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

Cyclohexene-Ring Flipping and Rigid-Chair Cyclohexane Ring in the Presence of Equatorial Halogen Atoms at C(8) and C(9)[1][2])

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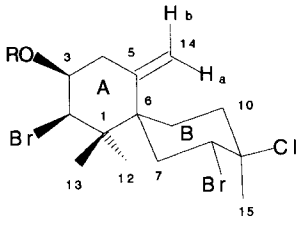
Temperature-dependent NMR spectra indicate that the α-chamigren-3-ones (−)-**11**, (+)-**12**, (+)-**14** (−)-**15**, (+)-**16**, **18**, and **19** bearing equatorial halogen atoms at C(8) and C(9) undergo slow conformational flipping of the envelope-shaped enone ring, while the cyclohexane ring is maintained in the chair conformation. The α-chamigren-3-ols (+)-**20** and (+)-**21**, obtained by hydride reduction of (+)-**12**, behave similarly, with slow half-chair inversion of the cyclohexenol ring. In each case, both conformers are about equally populated and detectable by NMR, except in the case of (+)-**15**, where repulsive interactions between Br–C(2) and H_{eq}–C(7) make the population of the conformer **15b** with Me–C(5) faced to H_{ax}–C(10) so low that it escapes direct ^{1}H-NMR detection. The energy barriers to these conformational motions are viewed to arise mainly from repulsive interactions between Me–C(5) and the axial H-atoms at C(8) and C(10), while, contrary to previous beliefs, no twist-boat conformations of the cyclohexane ring intervene. Similar conclusions hold for the 4,5-epoxides of both (−)-**6** and (+)-**7**. Clean *Jones* oxidation of (−)-**2** to **17**, where the CH_2=C(5) bond is maintained, and acid dehydration-isomerization of the α-chamigrene (+)-**21** to the β-chamigrene (+)-**24**, reflect the special stability of β-chamigrenes, providing a reason for their frequent occurrence in nature.

1. Introduction. – We recently reported on the conformational preferences and on the reactivity towards $Zn/Et_2O/AcOH$ of marine β-chamigrenes bearing equatorial halogen atoms at C(8) and C(9) besides, in certain cases, a further halogen atom at C(2). That work included rogiolol acetate ((+)-**1**), rogiolol ((−)-**2**), obtusol ((+)-**3**), and obtusol acetate ((−)-**4**) [1]. The energy barrier to these motions was attributed to mainly repulsive interactions between H_a–C(14) and the axial H-atoms at C(8) and C(10). We observed also that the conformer involving steric compression between Br–C(2) and H_{eq}–C(7) was thermodynamically so much disfavored to escape direct detection by NMR. The other large class of marine polyhalogenated chamigranes are the α-chamigrenes, with halogen atoms at the same positions as in the β-series [2]. The relevance and interest of compounds of both series are comparable with regard to *a*) marine pharmacology and ecology[3]), with bioactivities that seem to depend on the sense of chirality of the chamigrane C-skeleton [4], *b*) structure-reactivity relationships [1], *c*) the generally admitted

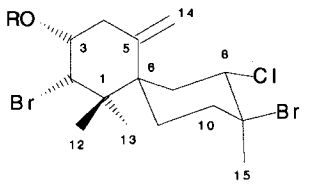
[1]) Presented in part by *G.G.* at both CISCI 90, S. Benedetto del Tronto, 30 September–5 October, 1990, and the Congresso Nazionale di Risonanze Magnetiche, Pisa, 22–24 October, 1990.

[2]) 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.*

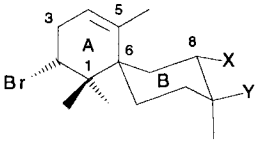
[3]) Many other compounds of red seaweeds are involved [3].



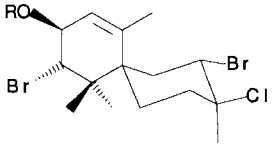
(+)-**1** R = Ac
(−)-**2** R = H



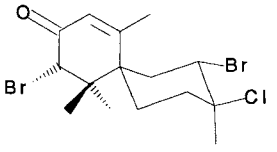
(+)-**3** R = H
(−)-**4** R = Ac



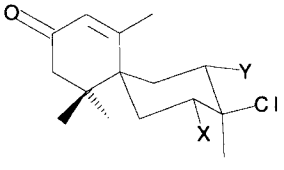
(−)-**5** X = Cl, Y = OH
(−)-**6** X = Br, Y = Cl



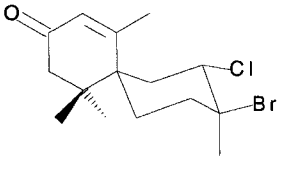
(+)-**7** R = H
(+)-**8** R = Ac



(−)-**9**



10 X = H, Y = Br
(−)-**11** X = Br, Y = H



(+)-**12**

(although not yet proven by biosynthetic experiments) central role of chamigrene precursors in the biogenesis of many sesquiterpene skeletons found in seaweeds of the genus *Laurencia* [2] [5], and *d*) a general interest in spirocyclic terpenes [4]. Since the bioactivity and the reactivity of chamigrenes are likely to depend largely onconformational factors, we deemed it interesting to investigate their conformational behavior.

In this paper, we study α-chamigrenes bearing equatorial halogen atoms at C(8) and C(9) and, in the accompanying paper, those having an axial substituent at C(8) [6]. Representative examples of the former were obtained by chemical transformations of the polyhalogenated β-chamigren-3-ols (+)-**1** to (−)-**4** [1] [9]. α-Chamigrenes of the first type for which the conformational behavior is already known include the α-chamigren-9-ol glanduliferol ((−)-**5**) and its 9-chloro analogue (−)-**6** [7] (isolated from *Laurencia glandulifera*), besides the α-chamigren-3-ol (+)-**7** (isolated from *Laurencia nipponica* collected at Hamamasu and other locations in Japan [7]), its acetate (+)-**8** [7], the α-chamigren-3-one (−)-**9** [7], and laurencenone D [8] (**10**; isolated from *Laurencia obtusa* collections of Jamaica). The structure of laurencenone D [8] (**10**) needs a revision, however [9]: probably it belongs to the above mentioned second type of α-chamigrenes [6].

^{1}H-NMR J data [7] indicate that in β-chamigrenes [1], ring A is a nearly perfect chair while in α-chamigrenes [7], it takes preferentially a distorted half-chair conformation, like in simple cyclohexenes [2]. Moreover, the preferred conformation of ring B in α-chamigrenes seemed to depend on the spatial position of the substituents at C(8) and C(9) [7]. Thus, twist-boat conformations of ring B were proposed for glanduliferol ((−)-**5**) and (−)-**6** to (−)-**9**, based on the similarity of $J(8,7\alpha)$ and $J(8,7\beta)$ at room temperature [7a]. In line with this, the coupling constants $J(8,7) = 11$ and 7 Hz for (−)-**9** at −30°, and the broadening of many signals at room temperature, were implicitly interpreted in terms of slowly equilibrating twist-boat conformations of ring B [7b]. However, this contrasts with ring B adopting an only slightly deformed chair in crystalline enone (−)-**9** [7b], and in the naturally occurring epoxide[4]) of (−)-**6** where the Br- and O-atoms are *cis*-related [10], as shown by X-ray diffraction analysis.

2. Results and Discussion. – 2.1. *α-Chamigren-3-ones.* Enone (−)-**11** was obtained from the dehydrobromination of rogiolol ((−)-**2**) in 3% KOH/MeOH [9]. Similarly, enone (+)-**12** was prepared from obtusol ((+)-**3**; see *Exper. Part*). The ^{13}C-NMR (*Table 1*), MS, and ^{1}H-NMR data (see *Exper. Part*) fully support structure (+)-**12**.

