75. Conformational Analysis of Marine Polyhalogenated β-Chamigrenes Through Temperature-Dependent NMR Spectra[1])

by **Graziano Guella, Giuseppe Chiasera, Ines Mancini,** and **Francesco Pietra***

Istituto di Chimica, Facoltà di Scienze MFN, Università di Trento, I-38050 Povo-Trento

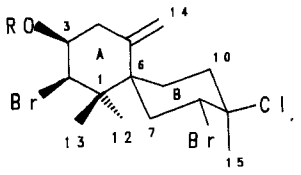
(15.II.91)

Temperature-dependent ^{1}H- and ^{13}C-NMR spectra reveal that polyhalogenated marine β-chamigrenes or synthetic derivatives thereof which are *trans*-diequatorially substituted at C(8) and C(9), such as rogiolol ((−)-**2**), obtusol ((+)-**3**), and their acetates (+)-**1** and (−)-**4**, undergo slow ring-A chair-chair inversion. Conformational equilibria and kinetics are investigated with the aid of synthetic model compounds and molecular-mechanics calculations. Thus, steric repulsions between Br_{ax}–C(2) and H_{eq}–C(7) are seen to disfavor thermodynamically conformers **1b**, **2b**, **3b**, and **4b**, which can only be detected through cross-saturation transfer, while additional steric repulsions between Me_{ax}–C(1) and OH_{ax}–C(3) make conformer **8b** of obtusol epimer so scarcely populated that it can not be detected. In agreement, with (+)-**9** and (+)-**10**, which have a trigonal C(2), two conformers can be directly observed by NMR. The kinetic barriers, which are seen to arise mainly from steric repulsions between H_{ax}–C(14) and the axial H or halogen atoms at C(8) and C(10), are calculated and discussed with respect to well documented exocyclicmethylidene-substituted cyclohexane(ene) systems. This helps to rationalize why in rogiolol acetate ((+)-**1**) ring B is unusually inert towards Zn/Et_2O/AcOH which causes bromohydrine-group elimination from ring A.

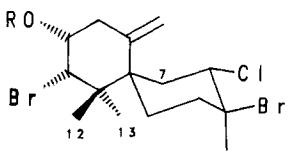
1. Introduction. – We have recently reported that the β-chamigrene derivative rogiolol acetate ((+)-**1**) is peculiar under at least three respects [1]. First, (+)-**1** was isolated from a marine sponge (*Spongia zimocca*) [1], which was a phylum unknown to contain chamigranes; possibly (+)-**1** is biosynthesized in this sponge from a precursor obtained from a nearby growing red seaweed of the genus *Laurencia* [1] (now identified as *Laurencia microcladia* KÜTZNING [2]), which would constitute an unprecedented example of food chain[2]). Second, ring B of (+)-**1** proved inert toward the reducing reagent Zn/Et_2O/AcOH, which was found to induce elimination of the bromohydrine group from ring A instead; this contrasts with the behavior of both obtusol ((+)-**3**) and isoobtusol ((+)-**5**)

[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.

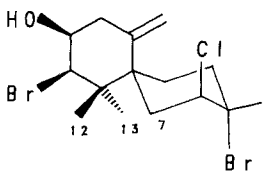
[2]) In a recent paper, *Coll* and *Wright* have reported (1*S*,2*S*,4*R*,8*R*,9*S*)-2,8-dibromo-1-chlorochamigr-11(12)-en-9-ol, isolated from the red seaweed *Laurencia majuscula* of the Great Barrier Reef, and its acetate derivative [3], which would thus be diastereoisomers of rogiolol ((−)-**2**) and rogiolol acetate ((+)-**1**), respectively [1]. Actually, polarimetric and (albeit much less detailed than ours [1] and affected by incorrect attributions too) NMR data of these compounds [3] match those of rogiolol ((−)-**2**) and rogiolol acetate ((+)-**1**) [1], so that their structures [3] have to be revised accordingly [1]. Unfortunately, *Coll* and *Wright* have also reported [3] incorrectly the configuration of obtusol, which appears correctly below (see (+)-**3**) [4], and of their compound **4** which, contrary to their desire, was drawn [3] in diastereoisomeric, and not enantiomeric, relationship to a compound which was reported as by *Suzuki et al.* [5]. This casts problems on the stereochemical implications about the photochemical interconversion between compounds **4** and **5** of *Coll* and *Wright* [3]. It must also be noticed that the NMR and polarimetric data of a compound reported by *Schmitz et al.* [6] as **6a** are identical to those of **5** [3], which, therefore, contrary to the statement in [3], is not new.



(+)-1[3]) R=Ac
(−)-**2** R=H



(+)-**3** R=H
(−)-**4** R=Ac



(+)-**5**

Table 1. *^{13}C-NMR Data* ($CDCl_3$) *for Some β-Chamigrenes*

	(−)-**2**	(+)-**3**	(−)-**4**[a])	(+)-**6**	(+)-**8**
C(1)	44.12 (br. *s*)	44.21 (br. *s*)	44.48 (br. *s*)	45.60 (*s*)	not det.
C(2)	70.13 (br. *d*)	70.06 (br. *d*)	62.28 (br. *d*)	67.87 (*d*)	72.39 (*d*)
C(3)	71.92 (br. *d*)	71.87 (br. *d*)	73.23 (br. *d*)	196.65 (*s*)	74.61 (*d*)
C(4)	38.55 (br. *t*)	37.07 (br. *t*)	37.06 (br. *t*)	48.66 (*t*)	37.21 (*t*)
C(5)	141.00 (br. *s*)	141.08 (br. *s*)	140.15 (br. *s*)	141.08 (*s*)	144.55 (*s*)
C(6)	48.77 (br. *s*)	50.20 (br. *s*)	50.15 (br. *s*)	49.65 (*s*)	not det.
C(7)	38.47 (*t*)	38.45 (*t*)	37.06 (*t*)	37.08 (*t*)	39.50 (*t*)
C(8)	60.97 (*d*)	67.55 (*d*)	67.50 (*d*)	67.09 (*d*)	67.67 (*d*)
C(9)	71.70 (*s*)	68.15 (*s*)	67.87 (*s*)	67.18 (*s*)	67.93 (*s*)
C(10)	38.73 (*t*)	40.44 (*t*)	40.49 (*t*)	40.50 (*t*)	40.22 (*t*)
C(11)	25.53 (*t*)	25.57 (*t*)	25.59 (*t*)	25.72 (*t*)	25.66 (*t*)
C(12)	24.16 (br. *q*)	24.13 (br. *q*)	24.17 (br. *q*)	23.06 (*q*)	23.59 (*q*)
C(13)	20.63 (br. *q*)	20.55 (br. *q*)	19.98 (br. *q*)	19.06 (*q*)	18.53 (*q*)
C(14)	117.81 (*t*)	117.84 (*t*)	117.84 (*t*)	117.88 (*t*)	117.07 (*t*)
C(15)	24.16 (*q*)	23.88 (*q*)	23.88 (*q*)	23.67 (*q*)	23.84 (*q*)

[a]) CH_3CO: 169.92 (*s*) and 20.97 (*q*).

which were found to undergo chloro-bromo-elimination by $Zn/Et_2O/AcOH$ at ring B (particularly rapidly in the case of (+)-**5**), while ring A remained intact [4]. Third, (+)-**1** showed temperature-dependent ^{1}H- and ^{13}C-NMR line widths, which suggested slow conformational motions [1]; this came to our surprise, in view of the enantiomeric relationship of the C-skeleton of (+)-**1** and obtusol ((+)-**3**), for which no NMR line broadening had been reported [4].

Actually, polyhalogenated β-chamigrene derivatives are known from X-ray diffraction studies to have both ring A and B in the chair form [4] [7]; however, their molecular dynamics remain scarcely investigated, which is also the case for chamigranes in general. The only reported dynamic ^{1}H-NMR study with β-chamigrenes concerns the enantiomer of our (see below) β-chamigradienone (+)-**10** [8a], isolated from *Laurencia nipponica* [8b]; this study [8a] revealed an equilibrium of two conformers, owing to ring-A flipping, although the reported data [8a] reveal inconsistencies (see below).

