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¹H, ¹³C NMR and X-ray crystallographic studies of highly polyhalogenated derivatives of costunolide lactone

D. Corona^{a,*}, E. Díaz^{a,*}, J.L. Nava^a, A. Guzmán^a, H. Barrios^a, A. Fuentes^b, S.A. Hernandez-Plata^b, J. Allard^c, C.K. Jankowski^c

^a Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, C.U. Coyoacán, 04510 México D.F., Mexico

^b Facultad de Química, Universidad Autónoma del Estado de México, Paseo Tollocán y Colón, Toluca 50000, Toluca, Estado de México ^c Faculté des Sciences, U de Moncton, Moncton, NB, Canada E1A 3E9

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Abstract

The costunolide lactone, a sesquiterpene compound isolated from *Zaluzania triiloba* species, reacted with several dihalocarbene sources produced by trihaloform-NaOH under successive phase transfer reactions yielding mono-, bis- and tris-dihalocyclopropane adducts. The structures, as well as the configurational assignments of the different derivatives, were established by ¹H and ¹³C NMR spectroscopy and assisted by X-ray crystallographic and molecular modelling studies.

The specific shielding of protons in the neighbourhood of different halogens on the cyclopropane moieties was correlated to the pseudocontact interactions.

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1. Introduction

Because of their magnetic sensitivity, their quadrupole moment and their associated line broadening [1–4] the four common halogen elements, except ¹⁹F, are not often used in organic NMR studies. For this reason, structural studies involving natural products containing chlorine, bromine and iodine, and their polyhalogenated derivatives are typically performed using ¹H and ¹³C NMR spectroscopy. More recently, the environmental occurrence of polyhalogenated compounds originated from the modification of natural products by widespread halogenation has attracted attention to this newer and still evolving branch of natural product chemistry.

Although their importance in synthetic organic chemistry is well known, the presence of halogen nuclei in the primary structures of natural products is less common: their occurrence is limited mainly to the marine natural products [5]. In this area, for example, some interesting acetylenic compounds were isolated from *L. grandulifera* showing the oxocin structures with one or two bromine atoms [6,7]. Fenical [8,9] reported on the isolation of bromo and chloro acetylenic alcohols from *Chondria oppositiclada* algae, and on the isolation from seaweed of the *Laurentia* species of an intriguing halogenated vinyl peroxide. Kazlauskas' [10] investigations of Antartic and Australian *Delisea fimbriata* led to the discovery of iodine-containing substances that differ structurally from the well-known naturally occurring iodinated products, in particular the thyroxine-related compounds.

Finally, several years ago Sims et al. [11] identified, in Antartic *D. fimbriata*, a series of C_8 ketones containing bromine, chlorine and iodine atoms, whose structures were confirmed by spectroscopic studies.

Natural occurring sesquiterpene lactones do not usually contain halogens. Among the interesting and simple synthetic methodologies developed to build such compounds the addition of the halocarbenes could be used to obtain their dihalocyclopropane adducts. Mathias and Weyerstahl

^{*} Corresponding authors. Tel.: +52 6224421; fax: +52 6162203. *E-mail address:* maudiaz@servidor.unam.mx (E. Díaz).

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[12] have described the preparation and spectroscopic properties of hetero-di-halosubstituted styrenes (pair of F and Cl; Br and I, etc.) and other olefins which display interesting NMR behaviour as far as the proton chemical shifts and their proton–proton coupling constants are concerned.

Despite experimental data accumulated in this field during the last decade, it should be noted that very few dihalocarbene additions to the double bonds of α , β -unsaturated carbonyls have been reported.

Our interest in difluoro carbene chemistry led to the synthesis and spectral description of several unsaturated sesquiterpene lactones after their exposure to a large excess of difluoro carbene (the small and easy-to-prepare source of the cyclopropane ring), and the investigation of the compounds formed [13–15].

Dichlorocarbenes have also been used as intermediates for the γ -lactone terpenes synthesis, in particular for the sesquiterpene lactone synthesis [16,17]. Dibromocyclopropane derivatives of the sesquiterpenes have also been used by our group for the synthesis of allene derivatives via the Hiyama red-ox Cr²⁺-catalyzed reaction [18] and more recently applied to some unusual rearrangements of dichlorocyclopropanes into dichloro methylvinylic derivatives and α , β -unsaturated aldehydes and acids [19].

Furthermore, since there are very few works reports on polyhalogenated derivatives of sesquiterpene lactones and in particular on their detailed NMR characteristics, we decided to undertake this study and report on the synthesis of polyhalogenated cyclopropane adducts attached to the costunolide lactone skeleton as well as to discuss the NMR properties of the protons attached to these structures and which are under the direct influence of the halogenated cyclopropane moieties.

Detailed studies of the high field 2D NMR spectra revealed a special behaviour of the protons attached to the sesquiterpene lactones with one, two or three different dihalocyclopropane rings. We linked this behaviour to their specific geometry and studied it with stereochemical data deduced from the X-rays and molecular modelling, particularly in the context of the pseudocontact interaction.

The shielding constant of nuclei is usually represented as a sum of two terms: a positive diamagnetic term and a negative, paramagnetic term.

The diamagnetic term largely depends on the electronic density of the nearby nucleus and remains almost constant in most chemical environments, even for heavy nuclei as the halogens are. The intramolecular influence [20] of one nucleus on the shielding of the other is called the heavy atom effect. In this case, the nuclear shielding of a lighter nucleus is translated into the change in its electronic energy level, on account of the spin-orbit coupling interactions derived from the neighbouring heavy nuclei.

On the other hand, the presence of a paramagnetic centre, either on the molecule itself or in the neighbourhood of the observed nuclei, can severely influence the observed nuclear shielding. The induced shielding effect may then be produced by two mechanism and experimentally observed shielding may be rationalized as being of either, or both, of two origins.

One of these gives rise to contact interactions as shown in the equation

$$\Delta B/B_0 = -a_\mathrm{n}g_\mathrm{e}^2 B_\mathrm{e}^2 S(S+1)/3g_\mathrm{N}B_\mathrm{N}KT$$

. .

whereas the other produces the dipolar or pseudocontact interactions given by equation

$$\Delta B/B_0 = -[(3\cos^2\theta - 1)B_e^2 S(S+1)/3r^3 KT]F(g)$$

In the equations presented, the paramagnetic-induced resonance shift ΔB is expressed as a function of the applied magnetic field B_0 , the hyperfine interaction constant a_n is expressed in Tesla, g_e is the rotationally averaged electronic value g, B_e is the Bohr magneton, g_n and B_N are the corresponding nuclear parameters, and S is the spin of unpaired electrons.