Table 1. *^{13}C-NMR Data* ($CDCl_3$) *for Some α-Chamigren-3-ones and α-Chamigren-3-ols Bearing Equatorial Halogen Atoms at C(8) and C(9)*

	12a	**12b**	(−)-**15**	(+)-**16**	(+)-**20**	(+)-**21**
C(1)	41.87 (*s*)	42.25 (*s*)	not det.	not det.	not det.	37.87 (*s*)
C(2)	48.69 (*t*)	48.50 (*t*)	65.78 (br. *d*)	67.24 (br. *d*)	42.56 (*t*)	42.61 (*t*)
C(3)	197.64 (*s*)	197.53 (*s*)	not det.	not det.	65.20 (*d*)	67.69 (*s*)
C(4)	127.89 (*t*)	128.32 (*d*)	126.57 (br. *d*)	126.99 (br. *d*)	126.70 (*d*)	126.84 (*d*)
C(5)	167.24 (*s*)	167.10 (*s*)	166.62 (br. *s*)	not det.	not det.	143.18 (*s*)
C(6)	47.17 (*s*)	46.63 (*s*)	not det.	not det.	not det.	44.59 (*s*)
C(7)	35.88 (*t*)	35.75 (*t*)	37.29 (br. *t*)	41.44 (br. *t*)	38.66 (*t*)	36.62 (*t*)
C(8)	68.87 (*d*)	67.73 (*d*)	68.37 (*d*)	65.75 (*d*)	69.63 (*d*)	68.42 (*d*)
C(9)	66.78 (*s*)	66.98 (*s*)	65.91 (*s*)	66.12 (*s*)	not det.	69.30 (*s*)
C(10)	41.65 (*t*)	42.47 (*t*)	41.44 (br. *t*)	42.30 (br. *t*)	42.36 (*t*)	42.05 (*t*)
C(11)	31.69 (*t*)	31.69 (*t*)	31.06 (br. *t*)	29.15 (br. *t*)	25.33 (*t*)	25.18 (*t*)
C(12)	24.73 (*q*)	24.07 (*q*)	24.61 (*q*)	24.65 (*q*)	25.32 (*q*)	24.66 (*q*)
C(13)	23.73 (*q*)	23.25 (*q*)	18.76 (*q*)	18.73 (*q*)	19.26 (*q*)	23.74 (*q*)
C(14)	26.70 (*q*)	26.31 (*q*)	26.62 (*q*)	26.22 (*q*)	26.02 (*q*)	26.08 (*q*)
C(15)	23.79 (*q*)	23.79 (*q*)	23.69 (*q*)	23.42 (*q*)	23.88 (*q*)	23.63 (*q*)

High-field ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) at room temperature showed for (−)-**11** [9] and (+)-**12** broad resonances of two conformers in a *ca.* 3:2 population ratio (see *Exper. Part*); cooling to −30° resulted in sharpening of the signals, H−C(8) showing up as a *dd* with coupling constants (see [9] and *Table 2*) typical for an only slightly distorted axial position at the cyclohexane ring. The dynamic process was monitored using this *dd* and, in the case of (+)-**12**, also using several ^{13}C-NMR signals, under full decoupling. The experimental and DNMR5-calculated [11] line shapes[5]) (*Fig.*) and the kinetic data (*Table 3*) can be rationalized in terms of interconverting envelope conformers [12] of ring A, while ring B remains a distorted chair (see **11a**⇄**11b** and **12a**⇄**12b** in *Scheme 1*).

[4]) It is shown below that α-chamigrenes and their 4,5-epoxides behave conformationally much the same.

[5]) This is a correct procedure while the method of coalescence, being applicable to *s* only, may lead to serious errors [11b].

Table 2. *^{1}H-NMR Data* (low-exchange limit; $CDCl_3$) *for the H–C(8)* dd *of Some α-Chamigren-3-ones and α-Chamigren-3-ols Bearing Equatorial Halogen Atoms at C(8) and C(9)*[a])

	δ	Obs. J	Calc. J[b])	T [°]
11a	4.87	13.0, 5.5	13.5, 4.4	−15
11b	4.53	13.2, 4.3	13.5, 3.6	
12a	4.85	12.6, 5.7	12.4, 4.1	−35
12b	4.49	13.0, 4.2	12.8, 3.4	
14a	4.88	12.6, 5.6	12.4, 4.1	−10
14b	4.47	13.0, 4.5	12.9, 3.1	
15a	4.84	12.2, 5.7	12.5, 3.9	−20
15b	4.55	/	12.6, 3.8	
16a	4.83	12.7, 6.8	12.4, 4.1	−50
16b	4.53	13.1, 4.6	12.8, 3.1	
20a	4.87	11.6, 5.8	12.3, 4.2	−65
20b	4.57	13.2, 4.5	12.5, 3.9	
21a	4.87	12.4, 5.7	12.3, 4.2	−65
21b	4.67	12.6, 4.8	12.5, 3.8	
24a	4.81	12.5, 5.2	12.1, 4.7	−30
24b	4.34	12.8, 4.7	12.9, 3.0	

[a]) Note that the closer the J values are to each other for a given conformer, the more flattened is the ring at C(8), *i.e.* the more deviates H–C(8) from the cyclohexane axial position.

[b]) Calculated by a modified *Karplus* equation [13c]; the relative torsional angles are evaluated from MM2-minimized structures [13b].

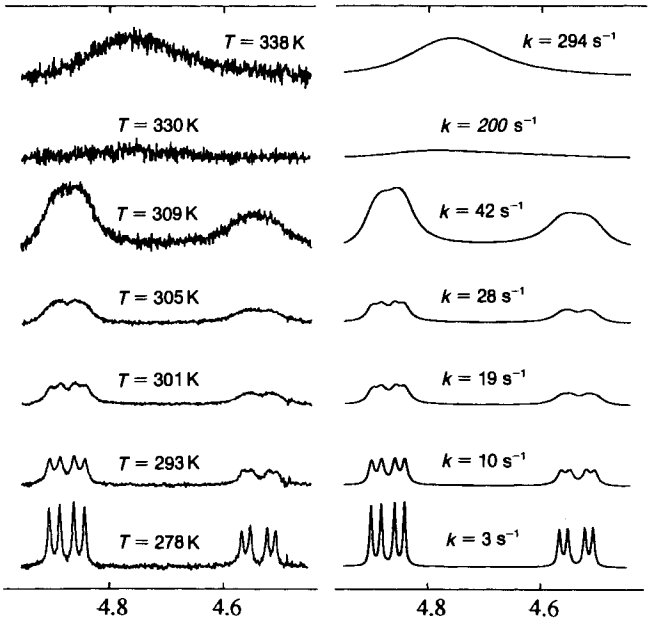


Figure. *Experimental* (left) *and DNMR5-computed* (right) *line shape of the* H–*C(8) signal of conformers* **12a** *and* **12b**

Table 3. *Experimental Thermodynamic and Kinetic Parameters for Ring-A Flipping of Various α-Chamigrenes Bearing Equatorial Halogen Atoms at C(8) and C(9)*[a])

	x_a/x_b[b])	$\Delta H^{\neq}$ [kcal/mol][c])	$\Delta S^{\neq}$ [cal/molK][c])	$\Delta G^{\neq}$ [kcal/mol][c])
(−)-**11**	62:38	14.0 ± 0.2	−6.5 ± 1	15.9 ± 0.2
(+)-**12**	62:38	14.0 ± 0.4	−6.0 ± 2	15.8 ± 0.2
(+)-**14**	65:35	11.1 ± 0.5	−16.1 ± 2	15.9 ± 0.2
(−)-**15**	92:8	–	–	15.9[d]) ± 0.2
(+)-**16**	12:88	–	–	15.9[d]) ± 0.2
(+)-**20**	80:20	8.7 ± 0.4	−16.2 ± 1	13.5 ± 0.2
(+)-**21**	32:68	8.9 ± 0.2	−11.8 ± 1	12.5 ± 0.2

