Carbohydrate-Based Enolates as Heterocyclic Building Blocks. Synthesis of the Herbicidin Glycoside

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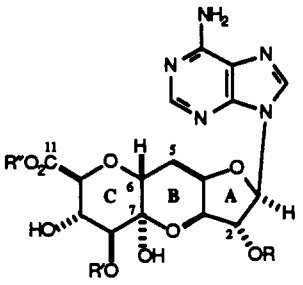
Between 1976 and 1979, the isolation and characterization of a series of undecose (C_{11}) nucleoside antibiotics from *Streptomyces saganonensis*, named collectively as the herbicidins, was described.[1-3] The glycosyl component of the herbicidins is based



1a: Herbicidin B (R=R″=Me, R′=H)
1b: Herbicidin G (R=H, R′=(E)-CO(Me)C=CHMe, R″=Me)
2: Aureonuclemycin (R=R′=R″=H)

on the unusual furo–pyrano–pyran skeleton, and while all members of this class incorporate an adenine unit, glycosyl substitution patterns do vary (as illustrated by herbicidin B (**1a**) and herbicidin G (**1b**)). Recently a closely related structure, aureonuclemycin (**2**), was reported, also from a *Streptomyces* culture.[4] The herbicidins exhibit herbicidal and antialgal activity, and herbicidins A and B (**1a**), as well as aureonuclemycin (**2**), are efficient inhibitors of *Xanthomanas oryzae*, a bacterium that causes leaf blight infection in rice crops.[1,4,5]

The herbicidins encompass a number of other interesting structural features. The C-ring substituents all occupy an axial orientation, and the B/C ring junction is held as an internal hemiacetal (at C-7) with a *C*-glycosyl linkage between C-5 and C-6. Assembling this class of natural products represents a significant challenge within carbohydrate chemistry, and we now describe in this report the first synthesis of the C_{11}-glycosyl core of the herbicidins.[6] The strategy that has been employed relies on the use of a carbohydrate-based ketone as a preformed heterocyclic unit displaying both the nucleophilic character (as an enolate) required for constructing the C-5/C-6 bond and the carbonyl functionality necessary to establish the hemiacetal at C-7. The relationship between these two features was central to our planning, but the successful implementation of this strategy relied on regiospecific generation of the requisite heterocyclic-based enolate. Such processes are, however, subject to quite rigid stereoelectronic considerations,[7] and enolization of both simple and more complex tetrahydropyran-3-ones takes place preferentially *away* from the ring-constrained heteroatom.[8,9] While solutions to this regiochemical problem have been examined,[10] our approach to the synthesis of the herbicidin glycoside (Scheme I) has focused on the use of a bicyclic constraint to enforce enolization in the sense required.

The 1,5:3,6-dianhydrohexulose derivative **3**, available in two steps (60% overall yield)[11] from 1,5:3,6-dianhydro-D-mannitol,[12] fulfils these requirements, and while there are a number of options available in terms of the oxidation level within the bridge (which corresponds to C-11 of the herbicidins), ether **3** is both the most accessible and synthetically useful variant currently available. Base-induced condensation of **3** with the D-glucose-derived aldehyde **4**[13] took place rapidly to give enone **5** in 60% yield as a single isomer (alkene geometry unknown). The stereochemistry at C-6 of the C-5/C-6 *C*-glycosyl bond was then set by face-selective hydrogenation of the enone and concurrent *O*-debenzylation occurred to provide directly hemiacetal **6** in 60% yield.[14] The structure of this key intermediate, which incorporates the furo–pyrano–pyran core of the herbicidins, was confirmed by an X-ray crystallographic analysis.

The diol function of **6** was then protected[15] to provide the corresponding cyclic carbonate **7** prior to oxidation and cleavage of the ether bridge. This oxidation step proved to be problematic, and a series of otherwise well-established and selective methods[16-20] for discriminating between -CH_2-O and >CH-O failed to achieve

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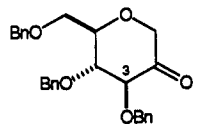

I

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(14) The origin of the selectivity observed in the reduction of enone **5** is less obvious, but small amounts (<10%) of the C-6 epimer of **6** have been isolated. The precise timing of enone reduction *vs* debenzylation is not clear but there are a series of alterative pathways feasible for the overall conversion of **5** to **6**.

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(16) For the oxidation of ethers using metal-based oxidants, as well as hydride acceptors, see: Godfrey, C. R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 235–250. RuO_4,[17] H^+/CrO_3,[18] and $BnNEt_3MnO_4$[19] failed to react with **7** and reaction with Mn_2O_7[20] (CCl_4, Me_2CO, –20 °C) resulted in hydroxylation at C-4 (stereochemistry unknown).

