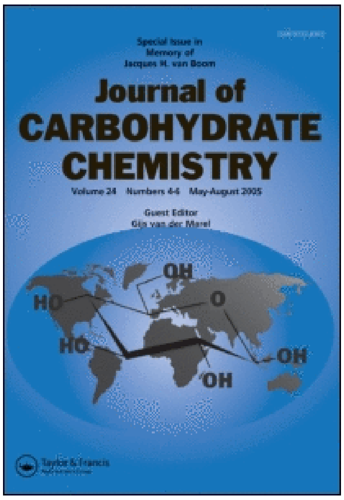

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STRUCTURAL IDENTIFICATION OF SUBSTITUTED C-1 SPIRO CYCLOPROPYL SUGARS.

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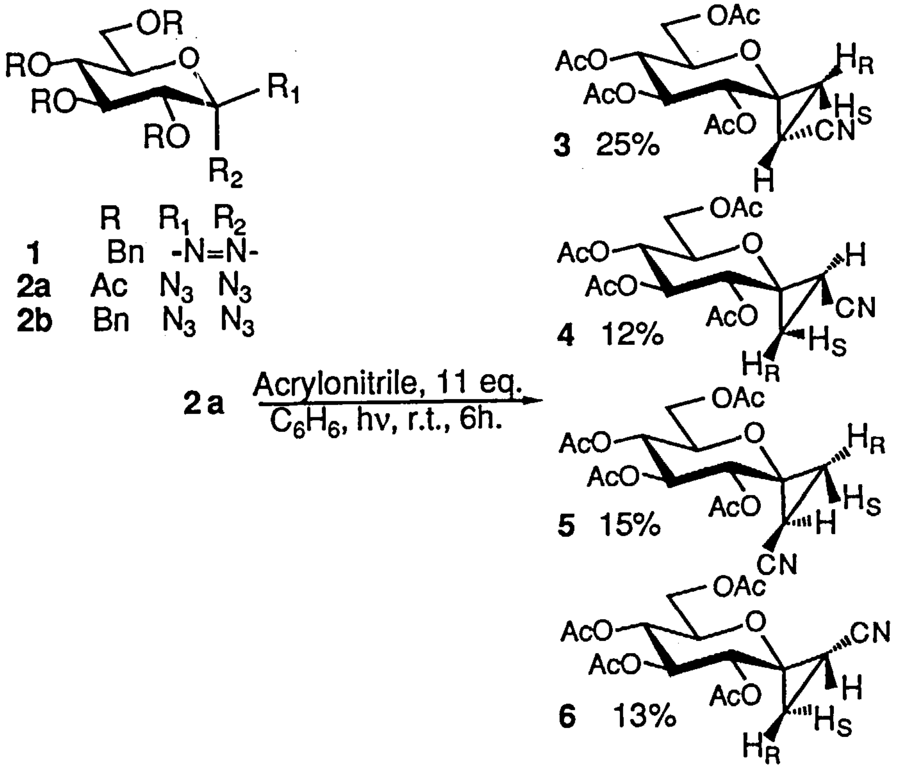
ABSTRACT

Photolysis of peracetylated D-glucopyranosylidene diazide in the presence of acrylonitrile in excess leads to new isomeric spiro C-1 cyclopropanic sugars (65% combined yield). Such structures, thus readily accessible by a new route which probably involves the addition of carbenic intermediates to an electrophilic alkene, have been identified by NMR investigations. In particular, the ^1H NMR spectra show that the location and the orientation of the cyano substituent on the cyclopropyl ring can be easily established by way of the deshielding effect (0.2 - 0.3 ppm) which is induced on a sugar ring proton attached at C-2, C-3 or C-5. In order to unambiguously identify the obtained spirosugars, the crystal structure of one of them was determined by X-ray analysis. $C_{17}H_{21}NO_9$, orthorhombic $P2_12_12_1$, a=9.093(1), b=9.933(1), c=21.588(3) Å, Z=4, R=0.041 for 1645 unique observed reflexions.