In the second equation several molecular geometry parameters appear. For instance, *r* is the separation between the resonating nuclei and the unpaired electrons (expressed in radians), θ is the angle between the vector defined by *r* and the principal axis of symmetry of the molecule, and *F*(*g*) is a function of the *g* tensor component. Substantial decrease and increase in nuclear shielding may then result from either the contact or dipolar interactions, or from both.

From these equations, we see that the paramagnetic influence on the nuclear shielding on protons in the NMR spectrum is of great importance when considering the heavy nuclei presence in the molecule. Distance and other geometrical considerations between protons and halogens should then be addressed, in order to explain the observed chemical shift for protons in the vicinity of halogen atoms.

As it has been said, the influence of fluorine, chlorine, bromine and iodide on the chemical shifts of protons or carbons is not well understood or explained. In this study, we used derivatives of sesquiterpenic costunolide lactone rigidified by introduction of dihalocyclopropane rings, in order to explain the trend in the shielding of selected proton, induced by different halogens placed in strictly geometrically defined positions. As can be noticed the exact interpretation of the proton spectra and the unambiguous assignment of protons is then the key starting point to this study. The geometrical features of the molecules should also be a credible; in this respect the X-ray and molecular modelling data were constantly challenged by the observed chemical shift, as compared to the estimated value.

2. Results and discussion

Because of the crucial importance of the correct, unambiguous assignment of the proton NMR spectra of the compounds chosen in this study, we present in the Section 5, the details of the data used to realize this objective. The tables of NMR data summarize the results used to correlate them to



Scheme 1.

the geometrical parameters deduced from X-rays or molecular modelling experiments for this group of compounds.

Several mono-, bis- and tris-dihalocyclopropane costunolide lactone adducts studied are presented in Scheme 1

The proton NMR spectra were analyzed on the basis of changes in halogen—carbon bond distances as well as on the contribution of pseudocontact effect induced by the distance and geometrical parameters of these changes. The complete ¹H and ¹³C assignments of the molecules described herein were achieved by means of the ¹H/¹H (COSY, NOESY) [21,22] and ¹H/¹³C correlation methods (HMQC, HMBC) [23–25].

For every adduct described, either 4α -15 α , 11α -13 α or 10α -14 α derivatives were obtained. On the ground of the configuration of the dihalocyclopropane adduct obtained, one would expect that H-5 α , H-7 α or H-1 α should undergo an

additional deshielding through the spatial interactions with the halogen atoms present on the cyclopropane moiety since the models may suggest a long range deshielding.

The stereochemistry of the dihalocyclopropane at C_4-C_{15} , $C_{10}-C_{14}$, $C_{11}-C_{13}$ in these compounds can be ascertained by the available NMR data and proved through the X-ray crystallographic studies as performed for the compounds **6** and **7**, as well as for the hexafluorinated adduct **13** described some years ago [13,14,26]. Derivative **13** was included in this study in order to afford the complete series of parameters such as size, bond distances and bond angles of derivatives containing several fluorine atoms.

The ¹H NMR spectrum of the adducts **2–12** displayed AB pattern corresponding to the methylene of the dihalocyclopropane attached on C₁₁–C₁₃, C₄–C₁₅ and C₁₀–C₁₄ which was unambiguously assigned through the COSY spectrum. For example, the dihalocyclopropane attached at C₁₁–C₁₃ in adduct **5** displayed at δ = 2.16 a doublet (*J* = 8.0 Hz) assigned to the *exo*-proton to the carbonyl lactone group, while the higher field doublet at δ = 2.02 was assigned to the *endo* proton.

The usual AB patterns in all adducts having the dihalocyclopropane moiety, either on $C_{11}-C_{13}$, C_4-C_{15} or $C_{10}-C_{14}$ double bond, showed the methylene geminal couplings between 7 and 8.0 Hz which enabled with help of the COSY spectrum, to assign the cyclopropane protons on C_{13} , C_{14} or C_{15} in the adducts.

Through the COSY spectrum, it was also possible to assign the key protons H-1, H-5 or H-7, since they shown the most relevant chemical shift changes which enabled to witness the pseudocontact contribution from the halogen atoms attached to the molecule.

With the complete proton assignment obtained from the COSY spectrum, ¹³C assignments were easily deduced from HMQC and HMBC spectra.

Table 1 presents the ¹H chemical shifts of the compounds **2–13**. In this table is also included some of the ¹³C chemical shifts of compounds **1**, **3–7** and **10** the assignments performed using DEPT, HMQC and HMBC experiments.

A general trend was observed for the proton chemical shift of the cyclopropane moieties in all of the haloderivatives studied. It was commonly observed that those protons on C-14 (compounds **2**, **4**, **6**, **9**, **11** and **12**; Table 1) displayed a highest chemical shift as well as the lesser chemical shift difference between both protons.

The X-ray crystallographic study of derivative **13**, previously reported [13] permitted us to extract several important parameters such as C–F, F–C–F bonds angles as well as spatial distances between H_7 – F_4 , H_7 – F_3 , H_5 – F_2 , H_5 – F_1 , H_1 – F_6 and H_1 – F_5 in particular (see Table 2).

Derivative 7 was used as model to investigate the crystallographic parameters involved in the diiodo cyclopropane moiety attached on C_{11} . In such a manner, C_{16} – I_2 , C_{16} – I_1 bond distances, I_2 –C– I_1 bond angle as well as H_7 – I_1 and H_7 – I_2 spatial distances were obtained. The data such as C–Br distance, Br–C–Br bond angle, etc. were extracted from the crystallographic studies of structures **6**, **7** and **13** and those for the structures **3**, **4**, **8–12** were obtained from molecular modelling data (Table 2).

