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Synthesis of Anomeric Spiro Uracil Nucleosides with an Orthoester Structure: Stereoselective Cyclization Controlled by the C6-Substituent

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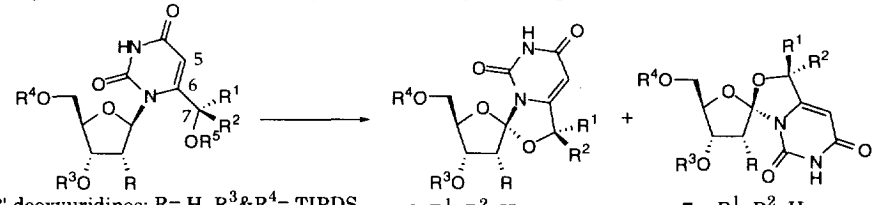
Abstract: *Uracil nucleosides having an anomeric orthoester structure were synthesized from 2'-deoxy-6-(hydroxyalkyl)uridines through hypoiodite-initiated cyclization. The hydroxyalkyl substituent at the 6-position was found to control the anomeric stereochemistry (β/α=7/1~1/46) of the cyclization. The transition state geometry of the reaction was postulated based on the X-ray crystallographic structure of the cyclized product 7α to elucidate the observed stereoselectivity.* © 1997 Elsevier Science Ltd.

Radical-mediated anomeric hydrogen abstraction in DNA is known to occur by certain antitumor antibiotics.[1] While the fate of the resulting DNA anomeric radicals has been well documented,[1] little is known about the method for generating nucleoside anomeric radicals or about the synthetic utility of such species.[2] Recently, we reported that the anomeric radicals can be generated from uracil and purine nucleosides *via* 1,5-translocation of vinyl radicals, which was followed by a 5-*endo*-*trig* cyclization to yield anomeric spiro nucleosides.[3,4] As a result of the above study, we became interested in the H-1' abstraction by an alkoxy radical, since DNA lesions produced by oxygen radicals are the subjects of extensive research.[5] In this communication, we wish to report the synthesis of novel spiro nucleosides having an anomeric orthoester structure[6] *via* hypoiodite reaction[7] of 2'-deoxy-6-(hydroxyalkyl)- and 6-(hydroxyalkyl)uridines (**1**-**3**, **5** and **6**),[8] in which the alkoxy radical-induced H-1' abstraction process would be involved.

Preparation of alcohols **1**-**3** was carried out by LDA lithiation of 3',5'-*O*-(tetraisopropyldisiloxan-1,3-diyl)-protected 2'-deoxyuridine. The resulting C6-lithiated species was reacted with an appropriate electrophile: DMF then $NaBH_4$ for **1** (53%); acetaldehyde for **2** (66%); acetone for **3** (24%).[8a] The secondary alcohol **2** was obtained as an inseparable mixture consisting of **2a** and **2b** (*ca.* 1.3:1). Chloroacetylation [$(ClCH_2CO)_2O$/DMAP/CH_2Cl_2] of the



2'-deoxyuridines: R= H, R^3&R^4= TIPDS
1: R^1=R^2=H, R^5=H
2a: R^1=H, R^2=Me, R^5=H
2b: R^1=Me, R^2=R^5=H
3: R^1=R^2=Me, R^5=H
4a: R^1=H, R^2=Me, R^5=$COCH_2Cl$
4b: R^1=Me, R^2=H, R^5=$COCH_2Cl$

7β: R^1=R^2=H
8β: R^1=H, R^2=Me
9β: R^1=Me, R^2=H
10β: R^1=R^2=Me
11β: R^1=R^2=R^3=R^4=H
12β: R^1=H, R^2=Me, R^3=R^4=H
14β: R^1=R^2=Me, R^3=R^4=H

7α: R^1=R^2=H
8α: R^1=H, R^2=Me
9α: R^1=Me, R^2=H
10α: R^1=R^2=Me
13α: R^1=Me, R^2=R^3=R^4=H

uridines: R=OR^3, R^3=isopropylidene, R^4=TBDMS
5: R^1=R^2=H
6a: R^1=H, R^2=Me
6b: R^1=Me, R^2=H

15β: R^1=R^2=H
16β: R^1=H, R^2=Me
17β: R^1=Me, R^2=H

15α: R^1=R^2=H
16α: R^1=H, R^2=Me
17α: R^1=Me, R^2=H

Scheme 1.

mixture enabled the separation of **4a** and **4b** by HPLC (hexane-EtOAc=1/1), each of which was then treated with NH_3/MeOH to give (*R*)-alcohol **2a** and (*S*)-alcohol **2b**. The stereochemistry of **2b** was unambiguously determined based on X-ray crystallographic analysis.[9]

