_{ax}–C(8) (X = Cl or Br) at ring B is then likely for laurencenone D. MM Calculations [7] indicate that, in accordance with the original experimental observations [5][7]), these two conformers have about the same

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[6]) Private communication *via* telephone of Dr. *D. J. Kennedy* [5] in spring 1990, when we first casted doubt on the validity of structure **7** for laurencenone D.

[7]) Originally, laurencenone D was described to exist in solution as two slowly equilibrating ring-B 'normal'-chair/inverted-chair forms, assigning a br. *dd* (*J* = 10 and 4 Hz) to H_{ax}–C(8) in the 'normal'-chair form, as depicted in **7**, and a br. *t* (*J* = 4 Hz) to H_{eq}–C(8) in the ring-B inverted-chair form [5].

weight independently from the relative positions of Br- and Cl-atoms. In contrast, for equatorial halogen atoms at ring B, as in structure **7** [5], a only negligible contribution by the ring-B inverted-chair conformation was calculated. No better evaluation of laurencenone D can be made since the observed relative populations of the conformers were not reported [5].

Recently, a confusing account on the structure of polyhalogenated α-chamigrenes appeared: a trihalogeno-α-chamigrene isolated from *Laurencia implicata* of the Great Barrier Reef was reported [12] to be identical to a compound previously isolated from *Laurencia sp.* of the Gulf of Mexico [13]. Actually, there is no such correspondence in either the depicted configuration or the NMR assignments, while neither chiroptical/mass data nor transformations to known compounds were reported for the Great-Barrier-Reef compound [12]. Therefore, the conclusion that this compound has *trans*-diaxial halogen atoms at C(8)/C(9) [12] is not warranted.

2.4. *MM Calculations with Polyhalogenated Chamigrenes.* In both our previous work on polyhalogenated β-chamigrenes [1] and the accompanying paper on α-chamigrenes that bear an equatorial substituent at C(8) [2], MM calculations [7] consistently reproduced the experimental data for observable conformers and could then be used to predict the behavior of non-observable conformers.

The case of α-chamigrenes bearing an axial halogen atom at C(8) is more complex. While MM calculations nicely fit the NMR data of both α-chamigrenones (+)-**8** and (+)-**15** and of the chamigrenol (+)-**12**, they fail in the case of chamigrenone (+)-**16** and α-chamigrenols (+)-**9**, (+)-**10**, (+)-**11**, and (+)-**13**. The latter are predicted to prefer the chair conformation with *trans*-diaxial halogen atoms at C(8) and C(9). However, agreement with the experimental data is obtained by adding 2 kcal mol^{-1} (see *Table 2*) to the calculated strain energy for all ring-B 'normal'-chair conformers that bear an axial halogen atom at C(8). In other words, our MM calculations [7] underestimate strain energies by 2 kcal mol^{-1} for these conformers. This is not surprising in view of the well known inaccuracies of *Allinger*'s force field, when the spatial orientation of vicinal polar bonds changes during the conformational process [7a] [14], as in the case of ring-B motions of chamigrenes. Ring-A motions of chamigrenes (see [1] and [2]) do not cause such problems. In any event, MM calculations, accounting for potential energy only, may be problematical when entropic terms become important in determining free energies, as in the case of (+)-**9**, (+)-**10**, (+)-**11**, (+)-**13**, and (+)-**16**.

2.5. *Bioactivity of Polyhalogenated Chamigrenes.* Polyhalogenated chamigrenes play an important ecological role in the sea, together with other metabolites of red seaweeds [15]. The bioactivity of polyhalogenated chamigrenes was related to the sense of chirality of their C-skeleton [10], relying on the observation that (+)-isoobtusol ((+)-**5**; isolated from *Laurencia obtusa* of the Canary Is. [16]) and (+)-elatol ((+)-**21**; isolated from *Laurencia elata* of New South Wales, Australia [17], or prepared by HBr elimination from (+)-**5** [18]) inhibit both gram-positive and gram-negative bacteria, and that (+)-**5** also displays cytostatic activity, albeit of modest level, while (+)-obtusol ((+)-**3**) has none of these bioactivities [19]. However, the extracts from various collections of *L. obtusa* of the Caribbean containing (−)-**21** inhibited the gram-positive bacterium *Bacillus subtilis* the more the higher was the concentration of (−)-**21** and displayed modest cytotoxicity toward cancerous CV-1 cells [20]. In the absence of quantitative data [10] [20], similar bioactivities for both enantiomers of elatol cast doubt on the existence of the suggested

simple relationship [10] between the bioactivity of polyhalogenated chamigranes and their sense of chirality. Results of biotests that are generally believed to be related to antineoplastic activity suggest that also other molecular features may determine the bioactivity of polyhalogenated chamigranes. Thus, both (−)-elatol and (6*S*)-elatone (the oxidation product of (−)-(6*S*)-elatol) inhibited the first cleavage of the fertilized eggs of the sea urchin *Strongylocentrotus purpuratus* as well as the incorporation of thymidine into DNA during this process, while the assembly of beef-brain microtubules was inhibited by (6*S*)-elatone only [21]. Clearly, the bioactivity of polyhalogenated chamigrenes warrants systematic investigation, and our conformational assessment will help rationalizing the area.

