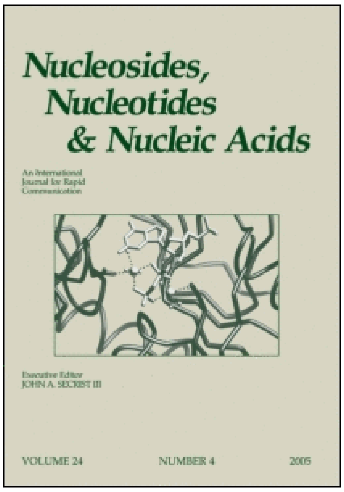

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Synthetic Studies on Guanofosfocin: Glycosylation of 8-Oxo-purine Nucleosides via Mitsunobu Reaction

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ABSTRACT

In model studies directed to the total synthesis of guanofosfocins, a unique glycosidic bond formation between the 8-oxo-purine nucleosides and mannopyranose derivatives under Mistunobu conditions is described.

Key Words: Guanofosfocin; 8-Oxo-purine nucleoside; 8-(Mannosyloxy)-purine nucleoside.

Guanofosfocin is a novel family of chitin synthase inhibitors isolated from the fermentation broths of *Streptmyces sp.* and *Trichoderma sp.*[1] Its structure is highly distinctive and contains a unique glycosidic bond between the 8-position of guanosine and α-D-mannopyranose moiety. In a previous study, we have disclosed that an 8-oxoadenosine derivative is successfully glycosylated using mannopyranosyl bromide in the presence of silver carbonate at 80°C for 20 h.[2] Herein, we describe an alternative approach for the construction of such a glycosidic linkage via Mitsunobu reaction under mild conditions.

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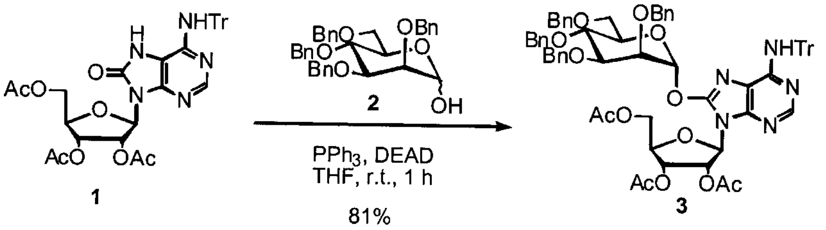
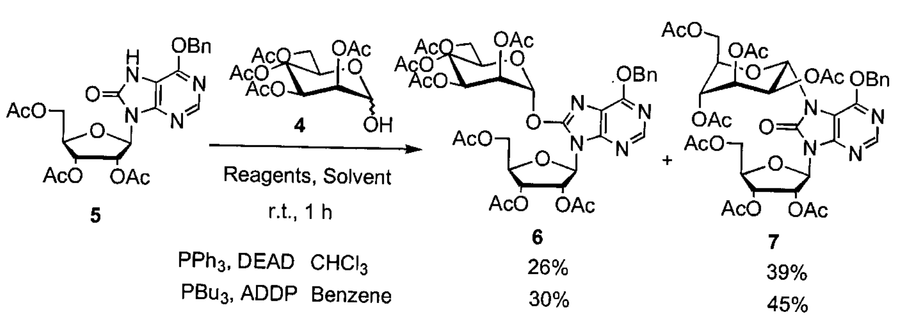
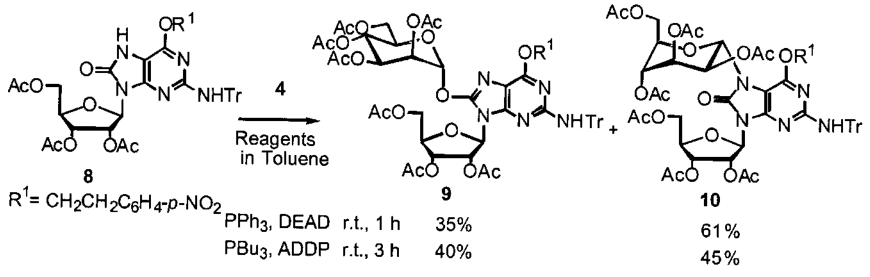
Several attempts have appeared on the application of Mitsunobu reaction for the glycosylation of nucleobases, involving some problems associated with regio- and stereoselecive requirements.[3] We first examined an 8-oxoadenosine derivative as the substrate for the proposed glycosylating strategy. Thus, 2′,3′,5′-tri-*O*-acetyl-6-*N*-trityl-8-oxoadenosine (**1**) was treated with 2,3,4,6-tetra-*O*-benzylmannopyranose (**2**) in the presence of 1.5 equiv. of triphenylphosphine and 1.5 equiv. of diethyl azodicarboxylate (DEAD) in dry THF at r.t. for 1 h. After silica gel chromatography, the single isolated product **3** (81% yield) was characterized by ^{1}H, ^{13}C NMR, showing the 8-*O*-α-glycosidic bond newly formed at the anomeric carbon of mannopyranose.



To our surprise, a similar reaction using 2′,3′,5′-tri-*O*-acetyl-*N*-1-benzyl-8-oxoinosine led to a mixture of both α and β stereoisomers of the 8-*O* and *N*-7 regioisomers. To suppress the production of the undesirable β-anomers, acetyl-protected mannose **4** was employed as the glycosyl donor instead of the benzylated sugar. As a result, the product bearing only α linkage was obtained in 82% yield, but the mannose was located at the undesirable *N*-7 position. When 2′,3′,5′-tri-*O*-acetyl-6-*O*-benzyl-8-oxoinosine (**5**) was used as the substrate, the desired 8-(α-mannopyranosyloxy) inosine derivative **6** was obtained in 26% yield, accompanied by 39% of the *N*-7 regioisomer **7**. Attempts to use another Mitsunobu reagents, a combination of tributylphosphine and azodicarbonyldipiperidine (ADDP),[3] gave similar results.



Finally, we applied this glycosylating method for the synthesis of 8-(mannopyranosyloxy) guanosine derivative. However, when suitably protected 8-oxoguanosine derivative **8** was conducted under the Mitsunobu conditions, two regioisomers,



6-*O*-mannosylated and *N*-7-mannosylated products, were produced again and, therefore, the yield of the desired product **9** was unsatisfactory.

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