The temperature-dependent NMR spectra of (+)-**1** could be preliminarily interpreted in terms of a single conformer [1], which is also an unusual condition of chemical exchange. Thus, rogiolol acetate ((+)-**1**) and its deacylated derivative (−)-**2** emerge as peculiar β-chamigrene derivatives, the dynamic NMR investigation of which is likely to contribute significantly to the understanding of the molecular properties of β-chamigrenes in general. The recognized ecological role in the sea of polyhalogenated β-chami-

grene derivatives of *Laurencia* species [7] [9], the dependence of their pharmacological activity on the sense of chirality of their C-skeleton [10] (and related implications on the structure of receptors), their variable and so far not rationalized chemical reactivity (see above), besides a general interest in spirocycles [10], prompted us to investigate the conformational preferences of polyhalogenated β-chamigrenes.

2. Results and Discussion. – 2.1. *NMR Dynamic Study.* Rogiolol acetate ((+)-**1**) revealed broad ^{1}H- and ^{13}C-NMR (300 and 75.43 MHz, resp.) resonances in $CDCl_3$ at room temperature[3]) (*Table 1*). This is typical of chemical-exchange phenomena, although only one conformer could be detected, even at −50° [1]. Monitoring the *H*−C(8) signal (δ = 4.72), the corresponding sharp *dd* at −50° changed to a very broad *d* at room temperature and to a sharp *dd* again at +50°. Neither for H−C(8) nor for any other proton of (+)-**1** could the resonance for the related exchanging site be detected. This is expected for a slow dynamic process with one of the two conformers being present at too low concentration to exhibit NMR signals, yet being present in sufficiently high amount to affect the spectral line width of the signals of the more abundant conformer [11].

If this is the case with (+)-**1**, a prerequisite to evaluate the kinetic parameters for the exchange process is to know the chemical shift of the exchanging sites for the two conformers and their relative concentrations. With (+)-**1**, a suitable signal on which to monitor is the ^{1}H-NMR signal of *H*−C(8); in fact, in a novel application of cross-saturation transfer [12], operating at −30°, we were able to locate the *H*−C(8) resonance for the minor conformer: the well-defined saturation transfer in *Fig. 1* constitutes evidence for a minor conformer in slow equilibrium with the major conformer. When the decoupler frequency was set 135 Hz upfield the *H*−C(8) signal (δ 4.72), the latter decreased by 50%. Thus, δ(H) 4.26 defines the center of a broad signal for *H*−C(8) in the minor conformer[4]).

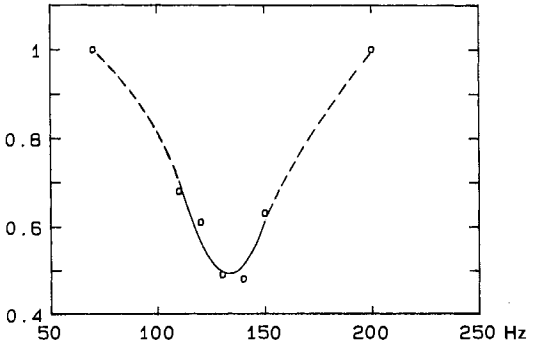


Fig. 1. *Saturation-transfer effect for H−C(8) of (+)-***1**. Abscissa: upfield shift in Hz of the decoupler frequency with respect to the *H*−C(8) frequency of conformer **1a** (= 0 Hz). Ordinate: resulting effect from the unperturbed signal area (1) to the maximum effect (*ca.* 0.5).

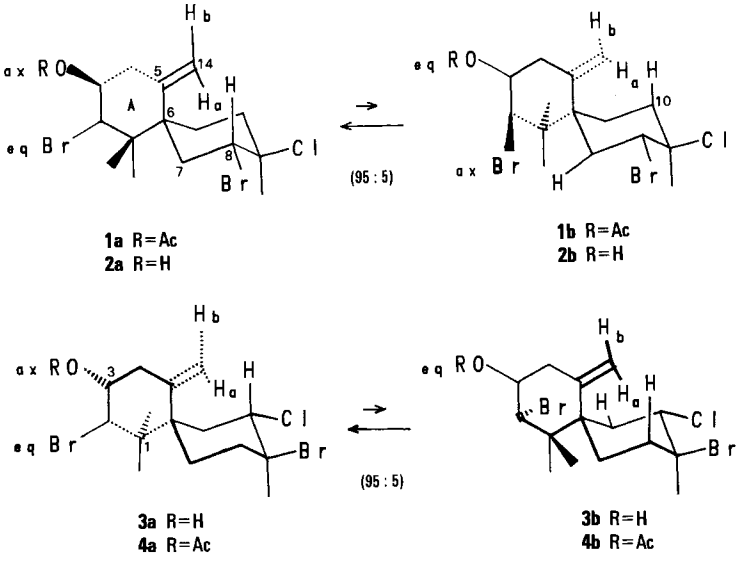
[3]) The same phenomenon was also observed in the solvents C_6D_6, $(CD_3)_2CO$, or CD_3OD. For convenience, the Me and methylidene groups of all β-chamigrenes are numbered sequentially throughout this paper.

[4]) For any future use of this novel application of cross-saturation transfer, one should be aware that the rate of the chemical exchange should not differ much from the longitudinal relaxation rate [12]; these conditions can be met by the proper choice of the temperature range.

The ratio of populations for the two conformers was first estimated by molecular-mechanics calculations [13] and then more accurately evaluated from the chemical shift of the *H*–C(8) signal in the fast-exchange limit; thus, a *ca.* 95:5 concentration ratio for the two conformers was calculated. Inspection of models suggested that displacement of the equilibrium toward conformer **1a** results from repulsive interactions between Br_{ax}–C(2) and H_{eq}–C(7) in conformer **1b**.

The fact that all ^{13}C-NMR signals for ring A, and only them, are exchange-broadened (*Exper. Part*) allowed us to assume that conformational motions are limited to ring A, while ring B behaves as a rigid chair[5]). The motion is imagined to consist of ring-A chair-chair inversion as depicted in *Scheme 1* where it is seen that H_a–C(14) faces H_{ax}–C(8) in the major conformer **1a** (which is supported by *J* and NOE data in the low-exchange limit [1]) and H–C(10) in the minor conformer **1b**.

Scheme 1



We were then in the position to study the dynamic phenomenon with (+)-**1** by monitoring the major conformer **1a** through the *H*–C(8) ^{1}H-NMR signal in $CDCl_3$ in the temperature range −20 to +50°. The dependence of the rate constant from the temperature was calculated with the DNMR5 computer program [14]; experimental and calculated line shapes are displayed in *Fig. 2* while the kinetic parameters, evaluated from the *Eyring*'s equation by least-squares fitting, are collected in *Table 2*.

A qualitative estimate of the energy barrier to be surmounted on going from conformer **1a** to **1b** *via* ring-A flipping was obtained from molecular-mechanics calculations with C(7)–C(6)–C(5)–C(14) as a driver angle [13]. In two sets of calculations, we obtained for $\Delta H^{\neq}_{ab}$ and $\Delta H^{\neq}_{ba}$ the values listed in *Table 3*. If boat-boat interconversion

[5]) In this view, hindrance to ring-B chair-chair inversion results from strong steric repulsions among the geminal dimethyl group at C(1) and the protons at C(8) and C(10).