3. Conclusions. – This work has shown that chair-chair inversion of ring B of α-chamigranes to the so far rare inverted-chair conformation, such as in (−)-**6** [4], can also occur in the absence of bonding interactions, contrary to previous views [10]. The driving force to ring-B chair inversion lies mainly in repulsive interactions between Me–C(5) and an axial substituent at C(8), while in β-chamigrenes, repulsive interactions between CH_2=C(5) and the axial substituents at C(8) and C(10) can be minimized in the ring-B 'normal'-chair conformation, at least in all cases studied so far [1].

Flattening of ring A by a carbonyl group at C(3) makes repulsive interactions between Me–C(5) and the axial substituent at C(8) less serious, such as in enones (+)-**8** and (+)-**15**, but extra factors may invert the situation, such as is enone (+)-**16**, as discussed above. Another case is enone (−)-**6** [4], where the additional driving force toward the ring-B inverted-chair conformation may be ascribed to the presence of the sterically demanding Me_{ax}–C(9) in the 'normal'-chair conformation. The reason why, in contrast, (+)-**8** has a ring-B 'normal'-chair conformation must be that an axial Br-atom at C(9) is less space demanding than a Me group.

The conformational behavior of isoobtusol ((+)-**5**; see [1]) is now also clarified: a single conformer with CH_2=C(5) pointing away from Cl_{ax}–C(8) is present.

We thank Prof. *J. D. Martín* for a generous gift of isoobtusol, Mr. *A. Sterni* for recording the mass spectra, and M.U.R.S.T. (Progetti di Interesse Nazionale) and C.N.R., Roma, for financial support.

Experimental Part

General. See [2]. Moreover: NMR[1]): in $CDCl_3$, unless otherwise stated; δ (H) and *J* values (in Hz) from differential double irradiations; assignments confirmed by COSY 120 experiments [22] with (+)-**9** to (+)-**13**, (−)-**15**, (+)-**17**, and (+)-**20** and by ^{13}C,^1H-shift correlations [23] using inverse detection [24] for (+)-**9**, (+)-**10**, (+)-**13**, and (+)-**16**; differential NOE (obtained with 4-s preirradiation): irradiated proton→NOE on the observed proton(s). *ΔH* values in *Table 3* were calculated using the default dielectric constant (ε = 1.5). Steps of 2° were used in driving the torsion angle to evaluate the kinetic activation parameters (*Table 3*).

1. *(+)-(6S,8S,9S)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((+)-**8**). Isoobtusol [1] ((+)-**5**; 0.042 g, 0.10 mmol) was stirred in 3% KOH/MeOH (4 ml) at r.t. for 30 min. The mixture was then neutralized with dil. aq. HCl soln. and evaporated, the residue extracted with Et_2O, and the org. extract evaporated. FC of the residue gave (+)-**8** (0.038 g, 90%). Colorless oil. $[\alpha]_D^{20}$ = +99 (*c* = 0.41, cyclohexane). ^1H-NMR: 2.51 (*d*, *J* = 18.3, H_{ax}–C(2)); 2.01 (*d*, *J* = 18.0, H_{eq}–C(2)); 5.84 (*q*, *J* = 1.4, H–C(4)); 3.04 (*dd*, *J* = 15.3, 4.7, H_{ax}–C(7)); 1.98 (*dd*, *J* = 15.3, 4.9, H_{eq}–C(7)); 4.57 (*td*, *J* = 4.8, 1.2, H–C(8)); 1.95 (*m*, H_{ax}–C(10)); 2.25 (*m*, H_{eq}–C(10)); 1.79 (*dtd*, *J* = 15.1, 4.4, 1.2, H_{eq}–C(11)); 2.20 (*m*, H_{ax}–C(11)); 1.18 (*s*, Me_{eq}–C(1)); 1.00 (*s*, Me_{ax}–C(1)); 2.23 (*d*, *J* = 1.4, Me–C(5)); 1.96 (*s*, Me–C(9)); NOE: 1.18→3.04, 2.20. MS: 336, 334, 332 (0.4, 0.9, 0.1, $M^{+\cdot}$), 280, 278, 276 (12, 61, 44, $[M - C_4H_8]^{+\cdot}$), 199, 197 (34, 100, $[M_4-C_4H_8-Br]^+$), 161 (47), 151 (56), 91 (48).

