Pure & Appl. Chem., Vol. 68, No. 3, pp. 589–592, 1996.
Printed in Great Britain.

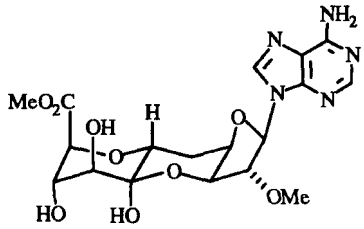
Carbohydrate building blocks in heterocyclic chemistry. Synthetic studies directed towards the herbicidins

Hayley M. Binch, Andrew M. Griffin and Timothy Gallagher*[1]

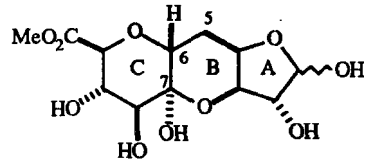
School of Chemistry, University of Bristol, Bristol BS8 1TS, UNITED KINGDOM

Abstract.-Recent synthetic studies directed towards the herbicidin class of nucleosides are described. Aldehyde **7**, incorporating the requisite adenine unit, has been prepared but failed to undergo base-induced aldol reactions with ketone **3**. This problem was overcome using the cerium enolate corresponding to **3**, which is generated from α-bromoketone **9**. Reaction of this species with aldehyde **7** leads to the enone **8**.

The herbicidins, exemplified by herbicidin B **1**, constitute a class of undecose (C_{11})-based nucleosides isolated originally from *Streptomces saganonensis*.[2,3] While the herbicidins are of limited biological value - they inhibit *Xanthomanas oryzae*, a bacterial form of leaf blight associated with rice - their unique structure poses a series of interesting questions and challenges to the synthetic chemist.[4]



1 Herbicidin B



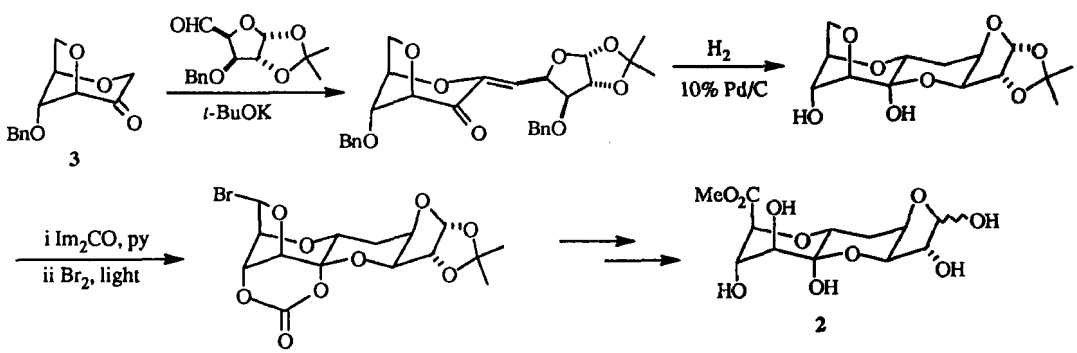
2

Our studies have focused on two objectives. The total synthesis of representative members of this class of natural products is our long term goal, but our initial target was to achieve the construction of the complex C_{11}-glycosyl component **2**. In approaching this task we identified three key structural features of **2** that controlled our synthetic planning:

- the presence of a hemiketal (a masked ketone) at C-7;
- the proximity of the C-glycosyl linkage (C-5/C-6) to the C-7 carbonyl function;
- the stereochemistry at C-6, given that all the *C*-ring substituents must occupy an axial orientation.

Synthesis of Glycoside 2.- The first phase of this programme has been successfully completed and a highly convergent synthesis of the C_{11}-glycosyl component **2** was achieved as outlined in ***Scheme 1***.[5]

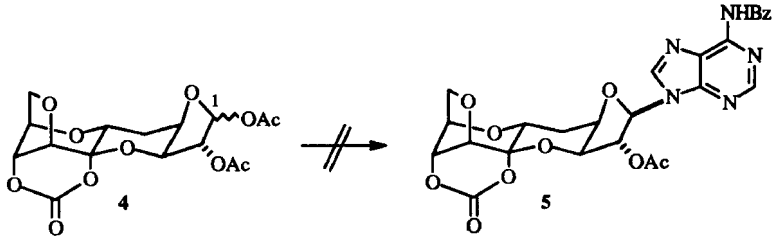
Scheme 1



The principle features of interest in this route were:

