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A Novel Photochemical Synthesis of Dideoxyfuranosyl Disaccharides

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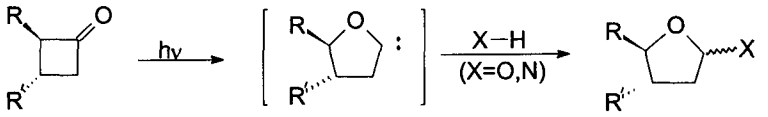
Abstract: A photochemical glycosylation is described using the chiral cyclobutanone **1**. Irradiation of ketone **1** in the presence of monosaccharides **2** and **3** gives photoadducts derived from OH insertion of the transient carbene. The carbene inserts into the N-H group in the case of nucleoside **4**.

Classical methods involving formation of *O*-glycosidic bonds generally demand time consuming protective chemistry and activation of a glycosyl donor.[1] A number of reports outlining the more popular methods of *O*-glycosylation have appeared.[2-4] Much of the focus of glycosylation reactions has shifted toward improving the efficiency by maximizing yields, regioselectivity and stereoselectivity. The glycosylation of hydroxyl groups generally proceeds by first activating one of the monosaccharide units in order to transform this into a glycosyl donor which would form a glycosyl bond with a free hydroxyl functionality present on the other saccharide reactant. The photochemical ring expansion of cyclobutanones to transient 2-oxatetrahydrofuranylidenes and insertion of these carbenes to O-H groups provides a general route for *O*-glycosylation and the preparation of 2-substituted furanosides.[5] Thus starting with an aglyconic unit a transient "glycosyl donor" is generated in one photochemical step under neutral and relatively mild conditions (Scheme 1).

Scheme 1



The ring-expansion step to produce the transient oxacarbene has been shown to proceed both regio- and stereospecifically.[6] With the increasing availability of chiral cyclobutanones[7], such a method could be utilized in the preparation of chiral furanosides. Indeed, we have shown that *N*-glycosylation can occur with chiral cyclobutanones to give ribonucleosides.[8-11] To explore the extension of this methodology to include the preparation of disaccharides, we initiated a study on the photochemistry of chiral cyclobutanones with a series of monosaccharides with emphasis on the regio- and stereoselectivity of the carbene insertion reaction (second step in Scheme 1). We report in this communication the photochemistry of chiral ketone **1**[12] with two monosacharides and a nucleoside, each substrate bearing at least one free hydroxyl group.

Chiral ketone **1** was prepared in >98% optical purity using a previously described method.[12] Photoaddition of ketone **1** with monosaccharides **2**, **3** and the nucleoside **4** was investigated .

Irradiation of a $4x10^{-3}$M solution of ketone **1** with five mole equivalents of glucofuranose **2** in chloroform solution for 3h[13] gave a mixture consisting of 8% of an anomeric mixture of **5** (α and β). The remaining components in the mixture were identified as unreacted ketone **1** (30%), (E)-butene-1,4-diol dibenzoate[9] (15%) and hemiacetal **6**[9] (5%), the latter two products arising from competing photocycloelimination and reaction with trace water associated with **2** respectively. The anomeric mixture **5** was separated into equal amounts of **5**-α and **5**-β and their stereochemical assignments based on 2D-NOESY spectra.[13]

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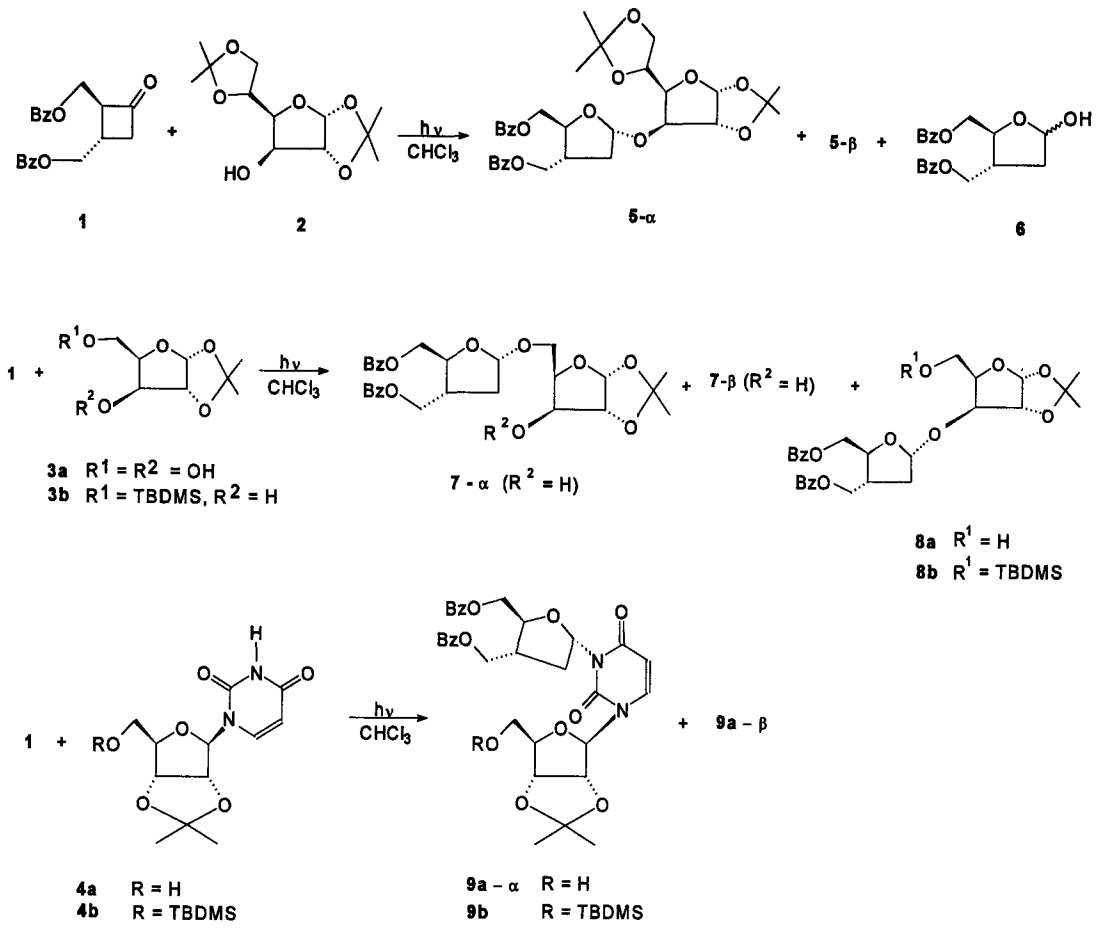

