A General Method for determining the Anomeric Configuration of *C*-Furanoside Derivatives: a ^{1}H Nuclear Magnetic Resonance Nuclear Overhauser Effect Study

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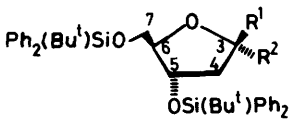
The nuclear Overhauser effect ^{1}H n.m.r. experiment was found to be an excellent method for *a priori* determination of the stereochemical configuration of a variety of *C*-furanoside derivatives. If the stereochemistry at one ring carbon atom is known, the methine proton at this centre may be used to determine the proton stereochemistry at neighbouring carbon centres and this can be repeated until the anomeric proton configuraton is determined. Certain protecting groups themselves may be used to report on the *C*-furanoside anomeric configuration, and this was demonstrated with methoxymethyl and *O*-isopropylidene derivatives.

Optically active *C*-furanosides (polysubstituted tetrahydrofurans) constitute an important class of molecules both as natural products [1] and as intermediates to the synthesis of other natural products. We have found considerable utility for these synthons in the stereoselective generation of chiral acyclic compounds [2] and, more recently, for the synthesis of the chiral precursor of the β-hydroxy-δ-lactone moiety of (+)-compactin and (+)-mevinolin.[3]

C-Furanosides are commonly synthesized by performing a Wittig reaction between a reducing sugar and a stabilized ylide,[1] and subsequent recyclization to afford the five-membered ring *via* an intramolecular Michael reaction. Reclosure of the ring often leads to a mixture of stereoisomers at what may be termed the anomeric carbon centre. In syntheses of chiral molecules, a key analytical step is the determination of the configuration at the newly formed asymmetric centre. At this time n.m.r. spectroscopy is the analytical method of choice [4] and several groups have developed criteria based on comparisons of chemical shifts or coupling constants to assist in this determination.[5–10] However, these procedures are not without their limitations, and may be restricted in their application to a particular series of furanosides or nucleotides; in many instances deviations from the rules have been reported. Clearly a need exists for an analytical procedure which confidently determines *a priori* the anomeric configuration of a single *C*-furanoside in a quick and reliable fashion, without the need for comparison with data for the complementary anomer.

Our approach with the *C*-furanoside synthetic intermediate of (+)-compactin and (+)-mevinolin [3] was to use ^{1}H nuclear Overhauser effect (n.O.e.) [11] measurements to determine anomeric configuration, and we now elaborate on this assignment and report the generality of the approach in a ^{1}H n.O.e. spectroscopy study of a variety of protected *C*-furanosides. In addition to n.O.e. experiments involving the furanose ring protons, the protecting group protons may, in favourable circumstances, report stereochemical features of the molecule.



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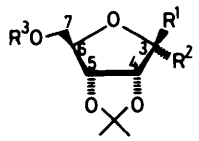
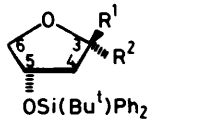
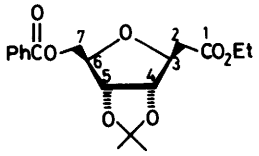


(3) R^1=CH_2CO_2Et, R^2=H, R^3=$Si(Bu^t)Ph_2$
(4) R^1=H, R^2=CH_2CO_2Et, R^3=$Si(Bu^t)Ph_2$
(5) R^1=CH_2CO_2Et, R^2=R^3=H
(6) R^1=H, R^2=CH_2CO_2Et, R^3=H



(7) R^1=C(I)HCO_2Et, R^2=H
(8) R^1=H, R^2=C(I)HCO_2Et
(9) R^1=CH_2CO_2Et, R^2=H
(10) R^1=H, R^2=CH_2CO_2Et



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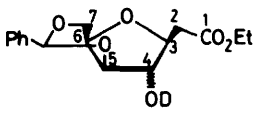

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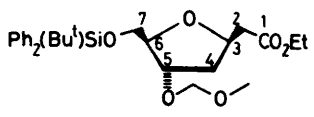


(13)

Results and Discussion

C-Furanosides (1)—(13)† were synthesized and analysed by ^{1}H n.m.r. spectroscopy. The exocyclic ethoxycarbonylmethylene side chain was utilized throughout this study for expediency and should not be construed as limiting. Reducing sugar precursors were chosen so as to afford exemplars of di, tri-, and tetra-substituted tetrahydrofuran ring systems, with varying relative stereochemistry and positional substitution. Thus, protected *C*-furanosides derived from D-ribose, 4-deoxy-D-ribose, D-xylose, and 4-deoxy-D-erythrose represent a useful selection of molecules. The procedure requires the ^{1}H n.m.r. spectrum to be fully assigned and all efforts to be made to minimize signal overlap.

† We use the numbering system indicated on the structures. Hence, what is termed here a 4-deoxyribofuranoside, *e.g.*, corresponds to a 2′-deoxyfuranoside using conventional nucleotide and *O*-furanoside nomenclature.

Table 1. ^{1}H N.m.r. chemical shifts of *C*-furanosides (δ from Me_4Si; 20 °C)

Compound	Solvent	2a-H	2b-H	3-H	4α-H	4β-H	5-H	6α-H	6β-H
(1)	$CDCl_3$	2.62	2.46	4.67	2.00	1.56	4.45	4.00	
(2)	$CDCl_3$	2.86	2.69	4.55	1.79	2.18	4.49	4.07	
(3)	$CDCl_3$	2.68	2.63	4.34		4.48	4.76	4.10	
(4)	$CDCl_3$	2.77	2.68	4.59		4.81	4.87	4.11	
(5)	$CDCl_3$	2.75	2.61	4.25		4.55	4.74	4.09	
(6)	$CDCl_3$	2.78	2.71	4.38		4.77	4.65	4.14	
(7)	$CDCl_3$	4.23		4.55	2.35	1.72	4.45	3.84*	3.88*
(8)	C_6D_6	5.04		4.68	2.22	1.71	4.05	3.90	3.32
(9)	$CDCl_3$	2.57	2.44	4.57	2.07	1.55	4.48	3.72	3.84
(10)	$CDCl_3$	2.84	2.66	4.30	1.75	2.16	4.43	3.81	3.62
(11)	$(CD_3)_2CO$	2.70	2.59	4.31		4.69	4.83	4.24	
(12)	$CDCl_3$–$(CD_3)_2CO$ (1:20, v/v)	2.95	2.80	4.26		4.17	4.37	4.01	
(13)	$CDCl_3$	2.65	2.48	4.50	2.16	1.72	4.36	4.02	