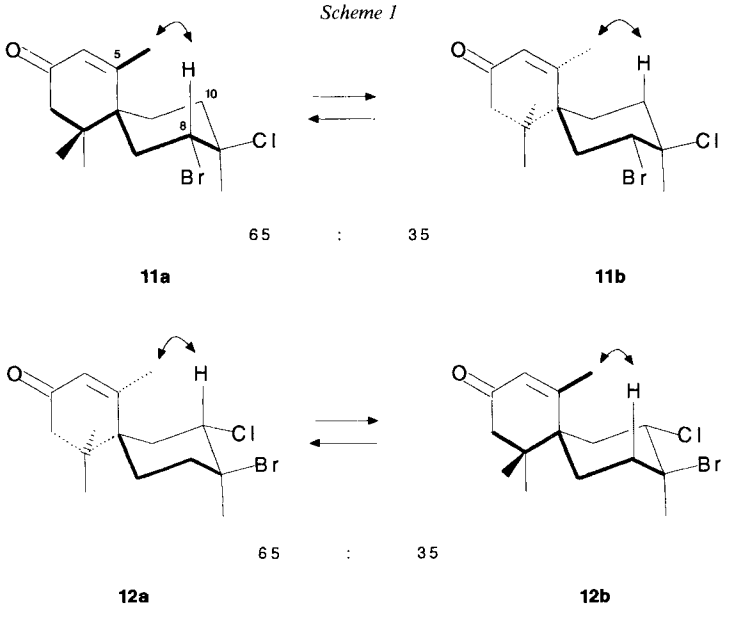
[a]) Statistical relative errors are indicated for $\Delta H^{\neq}$ and $\Delta S^{\neq}$, whereas errors in temperature and rate constants are reflected in the errors indicated for $\Delta G^{\neq}$.

[b]) Determined by either NMR-signal integration, when feasible, or $\Delta\delta$ at the fast-exchange limit.

[c]) Determined by least-square analysis of the DNMR5-derived kinetic data on the basis of the *Eyring* equation with transmission coefficient values of 1.

[d]) Determined by visual best fitting of the *H*–C(8) *dd* at −30° (slow-exchange limit).

Scheme 1



That the kinetic barrier arises mainly from repulsive interactions among Me–C(5), H_{ax}–C(8), and H_{ax}–C(10), is suggested by molecular mechanics (MM) calculations [13], which nicely reproduce the experimental population ratio x_a/x_b of the two conformers and give an estimate of the kinetic barrier (*Table 4*)[6]). The NMR data also suggest that

[6]) As in the case of the polyhalogenated β-chamigrenes (+)-**9** and (+)-**10** [1], these calculations could be directly carried out through the C(5)–C(6)–C(1)–C(13) dihedral-angle driver option [13b]; both the thermodynamic and the kinetic parameters were calculated from strain energies. Contrary to the β-chamigrenes, where flipping of ring A involves twist-boat intermediates [1], the calculations with α-chamigrenes indicate a single transition state in the interconversion between the two half-chair forms of ring A.

Table 4. *MM Calculations of Thermodynamic and Kinetic Parameters* (kcal/mol) *for Ring-A Flipping of Various α-Chamigrenes Bearing Equatorial Halogen Atoms at C(8) and C(9)*

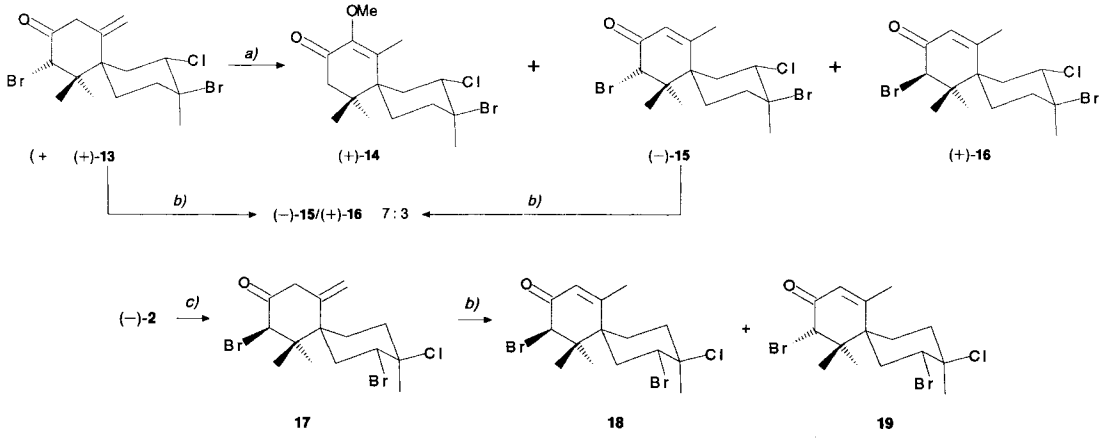
	ΔH^{a})	$x_a/x_b{}^{b}$)	$\Delta H_{ab}^{\neq c}$)	$\Delta H_{ba}^{\neq d}$)	$\Delta H^{\neq e}$)
(−)-**11**	0.17	58:42	12.84	12.67	12.7
(+)-**12**	0.17	58:42	12.84	12.67	12.7
(+)-**14**	0.17	58:42	11.69	11.42	11.5
(−)-**15**	1.14	87:13	13.33	12.19	12.4
(+)-**16**	0.70	23:77	12.24	12.94	12.4
18	1.13	87:13	13.29	12.20	12.4
19	0.70	77:23	12.96	12.26	12.4
(+)-**20**	0.54	72:28	9.31	8.77	8.9
(+)-**21**	0.36	35:65	8.81	9.17	8.9
(+)-**24**	0.10	55:45	11.23	11.13	11.2

[a]) Difference of strain energies between the **b** and **a** form.
[b]) Population ratio for the **a** and **b** ground states (x = molar fraction).
[c]) Difference of strain energies between the highest transition state and the ground state **a**.
[d]) Difference of strain energies between the highest transition state and the ground state **b**.
[e]) Calculated from $\Delta H^{\neq} = 1/2\,[\Delta H_{ab}^{\neq} + \Delta H_{ba}^{\neq} - (x_a - x_b)\,\Delta H]$.

distortion of H–C(8) from the axial position is more pronounced when H–C(8) is in close contact with Me–C(5) (ΔJ smaller than when H–C(8) is farther from Me–C(5), see *Table 2*). In agreement, the opposite is suggested for H–C(10) (see J values in *Exper. Part*).

Our observation of a distorted chair for ring B of enones (−)-**11** and (+)-**12** disagrees with *Suzuki*'s assumption of a twist-boat for ring B of enone (−)-**9** [7b]. To check if the lack of a Br-atom at C(2) in (−)-**11** and (+)-**12** is responsible for the different conformational behavior, we studied compound (−)-**15**. The latter was obtained in a mixture with, and was separated from (+)-**14** and (+)-**16** by treatment of (+)-**13** [1] with oxalic acid in

Scheme 2

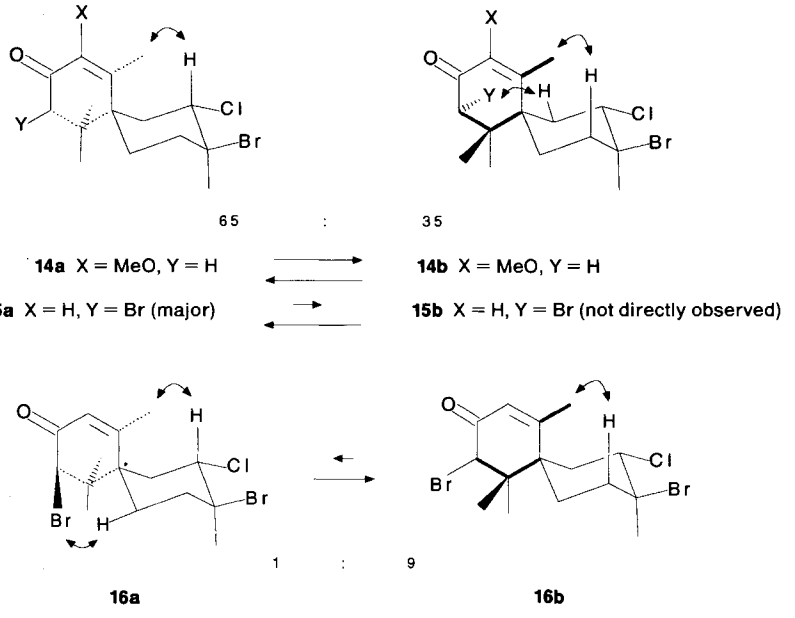


a) 5% $(COOH)_2$, MeOH, reflux, 10 h; 55% overall yield. *b*) TsOH, CCl_4, 55°, 2 h; 80% overall yield. *c*) *Jones* reagent, Me_2CO, r.t.; 75% yield.

