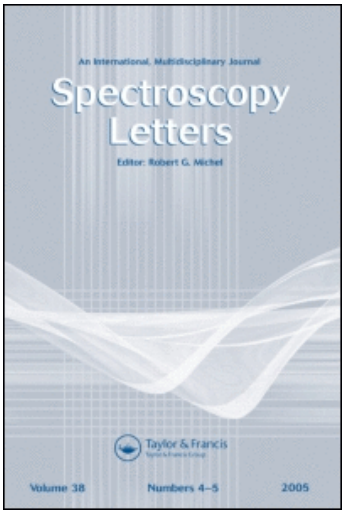

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Stereochemistry of a Guaianolide from *Cyathocline Purpurea* by High Resolution NMR Spectroscopy

P. Pradhan[a]; G. J. Chintalwar[a]; A. Banerji[a]
[a] Bio-Organic Division, Bhabha Atomic Research Centre, Bombay

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STEREOCHEMISTRY OF A GUAIANOLIDE FROM *CYATHOCLINE PURPUREA* BY HIGH RESOLUTION NMR SPECTROSCOPY

Key words : *Guaianolide, Stereochemistry, Samek Rule, Allylic coupling, NOESY, ROESY, HETCOR.*

P. Pradhan, G. J. Chintalwar and A. Banerji*

Bio-Organic Division
Bhabha Atomic Research Centre
Bombay 400 085

ABSTRACT

The stereochemistry of a sesquiterpene, 6α-hydroxy-4(14),10(15)-guaianadien-8β,12-olide (2) was established by high resolution and 2D-NMR spectroscopy. Careful analysis of the long range couplings along with vicinal spin-spin coupling constants predict a *trans* fusion of the lactone ring. Further information on the stereochemistry of 2 was obtained from 2D-NOESY and ROESY experiments.

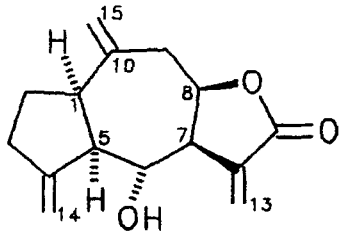
INTRODUCTION

Though versatile, use of X-ray crystallography is restricted to crystalline solids only. Recent advances in multi-dimensional

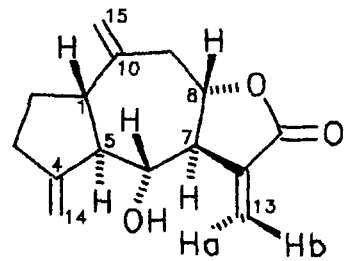
NMR spectroscopy provide a powerful alternative to X-ray crystallography for non-crystalline and liquid compounds. We have utilised high resolution NMR spectroscopy to establish structures and stereochemistry of a sesquiterpenoid, methyl picrotoxate[1] from the plant *Anamirta cocculus* and complex xanthonoids, zeyloxanthonone[2] and tomentonone[3] from *Calophyllum tomentosum*. A new guaianolide, isolated as its acetate by Nagasampagi *et al.*[4] from the plant *Cyathocline purpurea*, was assigned the structure, 6α-hydroxy-4(14),10(15)-guaianadien-8α,12-olide (1). The same compound was isolated by us from *C.purpurea* in the crystalline form.[5] Crystal structure by X-ray analysis established the structure as 6α-hydroxy-4(14),10(15)-guaianadien-8β,12-olide (2) thus necessitating the revision of the stereochemistry. In order to make a comparative evaluation, an independent study on the stereochemistry of 2 exclusively by NMR spectroscopy was undertaken. Stereochemical informations were derived from the observations based on ^3J and ^4J coupling constants. Possible nOe interactions between different nuclei were obtained from 2D NOESY and ROESY experiments. The assignment of carbon resonances in 2 were established from the HETCOR spectra.

