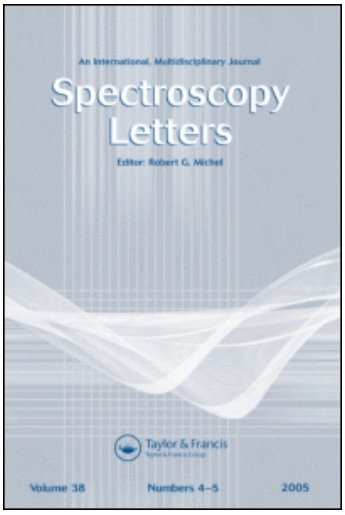

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The Use of Heteronuclear Shift Correlation ^{19}F-^{1}H. The Chemical Shift Assignment of Fluorinated (*mono, Bis*, and *tris* Gem Difluoro) Cyclopropane Derivatives of Sesquiterpene Lactones.

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THE USE OF HETERONUCLEAR SHIFT CORRELATION ^{19}F-^{1}H. THE CHEMICAL SHIFT ASSIGNMENT OF FLUORINATED (MONO, BIS, AND TRIS GEM DIFLUORO) CYCLOPROPANE DERIVATIVES OF SESQUITERPENE LACTONES.

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ABSTRACT

The ^{19}F-^{1}H heterocorrelated NMR experiments enable the final assignments of structures of six difluorocyclopropane (mono,bis and tris gem) sesquiterpene lactones of helenalin and parthenin series.

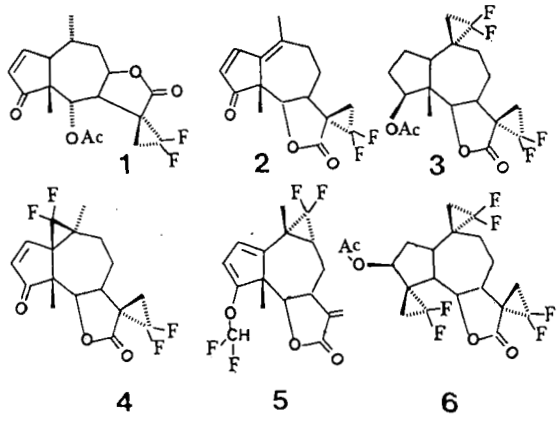
INTRODUCTION

In our previous work of fluorinated sesquiterpenes,the 1D NMR analysis of these compounds was reported[1,2].Several uncertainties remain unsolved due mainly to the high field proton signals which overlap even at 300 MHz or higher fields.

In continuation of this research[3],2D NMR heteronuclei experiments were used to unscramble the areas in proximity of fluorine atoms in particular and to further asign all proton signals.

DISSCUSSION

Six fluorinated sesquiterpene lactones (1-6) were studied(Scheme 1).These lactones have two,four, or six fluorine atoms attached on a cyclopropane ring at various possitions. The studies of fluoropseudoguayanolides and fluoroguayanolides provide interesting stereochemical data because the fluorine substituent effects gives information on the chemical shifts and coupling constants for both fluorines and protons in their proximity. The selected structures allow systematic examination of the effects mentioned above.



1 2 3 4 5 6

^{19}F NMR together with ^{1}H and ^{13}C high resolution NMR was used to examine the structures having the sesquiterpene fluorines at specific positions with a stereochemistry precisely established.

In order to identify and assign the newly observed ^{1}H-^{19}F long range coupling,the hetero equivalent of COSY experiment was used[4]. The experiment offers an additional benefit of phase sensitive detection[5,6].

Long range couplings between ^{1}H and ^{19}F nuclei has also been of interest from both stereochemical and theoretical point of view,since that type of interaction proceede by a through space mechanism[7]. The characteristic long range couplings with ^{19}F as well as ^{1}H, ^{13}C chemical shifts and ^{1}H-^{1}H, ^{1}H-^{19}F and ^{19}F-^{13}C coupling constants together with resulting multiplicity of signals are presented in Tables **1-3**.

The unambiguous chemical shift heteronuclear assignment of protons of compounds 1 and 2 were done using the HETCOR ^{1}H-^{13}C modulated experiment for $^{2}J_{C\text{-}H}$ and $^{3}J_{C\text{-}H}$ Cross sections through appropiate carbon signals from compound **2** enable to localize H-7 at δ=2.41 while the C-9 methylene protons appeared as a multiplet at δ=2.76(H-9) andδ=2.40 (H-9') with a geminal coupling of $^{2}J_{H\text{-}H}$=-19.5 Hz. Similarly the chemical shift assignment of H-8 and H-8' were made via correlation of the chemical shift of C-8 at δ_C=22.5 with the protons at δ=2.25 and δ=1.45 respectively.

