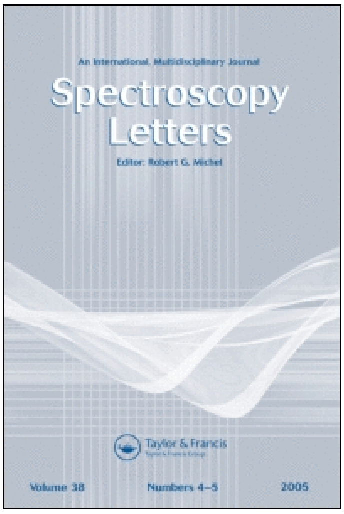

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STEREOCHEMICAL ASSIGNMENT OF TERTIARY HYDROXYL GROUP IN DITERPENE FURAN GLYCOSIDES BY PYRIDINE INDUCED SHIFTS, ^{13}C- AND 2D-NMR SPECTROSCOPY

KEYWORDS. *Tinospora cordifolia,* cordifoliside D, cordifoliside E, NOESY, γ-shift, pyridine induced shift (PIS).

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ABSTRACT

The stereochemistry of the tertiary hydroxyl group in diterpene furan glycosides *viz.* cordifolisides D (**1**) and cordifoliside E (**2**) has been assigned on the basis of pyridine solvent induced shifts (PIS) in the ^{1}H and ^{13}C NMR spectra. The methyl and the methylene groups occupying positions *vicinal*, 1,3-*diaxial* and *geminal* to the tertiary hydroxyl group were deshielded to different extent depending on the dihedral angle. The stereochemical assignments are well supported by ^{13}C- γ shifts and 2D Overhauser spectroscopy.

INTRODUCTION

Pyridine is a useful aromatic solvent for the NMR analysis of organic molecules containing hydroxyl functions due to solubility reason[1]. It coordinates at the electron deficient sites within a solute molecule and due to the large anisotropy in the magnetic susceptibility of aromatic system, protons situated in the vicinity of a polar functional group invariably experience large screening effect[2]. This often leads to increased spectral simplification relative to those in chloroform or carbon tetrachloride. The correlation of chemical shifts induced in benzene and pyridine (relative to chloroform) with specific structural features in a variety of carbonyl containing compounds is well known and has been amply demonstrated in structural analysis[3]. Subsequent studies revealed that pyridine may in addition serve as a useful solvent for characterization of hydroxylic compounds[4] and natural products[5,6]. In saturated cyclic systems, protons that are 1,3 diaxial, vicinal or geminal to a hydroxyl function experience significant down field pyridine-induced solvent shifts {PIS, $\Delta = \delta(CDCl_3) - \delta(C_5D_5N)$[4]. However, in phenolic systems protons *ortho* to hydroxyl function shows larger deshielding effects than protons in the *meta* or *para* positions. The shifts observed in pyridine have been rationalised in terms of solute-solvent interactions. Two distinct types of associations, *viz.* a hdrogen-bonding association and a collision complex association, have been tentatively proposed for the saturated alcohols. These studies revealed that pyridine induced solvent shifts can be useful in establishing location and stereochemistry of protons situated in the vicinity of hydroxyl function.

In our previous communications we have described the isolation and structural identification of several furan diterpene furan glycosides from the butanol extracts of the Indian medicinal plant *Tinospora cordifolia*[7,8]. Their stereochemical assignments were based on the qualitative inter proton distances inferred form the corresponding 2D-NOESY spectra. But the streochemistry of the tertiary hydroxyl groups present in the saturated cyclic systems of the norditerpene furan glycosides *viz.* cordifolisides D (**1**) and E (**2**) could not be assigned unambiguously[5]. The ^1H NMR resonances of the hydroxyl group in the aglycon moeities were unobservable either because of line broadening effects of chemical exchange or excessive signal overlapping hence could not be utilised for analysis. In the present communication, we discuss the utility of PIS, ^{13}C-γ-shift and 2D-NOESY in the stereochemical assignments of **1** and **2**.