2. *DIBAL Reduction of (+)-***8**. To (+)-**8** (0.040 g, 0.12 mmol) in dry THF (3 ml) was added 1.0M DIBAL in THF (120 µl). The mixture was stirred for 2 h at r.t. Then H_2O (3 ml) was added, the mixture concentrated and extracted with AcOEt, and the residue from evaporation of the org. layer subjected to HPLC (*Si-60*, hexane/i-PrOH 97:3): (+)-**9** (t_R 8.5 min; 0.013 g, 32%) and (+)-**10** (t_R 9.8 min; 0.013 g, 32%). Compound (+)-**9** (0.005 g) was treated with Ac_2O/dry pyridine 1:1 (1 ml) for 2 h at r.t., then with sat. aq. $CuSO_4$ soln. (1 ml) and then with Et_2O (10 ml). The mixture was percolated through a *Whatman* phase-separation filter, the filtrate evaporated, and the residue subjected to FC (*Si-60*, hexane/AcOEt gradient): (+)-**11** (0.005 mg, 89%).

*Data of (+)-(3*R,*6*S,*8*S,*9*S*)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-ol* ((+)-**9**). Colorless oil. $[\alpha]_D^{20} = +25$ ($c = 0.43$, CCl_4). ^{1}H-NMR: 1.61 (*m*, 2H–C(2)); 4.11 (br. *t*, $J = 7.5$, H–C(3)); 5.46 (*dq*, $J = 2.7$, 1.3, H–C(4)); 2.22 (*ddd*, $J = 15.2$, 4.9, 1.0, H_{eq}–C(7)); 1.85 (*dd*, $J = 15.2$, 11.5, H_{ax}–C(7)); 4.75 (*dd*, $J = 11.5$, 4.9, H–C(8)); 2.31 (*ddd*, $J = 15.0$, 6.9, 4.9, H_{eq}–C(10)); 2.49 (*ddd*, $J = 15.0$, 8.9, 5.4, H_{ax}–C(10)); 1.70 (*m*, 2H–C(11)); 1.17 (*s*, Me_{eq}–C(1)); 0.95 (*s*, Me_{ax}–C(1)); 1.79 (*t*, $J = 1.3$, Me–C(5)); 1.90 (*s*, Me–C(9)); NOE: 1.17→4.75, 2.49, 2.22; 0.95→4.11, 1.70; 4.75→2.22, 1.17. MS: 320, 318, 316 (0.4, 4.7, 2.4, $[M - H_2O]^{+\cdot}$), 282, 280, 278 (6, 23, 18), 254, 252, 250 (19, 75, 55), 201 (15), 135 (100).

*Data of (+)-(3*S,*6*S,*8*S,*9*S*)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-ol* ((+)-**10**). Colorless oil. $[\alpha]_D^{20} = +10$ ($c = 0.26$, CCl_4). ^{1}H-NMR: 1.55 (*dd*, $J = 13.6$, 7.2, H_{eq}–C(2)); 1.64 (*dd*, $J = 13.6$, 6.8, H_{ax}–C(2)); 4.11 (br. *t*, $J = 7.0$, H–C(3)); 5.48 (*dq*, $J = 2.6$, 1.3, H–C(4)); 2.22 (*ddd*, $J = 15.2$, 4.6, 1.4, H_{eq}–C(7)); 1.98 (*ddd*, $J = 15.2$, 11.2, H_{ax}–C(7)); 4.68 (*dd*, $J = 11.2$, 4.6, H–C(8)); 2.31 (*ddd*, $J = 14.7$, 5.2, 5.0, H_{eq}–C(10)); 2.55 (*ddd*, $J = 14.7$, 10.6, 5.7, H_{ax}–C(10)); 1.74 (*m*, 2H–C(11)); 1.13 (*s*, Me_{eq}–C(1)); 1.03 (*s*, Me_{ax}–C(1)); 1.82 (*t*, $J = 1.3$, Me–C(5)); 1.91 (*s*, Me–C(9)); NOE: 1.13→4.68, 2.55, 1.64; 1.03→4.11, 2.22. ^{1}H-NMR (C_6D_6): 1.36 (*dd*, $J = 14.3$, 7.4, H_{eq}–C(2)); 1.24 (*dd*, $J = 14.3$, 7.4, H_{ax}–C(2)); 3.79 (br. *t*, $J = 7.4$, H–C(3)); 5.27 (*m*, H–C(4)); 2.08 (*ddd*, $J = 15.2$, 4.6, 1.6, H_{eq}–C(7)); 1.78 (*ddd*, $J = 15.2$, 10.8, H_{ax}–C(7)); 4.64 (*dd*, $J = 10.8$, 4.6, H–C(8)); 1.97 (*ddd*, $J = 14.7$, 5.6, 5.6, H_{eq}–C(10)); 2.29 (*ddd*, $J = 14.7$, 10.8, 5.2, H_{ax}–C(10)); 1.32 (*ddd*, $J = 15.1$, 5.5, 5.5, H_{eq}–C(11)); 1.22 (*ddd*, $J = 15.1$, 10.8, 4.7, H_{ax}–C(11)); 0.79 (*s*, Me_{eq}–C(1)); 0.70 (*s*, Me_{ax}–C(1)); 1.49 (*t*, $J = 1.3$, Me–C(5)); 1.76 (*s*, Me–C(9)); NOE: 0.79→4.64, 2.29, 1.36; 0.70→3.79, 2.08; 4,64→0.79, 2.08, 1.36. MS: practically superimposable to that of (+)-**9**.