Results from the 2D NMR experiments for compound 3 are confirmed by the contour plot and the cross sections of all protons coupled to four fluorine atoms on C-13a and C-15a For example, H-13 and H-13'

Table 1 ^{1}H NMR chemical shifts[a] and coupling[b] constants for compounds 1-6

Position	1	2	3	4	5	6
1	3.06 ddd (3.0,2.0)		2.15			
2	7.70 dd (6.0,3.0)	8.01 d (5.6)	1.82, 1.40	7.40 d (6.0,1.5)	5.52m (2.8,1.2, 0.8)	
3	6.05 dd (6.0,2.0)	6.05 d (5.6)	1.51	6.30 d (6.0)	6.18 dd (4.5,2.8)	5.10
4			5.20			
5						1.50
6	5.06 d (0.5)	4.54 d (6.4)	4.70	4.88 d (7.0)	4.58	4.46
7	2.80 m (2.5,5.0,0.5)	2.41	3.18	2.72	3.10	2.70
8	4.93	2.45, 2.27	1.55	1.50	1.71, 1.60	1.30
9	2.50, 1.70	2.76, 2.40 (5.9, 19.5)	1.70, 1.65	2.00, 1.50	1.38 m (3.9,3.9, 10.5)	2.20, 1.50
10	2.13					
13	2.45, 2.27	2.15, 1.60	2.00, 1.72	2.15, 1.60	6.28, 5.65	2.00 1.72
14	1.06	1.42[c]	1.02	1.50	1.60	1.60
15	1.25	1.93	1.55, 1.08	1.32	1.48 (2.3,2.8)	1.15
OAc	1.93		2.10			2.02
17					6.42 dd (72.2, 74.8)	

a.) chemical shifts in ppm from internal TMS
b.) coupling constants in Hz given in parentheses
c.) obscured by other resonances

show correlations with fluorine attached on C-13a (δF_A=-135.22,δF_B=-138.61,^{2}J=-153.8 Hz) and the protons on C-15 correlated with fluorines at δF_a=-132.64 and δF_b=-134.4 ($^{2}J_{FF}$=-158.0 Hz). Similarly, application of the heteronuclear pulse sequence to the other compounds in this series enable the assignment of all long range ^{1}H-^{19}F couplings.

For the tetrafluorinated sesquiterpene derivatives **4** and **5** fluorine substitution on C-13a in compound **4** did not produce a large chemical shift change. The proton chemical shifts of C-13 methylene were readily assigned by comparison with compound **2**.

Table 2 ^{13}C NMR chemical shifts[a] and coupling constants[b] for compounds 1-5

Position	1	2	3	4	5
C-1	53.40	137.13	44.34	76.30?	139.25
C-2	162.00	155.81	22.56 (10.9)	159.6	128.0
C-3	128.90	126.87	26.71	130.50	105.40
C-4	208.50	209.20	79.81	208.50	158.41
C-5	54.40	49.15	51.50	54.00	57.35
C-6	74.70	79.03	88.00	81.60	79.42
C-7	43.90	38.64	38.26	41.30	40.53
C-8	79.80	22.53	23.64	23.80	27.88
C-9	40.20	34.70	29.70 (10.2)	36.20	28.47 (10.2)
C-10	25.80	136.77	30.92	28.20	29.50
C-11	37.50	36.95 (10.2)	34.35	37.50	140.88
C-12	170.80	170.50	171.03	169.50	169.30
C-13	18.00 (9.8)	17.42 (10.2)	18.20 (10.2)	19.20	122.82
C-14	17.00	18.91	9.37	23.40	22.58
C-15	20.50	21.30	16.70	17.80	16.78 (7.30)
C-13$_a$	110.40 (290.8)	110.20 (284.1,295.1)	110.20 (279.0,298.6)	115.0	
C-15$_a$			114.20 (287.0,290.0)	107.0	116.50 (263)
C-16					115.24 (210.0)
OAc	169.1,19.3		170.76,21.18.		

a.-) chemical shifts in ppm referenced to TMS
b.-) 13C-19F coupling constants in Hz given in parentheses

Substitution of a difluoromethylene at C1-C10, as illustred in compound **4**,(fig 3)leads to an AB pattern doublet in ^{19}F NMR and is showing a larger geminal coupling ($^2J_{FF}$=-160.0 Hz) than the usual range (-138 to -150 Hz). The higher value of such chemical coupling constants , compared with those observed on compound **5** for C-15a difluoromethylene ($^2J_{FF}$ =-150.2 Hz) , could be explained as a contribution of π orbitals of C2-C3 double bond. The fine splitting of both fluorines attached to C-15a in compound **4** (δF_A=-135.80 and δF_B=-138.30) was due to a long range coupling with C-15 methyl ($^4J_{H\text{-}F}$=1.5 Hz) as well as with C-9 methylene protons ($^4J_{H\text{-}F}$=1.5 Hz).