INTRODUCTION

For both theoretical[1] and synthetic reasons, reactions at the anomeric carbon of sugars have been receiving continuing attention, thus favouring the emergence of varied approaches for achieving stereocontrolled modifications at this centre. These methodologies usually involve anomeric carbenium intermediates,[2] but also carbanions[3] (umpolung) or, as it has been emphasized during the last decade, the corresponding free-



	R	R_1	R_2
1	Bn	-N=N-	
2a	Ac	N_3	N_3
2b	Bn	N_3	N_3

2a $\xrightarrow[C_6H_6,\ h\nu,\ r.t.,\ 6h.]{Acrylonitrile,\ 11\ eq.}$

3 25%

4 12%

5 15%

6 13%

SCHEME

radicals.[4,5] However, except for the recently reported decomposition of the glucopyranosylidene diazirine 1 (SCHEME) in the presence of 2-propanol[6] or substituted phenols,[7] neither the observation nor the utilization of transients related to anomeric carbenes have been reported. Therefore, the design of appropriate routes leading to such intermediates constitutes a stimulating challenge.

In this regard, the recently obtained glucopyranosylidene diazides 2[8] appeared of great interest. Though such diazides might be transformed using known procedures,[9,10] the cleavage of the azido groups of 2 under photolytic conditions with complete loss of nitrogen appeared a more promising alternative towards the desired carbenes, as suggested by a low temperature study of transients generated from aryl *gem* diazides.[11]

TABLE 1. Positional Parameters and Their Estimated Standard Deviations

Atom	x	y	z	B_{eq} (Å^2)
O1	0.2554(3)	0.2370(3)	0.0532(1)	4.73(5)
O2	0.2427(3)	0.3454(3)	0.2140(1)	5.11(5)
O3	0.4504(4)	0.4503(6)	0.2356(2)	16.6(2)
O4	0.1830(3)	0.5908(2)	0.1443(1)	4.81(5)
O5	0.0047(4)	0.5891(3)	0.2155(1)	8.14(8)
O6	0.0079(3)	0.5265(3)	0.0383(1)	4.73(5)
O7	0.1160(3)	0.6327(3)	-0.0409(1)	6.96(7)
O8	0.1345(3)	0.1768(3)	-0.0616(1)	6.12(7)
O9	0.3127(4)	0.2048(4)	-0.1309(2)	8.80(9)
N	0.0004(5)	-0.0273(4)	0.0676(2)	8.1(1)
C1	0.2470(4)	0.2261(4)	0.1183(2)	4.56(8)
C2	0.2628(4)	0.3597(4)	0.1483(1)	4.42(7)
C3	0.1463(4)	0.4563(4)	0.1249(1)	4.28(7)
C4	0.1412(4)	0.4570(4)	0.0539(1)	4.07(7)
C5	0.1349(4)	0.3145(4)	0.0283(2)	4.28(7)
C6	0.1532(5)	0.3129(4)	-0.0411(2)	5.28(9)
C7	0.1454(4)	0.1199(4)	0.1441(2)	5.13(8)
C8	0.3117(5)	0.1024(4)	0.1443(2)	6.0(1)
C9	0.0632(5)	0.0386(4)	0.1015(2)	5.9(1)
C10	0.3435(5)	0.3952(6)	0.2530(2)	7.9(1)
C11	0.2955(7)	0.3821(6)	0.3191(2)	9.4(2)
C12	0.1055(5)	0.6454(4)	0.1917(2)	5.52(9)
C13	0.1669(6)	0.7761(4)	0.2112(2)	7.8(1)
C14	0.0107(5)	0.6166(4)	-0.0088(2)	5.13(9)
C15	-0.1316(5)	0.6884(5)	-0.0156(2)	7.1(1)
C16	0.2185(5)	0.1336(4)	-0.1078(2)	6.1(1)
C17	0.1888(5)	-0.0060(5)	-0.1256(2)	7.5(1)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as : $B_{eq} = 4/3\ \Sigma_i \Sigma_j \beta_{ij} a_i a_j$