3. Tentative semi-empirical relation between observed chemical shift of the alpha to a cyclopropane proton and the nature and geometry of that cyclopropane

The cyclopropane proton data (chemical shifts, angular parameters) for these compounds were then examined searching first for a geometrical relation between the proton chemical shift on the methine α to cyclopropane-ring and the presence of the gem-dihalogens on the same cyclopropane ring. Such a semi-empirical relation should correspond to the already specified requirement of the angular-dihedral (or longer) angle and distance between halogen and the proton effect on the proton chemical shift. The correction parameters should be electronegativity (taking account of the nature of the halogen atom) and a constant which will serve to the statistical treatment of the ensemble, and it will combine other geometrical parameters used either as a multiplicatory or additive corrective term.



example = four bond angle θ between H and $F_{cis} = \theta_{H}$, F_{cis}

Our search was oriented first toward the homodihedral dependence of the chemical shift for the same proton on the H-Ca-Cb-Cc-X homodihedral angle different for each of two halogens (θ_{HXcis} or $\theta_{HXtrans}$). In this case the equation found for 46 data was established as:

$$\delta_{\rm H} \sim KA \frac{3\cos^2\theta - 1}{r^3} f(ax_n \text{ constant}),$$
 (1)

$$x_n =$$
electronegativity (Pauling scale) (1)

The coefficient of determination within this group was found to be only $R^2 = 48\%$. Following this track the search for better correlation enabled us to consider the dependence of the proton chemical shift on the dihedral angle between H-Ca-Cb-Cc, θ_{HCc} . Two halogens electronegativity was considered as the correction parameter to the equation.



Position	Compound																			
	1		$\delta_{\mathrm{H}}\left(2\right)$	3		4		5		6		7	δ _H (8)	δ _H (9)	10		$\delta_{\rm H}$ (11)	$\delta_{\rm H}$ (12)	δ _H (13)	
	$\delta_{\rm H}$	$_{\rm H}$ $\delta_{\rm C}$	δ_{H}	$\delta_{\rm C}$	$\delta_{\rm H}$	$\delta_{\rm C}$	δ_{H}	$\delta_{\rm C}$	$\delta_{\rm H}$	$\delta_{\rm C}$	$\delta_{\rm H}$	δ _C			$\delta_{\rm H}$	$\delta_{\rm C}$				
1	2.93	46.5	1.96	3.19	48.3	2.03	51.1	2.99	47.3	2.24	49.1	3.00	47.3	3.21	2.28	3.16	48.3	2.20	2.18	2.04
2	1.88	29.5	1.83	2.05	29.2	1.87	27.9	1.96	30.2	1.90	26.0	1.95	30.2	2.05	2.04	1.90	29.3	1.99	2.04	2.58
	1.80		1.79	1.87		1.80		1.91		2.05		1.91		1.85	1.95	2.0		1.96	1.98	1.92
3	2.52	32.1	2.55	2.13	33.6	2.55	29.6	2.56	32.6	2.06	30.8	3.02	33.2	2.10	2.14	2.10	31.7	2.11	2.04	5.15
	2.48		2.36	2.08		2.37		2.54		2.15		2.99		2.10	2.08	2.07		2.09	2.04	
4		152.1			39.1		148.4		151.1		38.9		151.2				39.9			
5	2.86	51.5	2.92	2.52	54.0	3.02	50.6	2.99	52.1	2.67	51.9	3.0	52.0	2.53	2.64	2.52	51.5	2.53	2.59	2.20
6	3.94	84.7	3.98	4.35	82.0	4.08	80.4	4.08	84.6	4.37	81.0	4.09	84.4	4.36	4.38	4.34	81.9	4.24	4.35	4.51
7	2.98	43.9	3.03	2.66	44.1	2.82	43.0	2.70	44.5	2.82	43.2	2.41	47.4	2.39	2.55	2.65	44.1	3.03	2.81	2.70
8	2.25	30.3	2.70	1.75	29.9	2.24	25.6	1.76	31.8	1.23	25.6	1.74	35.1	1.75	2.30	1.28	29.4	2.60	2.14	1.76
	1.32		1.44	1.28		1.20		1.21		2.26		1.20		1.25	1.22	1.75		1.53	1.26	1.33
9	2.41	35.8	2.34	2.34	29.9	2.30	27.7	2.43	35.7	2.39	27.5	2.44	35.7	2.35	2.39	2.34	29.3	2.41	2.39	2.25
	2.13		1.64	2.27		1.62		2.10		1.61		2.07		2.35	1.63	2.28		1.62	1.56	1.49
10		149.7			147.0		32.3		148.7		32.1		148.7				146.8			
11		139.8			36.0		37.0		35.6		36.4		31.9				35.7			
12		169.5			172.0		171.9		172.2		171.9		172.7				171.9			
13	6.04	119.9	6.27	2.15	31.8	2.21	31.7	2.16	31.2	2.20	31.8	2.27	32.7	2.28	2.33	2.15	29.5	6.27	2.19	2.01
	5.64		6.57	2.02		2.02		2.02		2.05		2.19		2.16	2.21	2.02		5.57	2.03	1.96
14	4.86	111.9	1.60	5.07	115.8	1.56	37.3	4.90	112.8	1.57	37.0	4.89	112.8	5.08	1.57	5.05	115.3	1.41	1.36	1.16
	4.74		1.50	4.89		1.49		4.82		1.55		4.82		4.90	1.54	4.90		1.39	1.38	1.16
15	5.08	108.2	5.31	2.36	30.4	5.30	112.5	5.28	109.7	2.33	31.0	5.29	109.7	2.37	2.32	1.47	28.1	2.22	2.14	2.06
	4.99		5.08	1.66		5.10		5.09		1.67		5.08		1.62	1.69	2.17		1.43	1.48	1.59
16					39.8		27.4		27.4		38.4		61.2				66.3			
17							36.7				27.2						27.4			
18											36.0									
Other																				OAc, 2.1