Compound	7a-H	7b-H	OCH_2CH_3	OCH_2CH_3	Bu^t		Others
(1)	3.36	3.22	4.15	1.25	1.07 0.91		Ph; 7.2—7.7
(2)	3.44	3.27	4.16	1.25	1.07 0.91		Ph; 7.2—7.2
(3)	3.79	3.73	4.15	1.24	1.06	1.55 (*endo*) 1.35 (*exo*)	Ph; 7.3—7.75
(4)	3.77	3.66	4.17	1.26	1.07	1.49 (*endo*) 1.35 (*exo*)	Ph; 7.3—7.8
(5)	3.82	3.65	4.16	1.26		1.54 (*exo*) 1.34 (*endo*)	OH; 2.55
(6)	3.62*	3.62*	4.16	1.27		1.49 (*endo*) 1.33 (*exo*)	OH; 2.11
(7)			4.24	1.29	1.09		Ph; 7.3—7.8
(8)			4.00* 3.96*	0.92	1.09		Ph; 7.2—7.8
(9)			4.15	1.26	1.06		Ph; 7.2—7.7
(10)			4.16	1.27	1.07		Ph; 7.2—7.7
(11)	4.45	4.38	4.08	1.19		1.50 1.32	Ph; 7.4—7.7 8.0—8.1
(12)	4.42	4.16	4.16	1.27			Ph; 7.3—8.0 PhC*H*; 5.47
(13)	3.70	3.56	4.14	1.25	1.05		Ph; 7.3—7.8 OCH_2OCH_3; 4.67 OCH_2OCH_3; 3.36

* Ambiguous assignments resulting from strong coupling.

Since no coupling constant or chemical-shift comparisons are made between anomers, one may make full use of solvent effects for this objective. The ^{1}H n.m.r. chemical shift and coupling constant data for (**1**)—(**13**) in the indicated pure or mixed solvents are in Tables 1 and 2. Although the anomeric configuration of some derivatives could have been determined at this point using literature procedures, this was reserved for confirmation.

The procedure has further generality in that the absolute stereochemistry at the anomeric carbon centre will be established if the absolute stereochemistry at any other ring carbon centre is known; if not, then relative stereochemistries will be afforded.

It is well known that the magnitude of n.O.e.s diminishes rapidly as the interproton distance is increased.[11a] Hence, when a ring proton is saturated in a steady-state n.O.e. difference spectroscopy (s.s.n.O.e.d.s.) experiment,[11b] one expects to observe a larger n.O.e. in a vicinal proton with the same stereochemistry than when the two protons have opposite stereochemistry. N.O.e.s may be observed over greater interproton distances and the presence or absence of these long-range interactions may serve as useful confirmatory evidence for a stereochemical assignment.

S.s.n.O.e.d.s. experiments were performed on (**1**)—(**13**) and the resultant data are in Table 3.

By inspection of the non-anomeric ring carbon stereochemistries of a particular *C*-furanoside, one may *predict* the relative magnitudes of n.O.e.s in various irradiation experiments based on considerations of relative proton juxtaposition. These are in Table 4.

To illustrate the method, let us consider two compounds of the β-4-deoxyribofuranoside series, (**1**) and (**13**). The stereochemistry at C-5 is that where the substituent has the α configuration and the proton, therefore, has the β configuration. It is conceptually feasible to irradiate 5-H and observe the n.O.e.s generated in 4-H_2; 4β-H should experience a larger n.O.e. than 4α-H since it is on the same (β) face of the molecule and, therefore, closer to 5-H. In practice, there is merit in simply performing n.O.e. irradiations of each 4-H. (a) They resonate to high field of the ring protons, often in a region of the spectrum which is less congested, (b) their chemical shifts are strongly affected by solvents, and (c) the magnitude of n.O.e.s from a

Table 2. ^{1}H n.m.r. coupling constants of *C*-furanosides (*J*/Hz)[a]

Compound	$J_{2a,2b}$	$J_{2a,3}$	$J_{2b,3}$	$J_{3,4\alpha}$	$J_{3,4\beta}$	$J_{4\alpha,4\beta}$	$J_{4\alpha,5}$	$J_{4\beta,5}$	$J_{5,6\alpha}$
(1)	15.4	7.4	5.7	4.8	10.7	12.6	1.5	5.3	1.2
(2)	15.2	7.2	6.7	4.5	7.3	13.0	3.3	6.3	3.0
(3)	15.5	6.0	7.1		4.7			6.5	3.4
(4)	16.4	6.9	6.9		3.9			6.2	0.0
(5)[b]	15.9	4.9	6.5		4.8			6.6	3.8
(6)[c]	16.8	6.6	7.0		4.1			6.2	1.2
(7)		8.7		5.8	9.0	13.3	1.3	5.3	2.0*
(8)[d]		10.5		3.2	8.1	13.6	1.5	5.4	1.8
(9)	15.2	7.2	5.9	5.6	9.6	15.6	1.8	5.6	2.6
(10)	15.4	7.3	6.4	5.7	7.5	13.1	3.4	6.3	2.8
(11)	15.6	5.6	7.3		3.9			6.6	4.0
(12)	16.8	6.2	8.5		2.1			<0.5	2.4
(13)	15.4	7.1	6.0	5.1	10.3	13.1	1.5	5.9	2.1