TABLE 2. Bond Distances in Angstroms

Bond	Distance	Bond	Distance	Bond	Distance
O1 - C1	1.410(4)	O7 - C14	1.193(5)	C4 - C5	1.521(5)
O1 - C5	1.443(4)	O8 - C6	1.432(5)	C5 - C6	1.508(5)
O2 - C2	1.436(4)	O8 - C16	1.328(5)	C7 - C8	1.522(6)
O2 - C10	1.339(5)	O9 - C16	1.217(5)	C7 - C9	1.435(6)
O3 - C10	1.177(6)	N - C9	1.135(6)	C10 - C11	1.498(6)
O4 - C3	1.439(4)	C1 - C2	1.484(5)	C12 - C13	1.475(6)
O4 - C12	1.356(4)	C1 - C7	1.509(5)	C14 - C15	1.485(6)
O5 - C12	1.191(5)	C1 - C8	1.474(5)	C16 - C17	1.464(6)
O6 - C4	1.434(4)	C2 - C3	1.516(5)		
O6 - C14	1.356(4)	C3 - C4	1.534(4)		

TABLE 3. Bond Angles in Degrees

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C1	O1	C5	111.8(3)	04	C3	C2	109.2(3)	N	C9	C7	178.7(5)
C2	O2	C10	119.8(3)	04	C3	C4	107.0(3)	02	C10	03	122.4(4)
C3	O4	C12	118.0(3)	C2	C3	C4	110.9(3)	02	C10	C11	111.6(4)
C4	06	C14	118.5(3)	06	C4	C3	105.2(3)	03	C10	C11	125.8(4)
C6	08	C16	117.9(3)	06	C4	C5	109.3(3)	04	C12	05	122.6(4)
01	C1	C2	111.2(3)	C3	C4	C5	111.1(3)	04	C12	C13	111.8(4)
01	C1	C7	117.0(3)	01	C5	C4	109.4(3)	05	C12	C13	125.5(4)
01	C1	C8	115.0(3)	01	C5	C6	106.4(3)	06	C14	07	122.7(4)
C2	C1	C7	121.5(3)	C4	C5	C6	111.5(3)	06	C14	C15	112.0(3)
C2	C1	C8	122.7(3)	08	C6	C5	107.6(3)	07	C14	C15	125.3(4)
C7	C1	C8	61.3(3)	C1	C7	C8	58.2(3)	08	C16	09	121.7(4)
02	C2	C1	109.3(3)	C1	C7	C9	118.4(3)	08	C16	C17	113.4(4)
02	C2	C3	107.6(3)	C8	C7	C9	117.1(3)	09	C16	C17	124.9(4)
C1	C2	C3	110.6(3)	C1	C8	C7	60.5(3)				