Table 2

Compound	Bond angle ($^{\circ}$)	Bond distance (Å)	H···X distance (Å)	Dihedral angle (°)
6 ^a	Br ₄ -C ₁₇ -Br ₃ : 110.7,	Br ₄ —C ₁₇ : 1.935,	$H_7 \cdots Br_4$: 2.922,	$H_1 - C_1 - C_{10} - C_{18}$: -32.9, $C_1 - C_{10} - C_{18} - Br_6$: -2.7,
	Br ₁ -C ₁₆ -Br ₂ : 108.7,	Br ₃ —C ₁₇ : 1.896,	$H_7 \cdots Br_3$: 4.303,	$H_1 - C_1 - C_{10} - C_{18} - Br_6: -35.6,$
	$Br_5 - C_{18} - Br_6$: 110.1	$Br_1 - C_{16}$: 1.917,	$H_5 \cdots Br_1: 2.735,$	$H_1 - C_1 - C_{10} - C_{18} - Br_5: -190.0, H_7 - C_7 - C_{11} - C_{17}:$
		$Br_2 - C_{16}$: 1.916,	$H_5 \cdots Br_2$: 4.533,	$36.9, C_7 - C_{11} - C_{17} - Br_4: 9.2, H_7 - C_7 - C_{11} - C_{17} - Br_4:$
		$Br_5 - C_{18}$: 1.942,	$H_1 \cdots Br_6$: 2.798,	$46.1, H_5 - C_5 - C_4 - C_{16}: 8.2, C_{16} - C_4 - C_5 - Br_1: 9.7,$
		$Br_6 - C_{18}$: 1.882	$H_1 \cdots Br_5$: 4.644	$H_5 - C_5 - C_4 - C_{16} - Br_1: 1.0, C_7 - C_{11} - C_{17} - Br_3:$
				$-143.8, H_7 - C_7 - C_{11} - C_{17} - Br_3: -105.0,$
				$C_1 - C_{10} - C_{18} - B_{15} - 157.0, C_5 - C_4 - C_{16} - B_{12}$
7 ^a	$I_1 - C_{16} - I_2 \cdot 109.1$	$I_1 - C_{16}$; 2, 162	$H_7 \cdots I_1 : 3.012$	$H_7 = C_7 = C_{11} = C_{16} \cdot 50 \cdot 2$, $H_7 = C_7 = C_{11} = C_{16} = I_1 \cdot 55 \cdot 6$
	1 010 12 100	$I_1 = C_{16}$; 2.125	$H_7 \cdots I_2$: 4.506	$C_7 - C_{11} - C_{16} - I_1; 5.4, H_7 - C_7 - C_{11} - C_{16} - I_2; -98.4.$
		-2 -10	/ -2	$C_7 - C_{11} - C_{16} - I_2: -148.6$
13 ^a	F ₄ -C ₁₇ -F ₃ : 107.9,	F ₃ -C ₁₇ : 1.342,	$H_7 \cdots F_4$: 2.580,	$H_5 - C_5 - C_4 - C_{16}$: -15.3, $C_5 - C_4 - C_{16} - F_2$: 8.6,
	F ₁ -C ₁₆ -F ₂ : 107.0,	$F_4 - C_{17}$: 1.344,	$H_7 \cdot \cdot \cdot F_3$: 3.840,	$H_5 - C_5 - C_4 - C_{16} - F_2: -6.7, H_7 - C_7 - C_{11} - C_{17}: 36.9,$
	F5-C18-F6: 107.1	$F_2 - C_{16}$: 1.360,	$H_5 \cdots F_2$: 2.425,	$C_7 - C_{11} - C_{17} - F_4$: 8.2, $H_7 - C_7 - C_{11} - C_{17} - F_4$: 45.1,
		F ₁ -C ₁₆ : 1.354,	$H_5 \cdots F_1$: 4.075,	$H_1 - C_1 - C_{10} - C_{18}$: -34.7, $C_1 - C_{10} - C_{18} - F_5$: -0.5,
		F ₅ -C ₁₈ : 1.357,	$H_1 \cdots F_5$: 2.488,	$H_1 - C_1 - C_{10} - C_{18} - F_5$: -34.2, $C_1 - C_{10} - C_{18} - F_6$:
		$F_6 - C_{18}$: 1.344	$H_1 \cdots F_6$: 4.135	$-151.2, C_5 - C_4 - C_{16} - F_1: -145.8,$
				$H_5 - C_5 - C_4 - C_{16} - F_1: -160.8,$
. h				$H_7 - C_7 - C_{11} - C_{17} - F_3 = 104.8$
9 ^b	$I_1 - C_{17} - I_2$: 111.5,	$I_1 - C_{17}$: 2.10, $I_2 - C_{17}$:	$H_7 \cdots I_1$: 2.996,	$H_7 - C_7 - C_{11} - C_{17}$: 35.6, $C_7 - C_{11} - C_{17} - I_1$: 9.8,
	Br_1 -C16-Br ₂ :	2.10, $Br_1 - C_{16}$: 1.909,	$H_7 \cdots I_2$: 4.488,	$H_7 - C_7 - C_{11} - C_{17} - I_1$: 45.4, $H_1 - C_1 - C_{10} - C_{18} - Br_4$:
	112.3, $Br_3 - C_{18} - Br_4$:	$Br_2 - C_{16}$: 1.91,	$H_5 \cdots Br_2: 2.735,$	-35.6 , $H_1-C_1-C_{10}-C_{18}$: -32.3 , $C_1-C_{10}-C_{18}-Br_4$:
	112.2	$Br_3 - C_{18}$: 1.909,	$H_5 \cdots Br_1$: 4.564,	$-3.3, H_5 - C_5 - C_4 - C_{16} - Br_2: 3.1, H_5 - C_5 - C_4 - C_{16}:$
		$Br_4 - C_{18}$: 1.909	$H_1 \cdots Br_4$: 2.80, $H_1 = Dr_2 \cdot A 68A$	$-8.7, C_5 - C_4 - C_{16} - Br_2: 9.8, C_7 - C_{11} - C_{17} - I_2:$ 144.8. H - C - C - C - L - 100.2
			$\Pi_1 \cdots \Pi_3$: 4.064	$-144.8, H_7 - C_7 - C_{11} - C_{17} - I_2; -109.2,$ $H_7 - C_7 - C_{12} - H_7 - I_2; -109.2,$
				-147.9
12 ^b	Br1-C17-Br2: 112.6	$Br_1 - C_{17}$: 1.90	$H_7 \cdots Br_1 : 2.885$	$H_1 - C_1 - C_{10} - C_{10} - 33.8 C_2 - C_{10} - C_{10} - C_1 - 1.8$
	$C_{1}-C_{16}-C_{12}$: 113.5.	$Br_2 - C_{17}$: 1.908.	$H_7 \cdots Br_2$: 4.292.	$H_7 - C_7 - C_{11} - C_{16}$; 37.6. $Br_1 - C_{16} - C_{11} - C_7$; 9.2.