MeOH (*Scheme 2*). Using TsOH in CCl_4, only the epimers (−)-**15**/(+)-**16** were formed from (+)-**13**. The same 7:3 mixture (−)-**15**/(+)−**16** was obtained from pure (−)-**15**; *i.e.* epimerization did not occur in the starting enone (+)-**13**. Along a similar procedure, enone **17** (obtained from *Jones* oxidation of (−)-**2**) gave the epimer mixture **18**/**19** which was separated by HPLC (*Scheme 2*). It should be noticed that compound **18** is enantiomeric to *Suzuki*'s α-chamigrenone (−)-**9**[7]). The structures of all these compounds are supported by ^{1}H-NMR and MS data (see *Exper. Part*).

A ^{1}H-NMR study at various temperatures and NOE investigations (see *Exper. Part*) of (−)-**15** revealed, at the slow-exchange limit, the presence of only one conformer **15a** (with *H*−C(8) showing up as a *dd* with coupling constants typical for an only slightly distorted axial position; see *Table 2* and *Scheme 3*). The other conformer, **15b**, must be

Scheme 3



scarcely populated, although not to a negligible extent, in order to account for broadening of the NMR lines of **15a**. The much lower population of conformer **15b** and, therefore, the much larger line broadening of its ^{1}H-NMR signals, as compared to **15a**, prevents direct detection of **15b** by NMR. This phenomenon was already observed for the β-chamigrenols rogiolol ((−)-**2**), obtusol ((+)-**3**), and their acetates [9]. Like in the case of (−)-**2**, the minor conformer **15b** was revealed by ^{1}H-NMR experiments of saturation transfer on H−C(8) at −10° [1], H−C(8) of **15b** lying 85 Hz upfield H−C(8) of the major

[7]) The low specific rotation of (−)-**9** [7] and the small amount of product in our hands prevented recording the optical rotation of **18**.

conformer **15a** (see *Exper. Part*)[8]). This is just what is expected from the presence of the sterically hindering Br-atom at C(2) in the minor conformer **15b** [1] (*Scheme 3*).

In agreement with the above observations, compound (+)-**14**, lacking a bulky substituent at C(2), showed up as two about equally populated conformers **14a** and **14b** (*Scheme 3*). The MM-calculated population ratio was 65:35, **14a** being the dominant conformer. At the low exchange limit, the ^{1}H-NMR signal of H–C(8) was that of a perfectly axial proton for **14b** and that of a slightly distorted axial proton for **14a** (*Table 2*). Also in line with the above observations is that the predominant conformer **16b** has Me–C(5) close to H_{ax}–C(10) (*Scheme 3*). Similar dynamic ^{1}H-NMR studies for enones **18** and **19** revealed that **18** behaves like (–)-**15**, and **19** like (+)-**16**. DNMR5-Analyzed line shapes of the H–C(8) resonance for (+)-**14**, (–)-**15**, and (+)-**16** (*Table 3*) are in good agreement with the results of MM calculations (*Table 4*).

The above results show that the interpretation by *Suzuki et al.* [7b] of the dynamic ^{1}H-NMR of (–)-**9** in terms of interconverting twist-boat conformations of ring B is untenable. It is likely that under *Suzuki*'s conditions of low-frequency (100 MHz) ^{1}H-NMR observations of (–)-**9** at room temperature, ring-A flipping gives rise to two conformers in conditions close to coalescence. At any event, the reported values $J(8,7) = 11$ and 7 Hz for (–)-**9** at –30° [7b] do not differ enough from our data for **18** (enantiomer of (–)-**9**) and (–)-**15** (very similar positional isomer of (–)-**9**) to warrant invoking twist-boat conformations of ring B (see *Table 2*). Using MM, we calculated that the twist-boat conformations proposed for ring B of (–)-**9**, with torsional angles H_{ax}–C(7)–C(8)–$H_{ax} = 140°$ and H_{eq}–C(7)–C(8)–$H_{ax} = 0°$ [7], have prohibitively high strain energies. We similarly calculated that even less strained conformations of (–)-**9**, with ring B as a twist-boat, where the above torsional angles take the values 170 and 56°, respectively, have at least 3.5 kcal/mol higher strain energy than conformers with ring B as a slightly distorted chair. Thus, ring-B twist-boat conformations for **18**, (–)-**15**, and (–)-**9** are ruled out.

2.2. *α-Chamigren-3-ols.* Polyhalogenated α-chamigren-3-ols are characteristic products of seaweeds of the genus *Laurencia* [2], like the above enones from which they are obtained by hydride reduction. Thus, diisobutylaluminium hydride (DIBAL) reduction of chamigrenone (+)-**12** gave a mixture of epimeric chamigrenols (+)-**20** and (+)-**21** which was separated by HPLC[9]) (*Scheme 4*). The ^{13}C-NMR (*Table 1*), MS, and ^{1}H-NMR data (see *Exper. Part*) fully support the structures of these compounds.

The ^{1}H-NMR spectra of chamigrenols (+)-**20** and (+)-**21** proved to be temperature-dependent, with coalescence temperatures –10° and –25° for the H–C(8) signal, respectively. In the case of (+)-**20**, at the low-exchange limit, two conformers, **20a** and **20b**, were observed, in a population ratio of 8:2 (*Scheme 4*), both H–C(8) and H–C(10) showing up as axial protons (*Table 2* and *Exper. Part*). It should be noticed that the OH group is pseudoequatorial in the major conformer **20a** and pseudoaxial in the minor conformer **20b**. At the fast-exchange limit, bot H–C(8) and H–C(10) of (+)-**20** showed up as only slightly distorted axial protons (see *Exper. Part*). These data suggest that (+)-**20** under-

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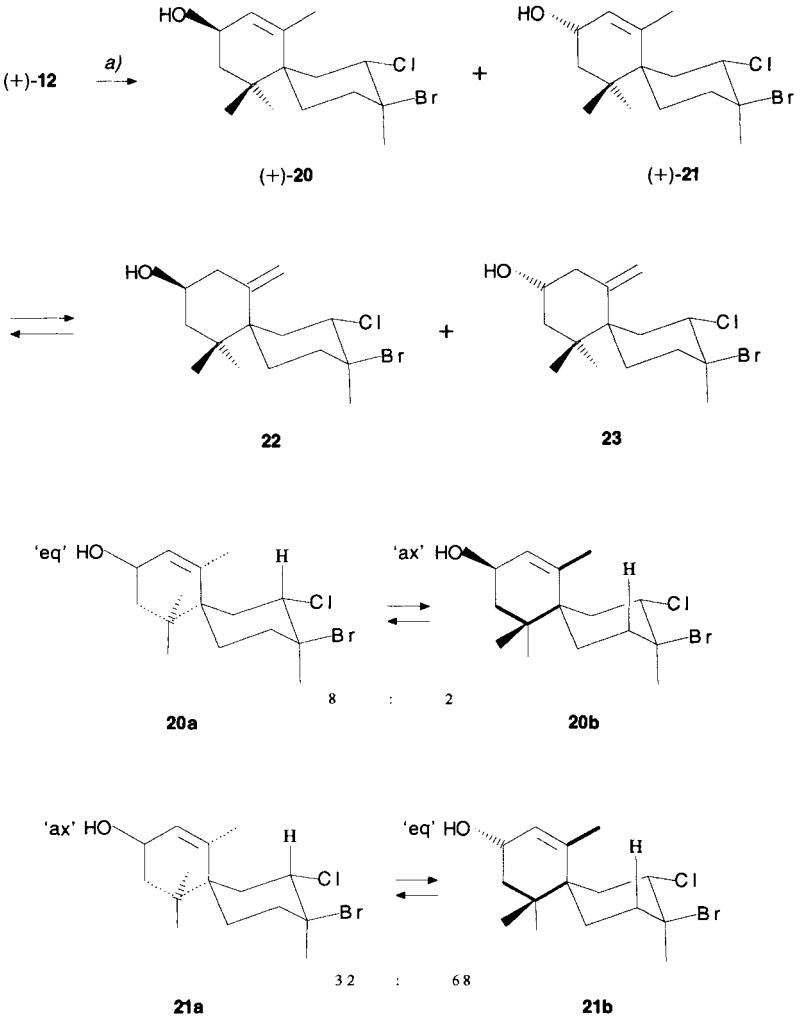
[8]) Further support for the occurrence of conformational phenomena was provided by the ^{13}C-NMR spectra of enone (–)-**15** where several signals were broad (*Table 1*).

