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Structures of Two Novel Triterpene Saponins from *Arenaira filicaulis* Boiss.†

M. Hani A. Elgamal,[1] Hesham S. M. Soliman,[2] Dalal T. Elmunajjed,[3] Gábor Tóth,[4]* András Simon[4] and Helmut Duddeck[5]*

[1] National Research Centre, Laboratory of Natural Products, Dokki, Cairo, Egypt
[2] Helwan University, Faculty of Pharmacy, Department of Pharmacognosy, Helwan, Egypt
[3] Faculty of Pharmacy, Damascus University, Damascus, Syria
[4] Technical University Budapest, Technical Analytical Research Group of the Hungarian Academy of Sciences, Institute for General and Analytical Chemistry, Szent Gellért tér 4, H-1111 Budapest, Hungary
[5] Universität Hannover, Institut für Organische Chemie, Schneiderberg 1B, D-30167 Hannover, Germany

Two novel triterpenoid saponins, Snatzkein A and B, were isolated from *Arenaria filicaulis* Boiss. One possesses an unusual 2′-*O*-hydroxyethylated glucose moiety. Their structure and conformational behaviour were investigated by one- and two-dimensional ^{1}H and ^{13}H NMR spectroscopy. © **1997 by John Wiley & Sons, Ltd.**

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INTRODUCTION

The rhizomes of *Arenaria filicaulis* Boiss. (syn. *Gypsophila filicaulis* Boiss., Borm.) are mainly used in the manufacture of a popular sweet diet (Halawa-Tahinia) and utilized in Syrian folk medicine as a diuretic, in bladder illness[1] and as a laxative and antirheumatic. Our continued interest in the saponins of *Caryophyllaceous* plants[2,3] has led to the isolation of two new saponins. In this paper, the isolation, structure elucidation, conformational behaviour and complete ^{1}H and ^{13}C NMR assignments of these compounds, Snatzkein A (**1**) and B (**2**) (Scheme 1), with a new lupane aglycone, are reported. The names Snatzkein A and B were chosen in commemoration of the late Professor Dr h.c.(H) Günther Snatzke (1928–92), the renowned stereochemist and spectroscopist and teacher of H.D., M.H.A.E. and G.T.

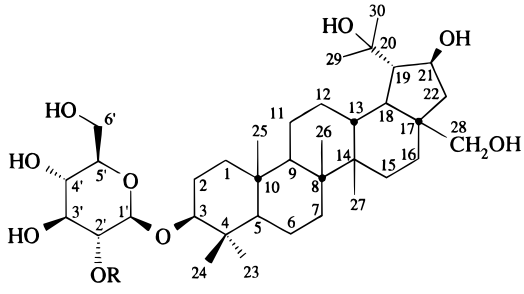
EXPERIMENTAL

Isolation

Arenaria filicaulis Boiss. was collected from the plains and areas around Damascus (Syria) and was identified by Professor A. El-Khatib, Damascus University. A voucher specimen is kept in the herbarium of the university.

The dried powdered rhizomes of the plant (3 kg) were exhaustively extracted with methanol and were finally distilled *in vacuo*. The residue was dissolved in water and successively extracted with diethyl ether and *n*-butanol. The *n*-butanol extract was dried and the residue (48 g) was applied to a silica gel column (Baker) and eluted with chloroform–methanol–water (100:10:1). The polarity of the solvent was increased by reduction of the amount of chloroform. When the composition of the solvent reached 50:10:1, 450 mg containing a major compound was collected. Purification was achieved by medium-pressure reversed-phase column chromatography (RP_8 column, 35% methanol as eluent). The product was finally filtered through Sephadex LH-20 (methanol) to give 40 mg of pure **1**, R_f = 0.36 using chloroform–methanol–water (9:4:0.5). M.p. 178–180 °C; $[\alpha]_D = -16.0$ (methanol, $c = 0.2$); IR (KBr), 3225 cm^{-1} (OH), 1070 cm^{-1} (C—O).

