Assignment of Anomeric Configuration of C-Glycopyranosides and C-Glycofuranosides. A ^1H, ^{13}C, and Nuclear Overhauser Enhancement Spectrometric Study

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The utility of ^1H, ^{13}C, and nuclear Overhauser enhancement spectrometries for assignment of C-glycopyranosides and C-glycofuranosides to α or β anomer series has been assessed. Specifically examined were ^1H–^1H coupling constants $J_{1',2'}$ and $J_{4',5'}$, ^1H chemical shifts $\delta_{H1'}$, ^{13}C chemical shifts $\delta_{C1'}$ and $\delta_{C5'}$, ^1H–^{13}C coupling constants $J_{C1',H1'}$, and nuclear Overhauser effects (NOE) observed upon irradiation of H1', H4', and H5'. While all of these data have been used for assignment of anomeric configuration of C-glycosides, this study demonstrates that the NOE obtained by irradiation of H1' is uniquely reliable. For β C-glycosides, in which H1' and H5' (C-glycopyranosides) or H1' and H4' (C-glycofuranosides) are on the same face of the carbohydrate ring, irradiation of H1' gives rise to the appropriate NOE. In no instance does irradiation of an α C-glycoside give rise to such an effect.

Introduction

C-Glycosides, stable analogues[1] of the ubiquitious classes of O- and N-glycosides present in nature, have become the subject of vigorous biological and chemical research.[2] The growing interest in C-glycosides has stimulated significant efforts directed toward their synthesis and chemical modification.[2,3] Synthesis and manipulation of C-glycosides[2,3] requires effective methods for unambiguous structure assignment. A problem of special importance is the assignment of configuration at the carbohydrate anomeric carbon, i.e., the assignment of C-glycosides to α or β anomeric series.[4] This problem has been especially challenging in cases where C-glycosyl bond-forming reactions, such as the regio- and stereospecific palladium-mediated glycal–aglycon couping reaction,[3] yield a single C-glycosyl product. In the present study, we present a detailed analysis of the ^1H and ^{13}C nuclear magnetic resonance (NMR) spectrometry of a series of pyranosyl and furanosyl C-glycosides and critically assess the utility of these data for assignment of anomeric configuration in C-glycosides.

The use of ^1H and ^{13}C NMR spectrometric data to assign anomeric configurations of C-glycofuranosides was reviewed in 1984 by Chu and co-workers.[5] In general, the methods used up to that time for assignment of both C-glycofuranosides and C-glycopyranosides depend on the availability of both anomers for reliable assignments. This critical stereochemical assignment problem continues to receive attention. In more recent reports, for example, differences in coupling constants ($J_{1',4'cis}$ vs $J_{1',4'trans}$) were used[6,7] for assignment of anomeric configuration to 2',3'-unsaturated furanosyl C-glycosides, and Panek and Sparks[8,9] and Bolin et al.[10] have introduced the comparison of $^1J_{C1',H1'}$ of C-glycoside anomer pairs for assignment of anomeric configuration. Wright and co-workers,[11] Brakta et al.[12,13] and Cornia et al.[14,15] have made extensive studies of ^{13}C and ^1H chemical shift and coupling constant data in connection with C-glycosyl anomer pair assignments. Nuclear Overhauser effects (nuclear Overhauser difference spectroscopy, NOE) have been used in support of assignment of anomeric configuration of C-glycosides.[12-21]

Results

Table I contains ^1H chemical shifts for two 2',3'-deoxy C-glycosyl α and β anomer pairs[4] (1-, 2α and -β); the

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(4) In a strict sense, treatment of C-glycosides as pentoses or hexoses with carbon appendages at the anomeric carbon is incorrect; however, designation of C-glycosides isomeric at this "anomeric carbon" as α- and β-anomers is more readily understood than the systematic notation and is used in this report. Following convention, the carbons of the "carbohydrate moieties" of C-glycosides are designated C1', C2', etc.
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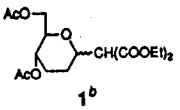
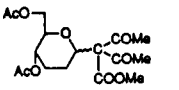
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) for 2′,3′-Dideoxy C-Glycopyranosides[a]

compd	anomeric config	H-1′	H-2′a	H-2′e	H-3′a	H-3′e	H-4′	H-5′	H-6′	H-6″	H-2
 1[b]	α	4.42	1.70		1.90	1.95–2.05	4.76	3.96	4.11	4.27	3.74
	β	4.02	1.50–1.60	1.90–1.97	1.50–1.60	2.20–2.30	4.65	3.58	4.08	4.18	3.46
 2	α	4.50	1.40–1.60		1.83–1.93	1.89–1.96	4.85	4.15	4.25	4.36	
	β	4.21	1.20–1.40	2.00–2.15	1.40–1.70	2.20–2.35	4.63	3.61	4.13		

[a] In $CDCl_3$. [b] See ref 22.

Table II. ^{13}C NMR Chemical Shifts (δ, ppm) and ^{1}H–^{1}H Coupling Constants (Hz) for 2′,3′-Dideoxy C-Glycopyranosides[a]

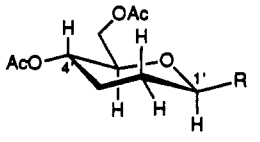
anomer	C-1′	C-2′[b]	C-3′[b]	C-4′	C-5′	C-6′	$J_{HC1',H1'}$	$J_{H1',H2'a}$	$J_{H1',H2'e}$	$J_{H4',H5'}$
1α	70.35	24.31	24.06	67.08	72.33	62.21	153.1	6.2	3.9	6.3
1β	75.78	28.07	28.73	67.71	77.70	63.27	146.7	11.2	2.4	9.8
2α	71.17	21.41	23.72	66.59	74.31	60.77	159.4	6.8	2.4	2.0
2β	77.34	25.99	28.59	67.32	78.20	62.86	139.7	12.0	2.1	10.5