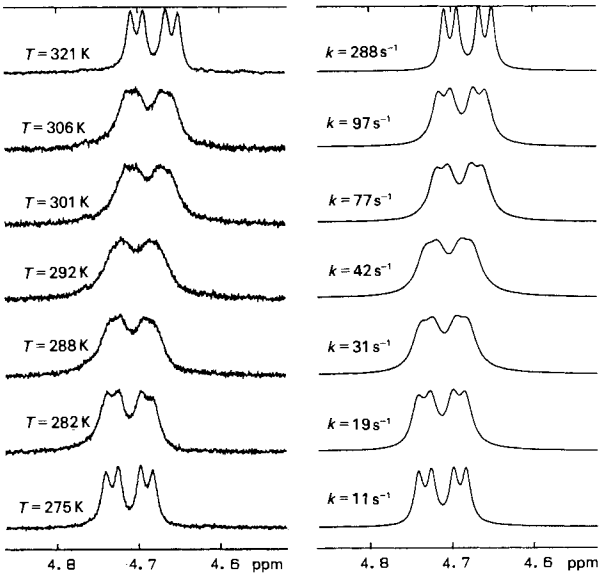


Fig. 2. *Experimental* (left) *and computed* (right) *line shape of the* H–*C(8) signal for conformer* **1a**

involves less energy than chair-chair interconversion, the overall barrier for chair-chair interconversion can be easily calculated ($\Delta H^{\neq}$, *Table 3*). The good agreement with the experimentally evaluated kinetic barriers (*Table 2*) justifies this approach.

Obtusol acetate ((−)-**4**), obtained by acetylation of natural obtusol ((+)-**3**)[6]), showed much the same behavior, and was, therefore, handled in the same way as (+)-**1** above[7]); the equilibrium position is the same as with rogiolol acetate ((+)-**1**). The *H*–C(8) ^{1}H-NMR resonance for the minor conformer **4b**, which results from chair-chair ring-A inversion (*Scheme 1*), was found to occur 145 Hz upfield the corresponding resonance (δ 4.70 (*dd*)) for the major conformer **4a**; a **4a**/**4b** population ratio of 95:5 could thus be estimated. The agreement between the experimentally evaluated (*Table 2*) and calculated kinetic parameters (with the driver-angle option of the molecular-mechanics program, *Table 3*) suggests that the kinetic barrier has the same origin as with (+)-**1**.

If the equilibrium of *Scheme 1* also is correct for obtusol ((+)-**3**), the **b**-type minor conformer of the C(3) epimer of obtusol should involve extra repulsive interactions between the axial OH group at C(3) and the axial Me group at C(1). To prove this point, we have synthesized the C(3) epimer of obtusol, *i.e.* (+)-**8**, by first oxidizing obtusol

[6]) Both obtusol ((+)-**3**) and rogiolol ((−)-**2**) showed qualitatively similar line-broadening phenomena. With the latter in $CDCl_3$, the paramagnetically induced shift of the ^{1}H-NMR signals was attented by either signal broadening at 0.2 or lower [(−)-**2**]/[[Eu(fod)$_3$]] ratios or sharpening at higher ratios. Shift-reagent binding either to both conformers equally (thereby locking the conformational motion) or to the major conformer preferentially (thereby making the other conformer uneffective) may be responsible for signal sharpening.

[7]) This was expected from the enantiomeric relationship of the C-skeleton of (−)-**4** and (+)-**1**. Therefore, in view of the fact that (−)-**2** and (+)-**3** show qualitatively similar exchange phenomena, previous failure to detect exchange broadening with the latter compound [4] has to be attributed to the low ^{1}H-NMR frequency used (100 MHz). This conclusion is further supported by the observation that at 80 MHz, all ^{1}H-NMR signals for rogiolol acetate ((+)-**1**) are sharp [1].

Table 2. *Experimental Thermodynamic and Kinetic Parameters for Ring-A Flipping of Various β-Chamigrenes*[a])

	x_a/x_b[b])	$\Delta H^{\neq}$ [kcal/mol][c])	$\Delta S^{\neq}$ [cal/mol K][c])	$\Delta G^{\neq}$ [kcal/mol][c])
(+)-**1**	95:5	11.7 ± 0.2	−9.7 ± 1	14.6 ± 0.2
(−)-**4**	95:5	12.6 ± 0.7	−6.1 ± 2	14.5 ± 0.2
(+)-**6**				*ca.* 9[d])
(+)-**9**	55:45			14.6 ± 0.2[e])
(+)-**10**	60:40	15.1 ± 0.4	−5.2 ± 1	16.7 ± 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 $\Delta\delta$ in the fast-exchange limit.

[c]) Determined by least-squares analysis of the DNMR5-derived kinetic data on the basis of the *Eyring* equation with transmission coefficient values of 1/2 for compounds (+)-**1**, (−)-**4**, and (+)-**6** or 1 for compound (+)-**9** and (+)-**10**. $\Delta G^{\neq}$ evaluated at 298 K.

[d]) Determined by visual best fitting of the *H*–C(8) *dd* at −70° (fast-exchange limit).

[e]) Determined by visual best fitting of the *H*–C(8) *dd* at −20° (slow-exchange limit).

Table 3. *Molecular-Mechanics Calculations of Thermodynamic and Kinetic Parameters* (kcal/mol) *for Ring-A Flipping of Various β-Chamigrenes*

	ΔH[a])	$x_a:x_b$[b])	$\Delta H_{ab}^{\neq}$[c])	$\Delta H_{ba}^{\neq}$[d])	$\Delta H^{\neq}$[e])
(+)-**1**	2.42	98:2	15.0	12.6	12.7
(−)-**2**	2.73	99:1	15.0	12.3	12.4
(+)-**3**	2.75	99:1	15.1	12.4	12.5
(−)-**4**	2.01	95:5	14.6	12.6	12.7
(+)-**5**	1.85	96:4	17.0	15.2	15.3
(+)-**6**	0.92	83:17	10.0	9.1	9.2
(+)-**8**	3.10	[f])	16.9	13.3	13.3
(+)-**9**	0.05	53:48	12.3	12.3	12.3
(+)-**10**	0.26	61:39	15.2	14.9	15.0
11	5.5	[f])	14.9	8.4	8.4
12	2.5	99:1	9.4	6.9	7.0
(−)-**13**	3.4	[f])	13.6	10.1	10.1

[a]) Difference of strain energies between the **b** and **a** form.

[b]) Population ratio for the **a** and **b** ground forms (x = molar fraction), on the assumption that the entropy difference ($\Delta S^{\neq}$) is negligible.

[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 groundstate **b**.

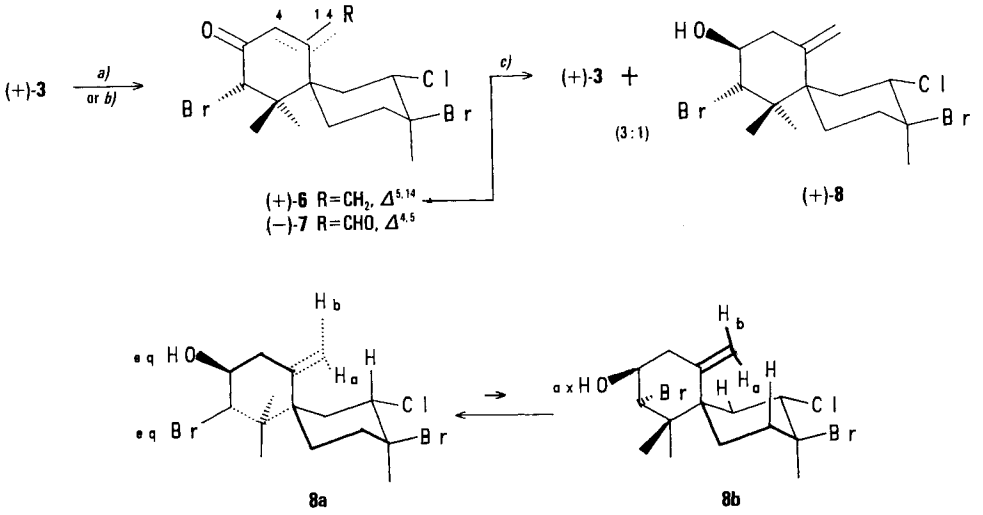
[e]) Calculated from $\Delta H^{\neq} = 1/2[\Delta H_{ab}^{\neq} + \Delta H_{ba}^{\neq} - (x_a - x_b)\Delta H]$.