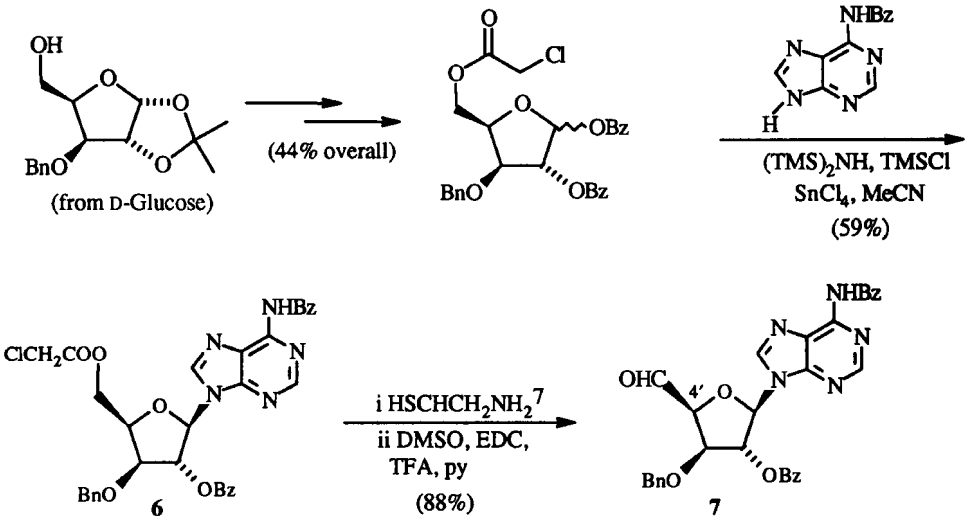
- regiocontrol of enolisation *via* the ether bridged bicyclic ketone **3**;[6]
- an intermolecular base-mediated aldol reaction to connect the *A* and *C*-rings;
- stereoselective enone reduction to establish the correct configuration at C-6;
- regioselective bromination at C-11 to enable cleavage of the ether bridge and introduction of the required carboxylic acid oxidation level at this site.

Incorporation of the adenine base.- Incorporation of the heterocyclic unit could be accomplished at various points on our synthetic pathway, but we were attracted towards doing this either at a very early or late stage. Late stage introduction of the base was studied on the model system **4** but we were unable to produce the corresponding nucleoside **5** under a variety of conditions.



This may be attributable to the sterically crowded environment at C-1 of **4** and this approach was set aside in favour of incorporation of the nucleoside unit at an **early** stage in the synthesis. This approach has the advantage that a high degree of convergency is retained although we also recognised that certain features of the chemistry shown in ***Scheme 1*** would not be compatible with the reactivity of the adenine moiety. The synthesis of the requisite *xylo*-nucleoside aldehyde **7** is shown below in ***Scheme 2***.

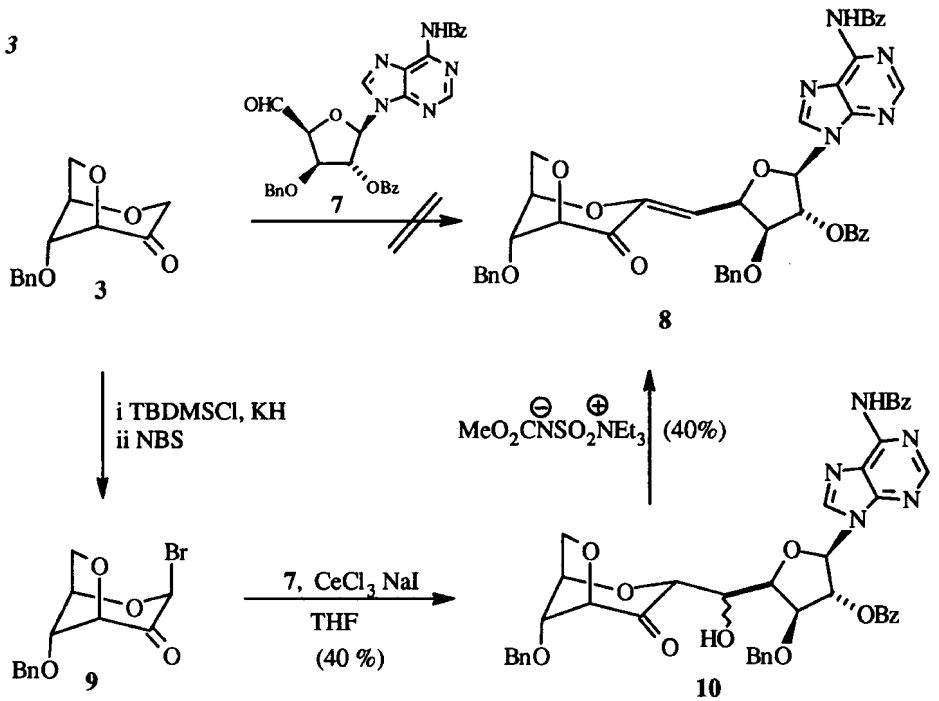
Scheme 2



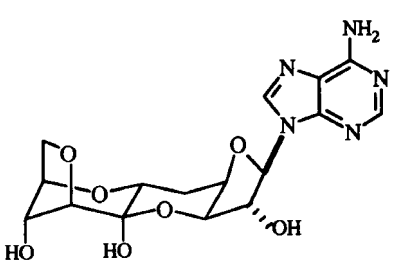
While the synthetic sequence was relatively straightforward, aldehyde **7** did prove to be extremely sensitive. Following a Moffat oxidation of the primary alcohol derived by deprotection[7] of chloroacetate **6**, attempts to purify **7** by chromatography led to essentially quantitative epimerisation at C-4'. However, this final transformation proceeded very cleanly and aldehyde **7** was used directly in subsequent transformations.