[a] Spectra were recorded in $CDCl_3$. [b] Assignments could be reversed.

corresponding ^{13}C chemical shifts and coupling constants, $J_{C1',H1'}$, $J_{H1',H2'a}$, $J_{H1',H2'e}$, and $J_{H4',H5'}$, are contained in Table II. Table III contains ^{1}H NMR chemical shifts for carbohydrate carbons of 11 2′,3′-unsaturated C-glycopyranosyl α and β anomer pairs (**3**–**13**α and -β) and an additional 2′,3′-unsaturated α C-glycopyranoside (**14**α). Corresponding ^{13}C chemical shifts are contained in Table IV; also in this table are coupling constants, $J_{C1',H1'}$ and $J_{H4',H5'}$. Tables V contains ^{1}H chemical shifts and coupling constants $J_{H1',H2'\alpha}$ and $J_{H1',H2'\beta}$ for six furanosyl C-glycosides (**15**–**19**β and **17**α); Table VI contains corresponding ^{13}C chemical shifts. 1-D Nuclear Overhauser effects observed upon irradiation of 1H′ (anomeric hydrogens), H5′, or an aglycon resonance for 13 C-glycopyranosyl anomer pairs (**1**-**13**α and -β), and one single anomer (**14**α) for the furanosyl C-glycosyl anomer pair **17**α and -β and for single anomers **15**β, **16**β, **18**β, and **19**β are contained in Table VII. Typical NOE data obtained in this study are illustrated for C-glycopyranosides in Figure 1 (**8**α and β) and Figure 2 (**13**α and β) and for a C-furanoside (**16**β) in Figure 3.

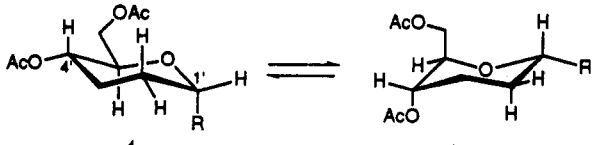
Discussion

^{1}H-^{1}H Coupling Constants. The most facile assignments of anomeric configuration involves saturated pyranosyl C-glycosides in which a single chair conformation is strongly favored.[27-31] In such cases, where the stereochemistry of other carbohydrate carbons is known (see **1** and **2**, Tables I and II), the anomeric configuration is readily deduced by the coupling constants for pyranosyl hydrogens. Thus, $J_{1',2'a}$ for **1**β and **2**β (Table II), 11.2 and 12.0 Hz respectively, indicate that the anomeric hydrogens (H1′) are axial, and $J_{4',5'}$ = 9.8 and 10.5 Hz indicate that H4′ and H5′ in these pyranosyl rings are also axial. These coupling constants establish the conformations of **1**β and **2**β in solution as $^4C_1$ and the anomeric assignments as β.[27-31] Coupling constant analysis for the corresponding α-anomers **1**α and **2**α is much less straightforward since these compounds are conformationally mobile involving interconverting $^4C_1$ and $^1C_4$ chair forms.[27]



$^4C_1$

1β, R = CH(COOEt)$_2$
2β, R = C(COMe)$_2$COOMe



$^4C_1$ $^1C_4$

1α, R = CH(COOEt)$_2$
2α, R = C(COMe)$_2$COOMe

Comparison of $J_{H4',H5'}$ for α- and β-anomers has also been used[17] in assignment of anomeric configuration of 2′,3′-unsaturated C-glycopyranosides; however, the $J_{H4',H5'}$ data in Table IV for eleven anomer pairs indicate that these data are of limited utility. Owing to the 2′,3′-unsaturation in the pyranosyl ring, β-C-glycopyranosides assume the half-chair $^OH_5$ conformation in which all pyranosyl substituents are pseudoequatorial; evidence for this conformation is provided by large (8–10 Hz) pseudo-axial–pseudoaxial values for $J_{H4',H5'}$ exhibited by the β-anomers in Table IV. As in the case of the saturated C-glycopyranosides (Tables I and II), 2′,3′-unsaturated C-glycopyranosyl α-anomers are more conformationally mobile, exhibiting $J_{H4',H5'}$ values ranging from 4.4 to 9.0 Hz indicative of differing contributions of $^OH_5$ and ^5H_O

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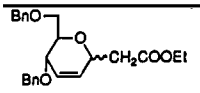
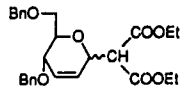
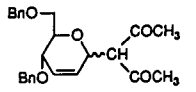
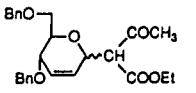
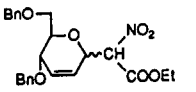
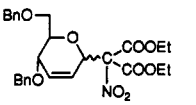
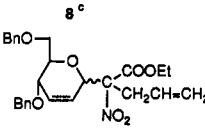
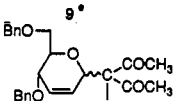
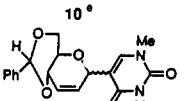
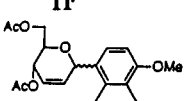
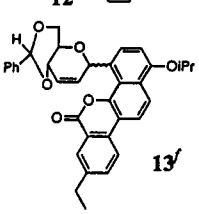
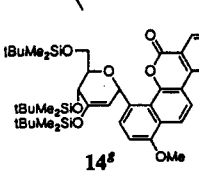
Table III. ^{1}H NMR Chemical Shifts (δ, ppm) for 2′,3′-Unsaturated C-Glycopyranosides[a]