[f]) Calculations indicated only one conformer.

((+)-**3**) to enone (+)-**6** in a clean reaction with *Jones* reagent[8]) (*Scheme 2*). Enone (+)-**6**, isolated by FC, was treated with $NaBH_4$ to give a 3:1 mixture of the starting obtusol ((+)-**3**) and the desired obtusol epimer (+)-**8**. In fulfillment of the above expectations, the β-chamigrene (+)-**8** showed only sharp NMR signals for a single conformer (**8a**, see *Scheme 2*); although the kinetic barrier to ring-A flipping was calculated to be about the same as for obtusol ((+)-**3**; *Table 3*), the population of conformer **8b** must be so low that the NMR line shape is not affected.

[8]) Pyridinium chlorochromate (PCC) proved inferior in this case, giving a 9:1 mixture of desired (+)-**6** and undesired (−)-**7**.

Scheme 2



a) *Jones* reagent, acetone, 30 min, r.t. *b*) PCC, CH_2Cl_2, 5 h, r.t. *c*) $NaBH_4$, Et_2O, 2 h, r.t.

The rationalizations in *Schemes 1* and *2* imply that, should C(2) be sp^2 hybridized, the repulsive interactions disfavoring the conformer of type **b** would vanish. In fact, with β-chamigradienone (+)-**10**, which was prepared *via* (+)-**9** from (−)-**2** (see [1] and *Scheme 3*), two conformers could be detected in nearly equal proportions[9]); a ^{1}H-NMR dynamic study monitoring both the $H-C(2)$ *d* and the $H-C(8)$ *dd* in the temperature range +20 to +55° (*Fig. 3*) led to the kinetic parameters of *Table 2*. The motion can be described in terms of ring-A flipping with the kinetic barrier arising from mainly repulsive interactions between H_a–C(14) and the axial protons at C(8) and C(10) (see *Scheme 3*). This is in accordance with molecular-mechanics calculations carried out with a change of the C(5)–C(6)–C(1)–C(12) (or C(7)–C(6)–C(5)–C(14)) driver angle from 61° (7°) in **10a** to 176° (125°) in **10b**; this led directly to the value $\Delta H^{\neq} = 15.0$ kcal/mol (*Table 3*) for the kinetic barrier, in good agreement with the experimental value (*Table 2*). With (+)-**9**, albeit on the basis of a less accurate analysis, we found similar results (*Tables 2* and *3*).

If the above conclusions are correct, replacing the C(8)–C(9) moiety with a C(8)=C(9) bond, fast flipping of ring A should occur. To prove the point, both (−)-**11** and (−)-**12** were synthesized from obtusol ((+)-**3**) or isoobtusol ((+)-**5**) according to

[9]) *Segawa et al.* have already found that with either the enantiomer of our (+)-**10** or with their 3-bromo derivative, slow ring-A flipping generates two conformers [8a]. Following the *s* of H_b–C(14) in the ^{1}H-NMR ((D_8)toluene) in the temperature range +40 to +60°, they reported for this conformational motion of the latter the kinetic parameters $\Delta G^{\neq}_{313}$ 18.2 kcal/mol, $\Delta H^{\neq} = 12.0$ kcal/mol, and $\Delta S^{\neq} = -20$ e.u. [8a]. However, *Segawa et al.* must have done an erroneous *Eyring* treatment of their kinetic data [8a]; when this is correctly done with the reported data [8a], $\Delta H^{\neq} = 8.8$ kcal/mol and $\Delta S^{\neq} = -28.5$ e.u. are obtained instead. But in either case, the values differ considerably from our data for (+)-**10** (*Table 2*) where, as expected for conformational processes [11], the main contribution to the barrier is enthalpic. Moreover, monitoring two *s* which collapse to a single line and exploring a very narrow range of temperatures as described in [8a] are well known sources of serious errors [11]. The factorization of the activation enthalpy for ring-A flipping given by *Segawa et al.* [8a] is, therefore, meaningless.

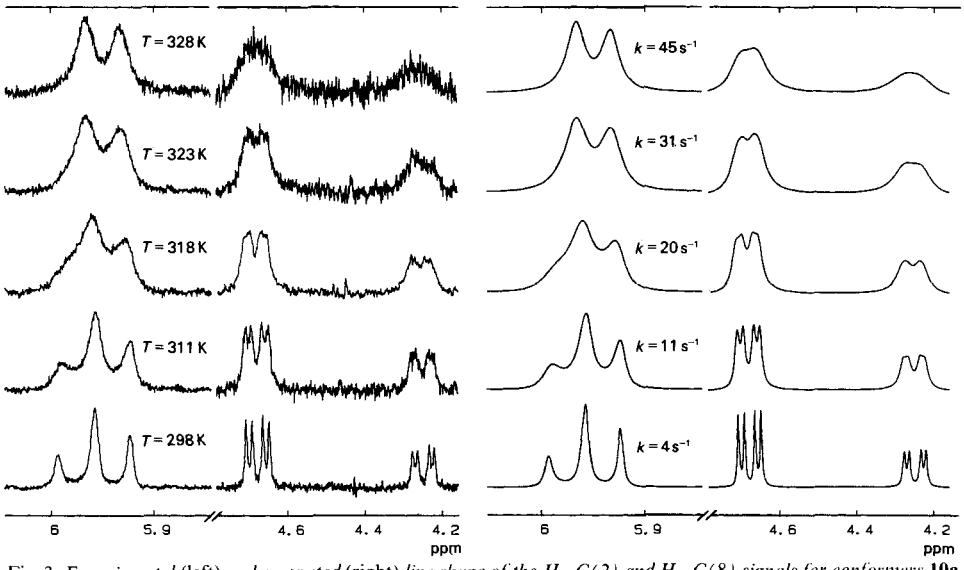
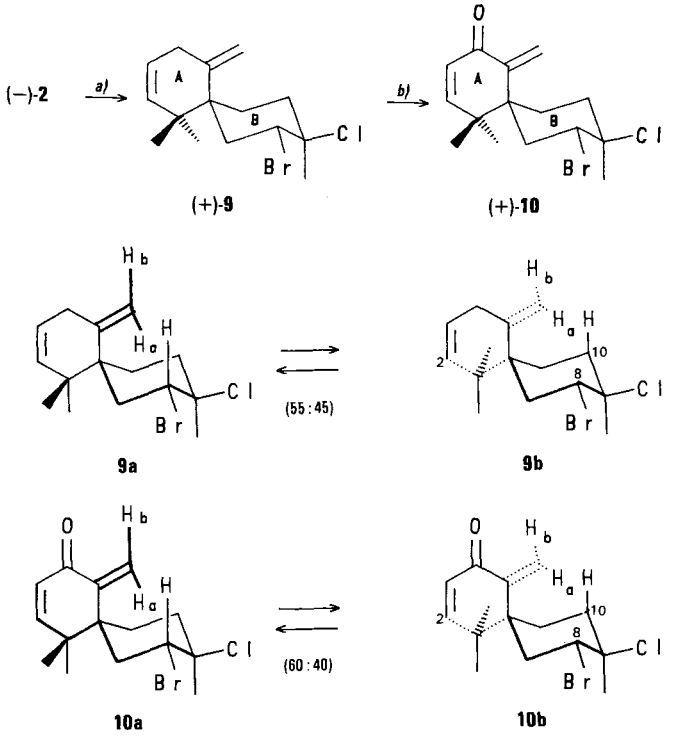