[9]) On elution of (+)-**20**/(+)-**21** from a silica-gel column (HPLC), some isomerization to the corresponding β-chamigrenes **22** and **23** was observed (*Scheme 4*).

Scheme 4

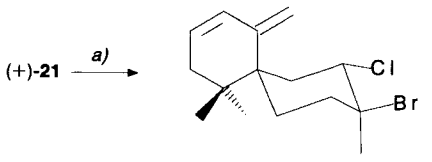


a) DIBAL, THF, r.t., 2 h; 64% yield.

goes, at the low-exchange limit, low-amplitude slow flipping of ring A, with Me–C(5) exploring a narrow area between H_{ax}–C(8) and H_{ax}–C(10) (see *Scheme 4* and *Table 3*). The data of *Table 2* and the *Exper. Part* suggest a similar situation for (+)-**21** (see *Scheme 4* and *Table 3*). Like for the above α-chamigrenones, MM calculations nicely reproduce the experimental findings for both (+)-**20** and (+)-**21** (*Table 4*).

In acids, chamigrenol (+)-**21** underwent a clean dehydration-rearrangement to diene (+)-**24** (*Scheme 5*), while **22** was recovered unchanged after exposure to acid. A dynamic ^{1}H-NMR study showed that (+)-**24** exists at room temperature as two conformers in a *ca.* 1:1 ratio, which result from the flipping of ring A, as expected for a β-chamigrene [1].

Scheme 5

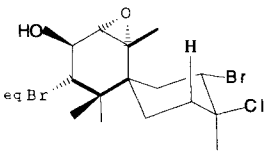


a) TsOH, $CDCl_3$, 40°, 10 min; 80% yield. (+)-**24**

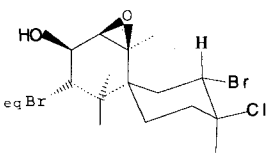
2. Conclusions. – This work has shown that conformational motions of α-chamigren-3-ones or -3-ols bearing *trans*-diequatorial halogen atoms at C(8) and C(9) and, or not, a further halogen atom at C(2) do not involve twist-boat conformations of ring B, which is contrary to current beliefs [2b] [7].

Our study allows to draw a number of other generalizations concerning the conformational behavior of α-chamigrenes: *a*) the population ratio of conformers depends primarily on the spatial position (pseudoequatorial *vs.* pseudoaxial) of the substituents at the two available positions of ring A (C(2) and C(3)), with predominance of the pseudoequatorially substituted conformer, particularly if this involves Me–C(5) being closer to H_{ax}–C(8) than to H_{ax}–C(10); *b*) ΔG^{+} for conformer interconversion is higher for α-chamigren-3-ones (15.8–16.0) than for α-chamigren-3-ols (12.3–13.0 kcal mol^{-1}), in line with what was observed for cyclohexane systems [13]; *c*) flipping of ring A induces solvent-independent ^{1}H-NMR shifts of 0.3–0.4 ppm for both H_{ax}–C(8) ($\delta(CDCl_3)$ 4.9–4.5) and H_{ax}–C(10) ($\delta(CDCl_3)$ 2.8–2.4) in the same conformer, the shift being downfield for H_{ax}–C(8) close to Me–C(5) and upfield for H_{ax}–C(10)[10]; *d*) resonances close to these limiting values indicate predominance of one conformer, while intermediate values indicate fast chemical exchange between about equally populated conformers; *e*) at the fast-chemical-exchange limit, distortion from the axial position of the protons at C(8) and C(10) is more marked than at the low-exchange limit; *f*) *Allinger*'s force field [13b] is a valid tool for the conformational analysis of polyhalogenated α-chamigrenes, the equi-

[10]) The same holds for 4,5-epoxides. Thus, in the case of epoxide (+)-**25**, which is structurally related to (+)-**7** and where, to maintain the Br-atom at C(2) in the equatorial position, Me–C(5) must be pushed away from H–C(8), the latter proton resonates at δ 4.78 (J = 13.1, 5.3), whereas in the case of the diastereoisomeric **26**, where, for the same reasons, Me–C(5) must point toward H–C(8), the latter proton resonates at δ 4.88 (J = 12.7, 5.6) [14]. Similar conclusions can be drawn for the epoxides of (–)-**6**: H–C(8) resonates at δ 4.77 (J = 12, 5) for the natural epoxide with *cis*-related Br-atom and epoxide group (Me–C(5) pointing away from H–C(8)) [15a] or at δ 4.88 (J = 11, 7) for the semisynthetic [15a] or natural [15b] diastereoisomer with *trans*-related Br-atom and epoxide group (Me–C(5) pointing toward H–C(8)). The latter is also the conformation in the crystalline state, as deduced from X-ray diffraction analyses [10].



(+)-**25**



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librium constant evaluated from the difference in strain energy between two conformers being in good agreement with the experimental value obtained from the integration of NMR signals, as expected for enthalpy-driven processes[11]).

The acid dehydration-isomerization of α-chamigrene (+)-**21** to give exclusively 3,4-didehydro-β-chamigrene (+)-**24** (no 2,3-didehydro-α-chamigrene which should be favored by the more substituted C=C bonds) is peculiar. We suggest that this reflects the stability of β- *vs.* α-chamigrenes. This is in line with our previous notice that polyhalogenated β-chamigrenes resist shift of the olefinic bond from the exocyclic to the endocyclic position under acidic conditions [1], unless α,β-conjugation occurs (see, *e.g.*, *Scheme 2*). This view is further supported by the partial isomerization of the α-chamigren-3-ols (+)-**20** and (+)-**21** to the corresponding β-chamigren-3-ols **22** and **23** on HPLC elution (see *Scheme 4*) where the particular chromatographic support must have been the catalyst (*cf. Exper. Part*). Resistance of β-chamigrene **22** to isomerize in acid media is in line with this rationalization. In accordance with the above conformational analysis of α-chamigrenes, the isomerization of (+)-**21** to (+)-**24**, which is against the rule of higher stability for the more highly substituted C=C bond, is driven by the relieve of repulsive interactions of the axial atoms at C(8) and C(9) with Me–C(5) in the α-chamigrene. If these observations are general, as further impressive examples in the accompanying paper [6] would suggest, it becomes clear why β-chamigrenes are so frequent in nature.