compound	anomeric config.	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′	H-6″	H-2
 3[b]	α	4.70	4.84	5.96	4.04	3.75	3.64	3.69	2.51, 2.72
	β	4.58	4.81	5.94	4.04	3.73	3.63	3.65	2.46, 2.63
 4[c]	α	4.86	5.98	6.02	4.04	3.65–3.75	3.60	3.71	3.75
	β	4.78	5.93	6.00	4.04	3.64–3.75	3.58	3.63	3.54
 5[c]	α	4.92	5.78	5.98	3.98	3.75	3.56	3.63	4.09[d]
	β	4.85	5.73	5.97	4.02	3.63–3.78	3.62	3.66	3.81[d]
 6[c]	α	4.84, 4.88	5.90, 5.92	5.99	3.99, 4.02	3.70–3.80		3.60–3.80	3.86, 3.94
	β	4.79, 4.82	5.83	5.91, 5.99	4.05, 4.07	3.60–3.80		3.60–3.80	3.60, 3.81
 7[c]	α	5.01, 5.02	5.89, 5.90	6.15	4.17	3.60–3.73	3.62	3.72	5.29, 5.35
	β	4.95, 5.00	5.85, 5.88	6.10	3.96, 4.08	3.60–3.75	3.63	3.72	5.09, 5.33
 8[c]	α	5.20	6.07	6.19	4.03	4.17	3.60	3.67	
	β	5.17	6.02	6.14	4.04	3.67	3.69	3.70	
 9[e]	α	4.86, 4.98	6.17	6.08	3.89	3.81, 4.01	3.57	3.64	
	β	4.82, 5.01		6.06–6.08	3.92, 4.04	3.58		3.75	
 10[e]	α	4.32	6.10	6.02	3.61	4.37	3.48	3.67	
	β	5.02	5.95	6.04	4.07	3.60		3.80	
 11[f]	α	5.45	5.74	6.20	4.20–4.23	3.43	3.80	4.20, 4.23	
	β	5.41	5.88	6.06	4.25	3.76	3.70	4.30	
 12	α	5.94	6.25	6.07	5.37	3.73	3.88	4.24	
	β	5.79	6.11	5.88	5.50	4.08	4.21	4.29	
 13[f]	α	7.07	6.15	6.23	4.37	3.63	3.78	4.02	
	β	7.06	6.20	6.10	4.44–4.47	4.21	3.92	4.44–4.47	
 14[g]	α	6.77	5.29		4.12	4.03	3.98	4.00	

[a] Spectra were recorded in $CDCl_3$. [b] See ref 13. [c] See ref 12. [d] H-3. [e] See ref 23. [f] See ref 24. [g] See ref 16; assignments have been reversed.

conformers.[17,32] While $J_{H4',H5'}$ values are useful in assessing conformations of 2′,3′-unsaturated C-glycopyranosides the overlap in values (see 3α and 3β, Table IV) preclude their use as a sole criterion for assignment of anomeric configuration.[12–14,24b,33,34] Similarly, assignment of anomeric configuration to C-glycofuranosides on the basis of ^{1}H NMR coupling constants is unreliable.[35–37]

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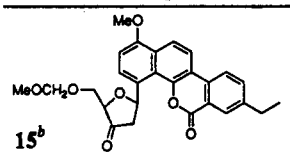
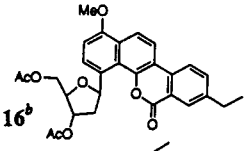
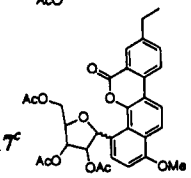
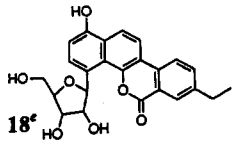
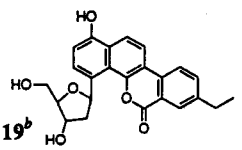
Table IV. ^{13}C NMR Chemical Shifts (δ, ppm) and Coupling Constants (Hz) for 2,3-Unsaturated C-Glycopyranosides[a]

anomer	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	$J_{C1'H1'}$	$J_{H4'H5'}$
3α	69.84	126.59	130.10	69.32	71.64	69.19		7.7
3β	71.58	126.99	130.30	70.38	77.64	69.58		7.7
4α	71.22	128.17	128.03	69.68	71.93	68.80		7.0
4β	73.25	128.25	128.16	70.10	77.75	69.45		8.2
5α	71.66	128.20	128.13	71.28	72.15	68.78		7.2
5β	73.57	128.18[b]	128.21[b]	72.20	77.28	69.42		8.4
6α	70.82, 71.29	c	c	69.52, 69.63	72.09, 72.17	68.85, 68.92		7.4
6β	73.20, 73.70	128.06, 128.17	127.80	69.91, 69.94	77.31, 77.49	69.28, 69.47		8.4
7α	70.16, 71.13	124.18, 124.82	130.88, 131.11	68.99, 69.21	72.27, 72.84	68.45, 68.78	156.0, 156.5	7.0
7β	72.89, 72.96	124.20, 124.74	129.96, 131.25	69.67	77.63, 78.05	68.91, 69.39	152.8	8.6
8α	72.64	123.64	131.04	68.84	72.85	68.78	157.4	6.7
8β	75.24	123.96	132.26	69.37	78.14	69.15	153.4	8.6
9α	71.26	126.37, 126.78	129.86, 130.22	68.70	73.25, 73.58	68.58		4.9, 5.2
9β	74.64, 75.77	126.04, 126.18	130.05, 130.51	69.72, 69.82	77.99, 78.38	69.12, 69.50		8.5
10α	69.51	125.67	129.56	67.91	74.17	67.68	152.7	4.4
10β	74.77	127.64	129.15	69.55	77.74	69.30	152.5	8.7
11α	68.35	129.66	126.94	74.93	64.73	69.42		9.0
11β	71.53	129.01	126.98	74.94	71.53	69.25		9.6
12α	71.15	131.86	126.16	65.57	68.52	62.86		8.0
12β	75.25	133.02	125.08	65.72	75.21	63.84		9.0
13α	73.08	131.10	126.16	75.68	64.13	69.86		6.1
13β	76.30	132.22	127.19	65.53	71.70	69.72		10.3
14α	70.07	108.37	147.32	67.28	80.16	62.18		8.9

[a] Spectra recorded in $CDCl_3$. [b] Assignments could be reversed. [c] Obscured by other resonances.