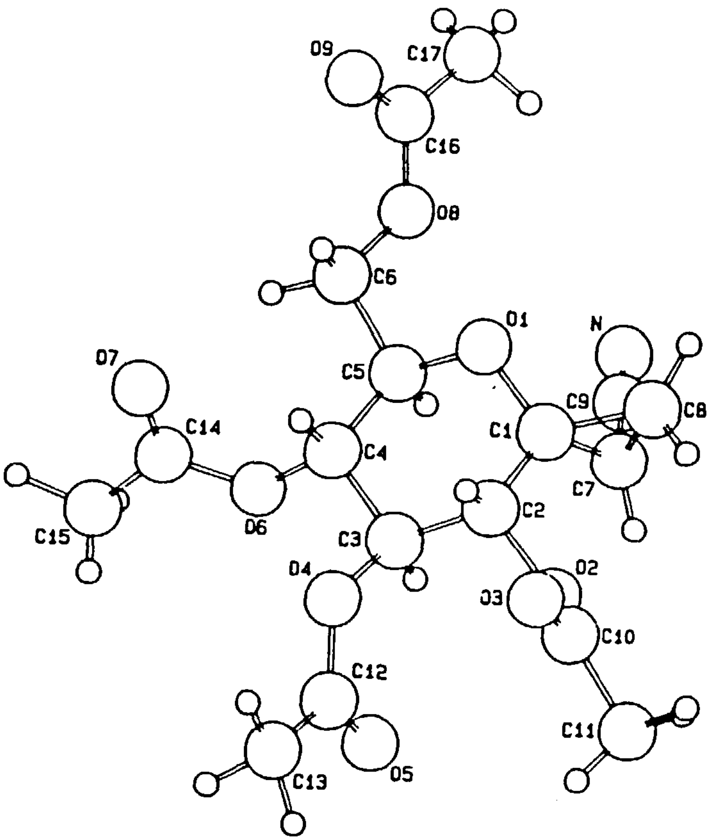


FIG. 1: PLUTO drawing of structure 3.

RESULTS AND DISCUSSION

Photolysis of **2a** and **2b** have been carried out in the presence of an excess of various alkenes (fumarodinitrile, dimethyl maleate, acrylonitrile).[12] While two isomeric tetrazoles were obtained in a 80% total yield from **2b**,[13] chromatographic purification of the products obtained from **2a** in the presence of the disubstituted alkenes afforded mainly the corresponding [2+2] cycloaddition adducts.[14] However, the validity of our approach was confirmed by the favourable outcome of the photolysis in the presence of acrylonitrile which is known to efficiently react with carbenes.[15] Careful column chromatography allowed the partial resolution of the mixture of four spiro cyclopropanic bis-C,C-glucosides: **3** (25%), **4** (12%), **5** and **6** (28%, 55-45 ratio) (SCHEME).

TABLE 4: ^1H and ^{13}C NMR data for compounds **3**, **4**, **5** and **6**. The missing chemical shifts are indicated in reference 22. a- These three protons appear as two 6 lines multiplets which are transformed into a doublet (5.21 ppm, spacing: 5.3 Hz, 2H) and a triplet (5.50 ppm, spacing: 4.7 Hz, 1H) by selective decoupling of H-5. b- This proton appears as a singlet by selective irradiation at 5.21 ppm. c- These coupling constants cannot be extracted from the spectra. d- These three protons give two multiplets. e- When studying the mixture **5** + **6**, these two protons give superimposed doublets of doublet which appear partially separated when applying a resolution enhancement sequence during the data treatment.

	H-2 $J_{2,3}$ C-2	H-3 $J_{3,4}$ to	H-4 $J_{4,5}$	H-5 $J_{5,6}$ C-5	H-6 $J_{5,6'}$ C-6	H-6' $J_{6,6'}$ C-1	H $J_{H,HR}$ CH	H_R $J_{H,HS}$ CH_2	H_S $J_{HR,HS}$ CN
3	$5.50^{a,b}$	5.21^a	5.21^a	4.02	4.29	4.17	1.84	1.65	1.24
	c	c	9.8	4.9	2.0	12.5	6.6	10.0	7.1
	73.5	67.7	66.8	75.5	61.4	62.7	5.3	16.0	117.4
4	$5.70^{b,d}$	5.21^d	5.21^d	3.67	4.20	4.03	1.94	1.65	1.38
	c	c	9.8	4.7	2.3	12.5	7.2	10.8	6.3
	74.0	67.9	65.5	75.2	61.4	62.7	8.5	14.1	116.7
5	5.61	5.41	5.22	3.77	4.22	4.05	1.69	1.62^e	1.25
	9.8	9.4	9.4	4.6	2.2	12.6	10.8	5.6	~ 6.3
	72.8	68.5	66.7	75.9	61.5	63.8	6.9	16.6	116.8
6	5.48	5.25	5.18	3.77	4.35	4.06	1.62^e	1.52	1.33
	8.9	9.3	9.2	5.0	2.3	12.4	10.0	~ 6.0	6.0
	73.6	68.4	66.9	75.8	61.5	61.7	7.5	14.8	116.50