When the composition of the solvent reached 30:10:1, another fraction (390 mg) was eluted and subjected to flash silica gel chromatography using chloroform–methanol (8:2) as the solvent. It yielded a partially pure saponin which was further purified by medium-pressure reversed-phase column chromatography (RP_8 column, 37% methanol as eluent). The product was filtered through Sephadex to give 23 mg of pure **2**, $R_f = 0.32$ using chloroform–methanol–water (9:4:0.5). M.p. 240–242 °C; $[\alpha]_D = -31.3$ (methanol, $c = 0.16$); IR (KBr), 3250 cm^{-1} (OH), 1073 cm^{-1} (C—O).



1 R = H

2 R = CH_2-CH_2-OH

Scheme 1. Structures of Snatzkein A (**1**) and B (**2**).

* *Correspondence to:* G. Tóth or H. Duddeck.

† Dedicated to Professor Adolf Zschunke on the occasion of his 60th birthday.

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Spectroscopy

NMR spectra were recorded in pyridine-d_5 at room temperature using a Bruker Avance DRX-500 spectrometer. Chemical shifts are given on the δ scale and were referenced to the solvent (C-β; $\delta = 123.4$; H-β; $\delta = 7.17$). In the 1D measurements (^{1}H, ^{13}C, DEPT), 64K data points were used for the FID.

The pulse programs of the following 2D experiments were taken from the Bruker software library and the parameters were as follows.

500/125 MHz gradient-selected HMQC[4] spectra: relaxation delay $D_1 = 2.0$ s; evolution delay $D_2 = 3.45$ ms; 90° pulse, 11.5 μs for ^{1}H, 10.0 μs for ^{13}C hard pulses and 65.0 μs for ^{13}C GARP decoupling; 1K points in t_2; spectral width, 8 ppm in F_2 and 130 ppm in F_1; 256 experiments in t_1; linear prediction to 512; zero-filling up to 1K.

500/125 MHz gradient-selected HSQC edited[4] spectra: relaxation delay $D_1 = 1.5$ s; evolution delay $D_2 = 3.45$ ms; 90° pulse, 11.5 μs for ^{1}H, 10.0 μs for ^{13}C hard pulses and 65.0 μs for ^{13}C GARP decoupling; 1K points in t_2; spectral width, 8 ppm in F_2 and 130 ppm in F_1; 256 experiments in t_1: linear prediction to 512; zero-filling up to 1K.

500/125 MHz gradient-selected HMBC[4] spectra: relaxation delay $D_1 = 1.5$ s; evolution delay $D_2 = 3.45$ ms; delay for evolution of long-range coupling $D_6 = 70$ ms ($J = 7$ Hz); 1K points in t_2; spectral width 8 ppm in F_2 and 180 ppm in F_1; 256 experiments in t_1; linear prediction to 512; zero-filling up to 1K.

500 MHz ROESY[5] spectra: relaxation delay $D_1 = 2.0$ s; 90° pulse for ^{1}H; spin lock 300 ms; 1K points in t_2; spectral width, 8 ppm in both dimensions; 256 experiments in t_1; linear prediction to 512 points; zero-filling up to 1K.

500 MHz TOCSY[6] spectra: relaxation delay $D_1 = 1.4$ s; 90° pulse for ^{1}H; 90° pulse for MLEV; TRIM pulse, 2.5 ms; mixing time, 80 ms; 1K points in t_2; spectral width, 8 ppm in both dimensions; 256 experiments in t_1; linear prediction to 512 points; zero-filling up to 1K.

500 MHz gradient-selected ^{1}H,^{1}H COSY[7] spectra: relaxation delay $D_1 = 1.0$ s; 90° pulse for ^{1}H; 2K points in t_2; spectral width, 8 ppm in both dimensions; 256 experiments in t_1; linear prediction to 512 points; zero-filling up to 2K.