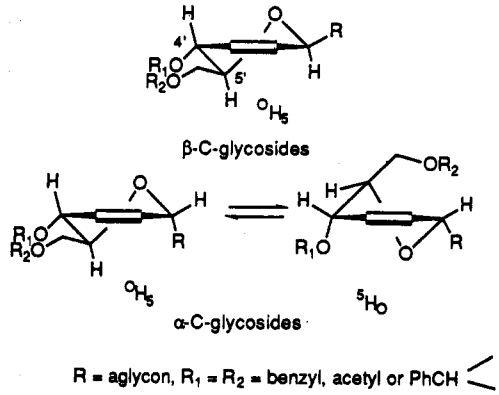
Table V. ^1H NMR Chemical Shifts (δ, ppm) and Coupling Constants (Hz) for C-Glycofuranosides[a]

compd	anom. confign	H-1′	H-2′	H-3′	H-4′	H-5′5″	$J_{H1',H2'\alpha}$	$J_{H',H2'\beta}$
 15[b]	β	6.58	α = 3.65 β = 2.39		4.38	4.00	6.1	10.0
 16[b]	β	6.45	α = 3.05 β = 1.93	5.24	4.42	4.33 4.47	5.2	9.7
 17[c]	α	6.72	6.35	5.69	4.50	4.34 4.49		
	β	6.58	5.59	5.16	4.56	4.46 4.53		3.5
 18[e]	β[d]	6.08	4.35	4.07	4.19	4.03 3.88	0.8	
 19[b]	β[f]	6.24	α = 2.70 β = 1.87	4.02	3.81	3.61 3.67	6.9	7.1

[a] Unless otherwise noted spectra were recorded using solutions of $CDCl_3$. [b] See ref 16. [c] See ref 25. [d] In DMF-d_7. [e] See ref 26. [f] In Me_2SO-d_6.

^1H Chemical Shifts. Axial hydrogens typically exhibit NMR resonances upfield of corresponding equatorial hydrogen resonances; this difference has been used for assignment of anomeric configuration.[27,38] It is noteworthy (Table I) that the relationship ($\delta_{H1'}$ for β-anomers upfield of $\delta_{H1'}$ for α-anomers) holds even though the anomeric hydrogens for these α-anomers are not, in general, completely equatorial; for 1α and 2α, $\delta_{H1'}$ represents a weighted average of the chemical shifts of this hydrogen in interconverting $^4C_1$ and $^1C_4$ conformers. Furthermore, for the 2′,3′-unsaturated C-glycopyranoside anomer pairs in Table III, $\delta_{H1'}$ for the β-anomer appears at higher field in eight (3–8, 11–12) of 11 pairs. For anomer pair 10, $\delta_{H1'}$ for the β-anomer appears 0.7 ppm downfield of that for the α-anomer, for anomer pair 9 the difference is slight (and for one diasteriometer is reversed from that expected), and for anomer pair 13 the $\delta_{H1'}$s are essentially identical. These data indicate clearly that assignment of anomeric configuration for 2′,3′-unsaturated C-glycopyranosides on the basis of the chemical shift difference for H1′ of α and β-anomers is not reliable. This is not surprising in light

(37) See, however: Francois, P.; Sonveaux, E.; Touillaux, R. *Nucleosides Nucleotides* **1990**, *9*, 379–382.
(38) Talshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518–522.



of the (solvent sensitive[27]) conformational mobility of these systems and the significant effects of the aglycon on chemical shifts ($\delta_{H1'}$ varies from 4.32 to 7.07, Table III).

It is noteworthy that the chemical shifts for H2′ and H3′ in these compounds are quite variable, ranging from δ 4.81 to 6.25, and, more importantly, that their relative positions can change. For most compounds in Table III, whether α or β anomers, $\delta_{H2'}$ is upfield of $\delta_{H3'}$; however, for **9**α, **10**α, **12**α and -β, and **13**β the upfield resonance is that of H3′. Assignments of these resonances must be made by a definitive method.[17]

For the single C-glycofuranoside anomer pair compared in this study (**17**, Table V) the chemical shift for H1′ of the β-anomer (δ 6.58) appears upfield of the corresponding α-anomer resonance (δ 6.72). This difference, commonly seen in ribofuranosyl N- and C-nucleosides,[5] is attributed to shielding of H1′ by the *cis*-hydroxy group at C2′ of β-anomers. For (2′-deoxyribofuranosyl)pyrimidine C-nucleoside anomer pairs H1′ for β-anomers resonate downfield of corresponding α-anomers.[35]

^{13}C Chemical Shifts. Data contained in Tables II and IV indicate that anomeric configurations of saturated and unsaturated C-glycopyranosides can be reliably assigned,[12,13,39,40] when both anomers are available, by comparison of the ^{13}C chemical shifts for C1′ and C5′. The γ-gauche effect[41] predicts that C1′ and C5′ of α C-glycopyranoside anomers will be shielded with respect to corresponding carbons of β anomers. Thus, for the anomer pairs reported in Tables II and IV, $\delta_{C1'}$ and $\delta_{C5'}$ for α anomers are 2–7 ppm upfield of corresponding resonances for β anomers. Unfortunately, this effect does not extend to C-glycofuranosides[5,11,35] (in which C4′ bears the same relationship to C1′ as C5′ does in C-glycopyranosides). For anomer pair **17** (Table VI), $\delta_{C1'\alpha}$ appears upfield of $\delta_{C1'\beta}$; however, $\delta_{C4'\alpha}$ is downfield of $\delta_{C4'\beta}$. Chu and co-workers[5] have reviewed ^{13}C chemical shifts in C-glycofuranosides; while assignments of anomeric configuration have been made using these data,[5] their utility for this purpose is questionable.