*Data of (+)-***11**. Colorless oil. $[\alpha]_D^{20} = +27$ ($c = 0.2$, CCl_4). ^{1}H-NMR: 1.61 (*m*, 2H–C(2)); 5.20 (*ddd*, $J = 9.1$, 7.0, 2.8, H–C(3)); 5.40 (*dq*, $J = 2.8$, 1.3, H–C(4)); 2.29 (*ddd*, $J = 15.2$, 4.8, 1.2, H_{eq}–C(7)); 1.88 (*dd*, $J = 15.2$, 11.0, H_{ax}–C(7)); 4.75 (*dd*, $J = 11.0$, 4.8, H–C(8)); 2.31 (*m*, H_{eq}–C(10)); 2.45 (*ddd*, $J = 15.0$, 9.0, 4.8, H_{ax}–C(10)); 1.70 (*m*, 2H–C(11)); 1.16 (*s*, Me_{eq}–C(1)); 0.99 (*s*, Me_{ax}–C(1)); 1.82 (*t*, $J = 1.3$, Me–C(5)); 1.90 (*s*, Me–C(9)); 2.03 (*s*, *Me*CO). ^{1}H-NMR (C_6D_6): 1.42 (*ddd*, $J = 13.5$, 7.0, 1.2, H_{eq}–C(2)); 1.53 (br. *dd*, $J = 13.5$, 8.9, H_{ax}–C(2)); 5.30 (*dddd*, $J = 8.9$, 7.0, 2.9, 1.2, H–C(3)); 5.48 (*dq*, $J = 2.9$, 1.3, H–C(4)); 2.16 (*ddd*, $J = 15.4$, 4.7, 1.2, H_{eq}–C(7)); 1.73 (*dd*, $J = 15.4$, 10.7, H_{ax}–C(7)); 4.67 (*dd*, $J = 10.7$, 4.7, H–C(8)); 1.90 (*ddd*, $J = 14.9$, 8.0, 4.4, H_{eq}–C(10)); 2.13 (*ddd*, $J = 14.9$, 9.1, 4.3, H_{ax}–C(10)); 1.32 (*ddd*, $J = 15.2$, 8.0, 4.4, H_{eq}–C(11)); 1.19 (*ddd*, $J = 15.2$, 9.2, 4.4, H_{ax}–C(11)); 0.77 (*s*, Me_{eq}–C(1)); 0.63 (*s*, Me_{ax}–C(1)); 1.43 (*t*, $J = 1.3$, Me–C(5)); 1.74 (*s*, Me–C(9)); 1.72 (*s*, MeCO); NOE: 0.77→4.67, 2.13, 1.42; 0.63→5.30, 1.32; 4.67→0.77, 2.13; 5.30→0.63, 1.42; 1.43→5.40, 1.90, 1.19. ^{1}H-NMR ($(CD_3)_2SO$): 1.65 (*m*, 2H–C(2)); 5.09 (br. *t*, $J = 7.5$, H–C(3)); 5.37 (*m*, H–C(4)); 2.19 (*dd*, $J = 15.3$, 4.6, H_{eq}–C(7)); 1.85 (*dd*, $J = 15.3$, 11.3, H_{ax}–C(7)); 4.77 (*dd*, $J = 11.3$, 4.6, H–C(8)); 2.50–2.20 (*m*, 2H–C(10), 2H–C(11)); 1.11 (*s*, Me_{eq}–C(1)); 0.96 (*s*, Me_{ax}–C(1)); 1.79 (br. *s*, Me–C(5)); 1.88 (*s*, Me–C(9)); 1.99 (*s*, MeCO). MS: 320, 318, 316 (21, 15, 10, $[M - AcOH]^{+\cdot}$), 282, 280, 278 (21, 100, 63), 254, 252, 250 (6, 24, 19), 201 (39), 185 (29), 157 (50), 145 (68).