A considerable change was observed in the ^{19}F spectrum of compound **5**.The fluorine atoms on C-16 appeared as a doublets of doublets of

Table 3 ^{19}F chemical shifts[a] and coupling constants[b] for compounds 1-6

Fluorine	1	2	3	4	5	6
C-13a F_2	-138.1 ddd- -138.4 ddd $^2J_{FF}$ -138 J_{FH} 9,10,5.5 $J_{HF'}$ 4.5,9	-133.27 ddd -134.80 ddd $^2J_{FF}$ -148 J_{FH} 11.8,7.5 $J_{F'H}$ 11.8,4.3	-135.22 ddd -138.61 m $^2J_{FF}$ -153.8 J_{FH} 7.9,12.1 J_{FH} 3,6 12.0 3.6	-133.3 ddd -134.7 ddd $^2J_{FF}$ -148 J_{FH} 11.0,9.5 $J_{F'H}$ 12.0,5.0		-135.45 ddd -139.93 m $^2J_{FF}$ -154 J_{FH} 4,12,3 $J_{F'H}$ 8.0,12
C-15a F_2			-132.64 m -134.36 m $^2J_{FF}$ -158.0 J_{HF} 12.8	-135.80 d -138.30 d $^2J_{FF}$ -160	-130.09 dd -139.95 d $^2J_{FF}$ -150.2 J_{FH} 14.7	-137.64 m -140.06 m $^2J_{FF}$ -160 J_{FH} 8.0,9.0
C-16 F_2					-83.82 ddd -85.41 ddd $^2J_{FF}$ -167.2 J_{FH} 74.8 J_{FH} 72.20 J_{FH} 1.7 J_{FH} 0.8	
C-14a F_2						-138.73 t J_{FH} 9.0

a.) chemical shifts in ppm referenced to internal $CFCl_3$ in $CDCl_3$.
b.) coupling constants in Hz

doublets at δ=-83.82 and δ=-85.41 with a $^2J_{FF}$=-167.2 Hz. This means that for both fluorine atoms a long range $^5J_{H\text{-}F}$ coupling 0.8 and 1.7 Hz respectively existed along with the coupling to the proton attached at C-3 (δ=5.52). The identification of long range coupling ^1H-^{19}F enable to assign with precision the stereochemistry of **5**. The compound 5 displayed a five bond coupling between H-2 and the fluorine attached on C-15a($^5J_{H\text{-}F}$=4.5 Hz). Its Dreiding model structures show that this coupling arises from the H-2 and the fluorine atom bonds along A-B rings junction ,being aligned in the coplanar extended "W" orientation.

Other non"W" type heteronuclear coupling to both fluorine atoms were also detected in 2D correlation spectra of compounds **1-5**. In the

