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

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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. 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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