2.1. Jones *Oxidation of (+)-***9**/*(+)-***10**. To a soln. of (+)-**9**/(+)-**10** 1:1 (0.005 g, 0.015 mmol) in acetone (2 ml) was added, by syringe, *Jones* reagent until persistency of the orange color (no (+)-**9**/(+)-**10** left). Then 5% aq. $NaHSO_3$ soln. (1 ml) was added and the mixture extracted with AcOEt (3 × 5 ml): (+)-**8** (0.0045 g, 90%; NMR analysis).

3. *Epoxidation of (+)-***9** *or (+)-***10**. To a soln. of (+)-**9** (0.005 g, 0.015 mmol) in dry CH_2Cl_2 (1 ml) were added 65% 3-chloroperbenzoic acid (6 mg) and $NaHCO_3$ (1 mol-equiv.) and stirred for 4 h at r.t. Excess 5% aq. $NaHCO_3$ soln. was added and the mixture percolated through a *Whatman* phase-separation filter. The filtrate was evaporated and the residue subjected to HPLC (*Si-60* hexane/i-PrOH 93:7): (+)-**12** (t_R 8.7 min; 0.004 g, 78%). By the same procedure, (+)-**10** gave (+)-**13** (t_R 11.9 min; 4 mg, 78%).

*Data of (+)-(1*S,*2*R,*3*R,*6*S,*8*S,*9*S*)-9-Bromo-8-chloro-1,2-epoxy-1,5,5,9-tetramethylspiro[5.5]undecan-3-ol* ((+)-**12**). Colorless oil. $[\alpha]_D^{20} = +32$ ($c = 0.2$, CCl_4). ^{1}H-NMR 1.37 (*ddd*, $J = 13.6$, 7.1, 1.2, H_{eq}–C(2)); 1.24 (*dd*, $J = 13.6$, 10.9, H_{ax}–C(2)); 4.00 (*dddd*, $J = 10.9$, 10.5, 7.1, 2.8, H–C(3)); 3.10 (*dd*, $J = 2.8$, 1.1, H–C(4)); 2.39 (*ddd*, $J = 15.5$, 4.1, 1.6, H_{eq}–C(7)); 2.49 (*dd*, $J = 15.5$, 4.3, H_{ax}–C(7)); 4.52 (*td*, $J = 4.2$, 1.6, H–C(8)); 2.01 (*ddd*, $J = 14.9$, 4.7, 3.6, H_{eq}–C(10)); 2.20 (*ddd*, $J = 14.9$, 12.4, 3.6, H_{ax}–C(10)); 1.68 (*dtd*, $J = 14.9$, 3.6, 1.6, H_{eq}–C(11));

1.96 (*ddd*, J = 14.9, 12.5, 4.7, H_{ax}–C(11)); 0.99 (*s*, Me_{eq}–C(1)); 0.87 (*s*, Me_{ax}–C(1)); 1.59 (*s*, Me–C(5)); 1.98 (*s*, Me–C(9)); 1.44 (*d*, J = 10.9, OH); NOE: 0.99→2.49, 2.39, 1.96; 0.87→4.00, 1.96; 1.59→3.10, 2.20. MS: 317, 315 (0.4, 0.4, $[M - Cl]^+$), 296, 294 (2, 2), 267, 265 (3, 3), 253, 251 (5, 5), 235 (8), 175 (47), 119 (30), 85 (41), 43 (100).