Nice single crystals were obtained for **3** from a diethyl ether - petroleum ether solution. In the absence of any known related stuctures[16,17] and in order to unambiguously identify the reaction products, a crystal structure determination was undertaken for **3** as a support of the comparative study of the four spirosugars **3**-**6**. The final atomic x, y, z and B_{eq} parameters for the C, N, O atoms are given in TABLE 1 whereas bond lengths and angles are gathered in TABLES 2 and 3. The anisotropic thermal parameters, list of observed and calculated structure factors x, y, z for the H atoms are given as supplementary material. The PLUTO[18] drawing (FIG. 1) shows clearly that the cyclopropanic bis-C,C-glucoside studied corresponds to structure **3** in which the pyranosyl ring adopts a $^4C_1$-D chair conformation. The carbon-carbon bonds in the three-membered ring are not identical, the axial one being longer (1.509 Å) than the equatorial one (1.474 Å).

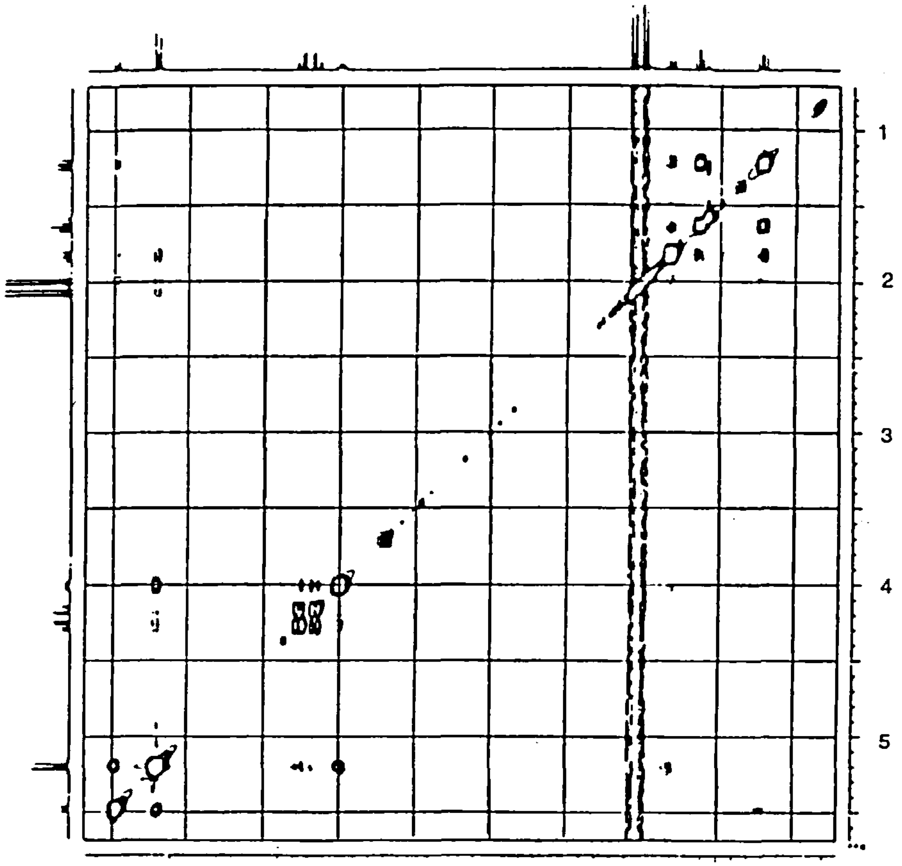


FIG. 2: 2D NOESY spectrum of compound 3.