Compound	$J_{5,6\beta}$	$J_{6\alpha,6\beta}$	$J_{6\alpha,7a}$	$J_{6\beta,7a}$	$J_{7a,7b}$	$J_{OCH_2,CH3}$
(1)			4.1	3.6	10.9	7.1
(2)			3.8	3.7	11.0	7.1
(3)			3.6	3.7	11.2	7.1
(4)			4.0	3.7	11.1	7.1
(5)[b]			2.9	3.4	12.1	7.1
(6)[c]			5.5	5.5		7.2
(7)	3.8*	9.4				7.1
(8)[d]	4.2	9.4				7.1
(9)	4.6	9.4				7.2
(10)	4.9	9.4				7.2
(11)			4.6	5.0	11.8	7.1
(12)			<0.5	2.1	13.1	7.1
(13)			3.8	5.6	10.8	7.1

[a] The signs of coupling constants were not determined. [b] $J_{7a,OH}$ 4.1 and $J_{7b,OH}$ 8.7 Hz [c] $J_{7a,OH} = J_{7b,OH} = 5.7$ Hz. [d] J_{OCH_a,OCH_b} (geminal) = 10.4 Hz. * Values may be interchanged as a result of an assignment ambiguity.

methylene proton to a methine will be larger than the opposite route, as a consequence of efficient mutual relaxation by methylene protons. Thus, 4-H_2 were stereochemically assigned in that 4β-H induced a stronger n.O.e. to 5-H (5.8—7.1%) than did 4α-H (1.7—1.5%). Most importantly, since this is the β anomer, irradiation of 4α-H induced a larger n.O.e. to the (anomeric) 3-H (7.7—8.3%) than when 4β-H was irradiated (1.1—2.8%). This effectively assigned the anomeric configuration.

It is useful to confirm this assignment by measuring the cross-ring 6-H to 3-H n.O.e.* Such an n.O.e. is measurable in the β *C*-furanosides of this genre, because 6-H and 3-H have a cisoid relationship. The ability to perform this cross-check experiment is useful as a confirmation, and may also serve as an alternative route to anomeric configuration determination if signal overlap precludes irradiation of the protons in the procedure detailed above.

The Utility of Protecting Groups.—Protecting groups which convert the *C*-furanoside into a fused bicyclic system, such as *O*-isopropylidene derivatives of ribose, confer rigidity on the furanose ring. Because of the imposed rigidity and the resultant conformation, these compounds may be stereochemically analysed using n.O.e. methods (Figure 1). The *exo* and *endo* methyl groups are oriented towards the β and α faces of the ribofuranose ring, respectively. Irradiation of the CH_3 (*endo*) protons† induced n.O.e.s to α protons at C-3 (1.5—2.2%) and C-6 (1.4—4.0%), *i.e.*, the β-furanoside was identified. In examples of α-furanosides (**4**) and (**6**), irradiation of the CH_3 (*endo*) protons resulted in an (0.6—0.9%) n.O.e. being observed in the exocyclic methylene 2a- and 2b-H protons. These observations are described in Table 5. Our data indicate that n.O.e. experiments where (*endo*)-*O*-isopropylidene protons are irradiated are useful in anomeric configuration determination.

This approach has some practical advantages over the n.O.e. experiments performed on ring protons. The *O*-isopropylidene protons resonate to high field of the spectrum and their chemical shifts may be influenced by solvents. In that the resonances appear as sharp singlets, they can be selectively irradiated using a very low decoupler power level. Indeed, with (**11**) dissolved in a variety of solvents, it was virtually impossible to perform unambiguous s.s.n.O.e.d.s. experiments on ring protons without unintentional partial saturation of other protons ('spillover'). The *O*-isopropylidene irradiation n.O.e. experiments were trivial and unambiguously assigned the anomeric configuration of this compound.

Our success with the *O*-isopropylidene proton n.O.e.s encouraged us to explore the potential for other protecting groups to render stereochemical information. The case of a 4-deoxy compound would be particularly interesting in that no *O*-isopropylidene derivative could be made, and the furanoside ring would be far less restricted to a rigid conformation. It was established that a suitably protected monocyclic furanoside may be of utility in this regard, provided the protecting group is sufficiently sterically unencumbered. Of the limited array of useful protecting groups that we have examined so far, the CH_2OCH_3 (MOM) ether was particularly interesting. When the MOM methylene or methyl protons of (**13**) were irradiated, n.O.e.s were observed (i) at the point of attachment of the MOM (5-H), and (ii) at protons α to the point of attachment which are on the same (α) face as the protecting group (4α-H and 6-H). The MOM proton singlets, too, were relatively easy to saturate selectively.

The t-butyldiphenylsilyl protecting group was not found to

* A similar cross-ring n.O.e. has been reported for a protected ribose nucleotide.[5c]

† Irradiation of the *exo* protons induced n.O.e.s to 4-H and 5-H (4.3—9.9%), but this has little diagnostic utility.