The hypoiodite reactions of these compounds shown in Scheme 1 were carried out by method A [$Pb(OAc)_4/I_2/h\nu$][7b] or B [(diacetoxyiodo)benzene (DIB)/$I_2/h\nu$].[7c] The following sequence of reactions would be involved in the cyclization: hypoiodite formation, photo-initiated generation of an alkoxy radical, its 1,5-translocation to yield an anomeric radical and finally cyclization through either radical or ionic substitution reaction of a C1'-iodo intermediate. Each cyclized product was isolated by HPLC (hexane-EtOAc=1/1), and the results are summarized in Table 1.[10,11] The primary alcohol **1** gave **7** with slight α-selectivity (entries 1 and 2). The stereochemistry of 7α was confirmed by X-ray crystallography and is depicted by ORTEP drawing in Fig. 1.[9]

Table 1. Hypoiodite reaction of 6-(hydroxyalkyl)uridine derivatives **1**-**6**.

entry	substrate	method[a]	irradiation time (min.)[b]	cyclized products (% yield by HPLC separation)		combined yield (%)	anomeric β/α ratio
1	**1**	A	15	**7**β (19.1)	**7**α (24.0)	43.1	1/1.3
2	**1**	B	60	**7**β (24.9)	**7**α (43.0)	67.9	1/1.7
3	**2a**	A	18	**8**β (61.9)	**8**α (9.5)	71.4	6.5/1
4	**2a**	B	45	**8**β (59.9)	**8**α (8.5)	68.4	7.0/1
5	**2b**	A	15	**9**β (2.0)	**9**α (66.5)	68.5	1/33.3
6	**2b**	B	45	**9**β (1.7)	**9**α (77.7)	79.4	1/45.7
7	**3**	A	15	**10**β (45.9)	**10**α (15.2)	61.1	3.0/1
8	**3**	B	45	**10**β (43.7)	**10**α (22.4)	66.1	2.0/1
9	**5**	B	30	**15**β (41.5)	**15**α (1.2)	42.7	34.6/1
10	**6a**	B	60	**16**β (61.9)	**16**α (1.8)	63.7	34.4/1
11	**6b**	B	30	**17**β (32.9)	**17**α (13.6)	46.5	2.4/1

a) method A: $Pb(OAc)_4$ (4.0 equiv.), I_2 (1.2 equiv.), $CaCO_3$ (4.0 equiv.); method B: DIB (2.4-3.0 equiv.), I_2 (1.1 equiv.); solvent system: cyclohexane-CH_2Cl_2 (6:1) for both methods. b) 250W tungsten lamp was used.

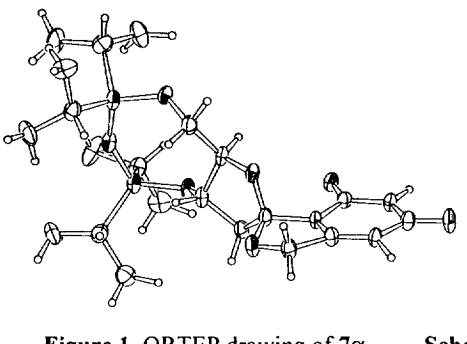
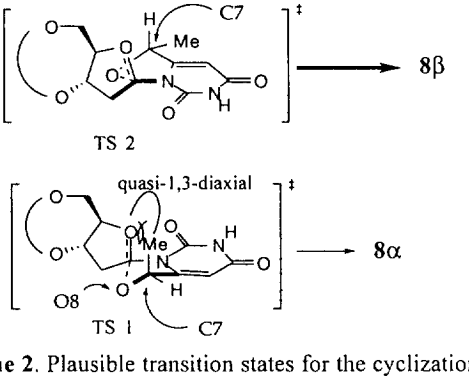


Figure 1. ORTEP drawing of 7α.



Scheme 2. Plausible transition states for the cyclization of **2a**.

In terms of the stereoselectivity in the cyclization, the most striking bias can be seen in entries 3-6. Namely, the (*R*)-alcohol **2a** gave the β-spiro nucleoside **8**β as the major product with a β/α ratio of 7/1, while the reaction of the (*S*)-alcohol **2b** resulted in dominant formation of the α-spiro nucleoside **9**α (β/α=1/46). One possible interpretation of these results comes from the transition state geometry of atoms, which is illustrated by the case of **2a** in Scheme 2. Based on the X-ray result of 7α in Fig. 1, it would be reasonable to assume that the newly

forming oxazolidine ring accommodates C1', N1, C6 and C7 atoms in the same plane as the uracil ring with only the oxazolidine oxygen forced to be located below the plane due to the anomeric effect of the furanose ring oxygen (O4').[12] Fig. 1 also shows that the *pro-R* hydrogen and the O4' atom are mutually in the quasi 1,3-diaxial disposition. If this hydrogen is replaced by a methyl group as in **2a**, there would be an enhanced steric repulsion between (7*R*)-Me and O4'. Therefore, the transition states TS2, which leads to **8**β, should be more favorable than TS1 in this particular case of **2a**. The reverse applies to **2b**.[13]