	$Cl_3 - C_{18} - Cl_4$: 113.6	$Cl_1 - C_{16}$: 1.757,	$H_5 \cdots Cl_1: 4.391,$	$H_7 - C_{16} - C_{11} - C_7 - Br_1: 46, C_5 - C_4 - C_{16} - Cl_2: 9.9,$
	5 10 4	$Cl_2 - C_{16}$: 1.758,	$H_5 \cdots Cl_2: 2.635,$	$H_5 - C_5 - C_{14} - C_{16}$: -9.2, $H_5 - C_5 C_4 - C_{16} - Cl_2$: 0°,
		Cl ₃ —C ₁₈ : 1.757,	$H_1 \cdots Cl_3: 2.70,$	$H_1 - C_1 - C_{10} - C_{18} - Cl_3: -35.6, C_1 - C_{10} - C_{18} - Cl_4:$
		Cl ₄ -C ₁₈ : 1.757	$H_1 \cdot \cdot \cdot Cl_4$: 4.475	-155.8, H ₁ -C ₁ -C ₁₀ -C ₁₈ -Cl ₄ : 190.0,
				$H_1 - C_1 - C_{10} - C_{18} - Cl_3: -36.2, C_5 - C_4 - C_{16} - Cl_1:$
				$-147.7, H_5 - C_5 - C_4 - C_{16} - Cl_1: -157.4,$
				$C_7 - C_{11} - C_{17} - Br_2$: -143.7, $H_7 - C_7 - C_{11} - C_{17} - Br_2$:
				-106.0
10 ^b	$Cl-C_{16}-Cl: 113.9,$	$Cl_1 - C_{16}$: 1.757,	$H_5 \cdots Cl_1: 2.648,$	$H_5 - C_5 - C_4 - C_{16}$: -17.3, $C_5 - C_4 - C_{16} - Cl_1$: 10.6,
	Br—C ₁₇ —Br: 112.0	$Cl_2 - C_{16}$: 1.757,	$H_5 \cdots Cl_2$: 4.394,	$H_5-C_5-C_4-C_{16}-Cl_1: -4.9, H_7-C_7-C_{11}-C_{17}: 46.3,$
		$Br_1 - C_{17}$: 1.909,	$H_7 \cdots Br_1$: 2.990,	$C_7 - C_{11} - C_{17} - Br_1$: 7.2, $H_7 - C_7 - C_{11} - C_{17} - Br_1$: 53.5,
		$Br_2 - C_{17}$: 1.908	$H_7 \cdots Br_2$: 4.323	$C_5 - C_4 - C_{16} - Cl_2$: -145.0, $H_5 - C_5 - C_4 - C_{16} - Cl_2$:
				-160.5, C/-C11-C1/-Br2: -145.6,
ap	$D_{m} = C_{m} = D_{m} = 112$	$D_{\pi} - C \rightarrow 1.000$	$II = D_{m} + 2.042$	$H_7 - C_7 - C_{11} - C_{17} - BF_2$: 99.5
5	$DI = C_{17} = DI: 112,$ $Pr = C_{17} = Pr: 111.4$	$BI = C_{17}$: 1.909, $Br = C_{17}$: 1.008	$\Pi_7 \cdots \Pi_1 : 5.045,$ $\Pi \Pi_{r_1} : 4.242$	$H_7 - C_7 - C_{11} - C_{17}$; 47.3, $C_7 - C_{11} - C_{17} - BI_1$; 0.8, $H_7 - C_7 - C_{11} - C_{17}$; 47.5, $C_7 - C_{11} - C_{17} - BI_1$; 0.8,
	ы-с ₁₆ -ы. пп.4	$Br = C_{17}$. 1.908, $Br = C_{17}$: 1.908	$H_7 \cdots BI_2$. 4.343, $H_7 \cdots Br_2$: 2.765	$H_5 - C_5 - C_4 - C_{16} - I_{5.0}, C_5 - C_4 - C_{16} - BI_{3.} I_{0.7},$ $H_7 - C_7 - C_4 - Br_{2.7} - 5.0 H_7 - C_7 - C_4 - BI_{3.} I_{0.7},$
		Br $-C_{16}$: 1.909, Br $-C_{16}$: 1.909	$H_5 \cdots BI_3 \cdot 2.703,$ $H_5 \cdots Br_4 \cdot 4.598$	-161.2 H ₂ -C ₁₆ -13.5 $-5.0, 115$ -5.5 -6.5 -16 -161.2 H ₂ -C ₁₇ -C ₁₇ -Br ₂ -54.3
		DI C ₁₆ . 1.909	115 B14. 4.590	$H_7 - C_7 - C_{11} - C_{17} - Br_2^* - 985 C_5 - C_4 - C_{16} - Br_4^*$
				-145.6 C ₇ -C ₁₁ -C ₁₇ -Br ₂ : -99.3
8 ^b	I-C ₁₇ -I: 110.9.	I-C ₁₇ : 2.10, I-C:	$H_7 \cdots I_1$: 3.133.	$H_7 - C_7 - C_{11} - C_{17}$; 45.0, $C_7 - C_{11} - C_{17} - I_1$; 7.4,
	Br-C ₁₆ -Br: 112.6	2.10, Br-C ₁₆ : 1.908.	$H_7 \cdots I_2$: 4.524.	$H_7 - C_7 - C_{11} - C_{17} - I_1$: 52.4, $C_5 - C_4 - C_{16} - Br_1$: 10.6.
	10	Br-C ₁₆ : 1.910	$H_5 \cdots Br_1: 2.758,$	$H_5-C_5-C_4-C_{16}$: -15.2, $H_5-C_5-C_4-C_{16}-Br_1$:
			$H_5 \cdots Br_2: 4.592$	$-4.6, H_5 - C_5 - C_4 - C_{16} - Br_2: -161.0,$
				$C_5 - C_4 - C_{16} - Br_2: -145.8, H_7 - C_7 - C_{11} - C_{17} - I_2:$
				$-101.2, C_7 - C_{11} - C_{17} - I_2: -146.2$
11 ^b	Cl—C ₁₆ —Cl: 113.8,	Cl—C ₁₆ : 1.757,	$H_5 \cdots Cl_3: 2.664,$	$Cl_3 - C_{16} - C_4 - C_5$: 7.8, $H_5 - C_5 - C_4 - C_{16}$: -18.9,
	Cl—C ₁₇ —Cl: 113.5	Cl—C ₁₆ : 1.757,	$H_5 \cdots Cl_4$: 4.434,	$H_5 - C_5 - C_4 - C_{16} - Cl_3$: 11.1, $H_1 - C_1 - C_{10} - C_{17}$: 47.2,
		Cl—C ₁₇ : 1.757,	$H_1 \cdots Cl_1: 2.832,$	$C_1 - C_{10} - C_{17} - Cl_1$: 8.0, $H_1 - C_1 - C_{10} - C_{17} - Cl_1$: 55.2,
		Cl—C ₁₆ : 1.757	$H_5 \cdots Cl_2: 4.147$	$H_1 - C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{10} - C_{17} - C_{12} = -100.0, C_1 - C_{17} - C_$
				-147.2, H ₅ -C ₅ -C ₄ -C ₁₆ -Cl ₄ -166.6,
				$C_5 - C_4 - C_{16} - Cl_4 = -147.7$