DISCUSSION

The NMR spectral data (Table 1) suggested that 2 is a



(1)



(2)

guaianolide with hydroxy group at C-6, a γ- lactone and three exocyclic double bonds at C-4, C-10, and C-11. The following stereochemical information could be inferred from the coupling constant

TABLE 1

^1H and ^{13}C NMR Spectra of 2

^1H			^{13}C			
proton number	chemical shift(ppm)	multi-plicity[c]	carbon number	chemical shift(ppm)	multi-plicity	J in Hz
13 H_a	6.299	dd	C-12	169.5	s	
13 H_b	6.268	dd	C-11	152.5	s	
14 H_a	5.042	bs	C-10	144	s	
14 H_b	5.044	bs	C-4	137.8	s	
15 H_a	4.998	bs	C-13	124.3	t	160
15 H_b	4.946	ddd	C-15	111.17	t	156
8 H	4.36	ddd	C-14	108.67	t	156
6 H	3.665	ddd	C-8	76.6	d	149
9 H_a	3.16	ddd	C-6	74.4	d	145
7 H	2.846	dddd	C-5	57.87	d	129
9 H_b	2.61	dd	C-7	52.88	d	130
1 H	2.55	dd	C-1	45.08	d	126
3 H_a	2.43	ddd	C-9	39.54	t	129
3 H_b	2.25	ddd	C-3	33.21	t	129
5 H	2.21	dd	C-2	29.33	t	128
2 H_a	1.73	m				
2 H_b	1.84	m				

[c] ^1H-coupling constants in Hz : $^4J_{7,13a}$ = 3, $^4J_{7,13b}$ = 3.6, $^2J_{13a,13b}$ = 1.3, $^3J_{7,8}$ = 9.7, $^3J_{8,9}$ = 4.3, 11, $^3J_{7,6}$ =9.3, $^3J_{5,6}$ = 9.2, $^3J_{6,3}$ = 3.4, $^2J_{9a,9b}$ =16, $^4J_{9,14}$ =2.1, $^3J_{5,1}$ =6.5.

data: (a) the observed value of four bond allylic coupling of 7-H with 13-H_a and 13-H_b are $^4J_{cisoid}$= 3.0 Hz and $^4J_{transoid}$= 3.6 Hz respectively. According to Samek's rule[7,8] this will suggest that the fusion of the lactone ring with the 7-membered ring in 2 is *trans*. (b) the magnitude of the vicinal coupling between 8-H and 7-H and 7-H and 6-H ($^3J_{7,8}$= 9.7 Hz, $^3J_{7,6}$= 9.3 Hz respectively) suggest an *anti*-relationship between them on the basis of Karplus Rule[9] and substituent effect on coupling constant[10]. Therefore, 7-H and 8-H are *trans* to each other and provides additional support