We thank Prof. *J. D. Martin* for a generous gift of obtusol, 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

1. *General.* See [1]. Moreover: ^{1}H-NMR: for (+)-**12**, (–)-**15**, and (+)-**20**, the assignments were confirmed by COSY 120 experiments [16] and ^{13}C,^{1}H shift correlations [17]. Differential NOE (obtained with 4-s-preirradiation): irradiated proton→NOE on the observed proton(s). Saturation transfer effects were obtained with the same pulse sequence as NOE (decoupler power optimized at $\gamma H_2 = 11$ Hz for the irradition of H–C(8) of (–)-**15** and (+)-**16**); the probe was calibrated as before (see [1]). EI-MS (*m/z*, %): *Kratos MS80* with home-built computerized acquisition system. Molecular mechanics calculations were performed by means of *Allinger*'s program [13b]. ΔH values (*Table 4*) were calculated using the default dielectric constant ($\varepsilon = 1.5$). Steps of 2° were used in driving the torsion angle to evaluate the kinetic activation parameters (*Table 4*). For the NMR line-shape simulation (*Fig.*), see [1].

2. *(+)-(6R,8S,9S)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((+)-**12**). Obtusol [1] ((+)-**3**; 0.050 g, 0.12 mmol) was stirred in 4 ml of 3% KOH/MeOH at r.t. for 24 h. The mixture was then neutralized with dil. aq. HCl soln. and evaporated. The residue was extracted with Et_2O. Evaporation of the extract and FC of the residue gave (+)-**12** (0.038 g, 95%). Colorless oil. $[\alpha]_D^{20} = +34.1$ ($c = 1.08$, cyclohexane). ^{1}H-NMR (low-exchange limit, –20°): **12a**: 2.51 (*d*, $J = 18.0$, H_{ax}–C(2)); 2.02 (*d*, $J = 18.0$, H_{eq}–C(2)); 5.86 (br. *s*, H–C(4)); 2.14 (*dd*, $J = 15.0$, 5.9, H_{eq}–C(7)); 1.99 (*dd*, $J = 15.0$, 12.6, H_{ax}–C(7)); 4.85 (*dd*, $J = 12.6$, 5.7, H–C(8)); 2.43 (*m*, H_{ax}–C(10)); 2.12 (*m*, H_{eq}–C(10)); 2.10 (*m*, H_{eq}–C(11)); 1.50 (*m*, H_{ax}–C(11)); 1.12 (*s*, Me_{eq}–C(1)); 0.95 (*s*, Me_{ax}–C(1)); 2.26 (br. *s*, Me–C(5)); 1.83 (*s*, Me–C(9)); **12b**: 2.53 (*d*, $J = 18.0$, H_{ax}–C(2)); 2.01 (*d*, $J = 18.0$, H_{eq}–C(2)); 5.86 (br. *s*, H–C(4)); 2.04 (*dd*, $J = 12.3$, 4.2, H_{eq}–C(7)); 2.38 (*dd*, $J = 14.3$, 13.0, H_{ax}–C(7)); 4.49 (*dd*, $J = 13.0$, 4.2, H–C(8)); 2.78 (*dt*, $J = 14.3$, 5.6, H_{ax}–C(10)); 2.20 (*m*, H_{eq}–C(10)); 1.81 (*m*, H_{eq}–C(11)); 1.61 (*m*, H_{ax}–C(11)); 1.12 (*s*, Me–C(1)); 0.93 (*s*, Me_{ax}–C(1)); 2.22 (br. *s*, Me–C(5)); 1.83 (*s*, Me–C(9)); NOE: 2.26→4.85,

[11]) The data in *Table 4* demonstrate also that on a suitable choice of the reaction coordinate, as it is optional in *Allinger*'s program [13b], $\Delta H^{\neq}$ is calculated in accordance with the DNMR5-derived experimental value, or, at the worst, as representing the dominant contribution to $\Delta G^{\neq}$; this allows one to predict the range of chemical-exchange rate for any couple of conformers at room temperature.

4.49, 2.78. MS: 336, 334, 332 (0.6, 1.6, 1.2, $M^{+\cdot}$), 280, 278, 276, (22, 83, 69, $[M - C_4H_8]^{+\cdot}$), 243, 241, (6, 6, $[M - C_4H_8{-}Cl]^+$), 199, 197, (33, 100, $[M - C_4H_8 - Br]^+$), 161 (63).

3. *(+)-(6R,8S,9S)-9-Bromo-8-chloro-2-methoxy-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((+)-**14**), *(−)-(4S,6S,8S,9S)- and (+)-(4R,6S,8S,9S)-4,9-Dibromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-one* ((−)-**15** and (+)-**16**, resp.). a) *With Oxalic Acid.* Compound (+)-**13** [1] (0.020 g, 0.05 mmol) was heated to reflux in 5% oxalic acid/MeOH (10 ml) until complete disappearance (10 h). The mixture was evaporated, H_2O (10 ml) added, the mixture neutralized with aq. Na_2CO_3 soln. and extracted with Et_2O, and the residue from evaporation of the org. phase subjected to HPLC (*CN*, hexane/i-PrOH 95:5): (+)-**14** (t_R 10.5 min; 0.004 g, 20%), (−)-**15** (t_R 16.5 min; 0.005 g, 25%), and (+)-**16** (t_R 15.0 min; 0.002 g, 10%).

b) *With TsOH.* Compound (+)-**13** (0.010 g, 0.025 mmol) and TsOH (0.002 g) were heated at 55° in CCl_4 (1.5 ml) until complete disappearance (2 h). The mixture was filtered and the residue from evaporation subjected to HPLC (*Si-60*, hexane/i-PrOH 98:2): (−)-**15** (t_R 8.5 min; 0.006 g, 60%) and (+)-**16** (t_R 7.8 min; 0.0025 g, 20%).

*Data of (+)-***14**. Colorless oil. $[\alpha]_D^{20} = +10$ ($c = 0.2$, CCl_4). ^{1}H-NMR (low-exchange limit; −20°): **14a**: 2.57 (*d*, $J = 18.1$, H_{ax}–C(2)); 2.11 (*d*, $J = 18.1$, H_{eq}–C(2)); 3.60 (*s*, MeO); 2.17 (*dd*, $J = 15.1$, 5.6, H_{eq}–C(7)); 1.99 (*dd*, $J = 15.1$, 12.6, H_{ax}–C(7)); 4.88 (*dd*, $J = 12.6$, 5.6, H–C(8)); 2.47 (*ddd*, $J = 14.3$, 13.4, 3.1, H_{ax}–C(10)); 1.50 (*m*, H_{eq}–C(11)); 1.27 (*m*, H_{ax}–C(11)); 1.10 (br. *s*, Me_{eq}–C(1)); 0.97 (*s*, Me_{ax}–C(1)); 2.21 (s, Me–C(5)); 1.83 (*s*, Me–C(9)); **14b**: 3.63 (*s*, MeO); 4.47 (*dd*, $J = 13.0$, 4.5, H–C(8)); 2.80 (*td*, $J = 14.3$, 5.6, H_{ax}–C(10)); 2.15 (*s*, Me–C(5)); NOE (r.t.): 2.21→4.88, 4.47, 2.47, 2.80. MS: 366, 364, 362 (3, 10, 8, $M^{+\cdot}$), 310, 308, 306 (5, 20, 15, $[M - C_4H_8]^{+\cdot}$), 285, 283 (2, 6, $[M - Br]^+$), 229, 227 (33, 100, $[M - C_4H_8 - Br]^+$), 180 (11), 163 (15).

*Data of (−)-***15**. Colorless oil. $[\alpha]_D^{20} = -16$ ($c = 0.2$, CCl_4). ^{1}H-NMR: 4.96 (br. *s*, H–C(2)); 6.00 (*q*, $J = 1.5$, H–C(4)); 2.52 (*dd*, $J = 15.1$, 5.7, H_{eq}–C(7)); 2.20 (*dd*, $J = 15.1$, 12.2, H_{ax}–C(7)); 4.84 (*dd*, $J = 12.2$, 5.7, H–C(8)); 2.47 (*dt*, $J = 14.1$, 3.9, H_{ax}–C(10)); 1.61 (*ddd*, $J = 13.7$, 3.5, 2.1, H_{ax}–C(11)); 1.37 (*m*, H_{ax}–C(11)); 1.33 (*s*, Me_{eq}–C(1)); 1.00 (*s*, Me_{ax}–C(1)); 2.34 (*d*, $J = 1.5$, Me–C(5)); 1.85 (*s*, Me–C(9)). MS: 335, 333, 331 (5, 19, 15, $[M - Br]^+$), 280, 278, 276 (19, 77, 59, $[M - C_4H_8]^{+\cdot}$), 199, 197 (33, 100, $[M - C_4H_8 - Br]^+$), 161 (37).