^{1}H–^{13}C Coupling Constants. It has been suggested[8-10] that comparison of $^1J_{C1',H1'}$ of C-glycoside anomer pairs is reliable for assignment of anomeric configuration. Values for $^1J_{C1',H1'}$ (Tables II and IV) indicate that the coupling constants for α anomers are generally larger than the corresponding coupling constants for β anomers[9] in accord with the expectation that coupling involving an equatorially disposed hydrogen is more effective.[10] However, values for $^1J_{C1',H1'}$ for anomer pair **10** (Table IV) are essentially identical, indicative that this criterion for assignment of anomeric configuration is also of limited utility.

Table VI. ^{13}C NMR Chemical Shifts (δ, ppm) for C-Glycofuranosides[a]

anomer	C-1′	C-2′	C-3′	C-4′	C-5′
15β	75.87	46.37		81.15	66.39
16β	79.16	41.88	76.54	81.01	64.48
17β	82.60	76.37	69.59	76.47	63.16
17α	80.59	73.02	73.66	77.71	64.40
18β[b]	78.06	82.78	69.71	86.33	61.79
19β[c]	77.73	44.15	71.05	86.39	62.21

[a] Unless otherwise noted spectra were recorded using solutions of $CDCl_3$. [b] In DMF-d_7. [c] In Me_2SO-d_6.

Nuclear Overhauser Effects. Table VII contains NOE data for 33 C-glycopyranosides and C-glycofuranosides; typical NOE spectra obtained in this study are exhibited in Figures 1–3. Figure 1 shows ^{1}H NMR spectra for 8α and 8β and the corresponding 1-D NOE spectra obtained upon irradiating the anomeric hydrogen resonances. Irradiation of H1′ of 8α gives rise to a strong effect only for H2′. This result has several implications. First, although H1′ is scalar coupled to H2′, H3′, and H4′ the observation of an effect only for H2′ is evidence that spin polarization transfer is not a problem. Second the single olefinic hydrogen NOE effectively distinguishes H2′ from H3′.[17] Finally, the failure to observe an NOE for H4′ is indicative that the average distance between H1′ and H4′ in C-glycopyranoside 8α, which exists in solution as a dynamic mixture of half-chair conformations $^0H_5$ and $^5H_0$ as shown by the intermediate value[27] of $J_{H4',H5'}$ (6.7 Hz, Table IV), is too great. Irradiation of H1′ of the β anomer 8β led to a spectrum exhibiting intense NOEs for H2′ and for H5′ (Figure 1). The conformation of 8β, $^0H_5$, brings H1′ and H5′, which occupy the same face of the glycopyranosyl ring, into close proximity.

NOE spectra for anomer pair **13** (Figure 2) are somewhat different. Irradiation of H1′ of **13**α gives rise to NOEs for H2′ and H4′. Presumably, the average distance of H1′ and H4′ in annelated C-glycopyranoside **13**α is somewhat less than in 8α permitting an NOE to be observed. The corresponding spectrum for **13**β contains NOEs for H2′ and H5′; in addition, an NOE for H3 of the anthracycline aglycon is also observed indicative that the conformation of **13**β in solution has H1′ of the carbohydate proximal to H3. The NOE spectrum for the β-C-glycofuranoside[42] **16**β (Figure 3) exhibits an NOE for H4′. The observation of strong effects for both H2's suggests that in this case spin polarization transfer may be occurring.

The data in Table VII demonstrate the utility of NOE for assignment of anomeric configuration in these C-glycosides. For every β C-glycoside, for which the configurations of carbons bonded to the ring oxygen (C1′ and C5′ for C-glycopyranosides, C1′ and C4′ for C-glycofuranosides) place the respective hydrogens on the same face of the

(39) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522–528.
(40) Bellosta, V.; Chassagnard, C.; Czernecki, S. *Carbohydr. Res.* **1991**, *219*, 1–7.
(41) (a) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1973; Chapter 3. (b) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1988; Chapter 3.

(42) For other NOE data for C-glycofuranosides see: Cookson, R. C.; Dudfield, P. J.; Klinkert, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 405–409. Rosenmeyer, H.; Seela, F. *Nucleosides Nucleotides* **1990**, *9*, 417–418. Rosenmeyer, H.; Toth, G.; Seela, F. *Nucleosides Nucleotides* **1989**, *8*, 587–597. Maeba, I.; Osaka, K.; Morishita, N.; Fujioka, K.; Ito, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 939–944. Seela, F.; Bourgeois, W. *Synthesis* **1988**, 938–943. Ito, Y.; Ito, C.; Maeba, I. *Heterocycles* **1991**, *32*, 1955–1959. Knutsen, L. J. S.; Judkins, B. D.; Newton, R. F.; Scopes, D. I. C.; Klinkert, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 621–630.

Table VII. Results of ^1H–^1H 1-D Nuclear Overhauser Enhancement Spectrometry Experiments[a]