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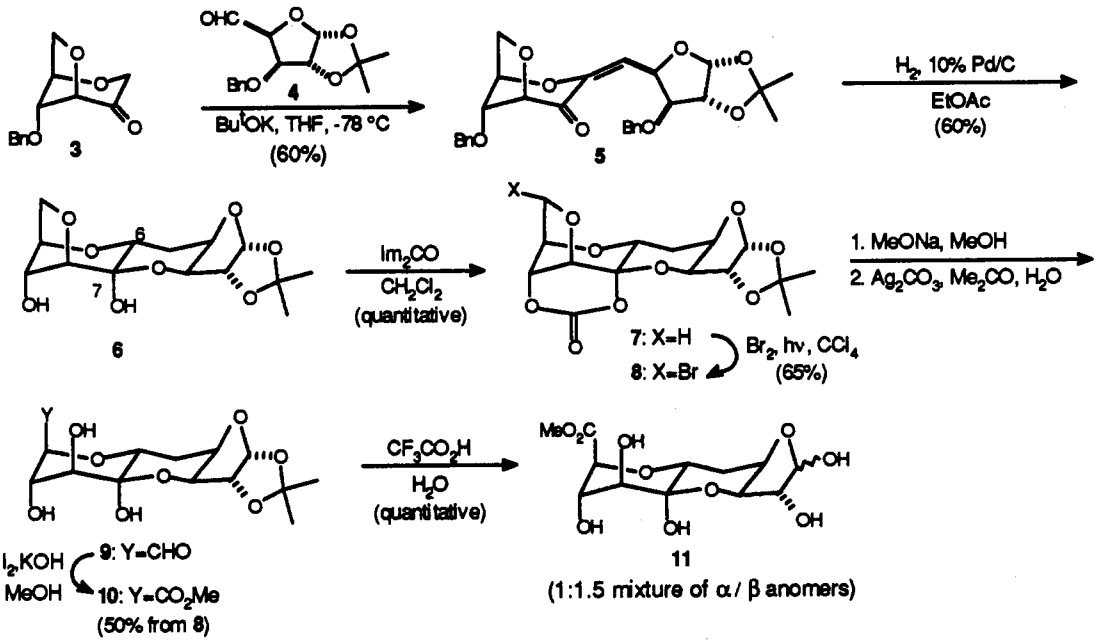
Scheme I



reaction at C-11 of **7**. However, free radical bromination[21] was both efficient and regioselective, providing the α-bromoether **8** in 65% yield. Methoxide-induced cleavage of the carbonate moiety followed by Ag(I)-mediated hydrolysis of the resulting α-bromoether gave aldehyde **9** which was used without further purification.[22] Selective oxidation[24] of the aldehyde function of **9** gave methyl ester **10** in 50% overall yield from α-bromoether **8**, and the structure of this intermediate was also established by an X-ray crystallographic analysis. Acetonide hydrolysis, under acidic conditions, completed the synthesis of the herbicidin glycoside **11**, which was obtained as a 1:1.5 mixture of α and β anomers at C-1.

The structural assignments of acetonide **10** and the deprotected glycoside **11**[25] are also consistent with ^{1}H NMR data reported for herbicidin B (**1a**)[1,2] and aureonuclemycin (**2**),[4] but the structure of acetonide **10** illustrates several interesting features. The distortion of the C-ring, due to the presence of adjacent axial substituents, is evident[26] and further details are available (see supplementary material).

In summary, we have described a direct and efficient synthesis of the undecose skeleton of the herbicidins using a carbohydrate-based ketone enolate as a preformed heterocyclic building block. Other structurally-related carbohydrate units are also now available and the more general application of this methodology to the construction of a wider range of *C*-glycosides is underway.

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Supplementary Material Available: Spectral and physical data for **5–11** and tables of crystallographic data together with ORTEP diagrams for **6** and **10** (25 pages). Ordering information is given on any current masthead page.

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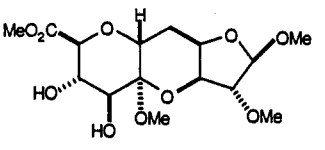

ii

(26) The distance between C-11 and the hydroxyl oxygen atom at C-8 is 2.78 Å; this compares to 1.45 Å for the equivalent distance in ether **6**. The distortion observed in **10** reflects the conformational relaxation required in the C-ring to accommodate four axial substituents and explains the thermodynamic preference for a hydroxy aldehyde rather than a hemiacetal in **9** as well as the extreme susceptibility of lactones related to **3** toward nucleophilic cleavage.