Compound	Bond angle ($^{\circ}$)	Bond distance (Å)	H···X distance (Å)	Dihedral angle (°)
4 ^b	Br—C ₁₇ —Br: 107.5, Br—C ₁₆ —Br: 112.5	Br- C_{17} : 1.909, Br- C_{17} : 1.913, Br- C_{16} : 1.908, Br- C_{16} : 1.909	$\begin{array}{l} H_7 \cdots Br_1: \ 2.906, \\ H_7 \cdots Br_2: \ 4.315, \\ H_1 \cdots Br_3: \ 2.794, \\ H_1 \cdots Br_4: \ 4.644 \end{array}$	$\begin{array}{c} H_1-C_1-C_{10}-C_{17}: -31.2, \ C_1-C_{10}-C_{17}-Br_3: -3.4, \\ H_1-C_1-C_{10}-C_{17}-Br_3: -34.6, \ H_7-C_7-C_{11}-C_{16}: \\ 38.6, \ C_7-C_{11}-C_{16}-Br_1: \ 8.4, \ H_7-C_7-C_{11}-C_{16}-Br_1: \\ 47.2, \ C_7-C_{11}-C_{16}-Br_2: -144.6, \\ H_7-C_7-C_{11}-C_{16}-Br_2: -136.0, \\ H_1-C_1-C_{10}-C_{17}-Br_4: -190.0, \ C_1-C_{10}-C_{17}-Br_4: \\ -158.7 \end{array}$

Table 2 (Continued)

^a Method: X-ray.

^b Method: molecular modelling.

In this case we arrived to Eq. (2) with the correlation using 23 proton chemical shifts. The measured data give a confidence of 43%. The use of the electronegativity of the different halogens enabled us to improve the coefficient of determination of 59%.

$$\delta_{\rm H} \ Kb \frac{n\cos^2\theta_1\cos^2\theta_2}{r^3} f(bx^n \text{ constant}) \tag{2}$$

As a result of these two correlations it seems that the chemical shift of alpha to cyclopropane proton is sensitive to both cis and trans halogens. This dependence however, could be presented as the trigonometrical function of the $\cos^2 \theta_{\text{H,Ca}}$, the angle between observed proton and the third carbon which is holder of two geminal halogens. The correlation with two individual halogen angles is not as important in this measurement as this first dihedral angle value is. It seems that the protons are shielding according to the combine effect of two halogens on this carbon, where both halogens act as a corrective term. The angle between these two halogens is related to its sp³ character, two bond X–Cc–X angle vary from 108° to 113°, which is not much different, for the entire halogen series. The dependence on the distance between the proton and the single halogen also seems to be already included in the angular term and from one compound to the other does not vary much. The partition of the X-Cc-X angle in projection to the observed proton ion as "homodihedral" partial angle which in principle should affect the r^{-3} , seems also to be of secondary importance because the measured difference between the homodihedral angles of H-Ca-Cb-Cc- X_{cis} and for the same proton H-Ca-Cb-Cc-X_{trans} (proton cis and

trans to the halogens) remains relatively constant and varies from 140° to 150° . In the calculations (Hyper Chem 6 Mm^+) the bond distances of Cc–X used were for F, Cl, Br and I, respectively, 1.34, 1.75, 1.91 and 2.16 Å.

The cyclopropane proton data for these compounds (chemical shifts and angular parameters) were then treated searching for other geometrical relation between the proton chemical shift on α - to cyclopropane ring and the influence of the gem-dihalogen atoms.

Such a semi-empirical relation should correspond to the already mentioned requirements of the angular (dihedral or other angle) and distance between halogen and the proton effects on the proton chemical shift. The correctional parameter should again be an electronegativity, which takes into account the nature of the halogen atom (the usual constant will serve the statistical treatment of the ensemble).

Following these calculations, two more correlations were made on the ensemble of geometrical parameters, because of the availability of separately, two homodihedral angles H–Ca–Cb–Cc–X for every proton. The semi-empirical equation was made with the assumption that, of two halogens placed in an space around a proton in specific manner, the *cis* halogen has different influence than the *trans* one. Reduction of this semi-empirical equation allowed to define the term $\delta_{\rm H}$ according to Eq. (3) (Table 3) and which for a given set of 23 data, showed an $R^2 = 16\%$ for *cis* and $R^2 = 54\%$ for *trans* without any corrective X_n term.