anomer	hydrogen irrad	obsd NOE						
1α	H-1′	H-5′ (no)	6α	H-1′	H-5′ (no)	11α	H-1′	H-5′ (no)
	H-5′	H-1′ (no)		H-5′	H-1′ (no)			
						11β	H-1′	H-5′ (yes)
1β	H-1′	H-5′ (yes)	6β	H-1′	H-5′ (yes)	12α	H-1′	H-5′ (no)
	H-5′	H-1′ (yes)		H-5′	H-1′ (yes)			
2α	H-1′	H-5′ (no)	7α	H-1′	H-5′ (no)	12β	H-1′	H-5′ (yes)
	H-5′	H-1′ (no)		H-5′	H-1′ (no)			
2β	H-1′	H-5′ (yes)	7β	H-1′	H-5′ (yes)	13α	H-1′	H-5′ (no)
	H-5′	H-1′ (yes)		H-5′	H-1′ (yes)			H-4′ (yes)
3α	H-2	H-5′ (yes)	8α	H-1′	H-5′ (no)	13β	H-1′	H-5′ (yes)
				H-5′	H-1′ (no)			H-4′ (no)
3β	H-2	H-5′ (no)	8β	H-1′	H-5′ (yes)	14α	H-1′	H-5′ (no)
		H-6′ (yes)		H-5′	H-1′ (yes)			
4α	H-1′	H-5′ (no)	9α	H-1′	H-5′ (no)	15β	H-1′	H-4′ (yes)
	H-5′	H-1′ (no)		H-5′	H-1′ (no)			
						16β	H-1′	H-4′ (yes)
4β	H-1′	H-5′ (yes)	9β	H-1′	H-5′ (yes)			
	H-5′	H-1′ (yes)		H-5′	H-1′ (yes)	17α	H-1′	H-4′ (no)
								H-3′ (yes)
5α	H-1′	H-5′ (no)	10α	H-1′	H-5′ (no)			
	H-5′	H-1′ (no)		H-5′	H-1′ (no)	17β	H-1′	H-4′ (no)
5β	H-1′	H-5′ (yes)	10β	H-1′	H-5′ (yes)	18β[b]	H-1′	H-4′ (yes)
	H-5′	H-1′ (yes)		H-5′	H-1′ (yes)			
						19β[c]	H-1′	H-4′ (yes)

[a] Unless otherwise noted experiments utilized C-glycoside solutions in $CDCl_3$. [b] In DMF-d_7. [c] In Me_2SO-d_6.

carbohydrate ring, irradiation of H1′ gives rise to the appropriate NOE. In contrast, in no instance does irradiation of H1′ of an α C-glycoside give rise to such an effect. Thus, following assignment of resonances present in the ^1H NMR spectrum of a C-glycoside, reliable assignment of anomeric configuration can be accomplished on the basis of a single NOE difference spectrum. That is, an experiment involving irradiation of the anomeric hydrogen and noting the presence or absence of the appropriate NOE permits unambiguous assignment of a C-glycoside to the α or β anomer series without need for comparison with the corresponding anomer.[43]

Experimental Section

General Comments. Thin-layer chromatography (TLC) was carried out on prescored silica gel GF plates (Analtech). Preparative TLC was carried out on 1-mm-thick 20 × 20-cm^2 silica gel GF plates (Analtech). Column chromatography was carried out on silica gel GF254 (230–400 mesh Merck). Synthesis of C-glycosides 1,[22] 3–11,[12,13,23,24] and 13–19[16,24,25] have been described.

NOE Experiments. The NOE difference measurements were obtained using the standard Bruker NOEDIFF microprogram. The anomeric hydrogens were preirradiated for 1 s at 35 dB attenuation of the low power decoupler (≈0.4 W). This was alternated every eight scans with off-resonance irradiation for the spectra that were to be subtracted.

Methyl 2-(4′,6′-Di-*O*-acetyl-2′,3′-dideoxy-D-*erythro*-hexopyranosyl)-2,2-diacetylacetate (2α and -β). A solution of 0.65 mmol of the unsaturated 4′,6′-di-*O*-benzyl C-glycoside 10α[23] or 10β[23] in 5 mL of ethanol was hydrogenated at atmospheric pressure and 25 °C in the presence of 30 mg of 10% Pd/C. After 12 h, filtration and concentration of the solution under vacuum gave the crude diol, which was dissolved in 5 mL of pyridine, and 1.5 mL of acetic anhydride was added at 0 °C. After 12 h the solvent was evaporated, and the crude residue was partitioned between water (5 mL) and CH_2Cl_2 (10 mL). Evaporation of the CH_2Cl_2 followed by column chromatography on silica afforded the acetylated product. 2α: yield 88%; oil; TLC R_f = 0.45 (AcOEt:hexane = 1:1); $[\alpha]^{20}_D$ = −32.9 (c 0.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40–1.60 (m, 1H, H-2′a), 1.83–1.93 (m, 2H, H-2′e and H-3′a), 1.89–1.96 (m, 1H, H-3′e), 2.06, 2.09 (2s, 6H, $OCOCH_3$), 2.25, 2.42 (2s, 6H, $COCH_3$), 3.80 (s, 3H, OCH_3), 4.15 (ddd, 1H, J = 7.6, 5.6, 2.0 Hz, H-5′), 4.25 (dd, 1H, J = 11.8, 5.6 Hz, H-6′), 4.36 (dd, 1H, J = 11.8, 7.6 Hz, H-6″), 4.50 (dd, 1H, J = 12.0, 2.4 Hz, H-1′), 4.85 (bs, 1H, H-4′); ^{13}C NMR ($CDCl_3$) δ 20.75, 21.06 (OCOMe), 21.41 (C-2′), 23.72 (C-3′), 28.90, 29.26 (COMe), 52.82 (OMe), 60.77 (C-6′), 66.59 (C-4′), 71.17 (C-1′), 74.31 (C-5′), 80.31 (C-quat), 167.40, 170.04 and 170.45 (OCOMe and CO_2Me), 200.32, 202.26 (COMe). Anal. Calcd for $C_{17}H_{24}O_9$: C, 54.8; H, 6.50. Found: C, 54.8; H, 6.02.