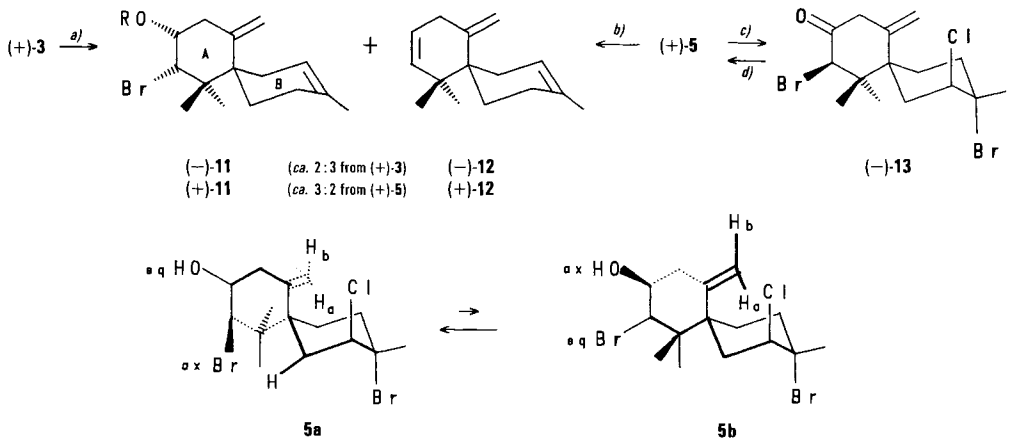
Fig. 3. *Experimental* (left) *and computed* (right) *line shape of the H–C(2) and H–C(8) signals for conformers* **10a** *and* **10b**

Scheme 3



a) $Zn/Et_2O/AcOH$, r.t., 48 h. *b*) PDC/*t*-BuOOH, *Celite*, benzene, r.t., 24 h [1].

Scheme 4



a) $Zn/Et_2O/AcOH$, r.t., 24 h. *b*) $Zn/Et_2O/AcOH$, r.t., 1 h. *c*) *Jones* reagent, acetone, 30 min, r.t. *d*) $NaBH_4$, Et_2O, 4 h, r.t.

Scheme 4. We were gratified by observing only sharp ^{1}H-NMR signals for both (−)-**11** and (−)-**12** in the temperature range −60 to +21°. This is also in accordance with molecular-mechanics calculations which indicate the large prevalence of one of the two enantiomers and a low kinetic barrier for the conformational inversion (*Table 3*).

It is well known that the cyclohexanones show lower kinetic barriers to ring inversion than the corresponding cyclohexanes [13]. This holds true with β-chamigrenes too, as revealed by the fact that line-broadening effects with β-chamigrene (+)-**6** could only be observed at temperatures below −50°. Molecular-mechanics calculations on the basis of our model above (*Table 3*) are in accordance with these conclusions. This view is further supported by the observation that the diastereoisomeric enone (−)-**13**, prepared from isoobtusol ((+)-**5**) as indicated in *Scheme 4*, showed NMR spectra in the fast-exchange limit at r.t., although practically only one conformation proved to be populated.

Isoobtusol ((+)-**5**) only showed sharp NMR signals in the temperature range −50 to +50°. This may result from only one conformation being populated (see **5a** in *Scheme 4*) since molecular-mechanics calculations, carried out with the driver-angle option as in the other cases above, failed to reveal high kinetic barriers to ring-A flipping. The alternative that **5a** represents a totally rigid C-skeleton, which was predicted on the basis of repulsive interactions between H_a–C(14) and the bulky axial Cl–C(8) by molecular-model inspection [10], is also compatible with the observed NMR spectra, however. This point can not be easily assessed given the difficulty of exploring all possible conformational motions with the molecular-mechanics program [21][10]).

[10]) Attempts to synthesize the C(3) epimer of isoobtusol ((+)-**5**) in order to further explore this problem were unsuccessful. Thus, (−)-**13**, obtained *via Jones* oxidation of (+)-**5**, gave mostly the starting (+)-**5** on treatment with $NaBH_4$ (*Scheme 4*); a by-product, possibly the desired C(3) epimer of (+)-**5**, was formed in less than 5% yield so that its structure could not be proven. The contrast with the successful preparation of (+)-**8** along similar lines is worth to be noticed, suggesting that the expected preferential axial attack by $NaBH_4$ [15] occurs with (+)-**6** (*Scheme 2*) preferentially in the minor conformation having an axial Br or with (−)-**13** exclusively in the more abundant conformation depicted in *Scheme 4*.

2.2. *Reactivity.* Both rogiolol ((−)-**2**) and rogiolol acetate ((+)-**1**) proved to react slowly with $Zn/Et_2O/AcOH$ at room temperature; while ring B was saved intact, *syn* elimination of the RO and Br substituents from ring A occurred, giving in good yield diene (+)-**9**, which could then be oxidized to enone (+)-**10** (*Scheme 3*) [1]. In contrast, the isomeric obtusol ((+)-**3**) or its acetate (−)-**4** showed a higher propensity of ring B than A to react with $Zn/Et_2O/AcOH$, affording a 3:2 mixture of (−)-**11** and (−)-**12** (*Scheme 4*). Isoobtusol ((+)-**5**) proved to behave as obtusol, giving the corresponding enantiomeric products (+)-**11** and (+)-**12**, albeit in a different relative ratio (2:3) and at higher rate (*Scheme 4*).

These results indicate that a Br-atom at a tertiary cyclohexyl center undergoes a facile attack by $Zn/Et_2O/AcOH$ resulting in its elimination, together with the vicinal Cl-atom (*Scheme 4*). This process is stereoelectronically aided by the *trans*-diaxial disposition of the two halogen atoms, resulting in a particularly rapid elimination of BrCl from isoobtusol ((+)-**5**). Either Br at a secondary center or Cl at a tertiary center of ring B are not reactive, so that the 1,2-RO,Br moiety at ring A is attacked instead, albeit slowly (*Scheme 3*). Our results are in keeping with literature indications as to a higher reactivity of the Br–C than Cl–C bond in 1,2-dihaloalkyl systems toward the $Zn/Et_2O/AcOH$ reagent [16].

What is finally worth to be noticed is the extraordinary aversion of these polyhalogenated β-chamigrenes to undergo a shift of the olefinic bond from the exocyclic to the endocyclic position, even under acidic conditions. This behavior, unpredictable on the basis of data from simple methylidenecyclohexanes, simplified our synthetic plans, allowing the transformation of β-chamigranes shown in *Schemes 2–4*.

3. Conclusions. – This work has revealed that with the 8,9-*trans*-diequatorially substituted β-chamigrenes (+)-**1**, (−)-**2**, (+)-**3**, and (−)-**4**, because of repulsive interactions between the $CH_2(14)$=C(5) group and the axial atoms at C(8) and C(10), chair-chair ring-A inversion is slow on the NMR time scale. The conformer involving repulsive interactions between the axial substituent at C(2) and H_{eq}–C(7) or H_{eq}–C(11) is thermodynamically so much disfavored that it was not directly detectable; it could be observed, however, using a novel application of cross-saturation transfer. This is of far-reaching value since the method proved applicable to all β-chamigrenes obtained by chemical modifications of the above ones. In fact, *i*) when there are additional repulsive interactions between Me_{ax}–C(1) and OH_{ax}–C(3), such as in the case of (+)-**8**, only one conformer is present (**8a**), whilst *ii*) when the spatial impedment at C(2) is removed, such as with β-chamigr-2-enes (+)-**9** and (+)-**10**, two conformers can be directly observed by NMR. Moreover, *iii*) removing the axial atoms at C(8) and C(9) by introducing a C(8)=C(9) bond, such as in (−)-**11** and (−)-**12**, leads to fast flipping of ring A; this is also favored by *iv*) the flattening of ring A on introduction of a 3-oxo function such as in (+)-**6** or (−)-**13**. The only dubious case remains isoobtusol ((+)-**5**): here, temperature-independent NMR spectra can either result from only one conformation being populated or from a totally rigid C-skeleton. We favor the first interpretation, since molecular-mechanics calculations, carried out sequentially on various conformations with the driver-angle option, indicate modest kinetic barriers. In all other cases, the results of this type of calculations are in accordance with experimental values for both the kinetic barriers and the positions of the equilibria.