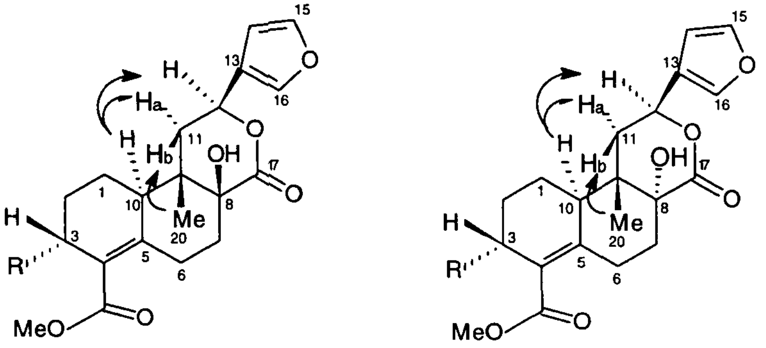
RESULTS AND DISCUSSION

The NMR spectra of compounds **1** and **2** were complicated due to a large number of overlapping multiplets. The structures were assigned[8] on the basis of two dimensional correlation spectroscopy *viz.* ^1H-^1H COSY, ^{13}C-^1H HETCOR and ^{13}C-^1H COLOC. Compounds **1** and **2** are isomeric norditerpene furan glycosides varying only in the stereochemistry of a tertiary hydroxyl group. Its position was fixed at the C-8 carbon (δ_C, 74.9 in **1a** and 88.8 in **2a**) based on its long range ($^3J_{CH}$) coupling to the neighbouring methyl (H-20), the methylene (H-6) and the methine (H-10) protons.

The relative stereochemistry of protonated sites were inferred from the nOe interactions. Both **1a** and **2a** showed nOe cross peaks (see *scheme 1*) between H-10 and H-12 suggesting *cis-* disposition between themselves. Absence of nOe between H-10/H-12 and H-20 indicated that the methyl is on the other side of the molecule. The other important nOe interactions are between H-10 and Ha-11, H-20 and Hb-11 and Hb-11 and H14. These NOE data established the stereochemistry of all chiral centers as shown in *scheme 1* except for the configuration of the tertiary hydroxyl at C-8.

Configuration of Tertiary Hydroxyl Group on the basis of ^{13}C NMR. Indirect evidences for the relative stereochemistry of the hydroxyl group in **1a** and **2a** come from the ^{13}C chemical shifts of the neighbouring carbons. It is known that shifts in ^{13}C chemical shifts of hydrocarbons due to the alkyl substitutions at α, β and γ-carbons are useful for structural characterisation[9,10]. Roberts *et al.* have shown that γ-shifts are very sensitive to steric effects and conformational changes in molecules with hydroxyl and other heteroatomic substitutions[11]. An upfield shift is generally observed for any carbon that can exist in cis-*gauche* orientation with respect to another carbon or heteroatom relative to the shielding of its *anti* counter part. Therefore, the relative shifts of the γ carbons *viz.* C-20, C-10 and C-6 in **1a** and **2a** are useful to find out the possible orientation of the hydroxyl groups. As listed in Table 1, C-20 resonated 4.0 ppm upfield in the ^{13}C NMR spectrum of **1a** (δ_C 15.8, $CDCl_3$) compared to that of **2a** (δ_C 19.8). Thus it clearly indicated that the methyl group at C-9 and `OH' group at C-8 are *cis-gauche* disposed in **1a** and *anti* disposed in **2a**. Molecular models of **1a** and **2a** constructed with DTMM software[12] on qualitative nOe and $^{13}$C guidelines suggested that the C-10 carbon is *anti* disposed to `OH' group at C-8 in **1a** and *cis-gauche* disposed in **2a**. The observed chemical shift of C-10 (δ_C 41.7, in **1a**) and (δ_C 38.8, in **2a**) are in complete agreement with this model. Hence, the hydroxyl and the methyl group have similar configuration (β) in cordifolisides D and opposite (α and β) in cordifoliside E, as shown in the structures **1a** and **2a** respectively. The third carbon (C-6) with a γ-hydroxyl substitution is also sensitive to steric effects. An upfield resonance for C-6 (δ_C 28.3) in **2a** suggested its *cis-gauche* relation with the hydroxyl group. In **1a**, it resonated downfield at δ_C 26.7 indicating the *anti* disposition of C-6 and the hydroxyl substitution.

