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Studies Directed Towards the Synthesis of Miharamycin B.

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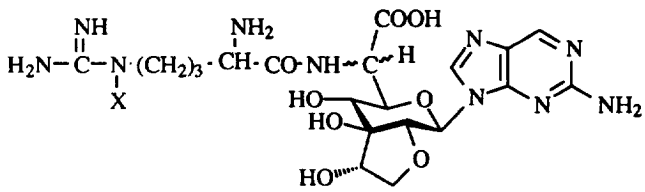
Abstract : *The northern part of Miharamycin B which differs from the natural product by the absence of a 2-carbon branched chain in the sugar moiety, was prepared by a sequence of selective transformations from methyl 2,3,4-tri-O-benzyl-α-D-gluco-hexodialdo-1,5-pyranoside 3. The key step is a regioselective glycosylation of 2-aminopurine.* Copyright © 1996 Published by Elsevier Science Ltd

Miharamycins A (**1**) and B (**2**) are complex nucleoside antibiotics which are produced by *Streptomyces miharaensis*. Although their high activity against *Pyricularia oryzae*, responsible for rice blast disease is known since almost thirty years,[1] their structures were determined only fifteen years later on the basis of ^{1}H and ^{13}C NMR data but the absolute configuration at C-6' remains to be established.[2]

The structural complexity of this molecule which contains a C-3 branched central carbohydrate unit bearing a heterocyclic base at the anomeric center and extended at C-6 by an aminoacid linked to an arginine prompted us to an exploration of its synthesis.

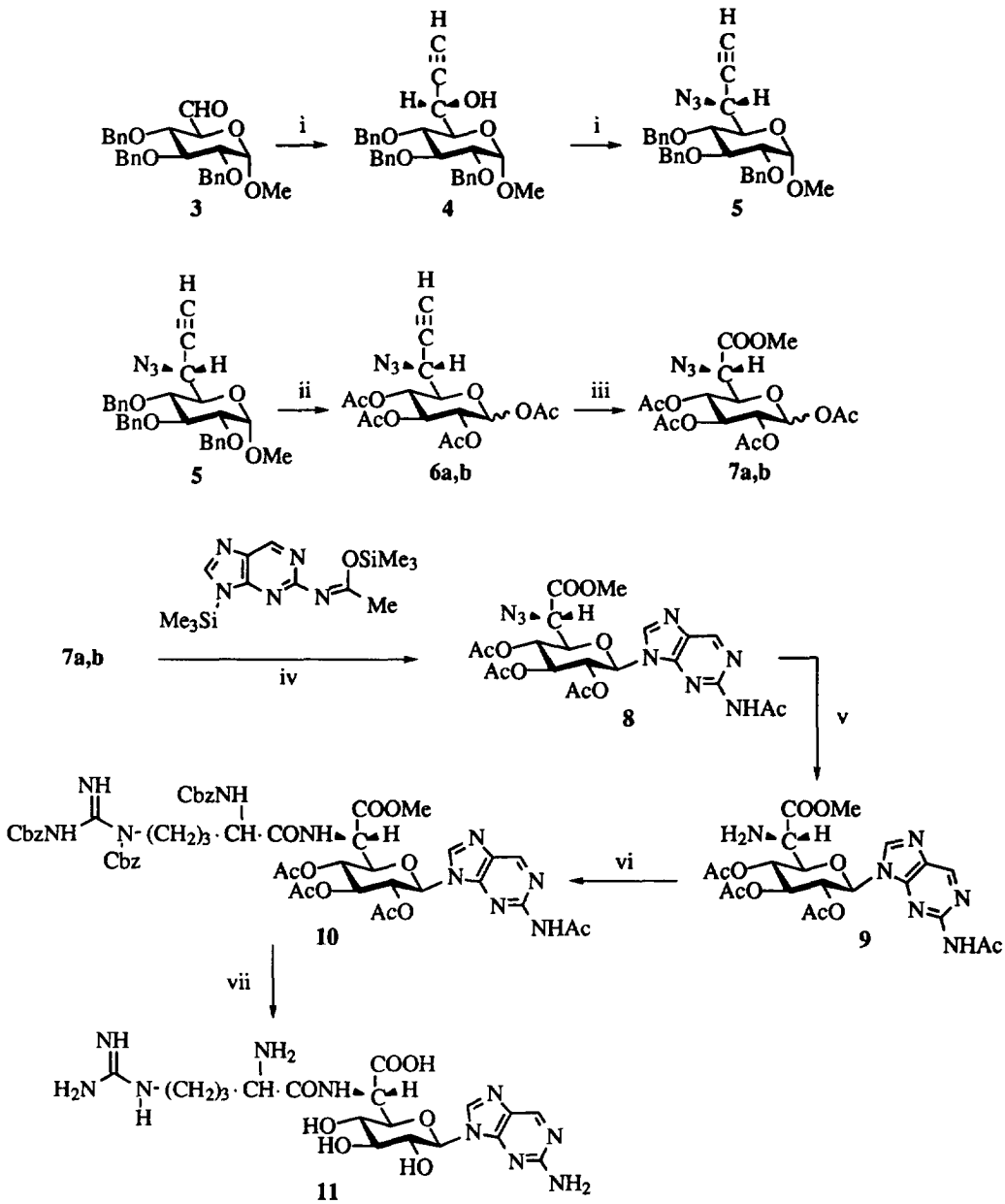


1 Miharamycin A: X= OH
2 Miharamycin B: X= H

We recently reported the synthesis of the central C-glycosylated amino-acid moiety of this molecule in which the key step was the stereocontrolled chain elongation of the dialdosugar derivative **3** using the ethynyl group as synthetic equivalent of the carboxylic acid functionality.[3] Replacement of the hydroxyl group by an azido group afforded compound **5** which was transformed into the C-glycosyl amino-acid present in Miharamycins.[3] We report herein the transformation of **5** into the northern part of Miharamycin B by a multistep sequence of selective reactions.