Table 3. N.O.e. values for *C*-furanosides[a]

Compound	Proton(s) irradiated	2a-H	2b-H	3-H	4α-H	4β-H	5-H
(1)	5-H				0.9	4.2	−93
	4α-H	−0.8	−0.4	8.3		17.7	1.7
	4β-H	1.8	1.5	1.1	18.5	−83	7.1
	3-H	2.2	2.7	−91	4.1		
	6-H			3.2			
(2)	4β-H			11.0	19.6	−69	6.4
	4α-H	1.1	2.0	2.2	−71	15.1	1.8
(3)	5-H					9.1	−85
	6-H			4.3		−2.3	3.0
	CH_3(*exo*)					4.3	6.3
	CH_3(*endo*)			4.0		0.5	0.6
(4)	3-H	1.9	3.1	−85		5.1	−3.7
	CH_3(*exo*)					4.2	5.1
	CH_3(*endo*)	0.6	0.9				
(5)	3-H[b]	2.5	1.4	−94		1.8	
	6-H[b]						1.2
	CH_3(*exo*)					5.8	4.9
	CH_3(*endo*)			2.7			
(6)	4-H	0.3	0.3	7.3		−87	n.r.
	3-H	2.0	2.0	−90		6.4	
	CH_3(*exo*)					4.0	3.7
	CH_3(*endo*)	(0.8)				0.5	0.5
(7)	4β-H			0.8	13.8	−64	5.6
	4α-H			4.4	−62	12.0	1.0
(8)	4β-H			7.6	14.4	−53	5.1
	4α-H			1.9	−57	9.2	1.4
	3-H			−80		3.1	
	6β-H						5.3
(9)	4β-H	1.3	1.1	0.9	10.9	−52	5.1
	4α-H			3.3	−76	n.r.	0.8
	6β-H						5.2
	6α-H			1.2			3.6
(10)	4β-H			3.7	n.r.	−66	4.3
	4α-H	0.4	0.8	1.0	−69	n.r.	1.2
	6β-H						4.4
	6α-H						7.7
(11)	CH_3(*exo*)					9.9	9.6
	CH_3(*endo*)			2.0			
(12)	3-H			−82			n.r.
	6-H			4.1			
	2b-H	15.0	−56	1.2		3.3	
(13)	5-H				1.3	4.3	−92
	4α-H			7.7	−63	15.5	1.8
	4β-H	1.1	1.2	2.8	17.5	−64	5.8
	OCH_2OCH_3				2.1		6.3
	3-H	2.3	2.4	−87	5.0		

Compound	Proton(s) irradiated	6α-H	6β-H	7a-H	7b-H	CH_3(*exo*)	CH_3(*endo*)	Other(s)
(1)	5-H	3.6		0.6	1.8			
	4α-H							
	4β-H			0.9	0.9			
	3-H	2.5						
	6-H	−93		2.1	3.6			
(2)	4β-H							
	4α-H	1.1						
(3)	5-H	2.6		1.2	1.2	0.9		
	6-H	−85		2.6	2.6			
	CH_3(*exo*)					−97	0.3	
	CH_3(*endo*)	1.8				n.r.	−95	
(4)	3-H			1.5	0.4			
	CH_3(*exo*)					−97	n.r.	
	CH_3(*endo*)	2.3				n.r.	−98	
(5)	3-H[b]	1.4					0.5	
	6-H[b]	−97		1.8	1.7			
	CH_3(*exo*)							
	CH_3(*endo*)	1.5						

Table 3 (*continued*)

Compound	Proton(s) irradiated	6α-H	6β-H	7a-H	7b-H	CH_3(*exo*)	CH_3(*endo*)	Other(s)
(6)	4-H							
	3-H			1.3	1.3			
	CH_3(*exo*)					−99	n.r.	
	CH_3(*endo*)	1.4						
(7)	4β-H							CHI 3.9
	4α-H	n.r.	n.r.					
(8)	4β-H							CHI 0.8
	4α-H							CHI 3.0
	3-H							
	6β-H	15.8	−72					
(9)	4β-H							
	4α-H							
	6β-H	n.r.	−59					
	6α-H	−56	n.r.					
(10)	4β-H					−99	n.r.	
	4α-H					n.r.	−97	
	6β-H	n.r.	−72					
	6α-H	−74	n.r.					
(11)	CH_3(*exo*)					−99	n.r.	
	CH_3(*endo*)	2.2				n.r.	−97	
(12)	3-H	3.2						
	6-H	−71		2.6	1.7			
	2b-H							
(13)	5-H	3.2		1.2	1.3			MOM; CH_2 1.1, CH_3 0.6
	4α-H							MOM; CH_2 = CH_3 = 1.0
	4β-H			−0.5	0.8			MOM; CH_2 0.8
	OCH_2OCH_3	2.5						MOM; CH_2 −88, CH_3 2.0
	3-H	3.8						

[a] N.O.e.s measured by % increase in summed peak heights. For each experiment (row), the % saturation is indicated. n.r. = value not recorded, usually due to decoupler spillover. [b] Experiment performed at 400 MHz using the method of Kinns and Sanders.[11c]

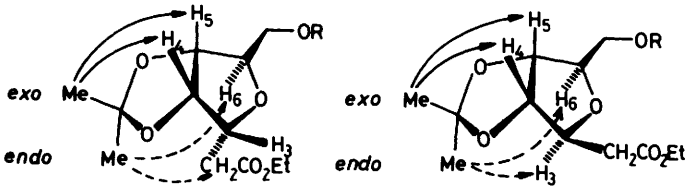


Figure 1. Three-dimensional depiction of *O*-isopropylidene derivatives of α- and β-ribofuranosides. The observed n.O.e.s resulting from irradiation of the *exo*- or *endo*-methyl protons are indicated with solid and broken lines, respectively

be useful in the assignment of ring proton stereochemistry; presumably, steric factors orient the protecting group moiety away from the ring protons.

These observations point to the immediate utility of the *O*-isopropylidene protecting group to determine the anomeric configuration of *C*-furanosides through n.O.e. experiments. Small protecting groups on monocyclic *C*-furanosides may offer some stereochemical information. These data signify a new consideration in the choice of a protecting group for synthetic strategies additional to classical ones of stability and reactivity. A protecting group's capacity to act also an 'n.O.e. probe' in the determination of anomeric configuration or stereochemistry would be a definite asset.