500/125 MHz HMQC-TOCSY[8] spectra: relaxation delay $D_1 = 1.5$ s; evolution delay $D_2 = 3.45$ ms; 90° pulse for ^{1}H and ^{13}C; 90° pulse for ^{13}C GARP decoupling; 90° pulse for MLEV; TRIM pulse, 80 μs; 1K points in t_2; spectral width, 8 ppm in F_2 and 130 ppm in F_1; 512 experiments in t_1; linear prediction to 1K.

RESULTS AND DISCUSSION

Signal and structural assignments

Structural determinations are based on the NMR spectral assignments, which were confirmed by DEPT, ^{1}H,^{1}H COSY, TOCSY, HMQC, edited HSQC, HMBC, ROESY and HMQC-TOCSY experiments. The ^{1}H and ^{13}C chemical shifts and $J(^1\text{H},^1\text{H})$ couplings of **1** and **2** are given in Table 1.

The ^{1}H signals and the proton connectivities of both compounds could be identified by the 2D ^{1}H,^{1}H COSY and TOCSY spectra. The COSY spectra gave the geminal and vicinal connectivities and the TOCSY spectra gave additional connectivities. The HMQC, HSQC and HMQC-TOCSY experiments provided the signals of the corresponding ^{13}C nuclei. To avoid some strong signal overlap in the HMQC spectrum, the edited HSQC proved to be the method of choice, affording CH_2 and CH/CH_3 signals separately. The HMBC spectra were very useful, in particular, for the assignment of the signals of the quaternary carbons since the cross peaks revealed the two- or three-bond correlation between protons and carbons. Figure 1 demonstrates the effectiveness of HMBC spectra in a section of the spectrum of **2**. ROESY spectra were measured for both compounds to determine internuclear spatial proximities. The α- and β-positions of the protons (stereochemical assignment) in the aglycone were determined from the coupling patterns, HMQC and HSQC rows and ROESY cross peaks. All connectivities obtained from these spectra are given in Tables 2 and 3.

The strategy applied for signal and structure assignments is discussed in the following using the example of compound **2**; that for **1** is analogous. The sugar moiety consists of five CH and three CH_2 fragments; the ^{13}C signals of two methylene groups are broadened at room temperature (see below). The aglycone part shows 30 carbon signals, i.e. seven CH_3, ten CH_2, seven CH and six quaternary carbons, all resonating in the sp^3 region. The determination of the atom connectivities started with the signals of C-3 and H-3, which are well separated and unambiguous to assign. HMBC correlations led from H-3 to C-4, C-23 and C-24, and then from H-24 to C-5. Further, we reached H-25 from C-5. H-25 led us to C-1, C-9 and C-10, and consecutively H-1 to C-2/H-2 (by TOCSY). A connectivity from C-9 to H-26 was obvious; the latter signal identified two quaternary carbons (C-8 and C-14) and also H-27. From H-27 we could proceed to H-13, one of few methine protons, and C-15. TOCSY/^{1}H,^{1}H COSY peaks indicated the coupling of H-15 and H-16. One HMBC cross peak connecting H-16β and C-14 allowed the differentiation of C-14 and C-8 (see above), and another one led to the remaining non-oxygenated quaternary carbon (C-17). C-17 correlates with the methylene protons of the only CH_2OH (ignoring those in the sugar moiety) so that this group contains C-28. Our way through the skeleton was pursued from H-13 to H-18 (TOCSY/^{1}H,^{1}H COSY) and then from H-18 to H-19 and further to H-21 and both H-22s. From the C-21 and H-21 chemical shifts it is clear that C-21 carries an OH group. HMBC peaks connect H-21 with C-17 and C-18, proving the existence of the five-membered ring. Moreover, H-21 correlates with C-20, the last quaternary carbon with a chemical shift ($\delta = 71.4$) indicating an attached oxygen atom. C-20 was reached from the two remaining methyl protons (H-29 and H-30) and from H-18. These two methyl groups are correlated with each