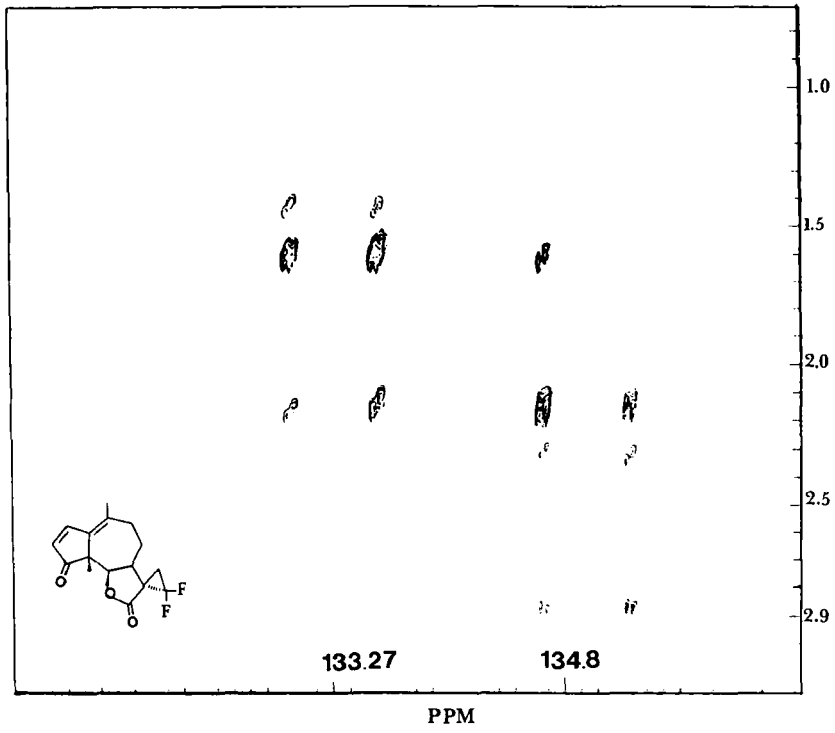


Fig 1.- Hetcor $^{1}H-^{19}F$ of compound 2

experiment mentioned previously a four bond $^{4}J_{H-F}$ couplings between CH_3-15 for both fluorine (2.0 Hz) is detected.Finally, a long range "W" is also observed for the fluorine attached to the C-15a and the β proton on C-8.

Carbofluorination of the guayanolide derivative from Zaluzanin D afforded the hexafluoroderivative **6**. X-ray crystallography data for this compound indicate that chiral centers were formed during the difluorocarbenation reaction [8,9] . A substitution performed on C-13a by a pair of fluorine atoms and the recording of its ^{19}F NMR spectra indicates the appearance of an AB doublet at δF_A=-135.45 δF_B=-139.93 with coupling established at $^{2}J_{FF}$=-154.0 Hz , indicating additional

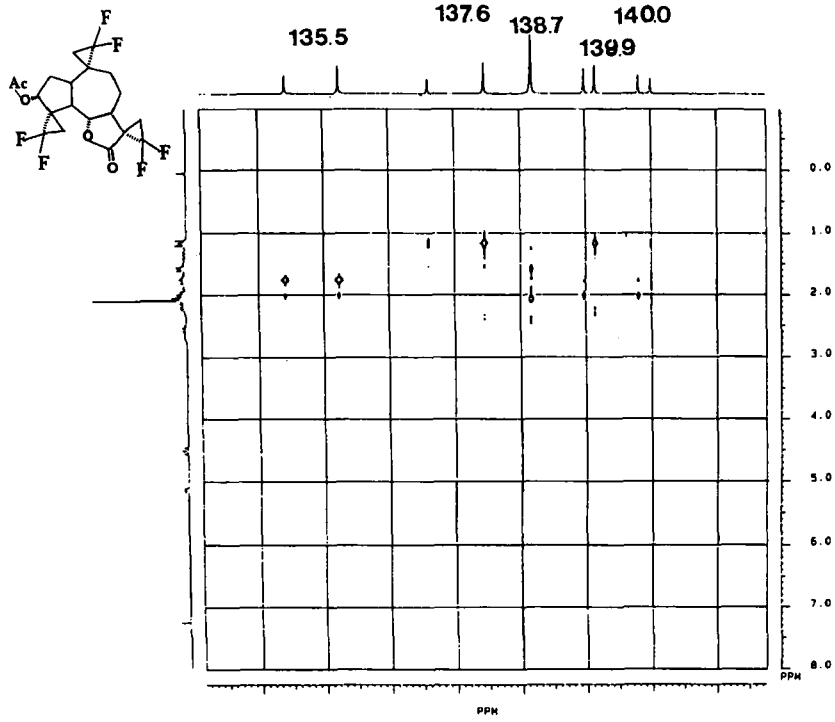


Fig 2.- Hetcor ^{1}H ^{19}F of compound 6

splitting with the protons attached to C-13.(Table 3). It was also possible to observe another broad AB pattern assigned to two fluorine atoms at C-15a. Fluorine atoms also showed the usual vicinal heteronuclear coupling with the C-15 protons. This broadening of signals was rationalized by a long range coupling with H-1 and with both protons attached on C-9.The cross section of such couplings from the heteronuclear ^{1}H-^{19}F correlation experiment, enables the assignment of the proton chemical shifts of protons coupled with all six fluorine atoms on the sesquiterpene framework .