When the electronegativity X_n is applied, as a corrective multiplicatory term according to Eq. (5) (Table 3) the

Table 3

Karplus-type equation between δH_x of the α - to cyclopropane proton and dihalocyclopropane nature and geometry

Formula of equation ^a	$R^2 (\%)^{b}$	
$\delta_{\rm H} \sim f(A_{\rm n};\cos^2 heta_{{\rm X},{ m H}_{cis}};C)$	(3)	16
$\delta_{\rm H} \sim f(A_{\rm n};\cos^2\theta_{{\rm X},{\rm H}_{trans}};C)$	(4)	54
$\delta_{\rm H} \sim f(A_{\rm n};\cos^2\theta_{{\rm X},{\rm H}_{cis}};C;X_{\rm n})$	(5)	51
$\delta_{\rm H} \sim f(A_{\rm n};\cos^2\theta_{\rm X,H_{trans}};CX_{\rm n})$	(6)	63
$\delta_{\rm H} \sim f[A_1(\cos^2\theta_{\rm X,H_{trans}};C_1) + B_1(\cos^2\theta_{\rm X,H_{cis}};C_2)]$	(7)	49
$\delta_{\rm H} \sim f[A_1(\cos^2\theta_{\rm X,H_{trans}};C_1) + B_1(\cos^2\theta_{\rm X,H_{cic}};C_2) + DX_{\rm n}]$	(8)	63
$\delta_{\rm H} \sim f[A_1(\cos^2\theta_{\rm X,H_{trans}};C_1) + B_1(\cos^2\theta_{\rm X,H_{cis}};C_2)X_{\rm n}]$	(9)	76 (64) ^c
$\delta_{\rm H} \sim f[A_1(\cos^2\theta_{\rm X,H_{trans}};C_1) + B_1(\cos^2\theta_{\rm X,H_{cis}};C_2)](D\sigma)$	(10)	75 (62) ^c

^a A, B, C, D – constants; X_n – electronegativity, Pauling scale; σ – Shoolery shielding effects; θ_x – angle as defined between X and H_x (H_{cis} or H_{trans}); X–F, Cl, Br or I (*cis* or *trans*); f=function of For detailed Eq. (9) for three halogens $\delta_H = (2.33 + 2.81 \cos^2 \theta_{X,H_{rins}} - 18.68 \cos^2 \theta_{X,H_{cis}})X_n$.

^b Coefficient of determination or R^2 .

^c For three halogens, except iodine

agreement reached was 51% but according to Eq. (3) reach only 16.5%.

Finally, the last semi-empirical equations were deduced with the emphasis on both halogens influence on the measured proton chemical shift. As a result the coefficient of determination for all 23 data (23 pair of coordinates) were at 49% without electronegativity term (Eq. (7)) and up to 63% with X_n additive term (Eq. (6)). The same term used as multiplicatory correction lead to 64% of correlation (Eq. (9)).

Last attempts were made assuming that the agreement of data for three of four halogen F, Cl and Br, is much better than when I is included into calculations. As a result of such a reduced set of data, of 20 instead 23 (or six values over 46 entries less) for the best equation (Eq. (9)) the agreement factor found was 76%. When additionally monitored by electronegativity, used as an additive term the correlation was at 64% and when the electronegativity was used as a corrective multiplicatory term, the R^2 within such a reduced set was at 74%.

From these nine models, the best semi-empirical equation found was by far Eq. (9) for the three halogens, which means that the dependence of the observed chemical shift of both halogens *cis* and *trans* to the methine proton in alpha-position to the dihalocyclopropane ring could be modulated via the homodihedral angle. When this "Karplus-type" equation was monitored by Shoolery shielding effect corrections, applied as multiplicatory term, the best fit of data for four halogens (F, Cl, Br and I) was found at $R^2 = 62\%$. When the same equation was recalculated on a reduced number of halogens (without iodine) this fit was improved to $R^2 = 75\%$ (Eq. (10)).

4. Conclusions

The interpretation of these results is leading to the conclusion that the induced proton chemical shift of the protons H₁, H₅ and H₇ is depending on the dihedral angle between halogen atoms in the vicinity as well as on the proton–halogen distance, according to the pseudocontact Eq. (2) where the later relationship shown a dependence on r^{-3} , and on the $\cos^2 \theta$ (homodihedral). As can be observed in Table 1, the protons H₁, H₅ and H₇ shown a paramagnetic shielding following the relationship I>Br>Cl>F which is opposite to the expected relationship coming from electronegativity (F>Cl>Br>I).

It is proposed a semi-empirical correlations in which the use of the corrective terms as electronegativity and the Shoolery shielding effects [30] only affords small improvements to such approaches.

5. Experimental

¹H and ¹³C NMR spectra were recorded on a Varian Unity 300 operating at 300.0 MHz for ¹H and 75.0 MHz for ¹³C. High resolution and 2D NMR spectra were recorded on a Varian Unity 500 operating at 500.0 MHz for ¹H and 125.0 MHz for ${}^{13}C$ spectra were obtained at 300 K and chemical shifts are expressed relative to TMS (0.00 ppm) for ${}^{1}H$. For ${}^{13}C$ NMR reference, the centre peak of the 1:1:1 multiplet of the CDCl₃ was assigned the value of 77.0 ppm.

The experiments were performed using an inverse detection 5 mm probe. The COSY, NOESY, HMQC and HMBC spectra were recorded using the standard Varian Unity programs.

The ¹H and ¹³C resonances were identified through interactive interpretation of NOESY, COSY, HMQC and HMBC spectra (Table 1).

For analytical purpose, the mass spectra were recorded on a JEOL JMS-5X 10217 instrument in EI/PI mode, 70 eV, 200 °C, via direct probe. Only the molecular ion (m/z) values are reported. IR spectra were recorded on a Nicolet Magna 55-X-FT instrument.

In order to prepare some fluorinated adducts derived from costunolide lactone, we performed two different unsuccessful reactions: CF_3HgPh/C_6H_6 /reflux (Seyferth reaction) [27–29]; or ClCF₂COONa /diglima/reflux. Both procedures failed due to the fact that costunolide lactone underwent undesirable fast polymerization.

Because we considered necessary to have available high resolution ¹H NMR data of tris-difluoro cyclopropane adduct to compare we have used as model the trisdifluorocyclopropane derivative of Zaluzanin C acetate (13) previously described [26] which enabled us to get the proton chemical shift sought.