Table 1. ^{1}H and ^{13}C NMR chemical shifts (ppm) and $J(^1H,^1H)$ couplings of 1 and 2

	1			2[a]		
	^{1}H	J(Hz)	^{13}C	^{1}H	J(Hz)	^{13}C
1 α	0.78		38.9	0.72		38.8
β	1.49			1.43		
2 α	2.22		26.7	2.11		26.4
β	1.79			1.78		
3 α	3.36	(11.8, 3.6)	88.8	3.28	(11.8, 4.3)	89.6
4	—		39.5	—		39.5
5 α	0.70	(11.8, 1.4)	55.7	0.64	(12.0, ~1)	55.6
6 α	1.44		18.4	1.44		18.3
β	1.25			1.24		
7 α	1.30		34.8	1.30		34.8
β	1.30			1.23		
8	—		41.7	—		41.6
9 α	1.26		50.6	1.23		50.5
10	—		36.8	—		36.8
11 α	1.44		21.6	1.40		21.5
β	1.16			1.13		
12 α	1.58		29.0	1.53		29.0
β	2.52			2.49		
13 β	2.15	(~12, 10.9, 3.6)	37.1	2.11		37.0
14	—		43.6	—		43.6
15 α	1.02		27.8	1.00		27.8
β	1.90			1.89		
16 α	1.34		32.1	1.33		32.1
β	2.10			2.08		
17	—		49.1	—		49.0
18 α	1.85	(10.9, 10.9)	49.3	1.83	(11.0, 11.0)	49.2
19 β	2.50	(10.9, ~3)	62.7	2.48	(11.0, 2.9)	62.7
20	—		71.4	—		71.4
21 α	4.50	(7.2, 3,1)	76.7	4.49	(7.1, 2.9)	76.7
22 α	1.55	(13.3, 7.2)	46.5	1.53	(13.0, 7.1)	46.5
β	2.41	(13,3, ~0)		2.40	(13.0, ~0)	
23 α	1.27		28.0	1.39		28.1
24 β	0.96		16.7	1.12		16.7
25 β	0.72		16.2	0.67		16.2
26 β	0.97		16.2	0.94		16.2
27 α	1.11		15.4	1.09		15.3
28 a	4.03		63.3	4.02		63.3
b	4.46			4.44		
29	1.41		26.6	1.39		26.6
30	1.73		32.3	1.71		32.2
1′	4.90	(8.0)	106.8	4.94	(7.6)	104.0
2′	4.01	(8.0, 8.6)	75.7	5.02	(8.9)	81.0
3′	4.22	(8.6, 8.8)	78.7	4.44	(9.2)	78.0
4′	4.18	(9.1, 8.8)	71.8	4.15	(9.2)	71.4
5′	3.98		78.2	3.87		77.6
6′ a	4.37	(11.7, 5.4)	63.0	4.21	(11.8, 5.5)	62.4
b	4.56	(11.7, 2.6)		4.44	(11.8, ~1)	

[a] (C-2′)-OCH_2CH_2OH: 3.82 (2H), 4.00 (2H); 72.7, 61.2.

other, showing their geminal position, so that the exocyclic carbinol moiety attached to C-19 was proved. The signals of H-6, H-7 and H-11 were difficult to identify owing to severe signal overlap. ROESY peaks established the spatial proximity of H-26 and H-7β as well as H-5α and H-7α. C-6, and hence the two H-6s, were reached from H-5. H-12 was connected with H-13. The identification of H-11β was achieved from its ROESY peaks with H-25 and H-26. The stereochemistry of the ring system, all atoms and all substitutions could be read beyond doubt from ^{1}H,^{1}H coupling constants, as far as identifiable, and ROESY cross peaks (see Scheme 1). In most instances pertinent information was redundant.