In any event, the especially facile chloro-bromo-elimination by $Zn/Et_2O/AcOH$ at ring B of isoobtusol ((+)-**5**) stems from the high mobility of a Br-atom at a tertiary C-atom (C(9)) and stereoelectronic factors; accordingly, with Cl at the tertiary C(9), such as in rogiolol acetate ((+)-**1**), ring B is inert, and elimination of the bromohydrine group from ring A occurs instead.

We are most grateful to Prof. *J. D. Martin* for comments and for generously sending us samples of natural obtusol and isoobtusol. We also thank Mr. *A. Sterni* for recording mass spectra and acknowledge financial support by *M.P.I.* (Progetti di Interesse Nazionale) and *C.N.R.*, Roma.

Experimental Part

General. All evaporations were carried out at reduced pressure below 40°. Yields are given on reacted compound. Flash chromatography (FC): *Merck Si60* (15–25 μm). HPLC: *Merck-LiChrosorb Si-60* (7 μm); for reversed-phase, *Merck-LiChrosorb RP-18* and *Merck-LiChrosorb CN* (7 μm); 25 × 1 cm columns; 5 ml min^{-1} solvent flux. M.p.: *Kofler* hot-stage microscope. Polarimetric data: *JASCO-DP-181* polarimeter. NMR[3]): *Varian-XL-300*; δ (ppm) rel. to internal Me_4Si (=0 ppm) and J in Hz; ^1H at 299.94 MHz, ^{13}C at 75.43 MHz (in $CDCl_3$, probe temp. 21° unless otherwise stated); multiplicities from DEPT [17]; both δ and J in ^1H-NMR from differential double irradiations; for (−)-**4**, (+)-**6**, (+)-**9**, (−)-**11**, (−)-**12**, and (−)-**13**, these assignments were confirmed by both COSY-120 experiments [18] and $^{13}C,^1H$ shift correlations [19]. Differential NOE (obtained with 5-s preirradiation): irradiated H → NOE on the observed H's. Saturation-transfer effects were obtained with the same pulse sequence as NOE (decoupler power optimized [20] at $H_2 = 11$ Hz for the irradiation of H–C(8) of (+)-**1** and (−)-**4**). The probe was calibrated as before [1]. EI-MS (*m/z*, %): home-built quadrupole mass spectrometer based on the *ELFS-4-162-8 Extranuclear* quadrupole [21]. Molecular-mechanics calculations were performed by means of *Allinger*'s program [22]. Initial geometries were given by inspection of *Dreiding* molecular models. ΔH values in *Table 3* were calculated using the dielectric constant of $CDCl_3$ ($\varepsilon = 4.8$). Steps of 2° were used in driving the torsion angle to evaluate the kinetic activation parameters (*Table 3*). NMR line-shape simulation (*Figs. 2* and *3*) was carried out by means of the computer program DNMR5 [14]. To this end, FID transfer of the experimental spectrum to the *Sun 3/60* work station was made through a magnetic-streaming tape; the resulting file was transferred to a 20 MHz 386 PC through a modem. The rate constants in *Figs. 2* and *3* were obtained as the best fitting from the iteration of the parameters describing the system under examination.

1. *Epimerization at C(3) of Obtusol* ((+)-**3**). 1.1. *Oxidation of* (+)-**3** *with PCC.* To a stirred soln. of ((+)-**3** (0.050 g, 0.12 mmol) in CH_2Cl_2 (2 ml) was added pyridinium chlorochromate (PCC; 0.6 mmol) in 2 portions. After 5 h (TLC: no (+)-**3** left), this suspension was filtered on silica gel, evaporated, and the residual oil subjected to FC (hexane/AcOEt gradient): (−)-**7** (0.004 g, 8%) and more polar (+)-**6** (0.030 g, 60%).

1.2. Jones *Oxidation of* (+)-**3**. To a soln. of (+)-**3** (0.050 g, 0.12 mmol) in acetone (2 ml) was added dropwise *Jones* reagent until persistency of the orange color (no (+)-**3** left). Then 5% aq. $NaHSO_3$ soln. (1 ml) was added and the mixture extracted with AcOEt (3 × 5 ml): (+)-**6** (0.045 g, 90%). An anal. sample was obtained by HPLC *CN* purification (hexane/i-PrOH 98:2).

1.3. *Reduction of* (+)-**6** *to* (+)-**3** *and Its C(3) Epimer* (+)-**8**. To a soln. of (+)-**6** (0.042 g, 0.10 mmol) in dry Et_2O was added $NaBH_4$ in large excess. After 2 h (TLC: no (+)-**6** left), this suspension was filtered and evaporated, and the residue was subjected to HPLC (hexane/i-PrOH 97:3): (+)-**3** (28 mg, 67%) and more polar (+)-**8** (9 mg, 22%).

(2S,6S,8S,9S)-2,9-Dibromo-8-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-one ((+)-**6**). Colorless crystals. M.p. (hexane) 118–120°. $[\alpha]_D^{25} = +25.8$ ($c = 0.10$, CCl_4). ^1H-NMR: 4.84 (br. *s*, H–C(2)); 3.33 (*m*, at −10° AB, $J_{AB} = 17.8$, 2 H–C(4)); 2.36 (br. *dd*, $J = 14.4$, 4.7, H_{eq}–C(7)); 2.07 (br. *dd*, $J = 14.4$, 12.5, H_{ax}–C(7)); 4.68 (*dd*, $J = 12.5$, 4.7, H–C(8)); 2.40 (*dt*, $J = 13.6$, 3.7, H_{eq}–C(10)); 2.23 (*ddd*, $J = 13.6$, 12.0, 3.7, H_{ax}–C(10)); 1.91 (*m*, 2 H–C(11)); 1.26 (*s*, 3 H–C(12)); 0.86 (*s*, 3 H–C(13)); 5.03 (br. *s*, H_a–C(14)); 5.36 (*t*, $J = 1.4$, H_b–C(14)); 1.86 (*s*, 3 H–C(15)); assignments based on extensive differential-decoupling and strong NOE: 5.03 → 4.68, 2.36; 1.26 → 2.07, 4.84; 0.86 → 2.36. MS: 335, 333, 331 (1, 4, 2, $[M-Br]^+$); 297, 295 (9, 9, $[M-Br-HCl]^+$); 278, 276 (4, 4); 252, 250 (3, 3); 217, 215 (15, 15); 199, 197 (17, 44); 171 (13), 169 (24); 161 (32); 133 (56); 199 (39); 105 (49); 91 (61); 83 (100).

(2S,6S,8S,9S)-2,9-Dibromo-8-chloro-5-formyl-1,1,9-trimethylspiro[5.5]undec-4-en-3-one (= *4,9-Dibromo-8-chloro-5,5,9-trimethyl-3-oxospiro[5.5]undec-1-ene-2-carbaldehyde*; (−)-**7**). Colorless oil. $[\alpha]_D^{25} = -30$ ($c = 0.03$, CCl_4). ^1H-NMR: 4.97 (br. *s*, H–C(2)); 6.55 (*s*, H–C(4)); 2,59 (*ddd*, $J = 14.5$, 5.7, 2.4, H_{eq}–C(7)); 2.10 (*dd*,

J = 14.5, 11.7, H_{ax}–C(7)); 4.98 (*dd*, J = 11.7, 5.7, H–C(8)); 2.43 (*dd*, J = 10.2, 3.6, H_{eq}–C(10)); 2.27 (*m*, H_{ax}–C(10)); 1.55 (*m*, 2 H–C(11)); 1.37 (*s*, 3 H–C(12)); 1.02 (*s*, 3 H–C(13)); 9.89 (*s*, H–C(14)); 1.85 (*s*, 3 H–C(15)). MS: 349, 347, 345 (0.4, 5, 3, $[M - Br]^+$); 311, 309, (2, 2, $[M - Br - HCl]^+$); 292, 290 (17, 17); 257, 255 (13, 13); 232, 230 (24, 14); 211 (49); 175 (74); 147 (93); 117 (60); 91 (100).