Configuration of tertiary hydroxyl group on the basis of pyridine induced shifts (PIS). Pyridine can coordinate to the hydroxyl group (i) by hydrogen bonding to the hydroxyl group where its N atom acts as a H-donor, or (ii) by



1. β-D-glucopyranosyl, *cordifoliside D*

1a. tetra-O-acetyl-β-D-glucopyranosyl, *cordifoliside D tetraacetate*

2. β-D-glucopyranosyl, *cordifoliside E*

2a. tetra-O-acetyl-β-D-glucopyranosyl, *cordifoliside E tetraacetate*

Scheme 1. Strucutures of norditerpene furan glycosides, arrows indicate nOe interactions.

forming collision complexes between the electron deficient centers and the aromatic π-clouds[3]. Hydrogen bonding with the hydroxyl group probably restricts the pyridine molecules to associate with the carbonyl group at C-17. Binding to the other oxygen atoms in **1a** and **2a** are weaker due to unavilibilty of stronger H-bond acceptor compared to the hydroxyl group. Hence, PIS will be significant at positions close to the hydroxyl group. The observed PIS for compounds **1a** and **2a** are listed in Table 1 and 2, respectively. In compound **2a**, the methyl group residing at C-9 position experienced a PIS of -0.15 ppm. On the other hand, the corresponding methyl group in **1a** had a larger PIS of -0.28 ppm. The larger PIS in **1a** could be attributed to the fact that the methyl protons are situated considerably closer to the ß-hydroxyl group at C-8 position and thus experience a greater deshielding effect from highly anisotropic pyridine molecule coordinated to the polar hydroxyl function. The relative magnitudes of vicinal deshielding in **1a** and **2a** could be explained on the basis of dihedral angles. Molecular models with DTMM software indicated dihedral angles of 36° and 163° respectively between the planes passing through O(8)-C(8)-C(9) and C(8)-C(9)-C(20) in **1a** and **2a** respectively. Other protons, which also showed considerable PIS were those of the methylene group at C-11 position. The PIS

TABLE 1: ^{1}H and ^{13}C pyridine induced shifts $\{\Delta = \delta(CDCl_3) - \delta(C_5D_5N)\}$ observed in Cordifoliside D tetraacetate (**1a**)

Pos	$\delta_H(CDCl_3)$ in ppm	$\delta_H(C_5H_5N)$ in ppm	Δ (ppm)	$\delta_C(CDCl_3)$ in ppm	$\delta_C(C_5H_3N)$ in ppm	Δ (ppm)
1	1.85	1.62	+ 0.23	16.9	17.5	- 0.6
	1.64	1.87	- 0.23			
2	1.53	1.52	+ 0.01	28.3	28.9	- 0.6
	2.15	2.27	- 0.08			
3	4.68	4.96	- 0.28	72.5	73.6	- 1.1
4				151.3	151.3	0
5				127.1	127.6	- 0.5
6	3.29	3.57	- 0.28	28.3	29.1	- 0.8
	1.90	2.13	- 0.23			
7	2.51	2.91	- 0.40	30.6	30.9	- 0.3
	1.80	2.12	- 0.32			
8				74.9	74.9	0
9				42.1	43.3	- 1.2
10	2.30	2.54	- 0.24	41.7	42.1	- 0.4
11	1.93	1.89	+ 0.04	33.9	34.3	- 0.4
	2.58	2.88	- 0.30			
12	5.43	5.64	- 0.19	71.5	71.6	- 0.1
13				124.7	126.5	- 1.8
14	6.50	6.72	- 0.22	108.8	109.6	- 0.8
15	7.47	7.81	- 0.34	139.7	140.5	- 0.8
16	7.40	7.60	- 0.20	143.9	143.8	+ 0.1
17				172.0	172.0	0
18				168.3	168.3	0
20	0.94	1.22	- 0.28	15.8	16.7	- 0.9