*Data of (+)-(1*R,*2*S,*3*S,*6*S,*8*S,*9*S*)-9-Bromo-8-chloro-1,2-epoxy-1,5,5,9-tetramethylspiro[5.5]undecan-3-ol* ((+)-**13**). Colorless oil. $[\alpha]_D^{20}$ = +16 (c = 0.15, CCl_4). ^{1}H-NMR: 1.26 (*dd*, J = 13.5, 6.0, H_{eq}–C(2)); 1.54 (*dd*, J = 13.5, 10.6, H_{ax}–C(2)); 4.00 (*dddd*, J = 10.6, 9.7, 6.0, 2.2, H–C(3)); 3.08 (*dd*, J = 2.2, 1.2, H–C(4)); 2.13 (*ddd*, J = 15.0, 4.5, 1.2, H_{eq}–C(7)); 2.02 (*dd*, J = 15.0, 12.8, H_{ax}–C(7)); 4.72 (*dd*, J = 12.8, 4.5, H–C(8)); 2.36 (*ddd*, J = 14.5, 4.3, 4.3, H_{eq}–C(10)); 2.65 (*ddd*, J = 14.5, 10.0, 8.9, H_{ax}–C(10)); 1.74 (*m*, 2H–C(11)); 1.11 (*s*, Me_{eq}–C(1)); 0.95 (*s*, Me_{ax}–C(1)); 1.31 (*s*, Me–C(5)); 1.90 (*s*, Me–C(9)); 1.41 (*d*, J = 9.7, OH). NOE: 1.11→4.72; 0.95→4.00, 2.13; 1.31→3.08, 2.02. MS: practically superimposable to that of (+)-**12**.

4. *(–)-(4*S,*6*R,*8*S,*9*S*)-4,9-Dibromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((+)-**15**) *and (+)-(4*R,*6*R,*8*S,*9*S*)-4,9-Dibromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((+)-**16**). Compound (–)-**14** [1] (0.010 g, 0.025 mmol) was heated in CCl_4 (1.5 ml) containing TsOH (0.002 g) at 55°, until complete disappearance (2 h). The mixture was filtered and the residue from evaporation of the org. phase subjected to HPLC (*Si-60*, hexane/i-PrOH 98:2): (+)-**15** (t_R 8.0 min; 0.004 g), (+)-**16** (t_R 9.2 min; 0.004 g).

*Data of (+)-***15**. Colorless oil. $[\alpha]_D^{20}$ = +48 (c = 0.14, CCl_4). ^{1}H-NMR: 4.93 (*s*, H–C(2)); 5.97 (*q*, J = 1.3, H–C(4)); 3.27 (*dd*, J = 15.0, 4.2, H_{ax}–C(7)); 2.06 (*dd*, J = 15.1, 3.0, H_{eq}–C(7)); 4.54 (*ddd*, J = 4.2, 3.3, 1.8 H–C(8)); 2.3–1.3 (*m*, 2H–C(10), 2H–C(11)); 1.39 (*s*, Me_{eq}–C(1)); 1.03 (*s*, Me_{ax}–C(1)); 2.30 (*d*, J = 1.3, Me–C(5)); 1.98 (*s*, Me–C(9)); NOE: 1.39→4.93, 3.27, 2.20. ^{1}H-NMR (C_6D_6): 4.55 (*s*, H–C(2)); 5.79 (*q*, J = 1.3, H–C(4)); 2.48 (*dd*, J = 15.3, 4.3, H_{ax}–C(7)); 1.31 (*ddd*, J = 15.1, 3.4, 1.9, H_{eq}–C(7)); 4.06 (*ddd*, J = 4.7, 3.7, 1.8, H–C(8)); 1.75–1.45 (*m*, 2H–C(10), H_{ax}–C(11)); 1.14 (*m*, H_{eq}–C(11)); 1.06 (*s*, Me_{eq}–C(1)); 0.77 (*s*, Me_{ax}–C(1)); 1.63 (*d*, J = 1.3, Me–C(5)); 1.68 (*s*, Me–C(9)); NOE: 1.06→4.54, 2.47; 4.54→1.31, 1.06. MS: 335, 333, 331 (5, 19, 15, $[M - Br]^+$), 280, 278, 276 (19, 77, 59, $[M - Br - C_4H_8]^+$), 199, 197 (33, 100), 161 (37).