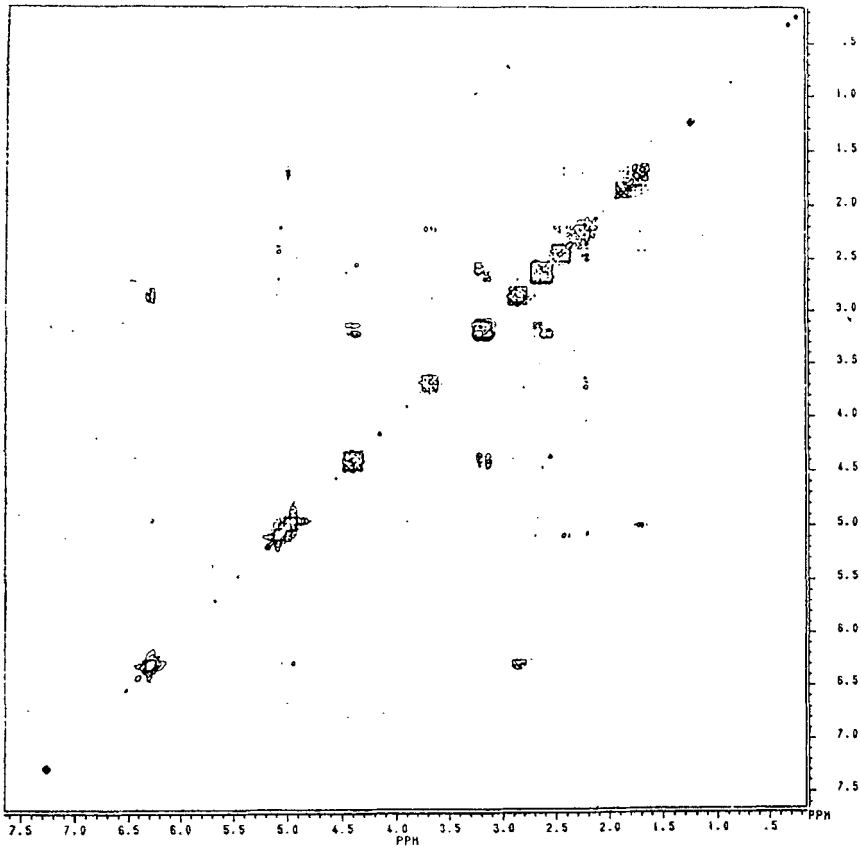


Figure 1. 2D-NOESY spectrum of 2 in $CDCl_3$

for the *trans* fusion of the lactone. Similarly 6-H and 5-H with $^3J_{6,5}$= 9.2 Hz also bear an *anti*-relationship with each other.

On the basis of the findings in (a) and (b) nOe interactions are expected between 6-H and 8-H and 7-H and 5-H but not between 7-H and 8-H. But none of these interactions were seen in 2-D NOESY spectra (Fig. 1). However, in small molecules weak and negative interactions which elude detection by 2D-NOESY can be observed by 2D-transverse nOe (ROESY) spectra. Thus in ROESY spectra (Fig. 2) of 2, clear nOe interactions between 6-H and 8-H, 6-H and 3-H and 7-H and 5-H were observed whereas there was