TABLE 2: ^1H and ^{13}C pyridine induced shifts {$\Delta = \delta(CDCl_3) - \delta(C_5D_5N)$} observed in Cordifoliside E tetraacetate (**2a**)

Pos	$\delta_H(CDCl_3)$ in ppm	$\delta_H(C_5H_5N)$ in ppm	Δ (ppm)	$\delta_C(CDCl_3)$ in ppm	$\delta_C(C_5H_3N)$ in ppm	Δ (ppm)
1	1.64	1.67	- 0.03	18.8	19.2	- 0.4
	1.90	1.98	- 0.08			
2	2.68	1.86	+ 0.82	26.0	27.1	- 1.1
	2.80	1.96	+ 0.84			
3	4.68	4.98	- 0.30	73.2	74.0	- 0.8
4				150.5	150.5	0
5				126.4	126.4	0
6	1.59	2.89	- 1.30	26.7	25.9	+ 0.8
	1.72	3.1	- 1.38			
7	1.96	2.06	- 0.10	29.6	30.9	- 1.3
	2.21	2.47	- 0.26			
8				88.8	88.8	0
9				50.1	50.8	- 0.7
10	2.60	2.70	- 0.10	38.8	38.9	- 0.1
11	2.04	2.33	- 0.29	44.4	44.7	- 0.3
	2.30	2.43	- 0.13			
12	5.22	5.39	- 0.17	73.0	72.0	+ 1.0
13				124.4	124.4	0
14	6.54	7.12	- 0.58	109.5	111.2	- 1.7
15	7.47	7.47	0	140.9	139.9	+ 1.0
16	7.35	7.35	0	143.4	144.0	- 0.6
17				177.9	177.9	0
18				167.9	167.9	0
19						
20	0.98	1.13	- 0.15	19.8	18.7	+ 1.1

for the H_a-11 and H_b-11 protons were +0.04 and -0.30 ppm in **1a** and -0.29 and -0.13 ppm in **2a**, respectively. These may be attributed to the 1,3 diaxial deshielding of pyridine. In **1a**, H_b-11 is disposed 1,3 diaxial with the -OH at C-8 whereas in **2a**, H_a-11 with higher PIS is 1,3 diaxial disposed with the -OH group. The larger 1,3 diaxial deshielding of methylene protons at C-6 carbon in **2a** (-1.30 and -1.38 ppm) is in agreement with the conclusion above with ^{13}C data that C-6 has a *cis-gauche* relationship with the hydroxyl group at C-8. On the other hand, the corresponding PIS in **1a** (-0.28 and -0.23 ppm) are less and hence justify the *anti-* relationship is predicted. The *vicinal* deshielding of protons at C-7 position (-0.40 and -0.32 ppm for **1a** and -0.10 and -0.26 ppm in **2a**) may have similar implications. The PIS observed for the carbon resonances are also significant but those for protons are more helpful due to their location at the periphery of the molecules. As expected, the ^{13}C- PIS of the methyl carbon at C-9 in **1a** is -0.9 ppm whereas that for **2a** is +1.1 ppm. All these data give confirmatory evidence to the stereochemistry as shown in the structures **1a** and **2a** for the cordifolisides D and E respectively.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively on a Bruker AC 200 NMR spectrometer at a normal probe operating temperature (~30° C). All the experiments were carried out with 0.01 M solutions in $CDCl_3$ and C_5D_5N using trimethyl silane as internal standard. For resonances not having first-order spectra chemical shift assignments were obtained from the HETCOR and COSY spectra. In NOESY and COSY, 32 transients were recorded for each t_1 experiment of 256 increments. These were then zero-filled to 512W. In the W_2 dimension 1K data points were recorded without zero-filling. A shifted square sine bell weighing function was used in both dimensions for signal processing. For NOESY a mixing time of 1 sec. was used.

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