Studies toward Stable Analogues of Guanofosfocins. Synthesis of the Protected Derivative of 8-(5a-Carba-α-D-mannopyranosyloxy)purine Nucleoside

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(Received September 26, 2006; CL-061120; E-mail: sugimura@edhs.ynu.ac.jp)

As a preliminary study directed towards the synthesis of a stable analogue of the guanofosfocins, a methylene analogue of the endocyclic oxygen atom in the mannose moiety, was designed. The construction of the pseudo-α-mannosyl linkage at the 8-position of the purine nucleoside was accomplished by the regioselective ring-opening substitution of the 1,2-*O*-cyclic sulfate derivative of 5a-carba-mannopyranose.

Guanofosfocins are a novel family of chitin synthase inhibitors, isolated from the fermentation broths of *Streptomyces* sp. and *Trichoderma* sp.[1] Despite their potent inhibitory activity against *Candida albicans* CHS 2, a further investigation of these fascinating molecules has been hindered by their low stability. In addition to their role as promising therapeutic agents against fungous diseases, the guanofosfocins contain a highly distinctive three component structure, a central part of which is a unique glycosidic type bond between the 8-position of guanosine and a D-mannose moiety. In earlier reports on the synthesis of 8-(mannopyranosyloxy)purine nucleosides, we disclosed that three different approaches were possible for the construction of such a glycosyl linkage.[2–5] However, at the same time the constructed glycosyl bonds were found to be easily hydrolyzed under acidic conditions, affording 8-oxopurine nucleosides. In contrast, an ethereal bond, for example, the 8-(cyclohexyloxy)-purine nucleoside, was shown to be quite stable under the same acidic conditions. Based on these findings, we designed the carba-sugar analogues of the guanofosfocins, in which the endocyclic oxygen atom of the mannose moiety is replaced by a methylene group, as stable guanofosfocin analogues (Figure 1, X = CH_2).[6] In this letter, we describe our preliminary studies of the synthetic route to 8-(5a-carba-α-D-mannopyranosyloxy)-purine nucleoside.

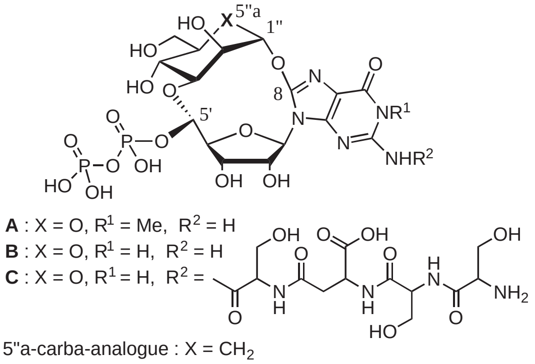
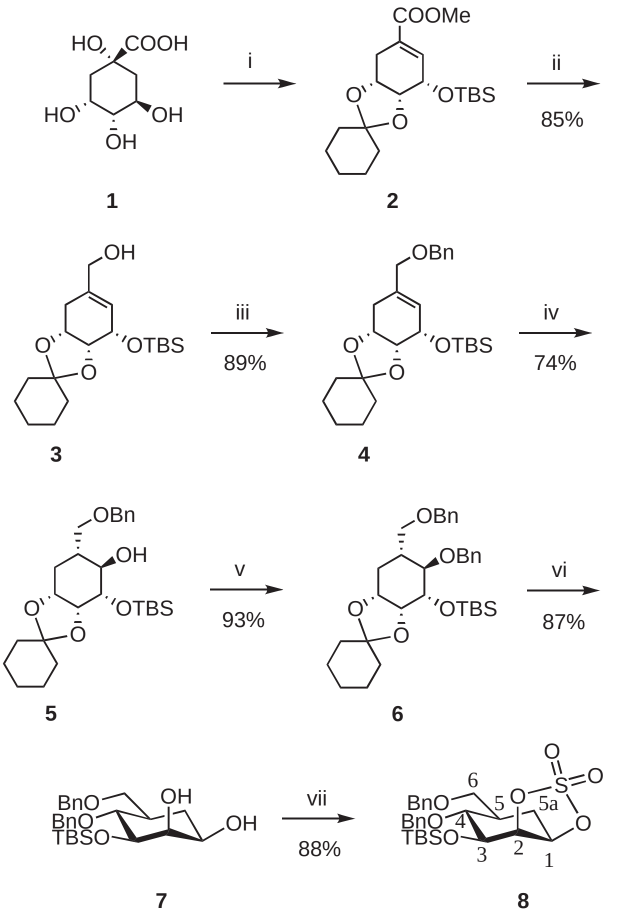


Figure 1. Structure of guanofosfocin A–C and their carba-analogues.

The synthesis of 5a-carbamannose from (–)-quinic acid was established by Shing and Tang.[7,8] Based on this protocol, our synthetic strategy for the stereoselective formation of the pseudo-α-mannopyranosyl linkage features the regioselective substitution of the 1,2-*O*-cyclic sulfate derivative of 5a-carba-β-D-mannnopyranose by a nucleophile, derived from the 8-oxopurine nucleoside.[9]