(2S,3S,6S,8S,9S)-2,9-Dibromo-8-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-ol ((+)-**8**). Semi-solid. $[\alpha]_D^{25}$ = + 18.3 (c = 0.06, CCl_4). ^{1}H-NMR: 4.27 (*d*, J = 10.4, H_{ax}–C(2)); 3.74 (*dddd*, J = 11,6, 10.4, 6.0, 2.1, H_{ax}–C(3)); 2.48 (br. *d*, J = 2.1, OH–C(3)); 2.62 (*dd*, J = 13.4, 6.0, H_{eq}–C(4)); 2.31 (*dd*, J = 13.4, 10.4, H_{ax}–C(4)); 2.24 (br. *dd*, J = 14.3, 4.8, H_{eq}–C(7)); 1.95 (*dd*, J = 14.3, 12.5, H_{ax}–C(7)); 4.71 (*dd*, J = 12.5, 4.8, H_{ax}–C(8)); 2.30–2.15 (series of *m*, 2 H–C(10)); 1.83 (*dd*, 14.0, 3.6, H_{eq} C(11)); 1.70 (*td*, J = 14.0, 3.6, H_{ax}–C(11)); 4.97 (br. *s*, H_a–C(14)); 5.39 (*d*, J = 1.5, H_b–C(14)); 1.15 (*s*, 3 H–C(12)); 0.95 (*s*, 3 H–C(13)); 1.82 (*s*, 3 H–C(15)). MS: 336, 334, 332 (0.6, 2.5, 1.5, $[M - Br]^+$); 319, 317, 315 (29, 100, 76, $[M - HBr - OH]^+$); 299, 297 (6, 6, $[M - Br - HCl]^+$); 237, 235 (20, 10); 199 (40); 185 (14); 157 (26); 143 (23); 105 (50); 91 (57).

2. *Treatment of either Obtusol* ((+)-**3**) *or Isoobtusol* ((+)-**5**) *with Zn-AcOH*. 2.1. (+)-**3**. To a soln. of (+)-**3** (0.070 g, 0.17 mmol) in Et_2O (2 ml) was added AcOH (0.3 ml) and activated Zn dust (0.4 g). After 24 h stirring at r.t., the mixture was filtered, the filtrate diluted with 5% aq. $NaHCO_3$ soln. (5 ml) and extracted with hexane, the org. layer evaporated, and the oily residue subjected to FC (hexane/AcOEt gradient): (–)-**12** (0.018 g, 53%) and more polar (–)-**11** (0.019 g, 35%).

2.2. (+)-**5**. As described in *2.1*, but with (+)-**5** (0.080 g, 0.19 mmol); reaction time, 1 h: (+)-**12** (0.015 g, 39%) and (+)-**11** (0.032 g, 53%).

2-Bromo-1,1,9-trimethyl-5-methylidenespiro[5.5]undec-8-en-3-ol (**11**). Colorless oil. (–)-**11** (2*S*,3*R*,6*S*): $[\alpha]_D^{25}$ = – 90.0 (c = 0.55, cyclohexane; [4a]: $[\alpha]_D$ = – 82). (+)-**11** (2*R*,3*S*,6*R*): $[\alpha]_D^{25}$ = + 95.0 (c = 0.79, cyclohexane; [4a]: $[\alpha]_D$ = + 82). ^{1}H-NMR: 4.67 (*d*, J = 2.9, H–C(2)); 4.13 (*quint.*, J = 2.9, H–C(3)); 2.16 (*dd*, J = 2.7, 1.7, OH–C(3)); 2.47 (*dd*, J = 14.5, 2.8, H_{eq}–C(4)); 2.69 (*dd*, J = 14.5, 3.3, 1.7, H_{ax}–C(4)); 2.21 (br. *ddd*, J = 17.5, 5.6, 2.8, H_{eq}–C(7)); 2.09 (br. *dd*, J = 17.5, 2.0, H_{ax}–C(7)); 5.28 (*m*, H–C(8)); 1.8–1.6 (series of *m*, 2 H–C(10), 2 H–C(11)); 1.03 (*s*, 3 H–C(12)); 1.04 (*s*, 3 H–C(13)); 5.08 (*t*, J = 1.6, H_b–C(14)); 4.80 (*t*, J = 1.7, H_a–C(14)); 1.57 (br. *s*, 3 H–C(15)); assignments based on extensive differential-decoupling and strong NOE: 4.80 → 5.28; 4.67 → 1.70, 1.03. ^{13}C-NMR: 43.21 (*s*, C(1)); 71.83 (*d*, C(2)); 72.40 (*d*, C(3)); 37.90 (*t*, C(4)); 141.21 (*s*, C(5)); 47.10 (*s*, C(6)); 30.07 (*t*, C(7)); 119.47 (*d*, C(8)); 132.65 (*s*, C(9)); 27.75 (*t*, C(10)); 25.94 (*t*, C(11)); 24.30 (*q*, C(12)); 20.81 (*q*, C(13)); 115.86 (*t*, C(14)); 23.07 (*q*, C(15)). MS: 300, 298 (9,9, $M^{+\cdot}$); 285, 283 (13, 13, $[M - Me]^+$); 218 (31, $[M - HBr]^{+\cdot}$); 203 (52, $[M - Me - HBr]^+$); 201 (76, $[M - HOBr]^{+\cdot}$); 159 (29), 145 (47), 119 (100), 105 (70), 91 (84).

1,1,9-Trimethyl-5-methylidenespiro[5.5]undeca-2,8-diene (**12**). Colorless oil. (–)-**12** (6*S*): $[\alpha]_D^{25}$ = – 67.0 (c = 0.60, cyclohexane; [4a]: $[\alpha]_D$ = – 32). (+)-**12** (6*R*): $[\alpha]_D^{25}$ = + 70.0 (c = 0.35, cyclohexane; [4a]: $[\alpha]_D$ = + 33). ^{1}H-NMR: 5.28 (*ddd*, J = 10.0, 2.8, 1.7, H–C(2)); 5.48 (*ddd*, J = 10.0, 4.4, 2.6, H–C(3)); 2.59 (*ddd*, J = 19.5, 4.4, 1.7, H_{eq}–C(4)); 2.92 (*d quint.*, J = 19.5, 2.8, H_{ax}–C(4)); 2.08 (*m*, 2 H–C(7)); 5.31 (*m*, H–C(8)); 1.75 (*m*, 2 H–C(10), H_{eq}–C(11)); 1.47 (*m*, H_{ax}–C(11)); 0.94 (*s*, 3 H–C(12)); 0.83 (*s*, 3 H–C(13)); 4.96 (*t*, J = 2.0, H_b–C(14)); 4.61 (*t*, J = 2.0, H_a–C(14)); 1.58 (br. *d*, J = 0.8, 3 H–C(15)). ^{13}C-NMR: 39.70 (*s*, C(1)); 137.46 (*d*, C(2)); 122.48 (*d*, C(3)); 32.68 (*t*, C(4)); 145.35 (*s*, C(5)); 43.78 (*s*, C(6)); 28.00 (*t*, C(7)); 119.60 (*d*, C(8)); 133.62 (*s*, C(9)); 28.78 (*t*, C(10)); 26.69 (*t*, C(11)); 23.22 (*q*, C(12)); 25.71 (*q*, C(13)); 110.62 (*t*, C(14)); 23.24 (*q*, C(15)). MS: 202 (16, $M^{+\cdot}$), 187 (64, $[M - Me]^+$), 159 (100), 145 (31), 131 (67), 119 (45), 105 (66), 91 (48).