The same all-*trans*-fused pentacyclic ring system was recently reported as an aglycone by Tsichritzis and Jakupovic,[9] but without the β-OH group at C-21. In the light of our present work, their ^{13}C signal assignment has to be revised for some atoms: C-4/C-10 (pairwise interchange), C-15/C-21 (pairwise interchange) and C-16/C-22 (pairwise interchange).

From ^{1}H and ^{13}C chemical shifts and ^{1}H,^{1}H coupling constants it is straightforward that the sugar moiety is β-glucose. It is attached to C-3, as proved by

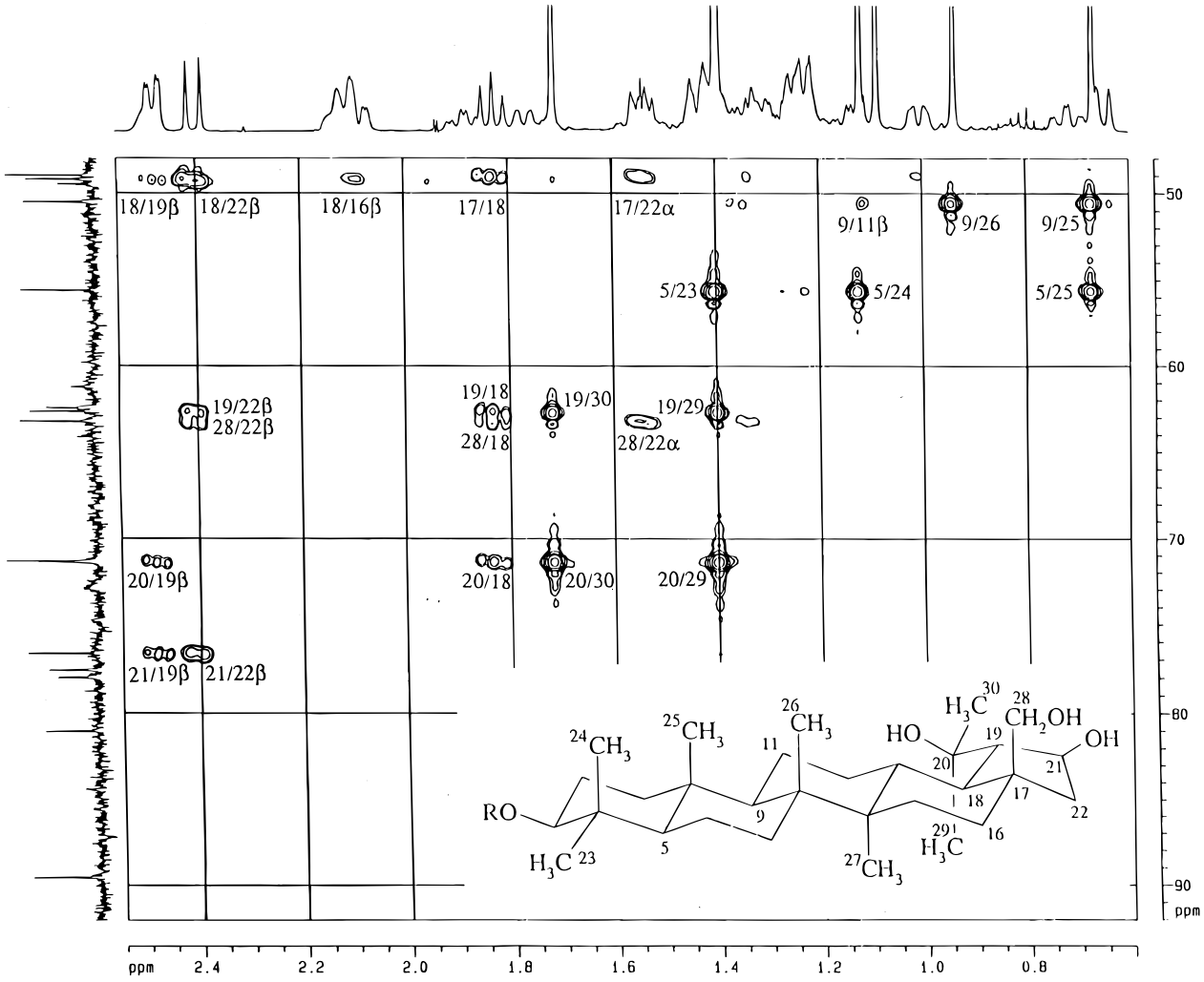

Figure 1. Section of the HMBC spectrum of **2**. In the identification of cross peaks the first number indicates the carbon and the second the hydrogen atom.

Table 2. Characteristic ^{13}C–^{1}H long-range correlations observed by HMBC measurements [$J(^{13}C,^{1}H) = 7$ Hz]

^{1}H	1 ^{13}C	2 ^{13}C
3 α	C-4; C-23; C-24; C-1′	C-4; C-23; C-24; C-1′
5 α	C-4; C-6; C-10; C-24; C-25	C-4; C-6; C-9; C-10; C-24; C-25
15 β	—	C-27
16 α	C-17	C-17; C-28
16 β	C-14, C-18	C-14, C-18
18 α	C-13, c-16, C-17; C-19, C-20, C-28	C-13; C-14, C-16, C-17; C-19, C-20, C-28
19 β	C-21	C-18; C-20; C-21; C-29
21 α	C-17, C-18, C-20	C-17, C-18, C-20
22 α	C-17, C-28	C-17, C-28