With aldehyde **7** available, we then examined its reactivity towards ketone **3** by analogy to the reaction used in ***Scheme 1***. However, all efforts to achieve the analogous aldol condensation were unsuccessful; aldehyde **7** was simply too sensitive to the basic conditions required and no evidence was found for the formation of the desired enone **8** (***Scheme 3***). A variety of modified reaction procedures were examined but it should be appreciated that the aldol reaction shown in ***Scheme 1*** is also highly sensitive to the conditions employed. Fortunately we quickly identified a solution to this difficulty. In concurrent studies we had examined the generation and reactivity of enolate derivatives derived by metal-mediated reductive cleavage of the α-bromoketone **9**.[8] Zinc enolates derived from glycos-2-ulosyl bromides have recently been described by Lichtenthaler and co-workers[9] and we have extended these elegant studies to include cerium enolates[10] derived from α-bromoketone **9**. Exposure of a mixture of aldehyde **7** and α-bromoketone **9** to $CeCl_3$/NaI in THF (conditions reported by Fukuzawa[10] for simple α-bromoketones) gave a 40 % yield of the aldol adduct **10** (as a mixture of two diastereoisomers) which underwent dehydration to give the target enone **8**.

Scheme 3



Our immediate objective is to complete the efficient construction of the ether bridged analogue **11**. This molecule will be used to probe the biological function and certain of the structural features of the herbicidins. Completion of the total synthesis of this class of natural products will require further modifications to our synthetic strategy - the adenine unit will not readily tolerate radical-mediated bromination - and these studies, which are aimed at more highly functionalised variants of ketone **3**, are underway.



11

Acknowledgements. We thank the EPSRC, Glaxo Research and Development and the University of Bristol for providing financial support, the Royal Society and the Indian National Science Academy Exchange Scheme for a travel award and Drs. M.V.J. Ramsay and S. Lister (Glaxo Research and Development) for their continued interest and support of this programme.

References.

1. *E-mail address:* t.gallagher@bristol.ac.uk
2. Isolation: M. Arai, T. Haneishi, N. Kitahara, R. Enokita, K. Kawakubo and Y. Kondo, *J. Antibiotics*, **1976**, *29*, 863; T. Haneishi, A. Terahara, H. Kayamori, J. Yabe and M. Arai, *J. Antibiotics*, **1976**, *29*, 870; Y. Takiguchi, H. Yoshikawa, A. Terahara, A. Torikata and M. Terao, *J. Antibiotics*, **1979**, *32*, 862.
3. Structural studies: A. Terahara, T. Haneishi, M. Arai, T. Hata, H. Kuwano and C. Tamura, *J. Antibiotics*, **1982**, *35*, 1711.
4. For other synthetic studies in this area, see: (a) F. Emery and P. Vogel, *Tetrahedron Lett.*, **1993**, *34*, 4209; (b) J.R. Bearder, M.L. Dewis and D.A. Whiting, *Synlett*, **1993**, 805.
5. N.J. Newcombe, D. Alker, M.F. Mahon, K.C. Molloy and T. Gallagher, *J. Am. Chem. Soc.*, **1993**, *115*, 6430; P.J. Cox, A.M. Griffin, N.J. Newcombe, S. Lister, M.V.J. Ramsay, D. Alker and T. Gallagher, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1443.
6. A.M. Griffin, N.J. Newcombe, D. Alker, M.V.J. Ramsay and T. Gallagher, *Heterocycles*, **1993**, *35*, 1247.
7. A.F. Cook and D.T. Maichuk, *J. Org. Chem.*, **1970**, *35*, 1940.
8. H.M. Binch, A.M. Griffin, S. Schwidetzky, M.V.J. Ramsay, T. Gallagher and F.W. Lichtenthaler, *submitted for publication.*
9. F.W. Lichtenthaler, S. Schwidetsky and K. Nakamura, *Tetrahedron Lett.*, **1990**, *31*, 71. A range of glycos-2-ulosyl bromides are available: E. Kaji and F.W. Lichtenthaler, *Trends Glycosci. Glycotechnol.*, **1993**, *5*, 121; F.W. Lichtenthaler and T. Schneider-Adams, *J. Org. Chem.*, **1994**, *59*, 6728.
10. S. Fukuzawa, T. Fujinami and S. Sakai, *J. Chem. Soc., Chem. Commun.*, **1985**, 777; S. Fukuzawa, T. Tsuruta, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1473.