Studies directed towards the synthesis of herbicidins. Model study based on late stage N-glycosylation

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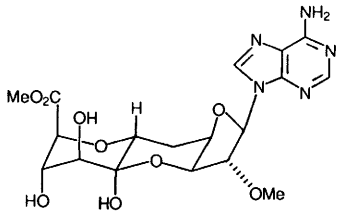
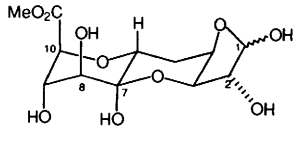
PERKIN 1 COMMUNICATION

The synthesis of nucleoside 6, *via* a regio- and stereoselective N-glycosylation of the undecose glycoside 4, is described. Nucleoside 6 is the first synthetic analogue of the herbicidin class of antibiotics to be reported and this model study also offers an insight into the scope and limitations associated with more general synthetic strategies based on a 'late stage' N-glycosylation.

The challenges associated with assembling complex nucleoside antibiotics continue to stimulate widespread interest.[1] The herbicidins,[2] exemplified by herbicidin B **1**, incorporate an unusual undecose moiety and, to date, all synthetic efforts reported have focused exclusively on constructing the tricyclic glycosyl core. Whiting[3] and Vogel[4] have both described studies aimed towards this particular goal and a synthesis of the fully elaborated undecose **2** has been achieved in our laboratory.[5]



1 Herbicidin B



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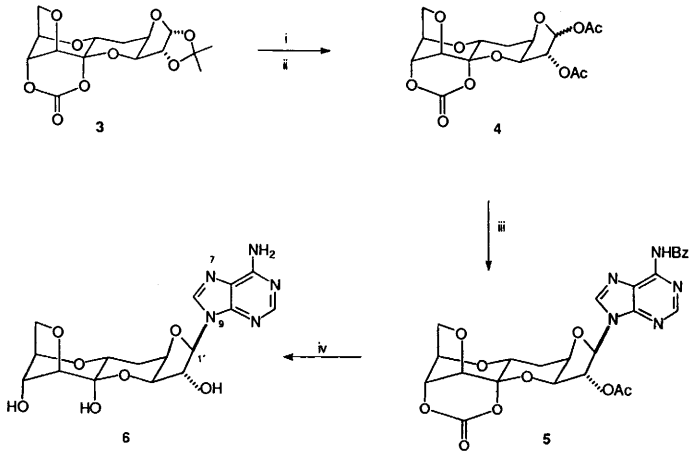
Extending these studies to encompass the synthesis of a complete herbicidin target incorporating the nucleoside moiety is our longer term goal. However, there are a series of important questions relating to N-glycosylation in this area that have yet to be addressed. This key step may be carried out at either an 'early' or 'late' stage in a total synthesis, that is, prior or subsequent to construction of the undecose glycoside. Our initial approach to the synthesis of the herbicidins involved establishing the nucleoside linkage at an early point in the synthetic sequence, but difficulties were encountered in this chemistry that have ultimately proven to be insurmountable.[6]

Late stage N-glycosylation, that is once the glycosyl core has been assembled, is an attractive alternative but this strategy also raises important issues. Firstly, glycoside **2** has two 'anomeric' sites (at C-1 and C-7) capable of activation under the conditions required for N-glycosylation.* Secondly, while the presence of a participating group at C-2 (*e.g.* OCOR) of **2** was predicted to control the stereochemistry of the newly-formed nucleoside linkage, we require that N-glycosylation at C-1 occurs on the concave and relatively hindered β-face of the undecose skeleton. This site is in close proximity to axial substituents at C-8 and C-10 and the steric demands imposed by these groups on N-glycosylation as well as nucleoside stability were unknown.

These issues have now been examined and in this paper we describe the synthesis of nucleoside **6** as shown in Scheme 1. Nucleoside **6** serves as a model for future synthetic studies in that this molecule incorporates the complete undecose framework and, more importantly, mimics closely the stereochemical features and demands associated with the naturally-occurring system.