*Data of (+)-***16**. Colorless oil. $[\alpha]_D^{20} = +78$ ($c = 0.08$, CCl_4). ^{1}H-NMR (low-exchange limit; −57°): **16a**: 4.13 (*s*, H_{ax}–C(2)); 5.98 (*s*, H–C(4)); 4.83 (*dd*, $J = 12.7$, 6.8, H–C(8)); 1.36 (*s*, Me_{eq}–C(1)); 1.10 (*s*, Me_{ax}–C(1)); 2.30 (br. *s*, Me–C(5)); **16b**: 4.98 (*s*, H_{eq}–C(2)); 6.02 (*s*, H–C(4)); 2.12 (br. *dd*, $J = 13.9$, 4.6, H_{eq}–C(7)); 2.48 (*dd*, $J = 13.9$, 13.1, H_{ax}–C(7)); 4.53 (*dd*, $J = 13.1$, 4.6, H–C(8)); 2.77 (*td*, $J = 13.9$, 5.1, H_{ax}–C(10)); 2.56 (br. *dd*, $J = 13.9$, 5.2, H_{eq}–C(10)); 1.94 (*td*, $J = 14.7$, 5.8, H_{ax}–C(11)); 1.70 (*m*, H_{ax}–C(10)); 1.33 (*s*, Me_{eq}–C(1)); 0.96 (*s*, Me_{ax}–C(1)); 2.26 (br. *s*, Me–C(5)); 1.85 (*s*, Me–C(9)). MS: practically superimposable to that of (−)-**15**.

4. *(2R,6R,8R,9R)-2,8-Dibromo-9-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-one* (**17**). To a stirred soln. of (−)-**2** (0.004 g) in acetone (0.5 ml) at r.t., *Jones* reagent was added dropwise until persistency of the orange color. Then 5% aq. NaHSO, soln. (0.5 ml) was added, the mixture filtered on a *Whatman* phase-separation filter, and the filtrate evaporated: 0.003 g (75%) of **17**.

Data of **17**. ^{1}H-NMR: 4.84 (*s*, H–C(2)); 3.33 (br. *s*, 2 H–C(4)); 2.55 (*ddd*, $J = 14.2$, 4.7, 3.1 H_{eq}–C(7)); 2.23 (*dd*, $J = 14.2$, 12.9, H_{ax}–C(7)); 4.69 (*dd*, $J = 12.9$, 4.7, H–C(8)); 2.32 (*m*, H_{ax}–C(10)); 2.03 (*m*, H_{eq}–C(10)); 1.85 (*m*, 2 H–C(11)); 1.27 (*s*, Me_{eq}–C(1)); 0.87 (*s*, Me_{ax}–C(1)); 5.03 (br. *s*, 1 H, CH_2=C(5)); 5.36 (*t*, $J = 1.4$, 1 H, CH_2=C(5)); 1.73 (*s*, Me–C(9)). MS: 335, 333, 331 (2, 8, 4, $[M - Br]^+$), 297, 295 (15, 15, $[M - Br - HCl]^+$), 278, 276 (10, 10), 252, 250 (7, 7), 217, 215 (15, 15), 199, 197 (17, 44), 171 (13), 169 (24), 161 (32), 133 (56), 119 (39), 105 (49), 91 (61), 83 (100).

5. *(2R,6R,8R,9R)- and (2S,6R,8R,9R)-2,8-Dibromo-9-chloro-1,1,5,9-tetramethylspiro[5.5]undec-1-en-3-one* (**18** and **19**, resp.). Compound **17** and TsOH were heated as described in *Exper. 3b*. HPLC (*Si-60*) gave **18** (1.1 mg; t_R 9.2 min) and **19** (0.8 mg; t_R 8.0 min).

Data of **18**. ^{1}H-NMR (−10°): 4.95 (*s*, H–C(2)); 6.01 (br. *s*, H–C(4)); 4.86 (*dd*, $J = 12.4$, 5.6, H–C(8)); 1.34 (*s*, Me_{eq}–C(1)); 1.00 (br. *s*, Me_{ax}–C(1)); 2.28 (br. *s*, Me–C(5)); 1.73 (*s*, Me–C(9)). MS: 335, 333, 331 (4, 15, 12, $[M - Br]^+$), 280, 278, 276 (19, 77, 59, $[M - C_4H_8]^{+\cdot}$), 199, 197 (33, 100, $[M - C_4H_8 - Br]^+$), 161 (41).

Data of **19**. ^{1}H-NMR (−10°): 4.94 (*s*, H–C(2)); 6.00 (br. *s*, H–C(4)); 4.53 (*dd*, $J = 13.2$, 4.5, H–C(8)); 1.33 (*s*, Me_{eq}–C(1)); 0.98 (br. *s*, Me_{ax}–C(1)); 2.25 (br. *s*, Me–C(5)); 1.73 (*s*, Me–C(9)). MS: practically superimposable to that of **18**.

6. *DIBAL Reduction of (+)-***12**. To (+)-**12** (0.020 g, 0.06 mmol) in dry THF (2 ml) was added 1M DIBAL in THF (60 µl) and stirred for 2 h at r.t. Then H_2O (1 ml) was added, the mixture evaporated and extracted with AcOEt, and the residue from evaporation of the org. layer subjected to HPLC (*Si-60*, hexane/i-PrOH gradient): (+)-**21** (t_R 9.3 min; 0.006 g, 30%), (+)-**20** (t_R 10.8 min; 0.0045 g, 22%), **22** (t_R 11.0 min; 0.9 mg, 5%), and **23** (t_R 12.4

min; 1.5 mg, 7%). The latter two compounds were absent from the mixture before HPLC (^{1}H-NMR) and after HPLC on a virgin *Si-60* column.

*Data of (+)-(3*R*,6*R*,8*S*,9*S*)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-ol* ((+)-**20**). Colorless oil. $[\alpha]_D^{20} = +34$ (*c* = 0.5, CCl_4). ^{1}H-NMR (+30°): 1.70 (*m*, H_{ax}–C(2)); 1.50 (*m*, H_{eq}–C(2)); 4.15 (*m*, H–C(3)); 5.45 (*dq*, *J* = 3.0, 1.5, H–C(4)); 1.97 (*m*, 2 H–C(7)); 4.80 (*dd*, *J* = 11.2, 6.8, H–C(8)); 2.60 (*dt*, *J* = 14.2, 4.6, H_{ax}–C(10)); 2.41 (*ddd*, *J* = 14.2, 4.7, 3.2, H_{eq}–C(10)); 1.57 (*ddd*, *J* = 14.3, 4.6, 1.4, H_{eq}–C(11)); 1.94 (*dt*, *J* = 14.3, 4.7, H_{ax}–C(11)); 0.99 (*s*, Me_{eq}–C(1)); 0.90 (*s*, Me_{ax}–C(1)); 2.01 (*t*, *J* = 1.3, Me–C(5)); 1.82 (*s*, Me–C(9)); NOE: 2.01→4.80, 2.60. ^{1}H-NMR (low-exchange limit; −65°): **20a**: 5.41 (*m*, H–C(4)); 4.87 (*dd*, *J* = 11.6, 5.8, H–C(8)); 2.52 (*td*, *J* = 14.1, 4.0, H_{ax}–C(10)); 0.99 (*s*, Me_{eq}–C(1)); 0.83 (*s*, Me_{ax}–C(1)); **20b**: 5.49 (*m*, H–C(4)); 4.57 (*dd*, *J* = 13.2, 4.5, H–C(8)); 2.73 (*td*, *J* = 14.5, 5.5, H_{ax}–C(10)); 0.98 (*s*, Me_{eq}–C(1)); 0.91 (*s*, Me_{ax}–C(1)). MS: 338, 336, 334 (0.1, 0.3, 0.2, $M^{+\cdot}$), 320, 318, 316 (0.5, 1.0, 0.6, $[M - H_2O]^{+\cdot}$), 282, 280, 278 (7, 28, 23), 254, 252, 250 (21, 84, 65), 239, 237 (3, 5), 163 (39), 135 (100).