Practical Considerations.—Since our protocol requires a comparison of relative strengths of n.O.e.s for a given compound, the experimental demands for rigorous s.s.n.O.e.d.s. (*viz.*, complete saturation, an irradiation time >5 T_1, *etc.*)[11a] may be relaxed. Reducing the decoupler power greatly enhances the frequency selectivity, although signal saturation may be less than complete. Saturation times set to *ca.* 1—2 T_1 will maximize direct dipolar interactions and minimize 'three-spin effects';[11b] signal acquisition will be expedited, too.

Since we make no comparisons of chemical shift or coupling constant data for different molecules, we need not concern ourselves with solvent effects.[12] Indeed, we can use these to full advantage so as to minimize signal overlap and facilitate the s.s.n.O.e.d.s. experiment. Figure 2 shows the 250 MHz ^{1}H n.m.r. spectra of (**10**) dissolved in the indicated solvents and these spectra amply illustrate the capability of solvent-induced shifts to induce dramatic effects on the ^{1}H n.m.r. resonance frequencies. In some instances a solvent mixture will be ideal; such was the case with (**12**), where the furanoside was initially dissolved in $CDCl_3$ and $(CD_3)CO$ was added in 10 μl aliquot portions until the requisite protons were shifted to a spectroscopically silent region and selective proton irradiations could be easily performed.

*Other N.m.r. Methods.**—As mentioned previously, other groups have devised criteria for nucleotide and *C*-furanoside anomeric configuration determination.[4] A full discussion of

* Since this study was initiated,[3] other groups have reported the utilization of the n.O.e. procedure to assign the stereochemistry of similar compounds.[5] These results are in full accord with the principles delineated here.

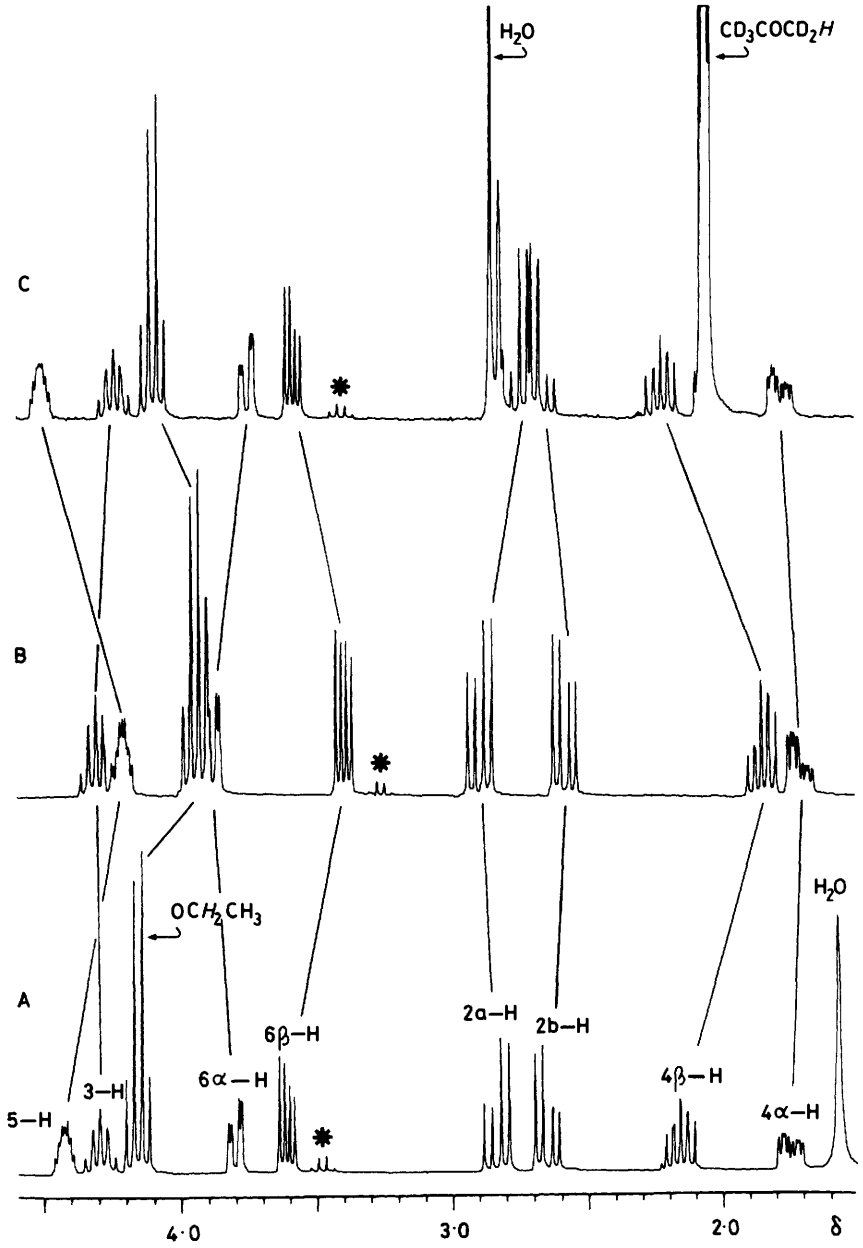


Figure 2. The ^{1}H n.m.r. spectra (250 MHz) of (**10**) dissolved in A, $CDCl_3$; B, C_6D_6; and C, $(CD_3)_2CO$, illustrates the strong effect of solvents on chemical shifts. Connecting lines indicate respective proton chemical shifts in the three solvents. Asterisks indicate the signals of small amounts of residual protonated solvent (diethyl ether)

these is not in order, but a number of points of comparison merit mention.

With fused bicyclic systems, vicinal coupling constants[6] may be useful; such is the case with *O*-isopropylidene derivatives of ribonucleotides.[7] The relative reliability of the procedure is, perhaps, partly a result of the imposed rigidity on the furanose ring. Using Ohrui's criterion for *C*-ribofuranoside stereochemistry,[7a] which relies on the magnitude of $J_{5,6}$, the assigned anomeric configurations of (**3**)—(**6**) and (**11**) were independently confirmed; there were no misassignments.