The dihalocarbene, generated by phase transfer reaction using HCX₃ (X = Cl, Br, I)/NaOH/Triton B has already been used to synthesize sesquiterpenic dihalocyclopropane lactones as well as the corresponding mono-, bis- and trisdihalocyclopropane adducts (see Scheme 1). Thus, when costunolide lactone **1** was reacted with HCBr₃/NaOH/Triton B, the mono-dibromocyclopropane adducts **2** and **5**, were obtained as well as the correspondent bis-dibromocyclopropane **3** and **4** and tris-dibromocyclopropane **6** derivatives. The structures of these compounds were characterized mainly by ¹H and ¹³C NMR spectra (see Table 1).

Compound 7 is a diiodine derivative obtained with the phase transfer reaction of the costunolide lactone 1 with CHCI₃. When this diiodocyclopropane derivative was later reacted with HCBr₃/NaOH/Triton B a new diiodo, dibromo adduct 8 as well as diiodotetrabromo adduct 9 were obtained.

Chlorinated derivatives were obtained when the source of the dihalocarbene was HCCl₃. Therefore, when costunolide lactone **1** reacted with HCCl₃/NaOH/Triton B one only tetrachlorinated adduct was obtained.

Likewise, adducts possessing in the molecule chlorine as well as bromine were obtained by two steps dicarbohalogenation (e.g. from compound **5** and compound **11**). When dibromo derivative **5** reacted with CHCl₃/NaOH/Triton B a new dibromodichloro adduct **10** was isolated. On the other hand, when the tetrachloro adduct **11** was reacted with HCBr₃/NaOH/Triton B a dibromotetrachloro derivative **12** was obtained. Compound **2**, m.p. 187–189 °C; $C_{16}H_{18}Br_2O_2$; MW 400. MS m/z 400 $[M^+]$, 402 $[M^+ + 2]$, 404 $[M^+ + 4]$, 321, 323, 256 (100).

Compound **3**, m.p. 140–141 °C; $C_{17}H_{18}O_2Br_4$; MW 570. MS *m*/*z* 570 [*M*⁺], 572 [*M*⁺ + 2], 574 [*M*⁺ + 4], 576 [*M*⁺ + 6], 578 [*M*⁺ + 8], 491, 493, 495, 497, 411, 413, 415, 388, 171, 256, 129, 57 (100); IR v_{max} (cm⁻¹) 2952, 2871, 1776, 1143.

Compound 4, m.p. 203–204 °C; $C_{17}H_{18}O_2Br_4$; MW 570. MS *m/z* 570 [*M*⁺], 572 [*M*⁺ + 2], 574 [*M*⁺ + 4], 576 [*M*⁺ + 6], 578 [*M*⁺ + 8], 495, 493, 491, 467, 413, 390, 386, 388 (1 0 0), 307, 227; IR ν_{max} (cm⁻¹) 2958, 2929, 1778, 1309, 1207, 1141, 1055.

Compound **5**, m.p. 110–111 °C; $C_{16}H_{18}O_2Br_2$; MW 400, MS EI *m*/*z* 400, 402 [*M*⁺ + 2], 404 [*M*⁺ + 4]; IR ν_{max} (cm⁻¹) 3086, 3006, 2943, 1772, 1641, 1323, 1240, 1152.

Compound **6**, m.p. 241–243 °C; $C_{18}H_{18}Br_6O_2$; MW 740. MS *m*/*z* FAB MH⁺ 741, 743 [MH⁺ + 2], 745 [MH⁺ + 4], 747 [MH⁺ + 6], 749 [MH⁺ + 8], 751 [MH⁺ + 10], 753 [MH⁺ + 12]; 665, 664, 663, 661, 648; IR ν_{max} (cm⁻¹) 2962, 2929, 2873, 1776, 1244, 1141.

Compound 7, m.p. 158–159 °C; $C_{16}H_{18}O_2I_2$; MW 496 MS FAB m/z MH⁺ 497, 154 (100), 136; IR ν_{max} (cm⁻¹) 3081, 2931, 2871, 1765, 1638, 1237, 1141, 1017.

Compound **8**, m.p. 68–70 °C; $C_{17}H_{18}O_2Br_2I_2$; mw 666. MS *m*/*z* 666 [*M*+], 668 [*M*⁺ + 2], 670 [*M*⁺ + 4], 391, 359, 337, 307, 263, 205; IR ν_{max} (cm⁻¹) 2954, 2933, 1768, 1303, 1137, 1029.

Compound **9**, m.p. 199–200 °C; $C_{18}H_{18}Br_4I_2O_2$; MW 836. MS *m*/*z* FAB MH⁺ 836, 838 [MH⁺ + 2], 840 [MH⁺ + 4], 842 [MH⁺ + 6], 844 [MH⁺ + 8], 154 (100), 136; IR ν_{max} (cm⁻¹) 2960, 2875, 1768, 1137, 1037.

Compound **10**, m.p. 148–149 °C; $C_{17}H_{18}O_2Br_2Cl_2$; MW 482. MS m/z 482 $[M^+]$, 484 $[M^++2]$, 486 $[M^++4]$, 488 $[M^++6]$; IR ν_{max} (cm⁻¹) 3080, 2952, 2873, 1776, 1467, 1417, 1327, 1238, 1201, 1143.

Compound **11**, m.p. 243–245 °C; $C_{17}H_{18}Cl_4O_2$; MW 394. MS m/z 312 [M^+ – 82], 314 [M^+ – 84], 316 [M^+ – 86], 230, 149 (1 0 0), 216 (85), 277 (35), 91 (50).

Compound **12**, m.p. 240–242 °C; $C_{18}H_{18}Cl_4Br_2O_2$; MW 564. MS m/z [M^+] 564, 566 [M^+ + 2], 568 [M^+ + 4], 570 [M^+ + 6], 572 [M^+ + 8], 574 [M^+ + 10], 533, 470, 435, 374 (1 0 0), 309 (30), 201 (50), 91 (70).

6. Calculations

The atomic coordinates used for these calculations were obtained from the crystallographic data or from the molecular modelling (Table 2). The homodihedral angles were calculated by optical superimposition of the first dihedral angle H–Ca–Cb–Cc on the second dihedral angle Ca–Cb–Cc–X, which indicates that the carbon Cb is not as important as the Cc for these estimations.

Two different mode of applications of the electronegativity as a corrective term to this equation were used to take into account the difference in the halogen atom nuclear characteristics: first, as an additive term to the equation or the second one as multiplicatory term. Both approaches are used in a series of such equations developed after seminal works of Karplus [31].

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