*Data of (+)-***16**. Colorless oil. $[\alpha]_D^{20}$ = +71 (c = 0.18, CCl_4). ^{1}H-NMR (fast-exchange limit; r.t.): 4.63 (*s*, H–C(2)); 5.97 (*q*, J = 1.3, H–C(4)); 2.88 (br. *d*, J = 15.8, H_{eq}–C(7)); 2.30 (*dd*, J = 15.8, 9.1, H_{ax}–C(7)); 4.72 (*dd*, J = 9.1, 4.7, H–C(8)); 2.44 (*m*, H_{eq}–C(10)); 2.27 (*m*, H_{ax}–C(10)); 2.09 (*ddd*, J = 15.3, 8.2, 4.5, H_{eq}–C(10)); 1.71 (*ddd*, J = 15.3, 8.6, 4.5, H_{ax}–C(10)); 1.29 (br. *s*, Me_{eq}–C(1)); 1.28 (br. *s*, Me_{ax}–C(1)); 2.16 (br. *d*, J = 1.3, Me–C(5)); 1.94 (*s*, Me–C(9)). ^{1}H-NMR (fast-exchange limit; r.t., C_6D_6): 4.30 (*s*, H–C(2)); 5.66 (*q*, J = 1.3, H–C(4)); 2.44 (br. *d*, J = 15.4, H_{eq}–C(7)); 1.89 (*dd*, J = 15.4, 10.2, H_{ax}–C(7)); 4.49 (*dd*, J = 10.2, 4.7, H–C(8)); 1.69 (*ddd*, J = 14.9, 7.5, 4.5 H_{eq}–C(10)); 1.99 (*ddd*, J = 14.9, 9.7, 4.5, H_{ax}–C(10)); 1.20 (*m*, H_{eq}–C(11)); 0.77 (*m*, H_{ax}–C(10)); 0.72 (*s*, Me_{eq}–C(1)); 0.82 (*s*, Me_{ax}–C(1)); 1.26 (br. *d*, J = 1.3, Me–C(5)); 1.61 (*s*, Me–C(9)); NOE (r.t.): 0.72→4.49, 4.30, 1.99; 0.82→4.49, 2.44. ^{1}H-NMR (low-exchange limit; –70°, $CDCl_3$): Conformer *ICβ*-**16**: 5.18 (*s*, H–C(2)); 5.99 (*s*, H–C(4)); 2.35 (*m*, 2H–C(7)); 4.80 (*dd*, J = 10.9, 6.6, H–C(8)); 2.70 (*td*, J = 13.9, 4.2, H_{ax}–C(10)); 2.42 (br. *d*, J = 13.9, H_{eq}–C(10)); 1.90 (br. *d*, J = 14.7, H_{eq}–C(11)); 1.60 (*td*, J = 14.0, 3.5, H_{ax}–C(11)); 1.43 (br. *s*, Me_{eq}–C(1)); 1.06 (br. *s*, Me_{ax}–C(1)); 2.05 (br. *s*, Me–C(5)); 1.91 (*s*, Me–C(9)); conformer *Cα*-**16**: 4.22 (*s*, H_{ax}–C(2)); 5.99 (*s*, H–C(4)); 4.59 (*m*, $w_{1/2}$ = 10, H–C(8)); 1.43 (br. *s*, Me_{eq}–C(1)); 1.12 (br. *s*, Me_{ax}–C(1)); 2.32 (br. *s*, Me–C(5)); 1.95 (*s*, Me–C(9)). MS: practically superimposable to that of (–)-**15**.

5. *Treatment of (+)-***9** *with Acid.* Compound (+)-**9** (0.006 g, 0.018 mmol) in CCl_4 (0.5 ml) containing TsOH (0.001 g) was heated at +40° for 20 min, whereby all (+)-**9** disappeared (TLC). H_2O (0.5 ml) was then added the mixture filtered on a *Whatman* phase-separation filter, the filtrate evaporated, and the residue subjected to HPLC (*Si-60*, hexane/i-PrOH 99.5:0.5): *(+)-(6*S,*8*S,*9*S*)-9-bromo-8-chloro-5,5,9-trimethyl-1-methylidenespiro[5.5]-undec-2-ene* ((+)-**17**; t_R 6.0 min; 0.005 g, 78%). Colorless oil. $[\alpha]_D^{20}$ = +24 (c = 0.15, CCl_4). ^{1}H-NMR: 2.10 (*m*, 2H–C(2)); 5.58 (*dddd*, J = 9.8, 4.9, 2.7, 1.5, H–C(3)); 6.10 (*dt*, J = 9.8, 2.1, H–C(4)); 2.14 (br. *dd*, J = 15.1, 2.1, H_{eq}–C(7)); 1.97 (*m*, H_{ax}–C(7)); 4.46 (*td*, J = 4.0, 1.5, H–C(8)); 2.62 (*m*, H_{eq}–C(10)); 2.30 (*m*, H_{ax}–C(10)); 1.00 (*s*, Me_{eq}–C(1)); 0.75 (br. *s*, Me_{ax}–C(1)); 5.06 (*s*, 1H, CH_2=C(1)); 4.98 (*s*, 1H, CH_2=C(1)); 1.93 (*s*, Me–C(9)). MS: 320, 318, 316 (4, 14, 10, $M^{+\cdot}$), 305, 303, 301 (1, 2.5, 2 $[M - Me]^+$), 283, 281 (2, 2), 239, 237 (20, 57), 238, 236 (24, 48), 223, 221 (8, 19).