Imbach's '$\Delta\delta$ criterion' for isopropylidene derivatives of ribonucleotides[8] has been demonstrated to be inapplicable in the case of *C*-furanosides,[7b] and our data concur with this.

Anomeric proton chemical-shift arguments used to assign configuration[4,9] do not universally apply to compounds studied here.* Our chemical-shift data for the 4-deoxyribofuranoside series, for which Srivastava *et al.* have devised chemical-shift relationships to determine anomeric configuration,[10] also failed to comply with his method.

Conclusions

The homonuclear ^{1}H n.O.e. experiment is a versatile and reliable method for the *a priori* determination of anomeric configuration of *C*-furanosides. Rules based on simple geo-

* Replacement of the silyl protecting group of (**7**) with a *p*-nitrobenzoate yielded crystalline material. *X*-Ray structure determination of this compound confirmed the β anomeric configuration (data to be published).

Table 4. Summary of diagnostic inter-ring proton n.O.e. comparisons in some *C*-furanoside molecules

Series	Expected n.O.e. observation[a]	Typical values (%; this study)
β-4-Deoxyribofuranoside	4β-H ⟷ 5-H > 4α-H ⟷ 5-H	4.2—7.1 > 0.9—1.8
	4α-H ⟷ 3-H > 4β-H ⟷ 3-H	4.1—8.3 > 0—2.8
	3-H ⟷ 6-H > 0	2.5—3.2
α-4-Deoxyribofuranoside	4β-H ⟷ 5H > 4α-H ⟷ 5-H	6.4 > 1.8
	4β-H ⟷ 3-H > 4α-H ⟷ 3-H	11.0 > 2.2
	3-H ⟷ 6-H = 0	0.0
β-Ribofuranoside	4-H ⟷ 5-H > 4-H ⟷ 3-H	9.1 > 1.8
	3-H ⟷ 6-H > 0[b]	1.4—4.3
α-Ribofuranoside	4-H ⟷ 5-H ≈ 4-H ⟷ 3-H	Data incomplete
β-4,6-Dideoxyribofuranoside	4β-H ⟷ 5-H > 4α-H ⟷ 5-H	5.1—5.6 > 0.8—1.0
	6β-H ⟷ 5-H > 6α-H ⟷ 5-H	4.4 > 1.7
	4β-H ⟷ 5-H > 4β-H ⟷ 3-H	5.6 > 0.8
	4α-H ⟷ 3-H > 4α-H ⟷ 5-H	4.4 > 1.0
α-4,6-Dideoxyribofuranoside	4β-H ⟷ 5-H ≈ 4β-H ⟷ 3-H	4.3—5.1 ≈ 3.1—7.6
	6β-H ⟷ 5-H > 6α-H ⟷ 5-H	4.4—5.5 > 1.7
	4α-H ⟷ 5-H ≈ 4α-H ⟷ 3-H	1.2—1.4 ≈ 1.0—1.9
	4β-H ⟷ 3-H,5-H > 4α-H ⟷ 3-H,5-H	3.1—7.6 > 1.0—1.9

[a] N.O.e.s between two protons are represented, *e.g.*, as '3-H ⟷ 6-H'. This denotes an n.O.e observed at 6-H when 3-H is saturated, or *vice versa*. [b] In one instance (**5**), a zero n.O.e. 6-H ⟶ 3-H was observed.

Table 5. Summary of diagnostic n.O.e. comparisons involving the 4,5-*O*-isopropylidene protecting group in *C*-ribofuranoside molecules [(**3**)—(**6**), (**11**)]

Anomer	Expected n.O.e. observations	Typical values (%; this study)
β	CH_3(*endo*) ⟶ 6-H ≈ CH_3(*endo*) ⟶ 3-H	2.0—4.0 ≈ 1.5—2.2
	CH_3(*exo*) ⟶ 4-H ≈ CH_3(*exo*) ⟶ 5-H	4.3—9.9 ≈ 4.9—9.7
	CH_3(*exo*) ⟶ 4-H,5-H > CH_3(*endo*) ⟶ 3-H,6-H	4.3—9.9 > 1.5—4.0
α	CH_3(*endo*) ⟶ CH_2CO_2R > 0	0.6—0.9
	CH_3(*exo*) ⟶ 4-H ≈ CH_3(*exo*) ⟶ 5-H	4.0—4.2 ≈ 3.7—5.1
	CH_3(*endo*) ⟶ 6-H > 0	1.4—2.3
	CH_3(*endo*) ⟶ 3-H = 0	0.0
	CH_3(*exo*) ⟶ 4-H,5-H > CH_3(*endo*) ⟶ 6-H	3.7—5.1 > 1.4—2.3

metrical criteria have been established for the comparative n.O.e.s expected in 13 common protected *C*-furanosides, and the s.s.n.O.e.d.s. experiments performed verified the protocol. It should be a simple matter to derive analogous rules for *C*-furanosides not specifically examined in this study.

It has been shown that protecting groups themselves may be an important route for the determination of the anomeric configuration using the n.O.e. experiment. This is particularly the case with *O*-isopropylidene derivatives of ribose, a common synthetic intermediate with nucleotides. N.O.e.s were also observed in proximal ring protons when MOM protons were irradiated. These data suggest that an additional consideration when protecting groups are chosen might be their potential to afford stereochemical information through s.s.n.O.e.d.s. experiments.

Although we have restricted our discussion to *C*-furanosides, we believe that the methodology is sufficiently general to accommodate nucleotides, *N*-furanosides, and *O*-furanosides, and these will be the topics of future studies.