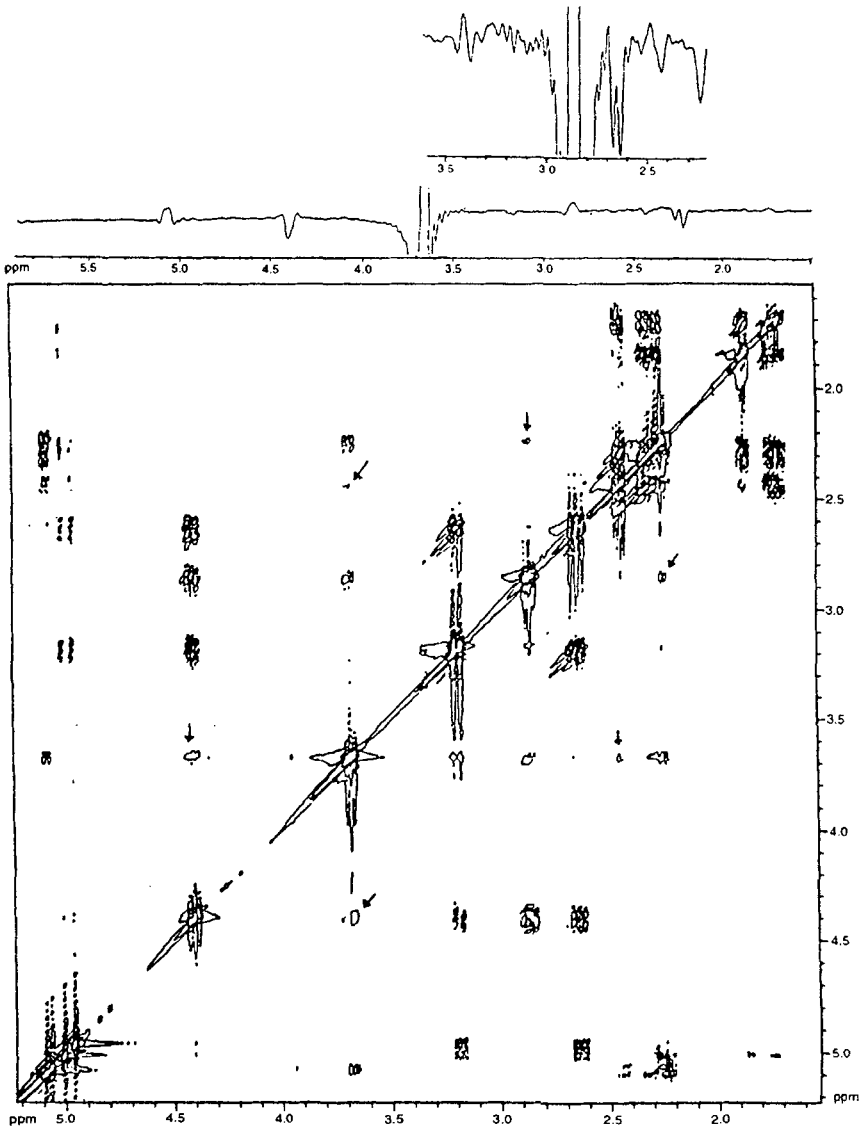


Figure 2. 2D-ROESY spectrum of **2** in $CDCl_3$. The cross peaks indicated by arrows in contour plot are due to nOe and have a sign opposite to diagonal peaks. The other cross peaks are artifacts due to Hartmann-Hahn effects. Two cross sections (with different vertical scale) taken parallel to the w_1 axes at the w_2 frequencies of 6-H and 7-H are shown at the top of the spectrum.Negative resonances in these sections are due to transverse nOe.

no such interaction between 7-H and 8-H. These observations reveal that 6-H and 8-H are on the same side of the molecule whereas 7-H is on the other side and thereby provides an absolute proof for the *trans*-fusion of the lactone ring. This also substantiates that 5-H and 7-H are both *trans* to 6-H and are *cis* to each other. In addition to the above information, NOESY and ROESY spectra were also useful in deriving other stereochemical details of 2. The nOe observed between the signals of 7-H and 13-$H_{a\&b}$ and between 5-H and 14-$H_{a\ \&\ b}$ suggest a *cis* disposition of protons 7-H and 5-H with the exocyclic double bonds at C-11 and C-4 respectively. The exocyclic double bond protons at C-15, do not show nOe with 1-H or 9-$H_{a\ \&\ b}$, but showed NOESY cross peaks with methylene protons at C-2. Thus 1-H is *trans* disposed to the double bond at C-10. The additional nOe between 8-H and the C-9 methylene protons indicates that the double bond at C-10 is pointing away from them. The *trans* disposition of 1-H and 5-H indicates a *trans* fusion of the cyclopantane and cycloheptane ring. The absence of nOe between H-1 and H-8 or H-1 and H-6 may be attributed to the fact that the hydroxyl group and γ -lactone at C-6 and C-8 respectively may prefer a pseudo equatorial position away from the inner part of the 7-membered ring.[11] Thus the stereochemistry of 2 is established as 6α-hydroxy-4(14),10(15)-guaianadien-8β,12-olide.

Moreover the assignment of carbon resonances were established by HETCOR spectra. The important ^{13}C-^{1}H correlations [δ_C(ppm)-δ_H(ppm)] are : (124.3 - 5.[illegible]), (111.5 - 4.97), (108.9 - 5.05), (76.6 - 4.36), (74.4 - 3.67), (57.9 - 2.2), (52.9 - 2.85), (45 - 2.66), (39.5 - 3.2 & 2.6), (33.2 - 2.4 & 2.25), and (29.3 - 1.65). The $^{1}J_{C-H}$ coupling constants (Table 1) were calculated from the noise-decoupled ^{13}C NMR spectra. Thus the complete assignment of NMR data using 1D and 2D techniques, allowed us to establish the structure of 2 independent of X-ray analysis.

EXPERIMENTAL

Compound 2 was isolated as a colourless crystalline solid from the aerial part of the plant *C.purpurea* and characterised on the basis spectral analysis and X-ray crystallography.[5]

^1H NMR spectra were measured at 200 MHz for a 36 mg/ml $CDCl_3$ solution at ambient temperature using a Bruker AC-200 spectrometer. The FIDs obtained were zero filled to 16K followed by Gaussian multiplication with GB = 0.4 and LB = -1. NOESY spectra were taken in absolute value mode with a mixing time of 1 sec. A spectral width of 1500 Hz used W_1 and W_2 dimensions. 1024 Data points for 256 increments with 32 transients were used for acquisition of the NOESY spectra. 2D ROESY of **2** (36mg/ml solution in $CDCl_3$) was recorded at 500 MHz in a Bruker AM-500 spectrometer in phase sensitive mode. The carrier frequency is positioned at an offset of δ 3.61 ppm and a 0.6 watt spin-lock field was used during 500 msec mixing period. 32 Scans were performed for every t_1 value and 512 x 2048 data set were acquired to a 1024 x 2048 part of the displayed spectrum.

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