*Data of (+)-(3*S*,6*R*,8*S*,9*S*)-9-Bromo-8-chloro-1,5,5,9-tetramethylspiro[5.5]undec-1-en-3-ol* ((+)-**21**). Colorless oil. $[\alpha]_D^{20} = +24$ (*c* = 0.15, CCl_4). ^{1}H-NMR: 1.55 (*dd*, *J* = 14.0, 6.9, H_{eq}–C(2)); 1.78 (*dd*, *J* = 14.0, 12.0, H_{ax}–C(2)); 4.12 (*m*, H–C(3)); 5.46 (*dq*, *J* = 3.0, 1.5, H–C(4)); 2.12 (*dd*, *J* = 14.5, 11.5, H_{ax}–C(7)); 2.02 (*ddd*, *J* = 14.5, 4.0, 1.7, H_{eq}–C(7)); 4.74 (*dd*, *J* = 11.3, 6.5, H–C(8)); 2.63 (*td*, *J* = 14.3, 4.7, H_{ax}–C(10)); 2.42 (*ddd*, *J* = 14.3, 5.1, 2.6, H_{eq}–C(10)); 1.37 (*ddd*, *J* = 14.5, 4.8, 1.6, H_{eq}–C(11)); 1.77 (*td*, *J* = 14.5, 4.7, H_{ax}–C(11)); 1.00 (*s*, Me–C(1)); 0.91 (*s*, Me_{ax}–C(1)); 2.01 (*t*, *J* = 1.3, Me–C(5)); 1.82 (*s*, Me–C(9)); NOE: 2.01→4.74, 2.63. ^{1}H-NMR (low-exchange limit; −65°): **21a**: 5.49 (*m*, H–C(4)); 4.87 (*dd*, *J* = 12.4, 5.7, H–C(8)); 2.73 (*td*, *J* = 14.3, 5.2, H_{ax}–C(10)); 0.99 (*s*, Me_{eq}–C(1)); 0.92 (*s*, Me_{ax}–C(1)); **21b**: 5.41 (*m*, H–C(4)); 4.67 (*dd*, *J* = 12.6, 4.8, H–C(8)); 2.56 (*td*, *J* = 14.3, 6.0, H_{ax}–C(10)); 1.00 (*s*, Me_{eq}–C(1)); 0.90 (*s*, Me_{ax}–C(1)). MS: practically superimposable to that of (+)-**20**.

*Data of (3*R*,6*R*,8*S*,9*S*)-9-Bromo-8-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-ol* (**22**). Colorless oil. ^{1}H-NMR: 1.56 (*m*, 2 H–C(2)); 3.74 (*m*, H–C(3)); 2.49 (*ddd*, *J* = 1.6, 5.6, 14.9, H_{eq}–C(4)); 2.27 (*dd*, *J* = 12.8, 14.9, H_{ax}–C(4)); 2.41 (*tdd*, *J* = 2.6, 3.8, 14.3, H_{eq}–C(7)); 1.90 (*dd*, *J* = 12.9, 14.3, H_{ax}–C(7)); 4.30 (*dd*, *J* = 3.8, 12.9, H–C(8)); 2.60 (*m*, H_{ax}–C(10)); 2.31 (*td*, *J* = 3.6, 13.9, H_{eq}–C(10)); 1.80–1.60 (*m*, 2 H–C(11)); 0.97 (*s*, Me_{eq}–C(1)); 0.82 (*s*, Me_{ax}–C(1)); 5.27 (*s*, 1 H, CH_2=C(5)); 4.82 (*s*, 1 H, CH_2=C(5)); 1.83 (*s*, Me–C(9)). MS: 320, 318, 316 (5, 20, 15, $[M - H_2O]^{+\cdot}$), 305, 303, 301 (2, 8, 6, $[M - Me - H_2O]^+$), 283, 281, (9, 9), 239, 237 (14, 39), 201 (48), 163 (26), 85 (100).

*Data of (3*S*,6*R*,8*S*,9*S*)-9-Bromo-8-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-ol* (**23**). Colorless oil. ^{1}H-NMR: 1.58 (*m*, 2 H–C(2)); 3.75 (br. *dd*, *J* = 5.7, 10.7, H–C(3)); 2.47 (*ddd*, *J* = 1.7, 5.7, 14.3, H_{eq}–C(4)); 2.19 (*dd*, *J* = 10.7, 14.3, H_{ax}–C(4)); 2.25–1.60 (series of *m*, 2 H–C(7), 2 H–C(10), 2 H–C(11)); 4.72 (*dd*, *J* = 4.8, 12.5, H–C(8)); 0.96 (*s*, Me_{eq}–C(1)); 0.84 (*s*, Me_{ax}–C(1)); 5.28 (*s*, 1 H, CH_2=C(5)); 4.85 (*s*, 1 H, CH_2=C(5)); 1.82 (*s*, Me–C(9)). MS: practically superimposable to that of **22**.

7. *Acid Treatment of (+)-***21**. Compound (+)-**21** (0.004 g) in $CDCl_3$ (0.5 ml) containing TsOH (0.001 g) was warmed for 10 min at +40° in the NMR probe until its complete disappearance. 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 97:3): (+)-**24** (t_R 4.5 min; 0.003 g, 80%).

*Data of (+)-***24**. Colorless oil. $[\alpha]_D^{20} = +27$ (*c* = 0.15, CCl_4). ^{1}H-NMR (low-exchange limit; −30°): **24a**: 2.10 (*m*, 2 H–C(2)); 5.58 (*m*, H–C(3)); 5.97 (br. *d*, *J* = 9.8, H–C(4)); 2.16 (br. *dd*, *J* = 14.0, 5.2, H_{eq}–C(7)); 1.97 (*dd*, *J* = 14.0, 12.5, H_{ax}–C(7)); 4.81 (*dd*, *J* = 12.5, 5.2, H–C(8)); 2.22 (*td*, *J* = 14.5, 4.7, H_{ax}–C(10)); 2.07 (*m*, H_{eq}–C(10)); 0.96 (*s*, Me_{eq}–C(1)); 0.73 (*s*, Me_{ax}–C(1)); 5.13 (*s*, 1 H, CH_2=C(5)); 5.00 (*s*, 1 H, CH_2=C(5)); 1.81 (*s*, Me–C(9)); **24b**: 2.10 (*m*, 2 H–C(2)); 5.58 (*m*, H–C(3)); 5.97 (br. *d*, *J* = 9.8, H–C(4)); 2.16 (br. *dd*, *J* = 14.0, 5.2, H_{eq}–C(7)); 1.97 (*dd*, *J* = 14.0, 12.5, H_{ax}–C(7)); 4.34 (*dd*, *J* = 12.8, 4.7, H–C(8)); 2.72 (*td*, *J* = 13.9, 5.3, H_{ax}–C(10)); 2.42 (*ddd*, *J* = 13.9, 4.8, 2.8, H_{eq}–C(10)); 0.95 (*s*, Me_{eq}–C(1)); 0.71 (*s*, Me_{ax}–C(1)); 5.11 (*s*, 1 H, CH_2=C(5)); 5.04 (*s*, 1 H, CH_2=C(5)); 1.82 (*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), 201 (100), 185 (46), 145 (56).

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