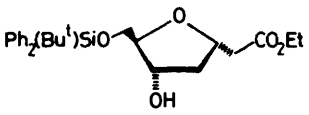
Experimental

Materials.—Dichloromethane, pyridine, triethylamine, and di-isopropylethylamine were distilled from CaH_2 prior to use. All reactions were carried out under argon. Crude products were purified by flash chromatography using 230—400 mesh silica gel (E. Merck). I.r. spectra were obtained with a Perkin-Elmer model 681 spectrophotometer. Mass spectra were obtained with a Hitachi–Perkin-Elmer RMU-6D instrument at an ionizing voltage of 70 eV. Elemental analyses were performed by Galbraith Laboratories Inc.

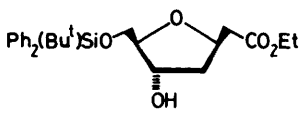
Compounds (**5**), (**6**),[8] (**9**), (**10**),[3] and (**11**)[13] were prepared as described previously. The synthesis of compounds (**7**), (**8**), and (**12**)* will be described later.

Preparation of the Common Precursors Ethyl 3,6-*Anhydro*-7-O-*t-butyldiphenylsilyl*-2,4-*dideoxy*-D-arabino- *and* -D-ribo-*heptanoate* (**14**) *and* (**15**).—A solution of ethyl 3,6-anhydro-2,4-dideoxy-D-*arabino*- and -D-*ribo*-hexanoate[2] (3.40 g, 16.6 mmol) in pyridine (83 ml) was treated with t-butyldiphenylsilyl chloride (21.6 mmol) at room temperature for 24 h. The solution was diluted with ethyl acetate (400 ml) and the mixture was washed successively with water (50 ml), 1.0N-HCl (3 × 50 ml),

* All new compounds gave satisfactory combustion analysis and exhibited spectral data (i.r., ^{1}H n.m.r., and mass spectroscopy) in accord with their assigned structures.



(14)



(15)

saturated aqueous $CuSO_4$ (3 × 50 ml), water (50 ml), and brine (50 ml). Drying ($MgSO_4$) and concentration afforded an oil which was purified by flash chromatography on silica gel. Elution with hexane–ethyl acetate (4:1) provided an inseparable mixture of the bis-silyl esters (**1**) and (**2**) (1.90 g), and pure α-siloxyalcohol (**14**) (2.04 g, 28%) as a viscous oil (Found: C, 67.4; H, 8.0. $C_{25}H_{34}O_5Si$ requires C, 67.8; H, 7.7%); $\nu_{max.}$(film) 3 450 (OH), 3 078 and 3 055 (aromatic C–H), 1 738 (ester C=O), 1 591 and 1 429 (aromatic C=C), 1 112 (ester C–O), and 740 and 701 cm^{-1} (aromatic C–H); *m/z* 385 (64%, M^+ − Bu^t) and 163 (100); δ($CDCl_3$) 1.05 (9 H, s, Bu^t), 1.25 (3 H, t, OCH_2CH_3), 1.80 (1 H, ddd, 4α-H), 2.42 (1 H, d, OH), 2.49 (1 H, m, 4β-H), 2.68 (2 H, m, $2\text{-}H_2$), 3.61 (1 H, dd, 7b-H), 3.75 (1 H, dd, 7a-H), 3.98 (1-H, m, 6-H), 4.15 (2 H, q, OCH_2CH_3), 4.48 (2 H, m, 3-H and 5-H), 7.40 (6 H, m, ArH), and 7.67 (4 H, m, ArH); a mixture of (**14**) and (**15**) (600 mg, 9%); and finally the pure β-siloxyalcohol (**15**) (1.88 g, 24%) as a viscous oil (Found: C, 67.8; H, 7.7%); $\nu_{max.}$(film) 3 448 (OH), 3 078 and 3 055 (aromatic C–H), 1 738 (ester C=O), 1 590 and 1 428 (aromatic C=C), 1 112 (ester C–O), and 740 and 701 cm^{-1} (aromatic C–H); *m/z* 385 (35%, M^+ − Bu^t) and 163 (100); δ($CDCl_3$) 1.05 (9 H, s, Bu^t), 1.25 (3 H, t, OCH_2CH_3), 1.75 (1 H, d, OH), 1.84 (1 H, ddd, 4β-H), 2.08 (1 H, ddd, 4α-H), 2.49 (1 H, dd, 2′-H), 2.64 (1 H, dd, 2-H), 3.59 (1 H, dd, 7a-H), 3.76 (1 H, dd, 7b-H), 4.89 (1 H, m, 6-H), 4.24 (1 H, q, OCH_2CH_3), 4.45 (1 H, m, 5-H), 4.56 (1 H, m, 3-H), 7.40 (6 H, m, ArH), and 7.67 (4 H, m, ArH).

Ethyl 3,6-*Anhydro*-5,7-*bis*-O-*t*-*butyldiphenylsilyl*-2,4-*dideoxy*-D-arabino-*heptanoate* (**2**).—To a cold (0 °C), stirred solution of the α-alcohol (**14**) (442 mg, 1.0 mmol) in dichloromethane (5 ml) were sequentially added triethylamine (278 μl, 2.0 mmol), 4-dimethylaminopyridine (12 mg, 0.1 mmol), and t-butyldiphenylsilyl chloride (416 μl, 1.6 mmol). Stirring was then continued at room temperature for 36 h. The mixture was then treated with saturated aqueous $NaHCO_3$ (5 ml) and partitioned with ether (50 ml). The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (5 ml), water (5 ml), and brine (5 ml), and dried ($MgSO_4$). Concentration gave a pale yellow oil which was purified by flash chromatography on silica gel. Elution with hexane–ethyl acetate (95:5) gave (490 mg, 72%) the α-bis-silyl ester (**2**) as a homogeneous oil (Found: C, 72.6; H, 7.9. $C_{41}H_{52}O_5Si_2$ requires C, 72.3; H, 7.7%); $\nu_{max.}$(film) 3 078 and 3 055 (aromatic C–H), 1 740 (ester C=O), 1 591 and 1 429 (aromatic C=C), 1 110 (ester C–O), and 739 and 702 cm^{-1} (aromatic C–H); *m/z* 623 (38%, M^+ − Bu^t) and 135 (100).