2β: yield 72%; oil; TLC R_f = 0.45 (AcOEt:hexane = 1:1); $[\alpha]^{20}_D$ = −21.1 (c 1.5, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.20–1.40 (m, 1H, H-2′a), 1.40–1.70 (m, 1H, H-3′a), 2.05, 2.06 (2s, 6H, $OCOCH_3$), 2.00–2.15 (m, 1H, H-2′e), 2.20–2.35 (m, 1H, H-3′e), 2.35, 2.42 (2s, 6H, $COCH_3$), 3.61 (ddd, 1H, J = 10.5, 4.2, 4.2 Hz, H-5′), 3.80 (s, 3H, OCH_3), 4.13 (bd, 1H, J = 4.2 Hz, H-6′), 4.21 (dd, 1H, J = 6.8, 2.1 Hz, H-1′), 4.63 (ddd, 1H, J = 10.5, 10.5, 4.8 Hz, H-4′); ^{13}C NMR ($CDCl_3$) δ 20.47, 20.77 (OCOMe), 25.99 (C-2′), 28.59 (C-3′), 28.76, 28.97 (COMe), 52.65 (OMe), 62.86 (C-6′), 67.32 (C-4′), 77.34 (C-1′), 78.20 (C-5′), 79.72 (C-quat), 166.97, 169.70, and 170.32 (OCOMe and CO_2Me), 200.03, 201.65 (COMe). Anal. Calcd for $C_{17}H_{24}O_9$: C, 54.8; H, 6.50. Found: C, 54.5; H, 6.72.

4-(4′,6′-Di-*O*-acetyl-2′,3′-dideoxy-D-*erythro*-hex-2′-enopyranosyl)-1-methoxynaphthalene (12α and -β). To a solution of 0.5 g (3.16 mmol) of 1-methoxynaphthalene and 1.29 g (4.74 mmol) of 3,4,6-tri-*O*-acetyl-D-glucal[44] in 50 mL of 1,2-dichloroethane at −22 °C was added $SnCl_4$ (0.32 mL of a 1 M solution in 1,2-dichloroethane). After 75 min, the solvent was removed and the residue was partitioned between CH_2Cl_2 and water. The residue obtained by evaporation of the CH_2Cl_2 solution was separated by column chromatography using CH_2Cl_2:AcOEt = 50:1 for elution to yield 1.1 g (94%) of a 1:1 mixture of 12α and 12β. Further separation by preparative TLC afforded the individual anomers which were recrystallized from $CHCl_3$–EtOH. 12β: R_f = 0.42 (CH_2Cl_2:AcOEt = 50:1); mp 125 °C; ^1H NMR ($CDCl_3$) δ 2.05, 2.12 (2s, 6H, $OCOCH_3$), 3.98 (s, 3H, OCH_3), 4.08 (ddd, 1H, J = 9, 6.1, 2.5 Hz, H-5′), 4.21 (dd, 1H, J = 12, 6.1 Hz, H-6′), 4.29 (dd, 1H, H = 6″), 5.50 (m, 1H, J = 9, 4.6, 3.2 Hz, H-4′), 5.79 (bd, 1H, J = 1.4 Hz, H-1′), 5.88 (m, 1H, J = 10.3, 4.6 Hz, H-3′), 6.11 (m, 1H, J = 10.3, 1.4 Hz, H-2′), 6.76 (d, 1H, J = 8 Hz, H-2), 7.43 (d, 1H, J = 8 Hz, H-3), 7.46, 7.52 (2m, 2H, H-6, H-7), 8.07 (d, 1H, H-5), 8.29 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 20.85, 21.10 (OCOMe), 55.54 (OMe), 63.84 (C-6′), 65.72 (C-4′), 75.21 (C-5′), 75.25 (C-1′), 103.05 (C-2), 122.66 (C-8), 123.40 (C-5), 125.08

(43) One can imagine unusual conformations, e.g., in which a β C-glycoside is contained in a strained cyclic array, where separation of H1′ and H4′ (furanosyl) or H5′ (pyranosyl) is large enough to preclude observation of an NOE.

(44) Roth, W.; Pigman, W. *Methods in Carbohydrate Chemistry*; Academic Press: New York, 1963; Vol. II, p 405.

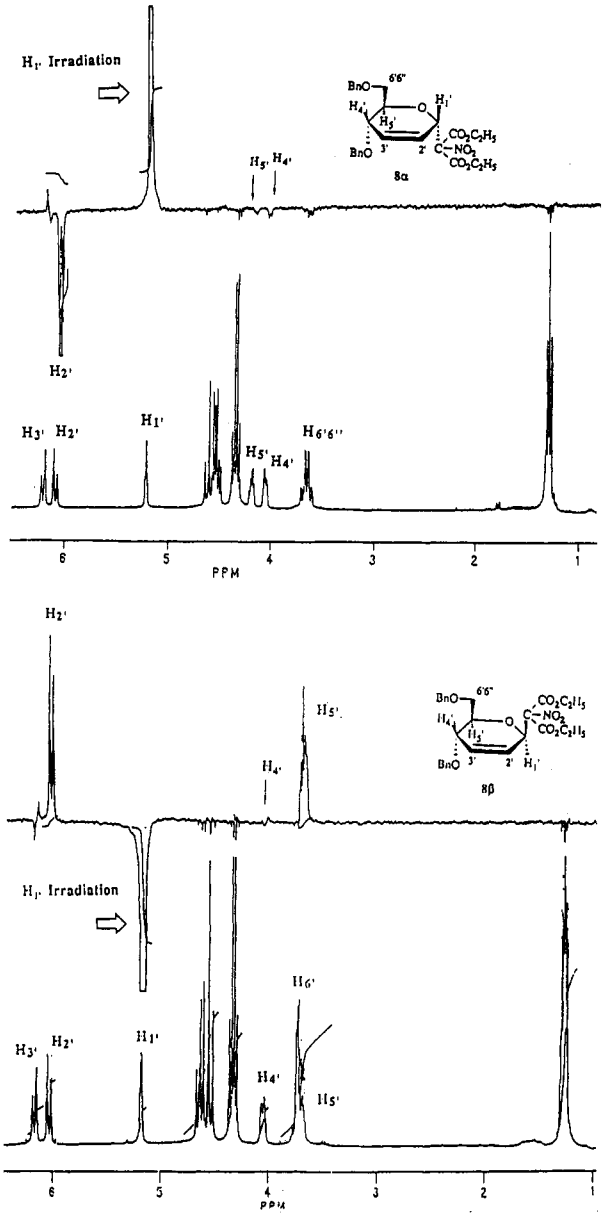


Figure 1. ^{1}H and NOE spectra for anomer pair 8. Top, (8α): irradiation of H1′ gives rise to a strong NOE only for H2′. Bottom (8β): irradiation of H1′ gives rise to strong NOEs for H2′ and H5′.

