

A Novel Approach Towards 2,3-Dideoxyriboside Synthesis

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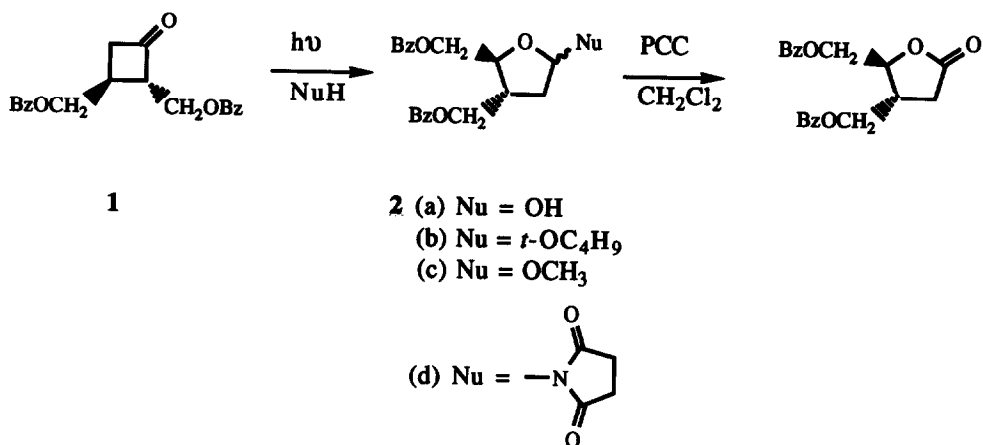
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Summary: A short synthesis of 2,3-dideoxy-3(S)-C-hydroxymethyl ribosides is described. The key step involves a photochemical ring-expansion of a chiral cyclobutanone which occurs stereospecifically.

There has been a recent flurry of activity on the preparation of nucleoside analogues related to oxetanocin which exhibit potent antiviral activity.¹⁻⁴ These compounds possess a four membered carbocyclic or heterocyclic oxetane ring with *vicinal* trans-disubstituted hydroxymethyl groups. In a recent report,⁵ a Swedish group showed that certain 2',3'-dideoxy-3'-C-hydroxymethyl nucleosides are very potent inhibitors of HIV. Our recent findings⁶ that the photochemical ring-expansion of cyclobutanones gives N-H insertion products (2-aminotetrahydrofurans) and that these ring expansion reactions occur with retention of configuration of the ring substituents⁷ prompted us to explore this route as a possible method for nucleoside synthesis. We report the successful application of this idea in the preparation of chiral 2,3-dideoxy-3(S)-C-hydroxymethyl ribosides starting with the optically pure protected 2,3-bishydroxymethylcyclobutanone **1**. This ketone was obtained by a modified procedure involving the stereospecific metal-catalyzed [2+2] cycloaddition of 1,1-dimethoxyethylene to (-)-dimethyl fumarate as the key step.^{2,13}

UV irradiation of ketone **1** in THF/water⁸ gave an epimeric mixture of hemiacetals **2(a)**⁹ (58%) ($[\alpha]_D = +13.2$, $c = 1M$, $CHCl_3$). The relative stereochemistry at the chiral centers C-3 and C-4 (sugar numbering) of **2(a)** was confirmed by its oxidation to lactone **3**.⁹ A single stereoisomer was produced as was evident from the ¹H-nmr spectrum. Homonuclear decoupling of the C-5 methylene protons showed a doublet for H-4 ($J = 3.4Hz$) typical for trans vicinal coupled protons.