Irradiation of ketone **1** with three mole equivalents of xylofuranoside **3a** in $CHCl_3$ gave three photoadducts **7-α**, (18%), **7-β** (22%) and **8a** (6%) formed as a single anomer as evident from the simplicity of the ^{1}H-NMR signal at δ5.39 for the anomeric proton at the newly formed anomeric center and the presence of the methyl proton resonances appearing as two singlets. In addition, small amounts of (E)-butene-1,4-diol dibenzoate (10%) and **6** (3%) were also isolated. The formation of what appears to be a single anomer of **8a** may be associated with intermolecular hydrogen bonding effects between diol **3a** and ketone **1**. Unequivocal regiochemical assignment for the structure of **8a** was obtained by irradiation of ketone **1** with the mono-protected *t*-butyldimethylsilyl ether (TBDMSO) derivative of xylofuranose[14] **3b** under the same conditions as above giving **8b** which was directly deprotected using $(n\text{-Bu})_4$NF in THF[15] giving **8a** as one of the components. The ^{1}H-NMR and IR spectra for this compound were identical with a sample of **8a** obtained by direct irradiation of ketone **1** with xylofuranoside **3a**.

Having shown that disaccharides can be prepared by photoglycosylation, we were interested in extending

this method to the preparation of 5′-*O*-glycosylated nucleosides (nucleoside disaccharides). A number of such nucleoside disaccharides have been implicated as regulators of phosphorylase or other enzymes of reserve carbohydrate metabolism exhibiting antibiotic properties.[20] Such compounds, found as natural products, exhibit significant *in vitro* and *in vivo* biological activities, ranging from antiviral to insecticidal properties[21-23] Irradiation of ketone **1** with 10 mole equivalents of 2′,3′-*O*-(1-methylethylidene)-uridine (**4a**) in acetonitrile gave an anomeric mixture of a photoadduct **9a** (20%) which was separated (**9a**-α, **9a**-β) by preparative TLC. The remaining products are derived from photocycloelimination and photoaddition to residual water as observed for the photoreaction of **1** with **2**. No 5′-*O*-glycosylation was observed, but instead, *N*-glycosylation by carbene insertion to the acidic imide N-H group of uridine took place. The regiochemical structure assignment of **9a** was based on its synthesis by an independent route. Irradiation of ketone **1** with the protected uridine **4b**[16] gave a photoadduct **9b** which upon deprotection with *n*-Bu_4NF gave a product **9a** whose spectral data matched those of the sample prepared from direct irradiation of **1** with **4a**. The regiospecificity for carbene insertion into **4a** would be expected on the basis of the relative acidic nature between imide N-H and O-H groups[17] and the nucleophilic (basic) nature of the transient oxacarbenes.[18]

Furthermore, 5′-*O*-glycosylations of nucleosides by standard methods have been shown to occur with great difficulty as a result of intramolecular hydrogen bonding between 5′-OH and the attached base, e.g. the 2-carbonyl group in 2′-deoxycytidine.[19]

In summary, a novel photochemical glycosylation reaction has been shown to be of potential use in the preparation of disaccharides. The method is based on the photoisomerisation of a cyclobutanone to a transient 2-oxatetrahydrofuranylidene and its insertion into O-H and acidic N-H groups with stereochemical retention of the ring substituents. Regioselectivity is observed for the insertion reaction with primary alcohol groups favoured over secondary ones. Insertion of the oxacarbene into the imide N-H function is preferred over the primary hydroxyl group in uridine. With the availability of chiral cyclobutanones, such method offers an alternative class of glycosyl donors which can be coupled under mild conditions without the adverse effects of protecting group degradation.

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13. Irradiations were performed using a Hanovia 450-W medium pressure mercury arc lamp in a water-cooled quartz immersion well. Pyrex tubes containing the solutions were strapped around the well and the assembly immersed in an ice-water bath. All reported yields are isolated yields after separation by column (flash grade silica gel) or thin-layer chromatography. ^{1}H-NMR spectra and MS parent ions as well as elemental analysis were consistent with the assigned structures.
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