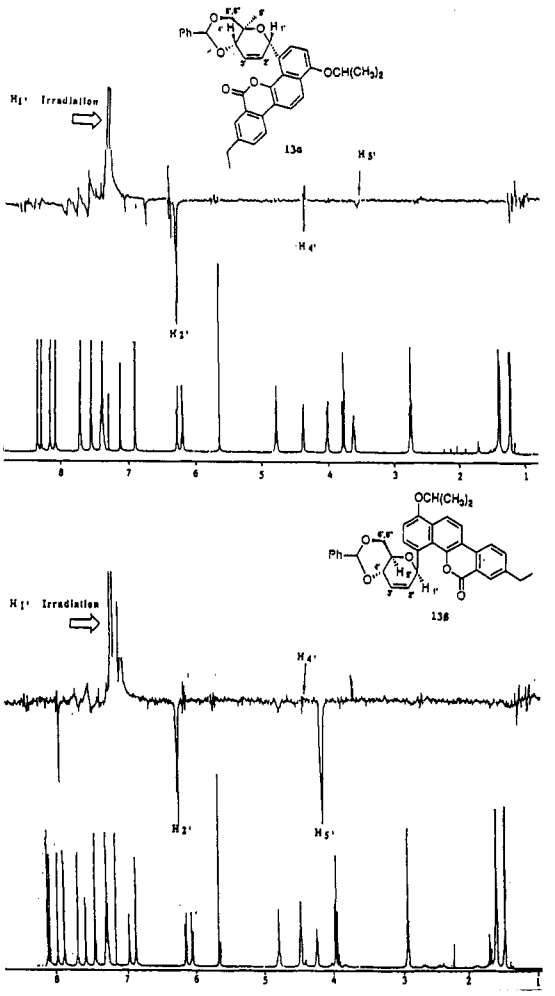


Figure 2. ^{1}H and NOE spectra for anomer pair 13. Top (13α): irradiation of H1′ gives rise to NOEs for H2′ and H4′. Bottom (13β): irradiation of H1′ gives rise to NOEs for H2′ and H5′.

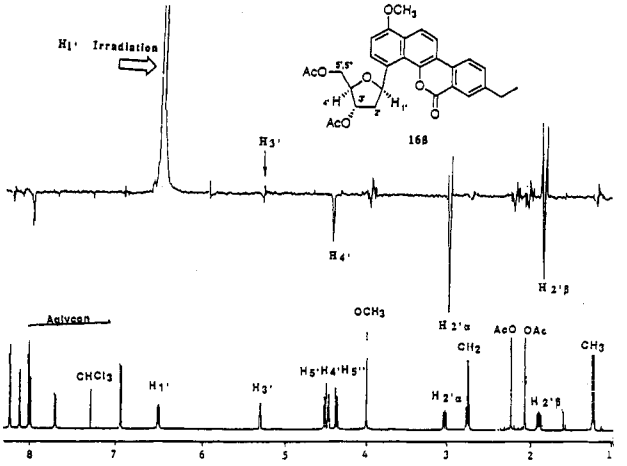


Figure 3. ^{1}H and NOE spectra for C-glycofuranoside 16β. Irradiation of H1′ gives rise to NOEs for both H2's and for H4′.

(C-3′, C-7), 125.87 (C-3), 126.06 (C-quat), 126.71 (C-6), 127.11 (C-quat), 131.91 (C-quat), 133.02 (C-2′), 155.89 (C-1), 170.45, 170.95 (OCOMe). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.1; H, 5.99. Found: C, 68.1; H, 5.86.

12α: R_f = 0.34 (CH_2Cl_2:AcOEt = 50:1); mp 133 °C; ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 3H, 4′-OCOCH$_3$), 2.07 (s, 3H, 6′-OCOCH$_3$), 3.73 (ddd, 1H, J = 8, 6.1, 2.9 Hz, H-5′), 3.88 (dd, 1H, J = 12, 2.9 Hz, H-6′), 4.00 (s, 3H, OCH$_3$), 4.24 (dd, 1H, H = 6″), 5.37 (m, 1H, J = 8, 4, 2.1 Hz, H-4′), 5.94 (b, 1H, J = 1.6 Hz, H-1′), 6.07 (m, 1H, J = 10.3, 4 Hz, H-3′), 6.25 (m, 1H, J = 10.3, 1.6 Hz, H-2′), 6.72 (d, 1H, J = 7.9 Hz, H-2), 7.35 (d, 1H, J = 7.9 Hz, H-3), 7.48, 7.56 (2m, 2H, H-6, H-7), 8.23 (d, 1H, H-5), 8.29 (m, 1H, H-8); ^{13}C NMR ($CDCl_3$) δ 20.59, 21.08 (OCOMe), 55.49 (OMe), 62.86 (C-6′), 65.57 (C-4′), 68.52 (C-5′), 71.15 (C-1′), 102.05 (C-2), 122.31 (C-8), 124.39 (C-5), 125.24, 126.90 (C-3, C-7), 125.60, 126.18 (C-quat), 126.16 (C-3′), 127.31 (C-6), 127.11 (C-quat), 131.86 (C-2′), 133.00 (C-quat), 156.13 (C-1), 170.48, 170.76 (OCOMe). Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.1; H, 5.99. Found: C, 68.1; H, 6.01.

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