3. *Attempted C(3) Epimerization of Isobtusol* ((+)-**5**). 3.1. Jones *Oxidation of* (+)-**5**. Using the same procedure and material amounts as described in 1.2.

(2R,6R,8S,9S)-2,9-Dibromo-8-chloro-1,1,9-trimethyl-5-methylidenespiro[5.5]undecan-3-one ((–)-**13**; 0.047 g, 94%) was obtained. Colorless crystals. M.p. (hexane) 125–127°. $[\alpha]_D^{25}$ = – 4.0 (c = 0.89, CCl_4). ^{1}H-NMR: 3.99 (br. *s*, H–C(2)); 3.06 (*dd*, J = 15.1, 1.9, H_{eq}–C(4)); 4.12 (*dt*, J = 15.1, 1.8, H_{ax}–C(4)); 3.18 (*dt*, J = 15.7, 2.8, H_{eq}–C(7)); 2.92 (*dd*, J = 15.7, 3.8, H_{ax}–C(7)); 4.50 (*ddd*, J = 3.6, 2.8, 2.2, H_{eq}–C(8)); 1.90 (*m*, H_{eq}–C(10), H_{eq}–C(11)); 2.25 (*ddd*, J = 15.7, 11.7, 3.0, H_{ax}–C(10)); 2.15 (*ddd*, J = 15.5, 11.7, 2.5, H_{ax}–C(11)); 1.31 (*s*, 3 H–C(12)); 0.98 (*s*, 3 H–C(13)); 4.96 (*d*, J = 1.7, H_a–C(14)); 5.15 (*d*, J = 1.9, H_b–C(14)); 1.94 (*s*, 3 H–C(15)); assignments based on extensive differential-decoupling and strong NOE: 4.96 → 2.25; 4.12 → 3.18; 1.31 → 3.99, 2.92, 2.15; 0.98 → 3.99, 1.90. ^{13}C-NMR: 42.13 (*s*, C(1)); 61.32 (*d*, C(2)); 200.82 (*s*, C(3)); 46.36 (*t*, C(4)); 144.54 (*s*, C(5)); 43.97 (*s*, C(6)); 33.23 (*t*, C(7) or C(10)); 64.92 (*d*, C(8)); 70,67 (*s*, C(9)); 33.12 (*t*, C(10) or C(7)); 25.45 (*t*, C(11)); 22.49 (*q*, C(12)); 23.84 (*q*, C(13)); 115.27 (*t*, C(14)); 32,97 (*q*, C(15)). MS: 416, 414, 412, 410 (0.4, 5, 9, 3, $M^{+\cdot}$); 335, 333, 331 (2, 11, 8, $[M - Br]^+$); 297, 295 (27, 27, $[M - Br - HCl]^+$); 278, 276 (14, 14); 252, 250 (15,15); 199, 197 (40, 100); 171 (35); 169 (69); 161 (88).

3.2. *Reduction of* (–)-**13**. To a soln. of (–)-**13** (0.030 g, 0.07 mmol) in dry Et_2O was added $NaBH_4$ in large excess. After 4 h (TLC: no (–)-**13** left), this suspension was filtered and evaporated: (+)-**5** (0.025 g, 83%). ^{1}H-NMR: ≤ 5% of another compound which was not investigated.

REFERENCES

[1] G. Guella, I. Mancini, G. Chiasera, F. Pietra, *Helv. Chim. Acta* **1990,** *73,* 1612.

[2] G. Guella, F. Pietra, *Helv. Chim. Acta* **1991,** *74,* 47.

[3] J.C. Coll, A.D. Wright, *Aust. J. Chem.* **1989,** *42,* 1591.

[4] A.G. Gonzáles, J. Darias, A. Diaz, J.D. Fourneron, J.D. Martìn, C. Perèz, *Tetrahedron Lett.* **1976,** 3051; A.G. Gonzáles, J.D. Martìn, V.S. Martìn, M. Martinez-Ripoll, J. Fayos, *ibid.* **1979,** 2717; A. Perales, M. Martinez-Ripoll, J. Fayos, *Acta Crystallogr., Sect. B* **1979,** *35,* 2771; J.D. Martìn, P. Caballero, J.J. Fernandez, M. Norte, R. Perèz, M.L. Rodriguez, *Phytochemistry* **1989,** *28,* 3365.

[5] M. Suzuki, A. Furusaki, N. Nashiba, E. Kurosawa, *Tetrahedron Lett.* **1979,** 879.

[6] F.J. Schmitz, D.P. Michaud, P.G. Schmidt, *J. Am. Chem. Soc.* **1982,** *104,* 6415.

[7] K.L. Erickson, in 'Marine Natural Products. Chemical and Biological Perspectives', Ed. P.J. Scheuer, Academic Press, New York, 1983, Vol. 5, p. 131; R. Sakai, T. Higa, C.W. Jefford, G. Bernardinelli, *Helv. Chim. Acta* **1986,** *89,* 91.

[8] a) M. Segawa, M. Suzuki, E. Kurosawa, H. Shirahama, M. Ikura, K. Hikichi, *J. Chem. Soc., Perkin Trans. 2* **1989,** 335; b) M. Suzuki, M. Segawa, T. Suzuki, E. Kurosawa, *Bull. Chem. Soc. Jpn.* **1983,** *56,* 3824.

[9] F. Pietra, 'A Secret World. Natural Products of Marine Life', Birkhäuser Verlag, Basel, 1990.

[10] J.D. Martìn, C. Pérez, J.L. Ravelo, *J. Am. Chem. Soc.* **1986,** *108,* 7801.

[11] G. Binsch, H. Kessler, *Angew. Chem. Int. Ed.* **1980,** *19,* 411.

[12] S. Forsén, R.A. Hoffman, *Acta Chem. Scand.* **1963,** *17,* 1787; S. Forsén, R.A. Hoffman, *J. Chem. Phys.* **1963,** *39,* 2892.

[13] U. Burkert, N.L. Allinger, 'Molecular Mechanics', ACS Monograph 177, American Chemical Society, Washington, D.C.,1982.

[14] C.B. LeMaster, C.L. LeMaster, H.S. True, 'Quantum Chem. Progr. Exch. 1989, QCMP 059', Indiana University, based on D.S. Stephenson, G. Binsch, 'Quantum Chem. Progr. Exch. 1978, QCPE 365', Indiana University.

[15] E. Volpi, G. Biggi, F. Pietra, *J. Chem. Soc., Perkin Trans. 2* **1973,** 571.

[16] M. Schlosser, in 'Methoden der organischen Chemie, Houben-Weyl', Ed. E. Müller, G. Thieme Verlag, Stuttgart, 1972, Vol. V/1b, p. 182–190.

[17] D.M. Doddrell, D.T. Pegg, M.R. Bendall, *J. Magn. Reson.* **1982,** *48,* 323; D.T. Pegg, D.M. Doddrell, M.R. Bendall, *J. Chem. Phys.* **1982,** *77,* 2745.

[18] V. Piantini, O.W. Sorensen, R.R. Ernst, *J. Am. Chem. Soc.* **1982,** *104,* 6800; A. Bax, R. Freeman, *J. Magn. Reson.* **1981,** *44,* 542.

[19] H. Kessler, C. Griesinger, J. Zarbock, H.R. Loosli, *J. Magn. Reson.* **1984,** *57,* 331.

[20] S. Patt, in 'Magnetic Moments', Ed. S.L. Patt, Varian Associates, Palo Alto, CA, 94303, 1990, Vol. IV, No. 2, p. 8.

[21] A. Slomp, G. Chiasera, C. Mezzena, F. Pietra, *Rev. Sci. Instrum.* **1986,** *57,* 2786.

[22] J.J. Gajewski, K.E. Gilbert (*Serena Software*), 'MMPMI (release February 25th, 1980) as adapted to MSDOS', Bloomington, Indiana, 1986.