Ethyl 3,6-*Anhydro*-5,7-*bis*-O-*t*-*butyldiphenylsilyl*-2,4-*dideoxy*-D-arabino-*heptanoate* (**1**).—This compound (65%) was prepared from the β-alcohol (**15**) (0.5 mmol) as described for the preparation of (**2**) (Found: C, 72.1; H, 7.9. $C_{41}H_{52}O_5Si_2$ requires C, 72.3; H, 7.7%); $\nu_{max.}$(film) 3 079 and 3 055 aromatic (C–H), 1 738 (ester C=O), 1 591 and 1 429 (aromatic C=C), 1 110 (ester C–O), and 740 and 701 cm^{-1} (aromatic C–H); *m/z* 623 (17%. M^+ − Bu^t) and 135 (100).

Ethyl 3,6-*Anhydro*-7-O-*t*-*butyldiphenylsilyl*-2-*deoxy*-4,5-O-*isopropylidene*-D-allo-*heptanoate* (**3**).—This compound (84%) was prepared from ethyl 3,6-anhydro-2-deoxy-4,5-isopropylidene-D-*allo*-heptanoate (1.0 mmol) as described for the preparation of (**2**) and was obtained as an oil (Found: C, 67.6; H, 7.7. $C_{28}H_{38}O_6Si$ requires C, 67.4; H, 7.7%); $\nu_{max.}$(film) 3 079 and 3 056 (aromatic C–H), 1 740 (ester C=O), 1 591 and 1 429 (aromatic C=C), 1 112 (ester C–O), and 740 and 702 cm^{-1} (aromatic C–H); *m/z* 483 (3%, M^+ − Me), 453 (8, M^+ − OEt), and 441 (100, M^+ − Bu^t).

Ethyl 3,6-*Anhydro*-7-O-*t*-*butyldiphenylsilyl*-2-*deoxy*-4,5-*isopropylidene*-D-altro-*heptanoate* (**4**).—This compound (81%) was prepared from ethyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene-D-*altro*-heptanoate[13] (0.5 mmol) as described for the preparation of (**2**) (Found: C, 67.6; H, 7.7. $C_{28}H_{38}O_6Si$ requires C, 67.4; H, 7.7%); $\nu_{max.}$(film) 3 079 and 3 055 (aromatic C–H), 1 740 (ester C=O), 1 592 and 1 430 (aromatic C=C), and 740 and 701 cm^{-1} (aromatic C–H); *m/z* 483 (3%, M^+ − Me) and 441 (100, M^+ − Bu^t).

Ethyl 3,6-*Anhydro*-7-O-*t*-*butyldiphenylsilyl*-2,4-*dideoxy*-5-O-*methoxymethyl*-D-ribo-*heptanoate* (**13**).—A cold (0 °C), stirred solution of the β-alcohol (**15**) (126 mg, 0.29 mmol) in dichloromethane (1.1 ml) was sequentially treated with diisopropylethylamine (1.7 mmol), 4-dimethylaminopyridine (0.05 mmol), and chloromethyl methyl ether (1.14 mmol). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 18 h. Saturated aqueous $NaHCO_3$ (2 ml) and ether (15 ml) were then added. After 10 min this mixture was partitioned with ether (50 ml) and the organic layer was sequentially washed with water (10 ml), 10% aqueous $NaHSO_4$ (2 × 10 ml), water (10 ml), and brine (10 ml). Drying ($MgSO_4$) and concentration afforded a pale yellow oil which was purified by flash chromatography on silica gel. Elution with hexane–ethyl acetate (4:1) gave the pure (129 mg, 93%) MOM ether (**13**) as an oil (Found: C, 66.7; H, 8.0. $C_{27}H_{38}O_6Si$ requires C, 66.6; H 7.9%); $\nu_{max.}$(film) 3 078 and 3 050 (aromatic C–H), 1 735 (ester C=O), 1 589 and 1 428 (aromatic C=C), and 700 cm^{-1} (aromatic C–H); *m/z* 441 (M^+ − C_2H_5O), 429 (M^+ − Bu^t), and 45 (100).

^{1}H *N.m.r.*—^{1}H N.m.r. spectra were recorded on a Bruker AM 250 spectrometer operating in the pulse mode. Compounds were dissolved in the indicated solvent (Table 1) and chemical-shift measurements were relative to internal Me_4Si, which was assigned δ 0. The probehead temperature was 20 °C. Solutions were not degassed. For all compounds except (**5**), the n.O.e. procedure was as follows. The standard Bruker library microprogram was used to perform steady-state n.O.e. difference spectroscopy. The experiments were performed with interleaving.[11b] Sixteen scans (preceded by two dummy scans to establish equilibrium) were acquired for each irradiation frequency, and the entire process was automatically repeated to afford the requisite signal-to-noise ratio. The irradiation time was typically 4 s, and the recycle time *ca.* 8 s. A 90° read pulse was employed in all cases. The decoupler power setting was chosen so as to minimize frequency spillover to neighbouring multiplets. The free induction decays were weighted with a 1—1.5 Hz exponential line-broadening factor prior to Fourier transformation and, finally, spectral subtraction. N.O.e. values were calculated by comparing summed peak heights in the vertically expanded difference spectra with the control irradiation spectrum. The error in these measurements is estimated to be ±5%.

With (**5**), the n.O.e. experiments on ring protons were performed on a Bruker WM 400 instrument, using the procedure of sequential multiplet line irradiation.[11c] The total irradiation time for each multiplet was 2.4 s. Irradiation experiments on *O*-isopropylidene methyl singlets were performed on the 250 MHz instrument, as described above.

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