22 β	C-17, C-18; C-19; C-21; C-28	C-17, C-18; C-19; C-21; C-28
23 α	C-4; C-5; C-24	C-4; C-5; C-24
24 β	C-4; C-5; C-23	C-4; C-5; C-23
25 β	C-1; C-5; C-9; C-10	C-1; C-5; C-9; C-10
26 β	C-7; C-8; C-9; C-14	C-7; C-8; C-9; C-14
27 α	C-8; C-13; C-14; C-15	C-8; C-13; C-14; C-15
28 a	C-17, C-18, C-22	C-17, C-18; C-22
28 b	C-16, C-17, C-18; C-22	C-16, C-17, C-18; C-22
29	C-19, C-20; C-30	C-19; C-20; C-30
30	C-19; C-20; C-29	C-19; C-20; C-29

Table 3. Characteristic ^1H–^1H proximities obtained by ROESY experiments

^1H	1 ^1H	2 ^1H
3 α	1α, 2α, 5α, 23α, 1′	1α, 2α, 5α, 23α, 1′, 2′
5 α	3α, 23α	3α, 7α, 9α, 23α
9 α	1α, 27α	1α, 27α
12 β	12α, 29	12α, 29
13 β	19β, 26β, 28a, 28b	19β, 26β, 28a, 28b
18 α	22α, 27α, 29	22α, 27α, 29, 30
19 β	13β, 28b, 29, 30	13β, 28b, 29, 30
21 α	22α, 29, 30	18α, 22α, 29, 30
22 β	16β, 22α	16β, 22α, 28a, 28b
23 α	3α, 5α, 6α, 24β, 1′	3α, 5α, 6α, 24β, 1′
24 β	2β, 23α, 25β	2β, 23α, 25β
25 β	1β, 2β, 11β, 24β, 26β	1β, 2β, 11β, 24β, 26β
26 β	11β, 13β, 15β, 25β	7β, 11β, 13β, 15β, 25β
27 α	9α, 12α, 16α, 18α	9α, 12α, 16α, 18α
28 a	13β, 15β, 28b	13β, 15β, 28b
28 b	13β, 19β, 28a	13β, 19β, 28a
29	18α, 19β, 21α, 30	18α, 19β, 21α, 30
30	19β, 21α, 29	19β, 21α, 29
1′	3α, 23α, 3′, 4′, 5′	3α, 23α, 3′, 4′, 5′