In order to be able to introduce the arginine moiety at the end of the synthesis, it was necessary to preserve the azido group along the whole sequence of reactions. The benzyl ethers which were required for the preparation of **4** due to the use of organolithium derivatives have to be replaced by acetyl groups at this stage of the synthesis for two reasons:

Scheme 1



Reagents and conditions: i; see ref. 3. ii; BCl_3, CH_2Cl_2, - 78 °C then Ac_2O, H_2SO_4, AcOH. iii; $RuCl_3$, $NaIO_4$, $CCl_4/CH_3CN/H_2O$ then CH_2N_2, Et_2O. iv; $SnCl_4$, $ClCH_2CH_2Cl$, 135 °C. v; H_2, Raney Ni, Ac_2O, THF. vi; protected arginine (ref. 9), DCC, HOBT, CH_2Cl_2, 0 °C. vii; LiOH, THF/H_2O, 0 °C then H_2, Pd/C, MeOH.

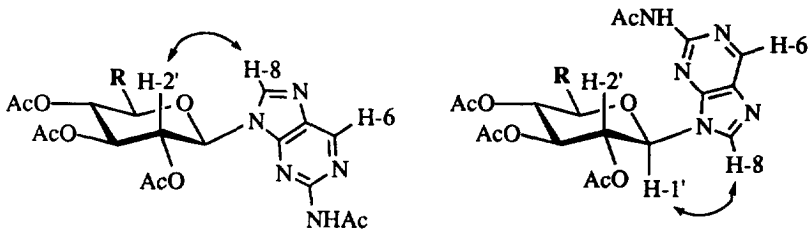
- the best reagent for the oxidative cleavage of the triple bond into a carboxylic acid is ruthenium trichloride under basic conditions.[4] Unfortunately, its use is precluded in the presence of benzyl ethers which are cleaved under these conditions.[3]

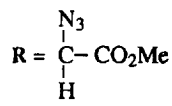
- benzyl groups are not compatible with strongly acidic conditions required for *N*-glycosylation of a heterocyclic base. Furthermore a participating group at C-2 is necessary to ensure formation of the desired β anomer.

Due to the presence of the triple bond and of the azido group, reductive cleavage of benzyl ethers was not possible. Consequently, boron trichloride was employed for that purpose at low temperature.[5] Under these conditions, the glycosidic linkage was also cleaved albeit in part. So the following acetylation of the crude mixture was performed in acidic conditions in order to ensure complete transformation at the anomeric center, thus affording an α/β mixture of tetraacetates **6a,b** in 68 % yield.[6]

After purification by flash chromatography, but without separation of anomers, **6a,b** were reacted with a catalytic amount of $RuCl_3$ (20 %) in the presence of $NaIO_4$ as reoxidant.[4] The resulting carboxylic acid was not isolated but treated with an excess of diazomethane to afford an α/β mixture of **7a,b** (83 %), a suitable synthon for coupling with an activated derivative of 2-aminopurine.

Coupling of **7a,b** with the *bis*-trimethylsilyl derivative of 2-aminopurine was promoted by $SnCl_4$ in 1,2-dichloroethane/acetonitrile solution and afforded a single product **8** in 74 % yield. As indicated by the chemical shift and coupling constant of H-1' (δ= 5.87 in $CDCl_3$, $J_{1',2'}$= 9.5 Hz) compound **8** was the β anomer.[7]





Glycosylation occurred exclusively at N-9 as indicated by NMR: Nuclear Overhauser effect was observed between H-8 and protons of the sugar ring and no effect could be detected between H-6 and any of them. This result is different from previous work relative to the coupling of simple glucopyranose derivatives by Garner *et al.*[8] who have noticed the formation of a 90/10 mixture of N-9 and N-7 glycosylated 2-aminopurine.

Reduction of the azido group proceeded smoothly (H_2, Ni Raney, THF) and the resulting **9** was directly reacted with protected arginine[9] in the presence of DCC and HOBT to afford **10** (40 %). Final deprotection with an aqueous solution of lithine afforded **11** in 60 % yield.

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6. All new compounds were fully characterized by elemental microanalyses and by spectroscopic methods.
7. Compound **8** exhibited the following representative physical data: mp = 90-92 °C. $[\alpha]_D^{20}$ = + 21.5 (*c* 0.53, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ = 1.77 (s, 3H); 1.98 (s, 3H); 2.00 (s, 3H); 2.56 (s, 3H); 3.77 (s, 3H); 4.34 (d, 1H, J = 2.4 Hz); 4.41 (dd, J = 9.6 and 2.4 Hz); 5.40 (t, 1H, J = 8.9 Hz); 5.48 (t, 1H, J = 9.5 Hz); 5.67 (t, 1H, J = 9.5 Hz); 5.87 (d, 1H, J = 9.5 Hz); 8.08 (s,1H); 8.64 (s,1H); 8.94 (s,1H). ^{13}C NMR (62.89 MHz, $CDCl_3$) δ = 20.12; 20.43; 20.49; 25.26; 53.10; 61.97; 67.58; 69.55; 72.76; 76.39; 80.40; 130.28; 142.04; 150.28; 152.14; 153.40; 166.73; 168.58; 168.8; 170.04; 171.00.
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