Furthermore, NOED experiments carried out for **3** indicated the trans relationship between the two benzoyloxymethyl groups. This is based on selective irradiation of the H-5 (δ 4.59) methylene protons and observation of signal enhancements for the H-4 (δ 4.80), H-3 (δ 2.95) and H-2 β (δ 2.90) protons. Since epimerization could only occur at C-4 upon photolysis of ketone **1** and a single stereoisomer **3** is produced in this sequence, the initial photochemical ring expansion reaction of the optically pure ketone **1** must have proceeded stereospecifically. Furthermore since the absolute configuration for ketone **1** has been assigned by X-ray crystallography of one of its analogs,³ the assignment of the 3(S), 4(R) configuration for hemiacetal **2**(a) is secure. Confirmation of the absolute configuration was obtained from the photoadduct **2**(c) obtained from the photolysis of **1** in methanol. The β -anomer which was separated by preparative chromatography has identical physical and spectral properties with those of a previously reported sample prepared by a different route.¹⁰

Similar irradiation of ketone **1** in THF containing *t*-butanol, methanol and succinimide gave adducts **2**(b)-(d) in varying yields (Table 1) depending on the extent to which water is rigorously excluded from the reaction. In addition to the photoadducts **2**, small amounts of the cycloelimination product, *E*-1,4-bis(benzoyloxy)-2-butene were produced. The extent of photocycloelimination in cyclobutanones is often solvent dependent.¹¹ In all cases, an anomeric mixture (about 1:1 mixture of α and β) was obtained as evident from the observation of two anomeric proton signals in the region δ 5.0-5.5 ppm in the ¹H-nmr spectra. Some stereoselectivity was observed in the case of the *t*-butanol photoadduct **2**(b) (4:1 in favour of the α epimer). The low yield in the case of *t*-butanol insertion may be attributable to steric factors in the bimolecular process favouring competing

unimolecular pathways such as photocycloelimination. Similar observations for other cyclobutanones have been reported.¹²

Table 1			<u>YIELDS OF PHOTOADDUCTS 2(a) - (d)^a</u>
<u>Solvent</u>	<u>Photoadducts (% Yield)</u>	<u>% Yield of Trans-Benzoyloxy-2-Butene</u>	
THF/H ₂ O	2(a) (58)	15	
THF/ <i>t</i> -C ₄ H ₉ OH	2(b) (9)	20	
THF/CH ₃ OH	2(c) (62)	33	
THF/Succinimide	2(d) (17) ^b	30	

a. Isolated yields.

b. Actual yield is 20%, based on unreacted starting material.

Since the methanol adduct 2(c) has been coupled with cytosine⁵ and a purine¹⁰ our method constitutes a formal synthesis of nucleosides. The direct insertion of the oxacarbene derived from 1 into N-H functions of purine and pyrimidine bases is under current investigation.⁶

Acknowledgements

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8. The irradiation was carried out using a Hanovia 450W lamp in a quartz immersion well. Pyrex tubes containing 0.02M solutions of ketone 1 in THF and nucleophile scavenger in pyrex tubes were strapped around the well and irradiated for two hours.
9. Spectral data: **2a** ^1H -nmr δ (ppm) 7.94-8.16, 7.35-7.65 (10H, aromatic benzoyl-H), 5.66, 5.60 (1H two dxd, anomeric H-1), 4.28-4.66 (5H, m, Bz-OCH₂ plus H-4), 3.06 (1H, br.s., OH), 2.90, 2.55 (1H, m, H-3), 2.31-2.47, 2.16-2.26 (2H, m, H-2); IR (cm⁻¹): 3430 (OH), 1710 (C=O); MS. 339 (M⁺-OH); analysis Calc. for C₂₀H₂₀O₆: C, 67.40; H, 5.66, Found C, 67.37; H, 5.90. Lactone **3**: ^1H -nmr δ (ppm): 8.01 (d, 4H, ortho benzoyl-H), 7.58 (t, 2H, para benzoyl-H), 7.44 (t, 4H, meta benzoyl-H), 4.80 (m, 1H, H-4), 4.59 (m, 2H, Bz-O-CH₂ at C-4), 4.44 (m, 2H, Bz-O-CH₂ at C-3), 2.95 (m, 1H, H-3), 2.90 (dd, 1H, H-2 β), 2.57 (m, 1H, H-2 α), IR(cm⁻¹): 1780 (C=O of lactone), 1715 (C=O of benzoyl group); MS.CI 355 (M⁺+H), 372 (M⁺ + NH₄).
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