Scheme 1 *Reagents and conditions:* i, CF_3CO_2H, H_2O, RT; ii, Ac_2O, py, CH_2Cl_2, RT (84% from **3**); iii, N^6-benzoyladenine, $SnCl_4$ (2.2 equiv.), $(Me_3Si)_2NH$, Me_3SiCl, MeCN, 80 °C, 55%; iv, MeONa, MeOH, 20 °C, 20%

Acetonide **3**, an intermediate in our earlier synthesis[5] of undecose **2**, was converted into the diacetate **4** in 2 steps (84% from **3**) as a 2:1 mixture of α- and β-anomers at C-1. N-Glycosylation of **4** was examined under various conditions and was finally achieved using a modification to Vorbrüggen's 'one-pot' procedure[7] leading to the protected nucleoside **5** (55%). This step required use of $SnCl_4$ (2.2 equivalents) in preference to $C_4F_9SO_3K$ as the Lewis acid component and no isomeric nucleoside products involving reaction at C-7 were detected. Deprotection of **5** to give the target nucleoside model **6** was carried out using NaOMe–MeOH, but the low yield (20%) obtained reflects a number of competing side reactions. These included facile cleavage of the nucleoside linkage, the sensitivity of which in these basic reaction conditions is particularly noteworthy.[8],† The structure of nucleoside **6** was established by direct correlation with spectroscopic data available from

* The 'glycosyl' function at C-7 of **4** (and related systems do display acetal reactivity at C-7[2]) may undergo activation under Lewis acid conditions and, though sterically hindered, the reactivity of this site had to be defined.

† Use of NH_3–MeOH gave **6** in 15% yield. The C-7′ hemiacetal moiety is not inert with respect to ring-opening to liberate the corresponding C-3-OH and C-7-ketone units[5b] and we cannot exclude such a process in any side reactions observed.

intermediates in the synthesis of undecose **2**. These correlations, based on crystallographic data, confirmed that the integrity of the undecose moiety has been maintained and the β-stereochemistry at C-1′ of **6** was verified by ^{1}H NMR ($^3J_{1',2'}$ 0.7 Hz). Finally, the course of the N-glycosylation step (alkylation at N-9 rather than at N-7) was deduced by a combination of ^{13}C NMR [9] and UV spectroscopy.[10]

In summary, the synthesis of nucleoside **6**, the first example of a nucleoside that bears a close structural relationship to the herbicidins, has been achieved in a regio- and stereo-selective fashion. This study establishes the viability of a 'late stage' N-glycosylation strategy and we now intend to apply the methodology developed to fully functionalised variants of undecose **2**.‡ In addition, nucleoside **6** also represents the first example of a synthetic analogue of the herbicidins and may provide an insight into the as yet unknown biological mode of action of this class of natural products.

Experimental

N-Glycosylation of 4

A solution of diacetate **4**[5] (95 mg, 0.25 mmol) and N^6-benzoyladenine (67 mg, 0.28 mmol) in freshly distilled acetonitrile (2 cm^3) was treated consecutively with $SnCl_4$ (63 mm^3,§ 0.54 mmol), HMDS (1,1,1,3,3,3-hexamethyldisilazane; 42 mm^3, 0.20 mmol) and TMSCl (trimethylsilyl chloride; 25 mm^3, 0.20 mmol). The reaction mixture was heated at reflux under nitrogen for 15 min and then stirred and allowed to cool to room temp. over 35 min. After this time, the mixture was diluted with CH_2Cl_2 (30 cm^3) and saturated aq. sodium hydrogen carbonate (20 cm^3) was added. A fine precipitate formed, the mixture was filtered through Florisil and the solids were carefully washed with CH_2Cl_2 (10 cm^3). The phases of the filtrate were then separated and the aqueous phase was extracted with CH_2Cl_2 (10 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (eluting with EtOAc) to give nucleoside **5** (76 mg, 55%) as a colourless solid; mp 184 °C (EtOAc–light petroleum), $[\alpha]_D^{23}$ +54 (*c* 0.5 in $CHCl_3$) (Found: C, 54.9; H, 4.0; N, 12.1. $C_{26}H_{23}N_5O_{10}$ requires C, 55.22; H, 4.1; N, 12.4%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3405 and 1776; δ_H(300 MHz, $CDCl_3$), 2.18 (3 H, s, CH_3), 2.30 (1 H, td, $J_{5a',5e'}$ and $J_{5a',6'}$ 12, $J_{5a',4'}$ 2,¶ 5a′-H), 2.40 (1 H, m, 5e′-H), 4.15 (1 H, dd, $J_{11',11'}$ 12, $J_{11',10'}$ 3, 11′-H), 4.25 (1 H, d, $J_{11',11'}$ 12, 11′-H), 4.25 (1 H, d, $J_{8',9'}$ 6, 8′-H), 4.45 (1 H, dd, $J_{6',5a'}$ 12, $J_{6',5e'}$ 5, 6′-H), 4.55 (1 H, t, $J_{10',9'}$ and $J_{10',11'}$ 3, 10′-H), 4.61 (1 H, q, $J_{4',3'}$ and $J_{4',5'}$ 2, 4′-H), 4.72 (1 H, d, $J_{3',4'}$ 2, 3′-H), 4.94 (1 H, dd, $J_{9',8'}$ 6, $J_{9',10'}$ 3, 9′-H), 5.40 (1 H, br s, 2′-H), 6.43 (1 H, br s, 1′-H), 7.50–7.65 (3 H, m, ArH), 8.01–8.05 (2 H, m, ArH), 8.45 (1 H, s), 8.83 (1 H, s) and 9.12 (1 H, br s, NH); δ_C(75.45 MHz, $CDCl_3$) 20.6 (CH_3), 24.5 (CH_2), 67.5 (CH), 69.0 (CH_2), 75.3 (CH), 75.9 (CH), 76.3 (CH), 77.1 (CH), 77.2 (CH), 81.5 (CH), 86.7 (CH), 100.1 (C), 127.9 (CH), 128.9 (CH), 132.9 (CH), 133.5 (C), 141.5 (CH), 145.4 (C), 149.6 (C), 152.0 (C), 153.0 (CH), 164.7 (C) and 169.1 (C); *m/z* (CI) 566 [(M + H)$^+$, 41%] and 240 (100).