To see if the above explanation holds in the case of a different type of substrate, the 5'-*O*-(*tert*-butyldimethylsilyl)-2',3'-*O*-isopropylideneuridine derivatives **5**, **6a** and **6b** were prepared. The depicted C7-configurations of **6a** and **6b** are consistent with ^{1}H NMR evidence of their *O*-methylmandelates[14a] and Mosher's esters.[14b] It was anticipated that, in the transition state, the presence of 2',3'-*O*-isopropylidene group would prevent the bulkier uracil ring occupying the α-face, thereby rendering the cyclization in favor of β-anomer formation. This turned out to be the case for the cyclization of **5** (entry 9). As shown in entry 10, when the above mentioned steric demand matched the configuration at the 7-position, again a high β/α ratio became actual issue. In contrast, when mismatched (entry 11), the ratio decreased significantly. Almost identical β/α ratios observed in the reactions of **5** and **6a** suggest that the 2',3'-*O*-isopropylidene group plays an overwhelmingly important role in controlling the stereoselectivity.

For the tertiary alcohols **3**, neither TS1 nor TS2 is considered to be suitable for the cyclization, the result of which will lead to its poor cyclization efficiency. However, when **3** was subjected to the hypoiodite reaction, comparable combined yields of the products (**10**) were obtained as given in entries 7 and 8. It would be worth noting that the H-1' resonance of **3** appeared at δ 6.86 ppm in $CDCl_3$ which is significantly deshielded when compared with those of other alcohols **1**, **2a** and **2b** (δ 5.99-6.10 ppm). We assumed, therefore, that the hydroxyl group of **3** is in close proximity to H-1' due to the presence of the bulky geminal dimethyl group which cetainly encourages 1,5-translocation of the initially formed alkoxy radical.

Some of the spiro nucleosides (**7**β, **8**β, **9**α, and **10**β) synthesized in the present study were deprotected in the conventional way (Bu_4NF in THF) to furnish the corresponding free nucleosides (**11**β, **12**β, **13**α, and **14**β) in high yields.

In summary, a synthetic method is disclosed for novel types of anomeric spiro nucleosides with an orthoester structure. Based on the X-ray crystallographic result of the product, the geometry of the transition state has been proposed to elucidate stereoselectivity of the cyclization at the anomeric position. The possibility of introducing such an acid labile component into oligonucleotides is currently under investigation.[15]

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9. Experimental details of the X-ray structure determination, ORTEP representations and tables of fractional atomic coordinates, thermal parameters, interatomic distances and angles for **2b**, **7α** and **11β** were deposited by the editor at the Cambridge Crystallographic Data Center.
10. For convenience, the α-spiro nucleosides refer to the compounds in which the base moiety occupies the opposite face to the 4'-hydroxymethyl group.
11. In uracil spiro nucleosides, since the C2 carbonyl group is always fixed in the *syn* region, the anisotropic effect toward the H2'β or H2'α/H4' (NOE between H2'α and H4'=3.6~7.6%) could be taken into account for determination of the anomeric β/α configuration.[3a,4a,b] For example in β-nucleoside **7β**, chemical shifts of H2'β, H2'α and H4' in $CDCl_3$ are δ 3.20, 2.49, and 3.89 ppm, and those for the corresponding α-nucleoside **7α** are δ 2.42, 3.43 and 4.22 ppm, respectively. All compounds are in agreement with spectral data (^1H NMR, FAB Mass, elemental analysis, UV).
12. In this system, the O8 atom can take only two possible envelope conformations for a 5-memberd ring puckering, *i.e.* over or below the plane. For anomeric effect of the spiro ketal system, see: Deslongchamps P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 4-53.
13. The same discussion is possible based on the X-ray crystallographic structure of the free β-nucleoside **11β**.[9] It is also clear that *pro-S* hydrogen undergoes quasi 1,3-diaxial interaction with the O4' atom in this case.
14. a) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370-2374. b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakizawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
15. For example, compound **11β** is stable under conditions of DMTr deprotection: 3% Cl_3CCO_2H in MeOH-MeCN (1:9)/30 min, TFA (6.5 eq) in MeOH-CH_2Cl_2 (1:9)/20 min, and 80% AcOH/rt/2.5 h.

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