As seen from TABLE 4, the ^{13}C NMR data confirm the presence in each structure of a quaternary anomeric carbon (~ 61 ppm), a nitrile group (~ 117 ppm) and, in the high field region, a secondary and tertiary carbon atom. The complete structure assignment relies upon the comparison of the ^{1}H NMR spectra which show a deshielding effect for the protons located in the vicinity of the nitrile group. Since such a deshielding amounts to 0.3 and 0.4 ppm for the H-3 and H-5 protons of the peracetylated-α-D-glucopyranosyl cyanide,[19] as compared to its β-counterpart, smaller effects are to be expected for H-5 (3), H-2 (4) and H-3 (5) (0.3, 0.2 and 0.2 ppm respectively) as a result of larger interatomic distances. Furthermore, these structural assignments were confirmed by the analysis of the 2D-spectra (NOESY) recorded for the known compound 3 (FIG. 2) and

4. The identification of all the NOESY cross peaks observed for the various neighbouring nuclei (3: H-2 / H_S and H-3 / H; 4: H-3 / H_R and H-5 / H_S, in particular) allows an unambiguous[20] assignment of both the heterocyclic and cyclopropanic protons.

The coupling constants (in Hz) observed for the cyclopropanic protons (*Jgem* $\sim$ -7, *Jcis* $\sim$ +10, *Jtrans* $\sim$ +7) are in agreement with those recorded for similarly substituted cyclopropyl derivatives.[21] The vicinal coupling constants (9-10 Hz) observed for the protons H-2, H-3 and H-4 in compounds **5** and **6** indicate a $^4C_1$-D chair conformation in solution, as observed for **3** in the solid state.

EXPERIMENTAL

Crystal structure determination. Crystal data for $C_{17}H_{21}NO_9$, M_r = 383.3, orthorhombic $P2_12_12_1$, a = 9.093(1), b = 9.933(1), c = 21.588(3) Å, V = 1949.8 (7) Å^3, Z = 4, D_x = 1.31g.cm^{-3}, λ (CuKα$^-$) = 1.5424 Å, μ = 9.3 cm^{-1}, F(000) = 808, T = 295 K. The diffraction data were obtained from a single crystal of 0.5 x 0.5 x 0.1 mm studied on a Nonius CAD-4 diffractometer. The unit-cell parameters were refined from setting angles of 25 selected reflections ($64 < 2\theta < 81°$). Intensities were collected using ω-4/3 θ scan. A total of 2235 independent reflections were measured and only 1645 were considered as observed ($I > 3\sigma(I)$).

The structure was solved using MULTAN78[23] and refined by full-matrix least squares based on F. All the hydrogen atoms were located from ΔF syntheses and assigned with the isotropic thermal parameters B_{eq} of bearing carbon atoms. The final refinement involved the x, y, z parameters of all the atoms and the β_{ij} parameters for the non-hydrogen atoms. The final agreement indice was R = 0.041. All the calculations were carried out on a DEC Microvax II computer using the Enraf-Nonius SDP system.[24]

NMR Analysis. The ^{1}H and ^{13}C NMR spectra were obtained from $CDCl_3$ solutions containing TMS and using a Bruker AM 300 spectrometer. The 2D NOESY spectra were recorded in the phase sensitive mode[25] with the standard BRUKER NOESY sequence using TPPI for quadrature detection in F1 dimension. A random variation of ± 2 % was applied to τ m in view of attenuating zero quantum coherences between close coupled protons.[26] Prior to starting NOESY experiments, a T1 measurement was performed. The mixing time τ m and the relaxation delay D1 were chosen as a function of the average T1 and fixed respectively to T1 and 3.T1. Spectra were recorded in an overnight experiment on 10 mg samples, dissolved in 0.5 mL of deuterated chloroform at 22°C with : acquisition time AQ =0.34 s, SI2 = 2048, D1 = 6s, τ m = 2s, NE = 512, NS = 8 accumulations.

Prior to 2D Fourier transformation and in order to attenuate the effect of signal truncation, the data were multiplicated by a squared shifted sine-bell (π / 2) in F2 and F1 dimensions, and zero-filled to 2K in the F1 dimension to increase digital resolution.

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