6. *(+)-(6*S*)-1,5,5,9-Tetramethylspiro[5.5]undeca-1,8-dien-3-one* ((+)-**18**). To a stirred soln. of (+)-**8** (0.030 g, 0.09 mmol) in Et_2O (2 ml) was added AcOH (2 ml) and activated Zn dust (0.2 g). Stirring was continued for 2 h, then the mixture filtered, diluted with 5% aq. $NaHCO_3$ soln. (1 ml), and extracted with hexane, and the residue from evaporation of the org. phase subjected to FC (hexane/AcOEt gradient): (+)-**18** (0.018 g, 92%). Colorless oil. $[\alpha]_D^{20}$ = +65 (c = 0.45, CCl_4). ^{1}H-NMR (C_6D_6): 2.73 (br. *d*, J = 18.5, H_{eq}–C(2)); 2.23 (*d*, J = 18.5, H_{ax}–C(2)); 6.02 (*q*, J = 1.2, H–C(4)); 2.17 (br. *d*, J = 14.1, H_{eq}–C(7)); 2.00 (*m*, H_{ax}–C(7)); 5.48 (*m*, H–C(8)); 1.90 (*m*, 2H–C(10)); 1.75 (*m*, 2H–C(11)); 1.03 (*s*, Me_{eq}–C(1)); 0.94 (*s*, Me_{ax}–C(1)); 2.00 (*d*, J = 1.2, Me–C(5)); 1.66 (*s*, Me–C(9)). MS: 218 (22, $M^{+\cdot}$), 203 (7, $[M - Me]^+$), 190 (11), 162 (15), 151 (100), 147 (76).

7. *(+)-(6S,8R,9S)-8-Acetoxy-9-hydroxy-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one (= (+)-(2R,3S,6S)-3-Hydroxy-3,7,11,11-tetramethyl-9-oxospiro[5.5]undec-7-en-2-yl Acetate; (−)-***20***). To a stirred soln. of (+)-**18** (0.010 g, 0.046 mmol) in dry pyridine (0.5 ml) at r.t. was added a molar excess of OsO_4 (0.016 g). The mixture was stirred for 4 h and then treated in turn with 5% aq. $NaHSO_3$ soln. (1.5 ml), sat. aq. $CuSO_4$ soln. (2 ml), and AcOEt (6 ml). The resulting mixture was percolated through a *Whatman* phase-separation filter and the filtrate evaporated: 0.008 g of **19**. ^{1}H-NMR ($CDCl_3$): 2.61 (br. *d*, J = 17.4, H_{ax}–C(2)); 5.84 (br. *s*, H–C(4)); 1.13 (*s*, Me_{eq}–C(1)); 0.96 (*s*, Me_{ax}–C(1)); 2.13 (*m*, Me–C(5)); 1.32 (*s*, Me–C(9)).

The NMR $CDCl_3$ soln. of **19** was evaporated and the residue treated with Ac_2O/dry pyridine 1:1 (1 ml) at r.t. for 6 h. Workup as described above for (+)-**11** gave (−)-**20** (0.007 g, 52% from (+)-**18**). Colorless oil. $[\alpha]_D^{20} = -15$ (c = 0.20, CCl_4). ^{1}H-NMR (low-exchange limit; −15°): **20a**: 2.59 (*d*, J = 18.1, H_{ax}–C(2)); 2.00 (*d*, J = 18.1, H_{eq}–C(2)); 5.84 (*q*, J = 1.3, H–C(4)); 2.19 (br. *dd*, J = 15.1, 5.8, H_{eq}–C(7)); 1.81 (*dd*, J = 15.1, 10.6, H_{ax}–C(7)); 5.09 (*dd*, J = 10.8, 5.8, H–C(8)); 2.40–1.50 (several *m*, 2H–C(10), 2H–C(11)); 1.09 (*s*, Me_{eq}–C(1)); 0.91 (br. *s*, Me_{ax}–C(1)); 2.25 (*d*, J = 1.3, Me–C(5)); 1.23 (*s*, Me–C(9)); 2.03 (*s*, MeCO); **20b**: 4.91 (*dd*, J = 12.2, 4.6, H–C(8)); 2.16 (*d*, J = 1.3, Me–C(5)). MS: 294 (2, $M^{+\cdot}$), 238 (3, $[M - C_4H_8]^{+\cdot}$), 234 (4, $[M - AcOH]^{+\cdot}$), 178 (100), 163 (28), 145 (27), 135 (25).

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