the C-3 chemical shift and HMBC and ROESY cross peaks. Surprisingly, it turned out that in **2** a glycol unit is linked to C-2′, the only structural difference between **2** and **1**. This is evident from a comparison of the ^{13}C chemical shifts of C-1′, C-2′ and C-3′ in these compounds. Reuben[10] has reported substituent effects deduced for hydroxyethyl groups attached to various oxygen atoms in glucose. The β and γ effects (strongly positive and moderately negative, respectively) are most diagnostic, although the magnitudes of the β effects are somewhat different. Such hydroxyethylated sugars seem to be very strange in natural product chemistry. The extraction and chromatographic procedures for **2**, however, do not give any indication that this compound was formed from **1** during the isolation. Nevertheless, we cannot exclude that **2** was formed by hydrolysis of a larger molecule.

Conformational analysis

The five-membered ring in the aglycone is fairly rigid owing to the *trans*-ring junction and substitution. The atoms C-18, C-19, C-21 and C-22 are more or less coplanar whereas C-17 is the out-of-plane atom of the envelope. This is evident from J(H-21α,H-22β) ≈ 0 Hz and J(H-21α,H-19β) = 2.9 Hz.

The rotation about the C-19–C-20 bond is restricted in that the carbinol substituent adopts preferentially one conformation as depicted in Fig. 2, where the hydroxy group is directed towards C-12. The methyl group 29 is pro-*R*. Its ^{13}C chemical shift is $\delta = 26.6$, which is 5.6–5.7 ppm smaller than that of the other (C-30: $\delta = 32.2$). This is due to the diamagnetic γ-effect; there are two carbon atoms *gauche*-oriented with respect to C-29, namely C-18 and C-21, whereas there is

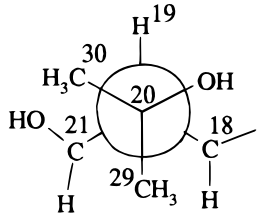

Figure 2. Conformation of the C-19 side chain.

only one for C-30, namely C-21. Moreover, we found a ROESY peak for the proton pair H-29 and H-18α, but not for the pair H-30 and H-18α.

The chemical shifts of the methylene protons of the 28-CH_2OH group are significantly different ($\Delta\delta = 0.42$–0.43). The ROESY spectrum indicated that the proton with the larger chemical shift (H-28b) is closer to H-19β, whereas H-28a is closer to H-15β. An orientation of the OH group at C-28 towards C-13 would create considerable steric hindrance. Thus, a stereochemical differentiation is possible: H-28a is pro-*R* and H-28b is pro-*S*.

ROESY cross peaks indicating spatial proximity between protons in the aglycone and the carbohydrate moiety are restricted to H-1′, H-3 and H-23α. Taking into account a stabilization by the well known *exo*-anomeric effect,[11] a preferred conformation as depicted in Fig. 3 is suggested.

As mentioned above, the carbon signals of the hydroxyethyl side chain of **2** are broadened at room temperature. At 330K, however, their linewidths adopt the values of all other carbon signals. Therefore, we have to assume that the mobility of the side chain is severely restricted (coalescence at room temperature), i.e. that at least two different conformations exist which are separated by a high energy barrier. A reason for this might be intramolecular hydrogen bond formation, either towards 3′-OH or the oxygen atom between C-1′ and C-3.

Acknowledgements

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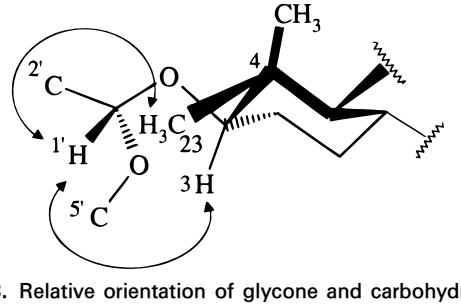

Figure 3. Relative orientation of glycone and carbohydrate moieties.

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