Deprotection of 5 and synthesis of nucleoside 6

The protected nucleoside **5** (34 mg, 0.06 mmol) in MeOH (1 cm^3) was treated with a solution of NaOMe [generated *in situ* from sodium (2 mg, 0.08 mmol)] in MeOH (1 cm^3) at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 1 h and allowed to warm to 10 °C after which it was neutralised with hydrochloric acid (2 mol dm^{-3}) and concentrated under reduced pressure. The residue was taken up in water (10 cm^3) and washed with CH_2Cl_2 (5 cm^3) and the organic extracts were extracted with a further portion of water (5 cm^3). The combined aqueous extracts were lypholised to give a pale yellow foam, which was purified by HPLC (Spherisorb ODS2; 15% MeCN, 85% H_2O) to give the deprotected nucleoside **6** (5 mg, 20%) as an amorphous solid, mp 148–150 °C (decomp.); $[\alpha]_D^{26}$ +17 (*c* 0.3 in MeOH) [Found: (M + H)$^+$, 394.1370. $C_{16}H_{20}N_5O_7$ requires *M*, 394.1363]; $\lambda_{max}(H_2O)$/nm 260 (ε 9900); δ_H(400 MHz, CD_3OD) 2.06 (1 H, bd, $J_{5e',5a'}$ 12.5, 5e′-H), 2.34 (1 H, td, $J_{5a',5e'}$ and $J_{5a',6'}$ 12.5, $J_{5a',4'}$ 3, 5a′-H), 3.91 (1 H, d, $J_{8',9'}$ 5.9, 8′-H), 4.04 (1 H, dd, $J_{11',11'}$ 11.0, $J_{11',10'}$ 2.7, 11′-H), 4.11 (1 H, d, $J_{11',11}$ 11.0, 11′-H), 4.19 (1 H, t, $J_{10',9'}$ and $J_{10',11'}$ 2.7, 10′-H), 4.26–4.33 (3 H, m, 3′-H, 6′-H, 9′-H), 4.39 (1 H, s, 2′-H), 4.57 (1 H, q, $J_{4',3'}$ and $J_{4',5'}$ 3.0, 4′-H), 6.17 (1 H, d, $J_{1',2'}$ 0.7, 1′-H), 8.22 (1 H, s) and 8.67 (1 H, s); δ_C(75.45 MHz, CD_3OD) 26.3 (CH_2), 69.8 (CH_2), 69.9 (CH), 74.1 (CH), 75.7 (CH), 77.9 (CH), 78.1 (CH), 80.3 (CH), 82.5 (CH), 90.9 (CH), 95.8 (C), 119.3 (C), 142.1 (CH), 150.8 (C), 154.1 (CH) and 157.3 (C); *m/z* (CI) 394 [(M + H)$^+$, 24%] and 136 (100).

Acknowledgements

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‡ All attempts to functionalise at C-11′ of **5** *via* selective radical-mediated bromination (as used in the synthesis of undecose **2**[5]) have been unsuccessful.

§ 1 mm^3 ≡ 1 μl.

¶ *J* values in Hz.

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