The ^{19}F signals studied here exhibited mainly a large $^{2}J_{FF}$ and vicinal $^{3}J_{H\text{-}F}$ couplings while the long range heteronuclear coupling contributes to a broadening of the ^{19}F multiplet transitions. Some long range ^{1}H-^{19}F

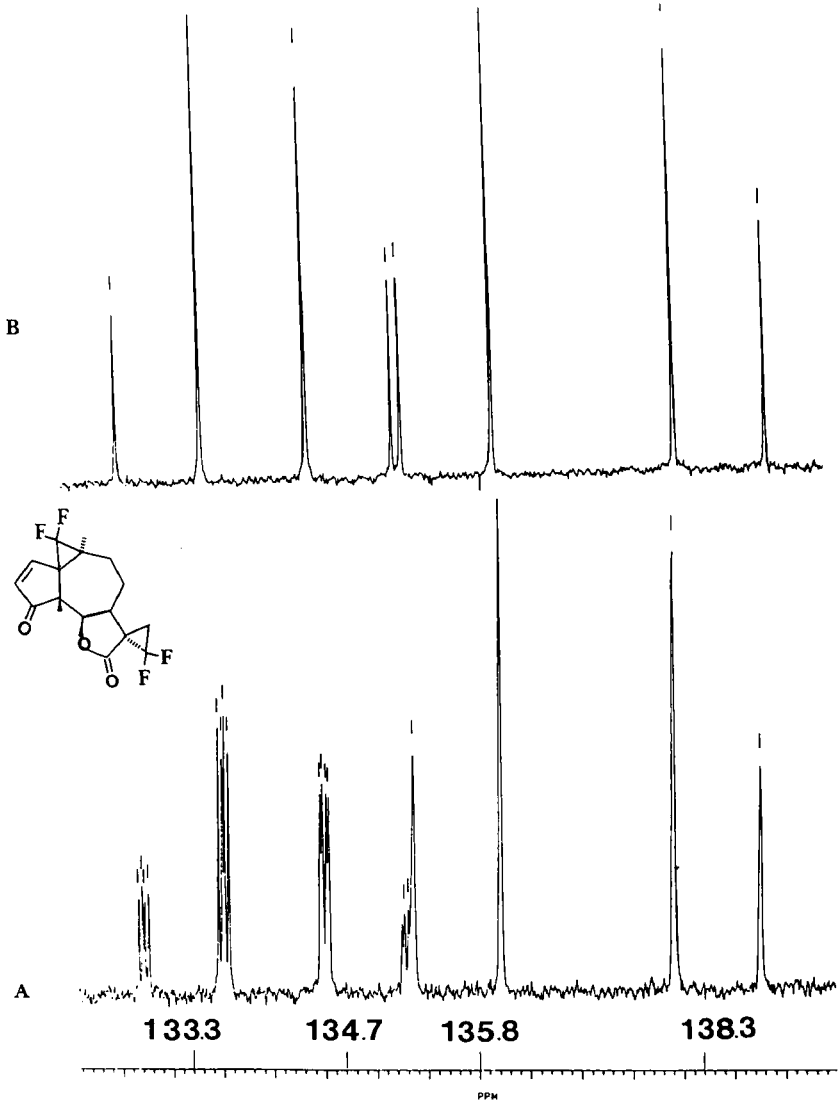


Fig 3.- ^{19}FNMR Spectra 235.36 MH$_z$

a) ^{1}H coupled Spectrum of compound 4

b) ^{1}H decoupled spectrum of compound 4

coupling constants were unresolved in the ^{19}F spectra.The geminal $^{2}J_{FF}$ coupling only was observed with sharper signals in the proton decoupled spectra. All the heteronuclear coupling interactions were determined using ^{1}H-^{19}F two dimensional correlation experiment,which detects all heteronuclear coupling up to the limit imposed by the natural line width of the signals in the spectrum.

NMR Spectroscopy experimental part.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 360 Fourier Transform spectrometer operating at 360.13 MHz for ^{1}H and 90.56 MHz for ^{13}C. Spectra were obtained at 305K and chemical shifts are expressed relative to $CHCl_3$ residual signal set to 7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C. All spin systems were identified by standard COSY and DEPT 135 experiments.[10] Heterocorrelated ^{1}H-^{13}C experiments were performed in the inverse mode according to Bax's HMQC for direct coupling[11] and HMBC for long distance coupling sequences[12]. ^{19}F spectra were recorded on a Bruker AC 250 NMR spectrometer operating at 235.36 MHz. The deuteriochloroform solutions were referenced to internal $CFCl_3$.

In order to identify and assign the new long range ^{1}H-^{19}F couplings the heteronuclear equivalent of COSY experiment was used.

^{1}H $\quad 90° - t_1 - 90°$

^{19}F $\quad 90°$ Aqn.

2D data acquisition were performed using 1024 time domain data points and 512 increments.After a zero filling in F_1 dimension data processing were carried out with the UXNMR program on a X32 Bruker computer.

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