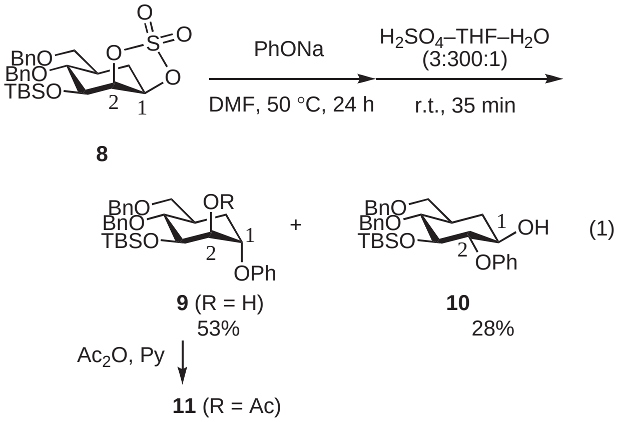
The cyclohexene derivative **2** was obtained in five steps from commercially available (–)-quinic acid (**1**) as described by Shing and Tang.[7,8] Treatment of the methyl ester **2** with DIBAL-H afforded the alcohol **3**, which was protected as a



Scheme 1. *Reagents and conditions*: (i) Refs. 7 and 8; (ii) DIBAL-H, THF, −20 to 0 °C; (iii) BnBr, NaH, DMF, 0 °C; (iv) 9-BBN, THF, reflux, then H_2O_2 aq, NaOH aq, r.t.; (v) BnBr, NaH, DMF, 0 °C; (vi) PrSH (2 equiv.), $BF_3 \cdot OEt_2$ (0.2 equiv.), −78 to −20 °C; (vii) $SOCl_2$, Py, CH_2Cl_2, 0 °C, $RuCl_3/n\text{-}H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, r.t.

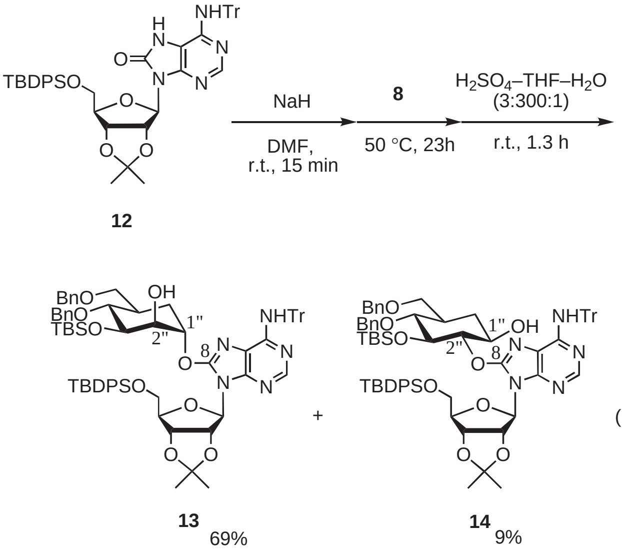
benzyl ether to yield the cyclohexene **4**. The double bond in **4** was subjected to a stereocontrolled hydroboration–oxidation sequence at the less hindered β-face, exclusively furnishing the cyclohexane derivative **5**. After protection of the hydroxy group as a benzyl ether, the attempt to remove the cyclohexylidene acetal in **6** under acidic conditions failed due to the simultaneous cleavage of the TBS group. However, selective removal of the cyclohexylidene group was fortunately accomplished under acetal exchange conditions. The treatment of **6** with two equiv. of PrSH in the presence of a catalytic amount of $BF_3 \cdot OEt_2$ afforded a good yield of the diol **7**, which was converted into the cyclic sulfate **8** by the Sharpless method (Scheme 1).[10]

The ring-opening substitution reaction was initially explored by employing sodium phenoxide as a simple nucleophile. Treatment of the cyclic sulfate **8** with sodium phenoxide in DMF at 50 °C for 24 h, and then under acidic conditions, furnished a mixture two phenoxy alcohols **9** and **10** with the desired regioisomer as the predominant product. The regio- and stereochemical assignments were based on the ^{1}H NMR spectral analyses of the alcohol **10** and an acetate derivative **11** due to signal overlapping in **9**. H-2 in **10** resonated at δ 4.24 as a triplet ($J = 9.2$ Hz), indicating that the C-2 phenoxy group was at the equatorial position. H-1 in **11** appeared at δ 4.53 ($J_{1,2} =$ 5.1 Hz), demonstrating that the C-1 phenoxy group was at the axial position.



(1)

As the model reaction using sodium phenoxide showed a preferential regioselectivity, a purine nucleoside was next employed as the nucleophile. The 8-oxoadenosine derivative **12**, easily accessible from the commercially available 2′,3′-*O*-isopropylideneadenosine in four steps, was treated with sodium hydride in DMF at r.t. for 15 min, and then added to the DMF solution of **8**. After stirring at 50 °C for 23 h, acid-hydrolysis afforded the desirable substitution product **13** in 69% yield along with the 9% yield of the regio isomer **14**. In this case, the good regioselectivity observed was most likely due to the bulkiness of the nucleophile **12** that would preferentially attack the sterically favorable C-1 position in **8**. Again, H-2$''$ in **14** appeared at δ 5.21 as a triplet ($J = 9.5$ Hz), reflecting the doubled *ax–ax* couplings, whereas H-1$''$ in **13** appeared at δ 5.30 as a broad singlet.



(2)

In conclusion, the ring-opening substitution of the 1,2-*O*-cyclic sulfate of the 5a-carbamannopyranose derivative predominately proceeded at the C-1 position, affording 8-(5a-carba-α-D-mannopyranosyloxy)purine nucleoside in good yield. A further investigation employing an 8-oxoguanosine derivative as a nucleophile as well as the ring-closure reaction between the 5′-position of the nucleoside and 3-OH of the pseudo-mannose is currently underway.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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Published on the web (Advance View) December 2, 2006; doi:10.1246/cl.2007.36