Natural Product Synthesis

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Stereoselective Total Syntheses of Herbicidin C and Aureonuclemycin through Late-Stage Glycosylation

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Nucleosides and their phosphates are involved in innumerable biochemical pathways, serving, for example, as building blocks for nucleic acids or as enzymatic cofactors. As such, it is not surprising that secondary metabolites have evolved that interfere with their elementary role in life. Many of these are nucleosides themselves that retain the canonical nucleobases, but feature more sophisticated carbohydrate residues than ribose. An important subclass are the so-called undecose nucleoside antibiotics, which include the herbicidins,[1] represented by herbicidin A (**1**), B (**2**), C (**3**), and aureonuclemycin (**4**),[2] as well as the tunicamycins (**5**)[3] and hikizimycin (**6**)[4] (Figure 1). All of these natural products contain a linear chain of 11 carbon atoms that can be incorporated in a variety of heterocyclic ring systems.

The herbicidins were isolated from different strains of *Streptomyces* and exhibit several interesting biological activities.[1a–d,g,2,5] For example, herbicidins A (**1**) and B (**2**) are efficient inhibitors of *Xanthomas oryzae*, a bacterium that causes leaf blight infection in rice crops. Furthermore, reduced seed germination and diminished algal growth, as well as selective toxicity towards dicotyledonous plants, but no toxicity against animals, was observed.[1a,b]

Structurally, the herbicidins also show a number of intriguing characteristics. Their common undecose sugar moiety comprises a linear carbon chain that is folded into a tricyclic furano-pyrano-pyran skeleton, which includes nine stereogenic centers. Adenine, as the nucleobase, resides in a sterically congested concave position. In addition, the hemiketal at C-7 fuses the pyrano-pyran system in such a way that all of its substituents adopt axial orientations. Their individual members differ from each other through various methylation and esterification patterns.

As a consequence of their structural beauty and potent biological activities, the undecose nucleoside antibiotics have attracted much attention from the synthetic community.[6] However, despite considerable efforts, only one total synthesis of a herbicidin, namely herbicidin B (**2**) has been reported to date.[6l] The synthesis started with adenosine, with the purine base carried through the whole pathway. All other published approaches to the herbicidins opted for introduction of the nucleobase at a late stage, but have not yet reached their intended target.[6a–k,m] We now report a total synthesis of herbicidin C (**3**) and its hydrolysis product aureonuclemycin (**4**) which is based on a late-stage glycosylation strategy and marked by a high degree of stereoselectivity.

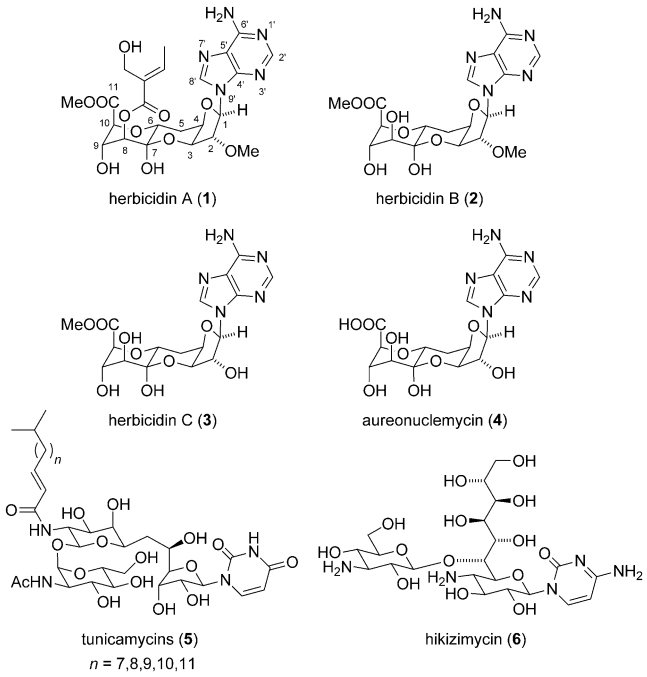

Figure 1. Congeners of undecose nucleoside antibiotics.

Our retrosynthetic analysis of herbicidin C (**3**) is shown in Scheme 1. We reasoned that the challenging late-stage glycosylation could be stereochemically controlled by a neighboring benzoate at C-2, thereby yielding hemiacetal **7** as a logical precursor. This intermediate, in turn, could be traced back to C-glycoside **8**, wherein C-7 and C-11 already possess the correct oxidation state. Further retrosynthetic simplification of the side chain would give ester **9**, which could be ultimately derived from glucose (**10**).

In the forward direction, glucose (**10**) was converted into the protected anhydro sugar **11**, by combining a practical, large-scale synthesis for 1,6-anhydrohexopyranoses with a standard benzylation protocol (Scheme 2).[7] Reaction of compound **11** with allyltrimethylsilane in the presence of a Lewis acid gave the known C-glycoside **12**.[7b,8] This compound could be selectively debenzylated through a two-step protocol involving formation of the iodo ether (→**13**)

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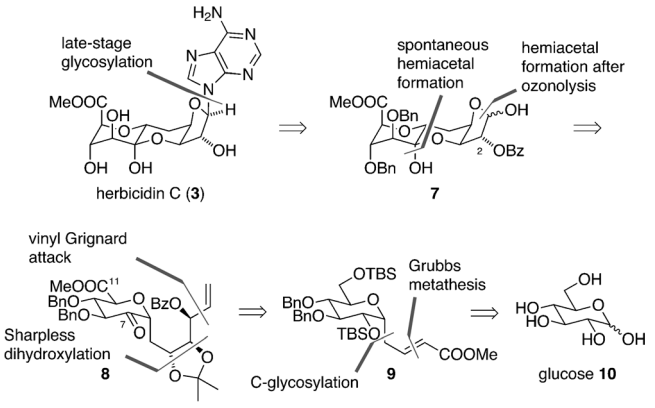
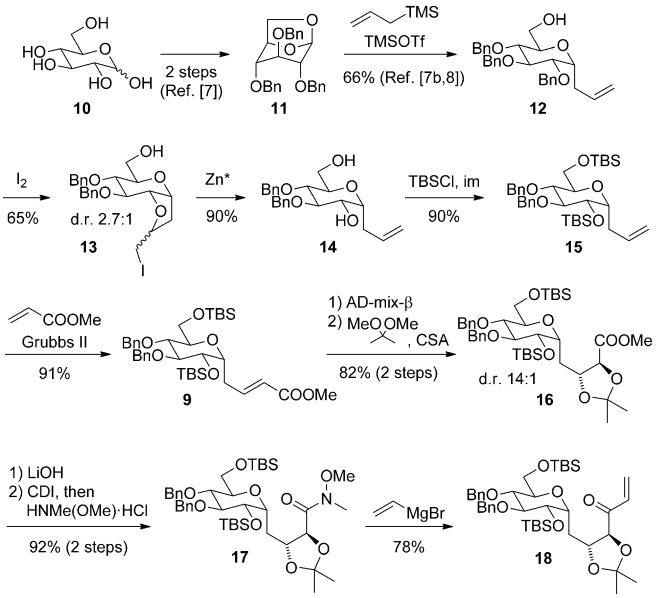


Scheme 1. Retrosynthetic analysis for herbicidin C (**3**). Bz = benzoyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

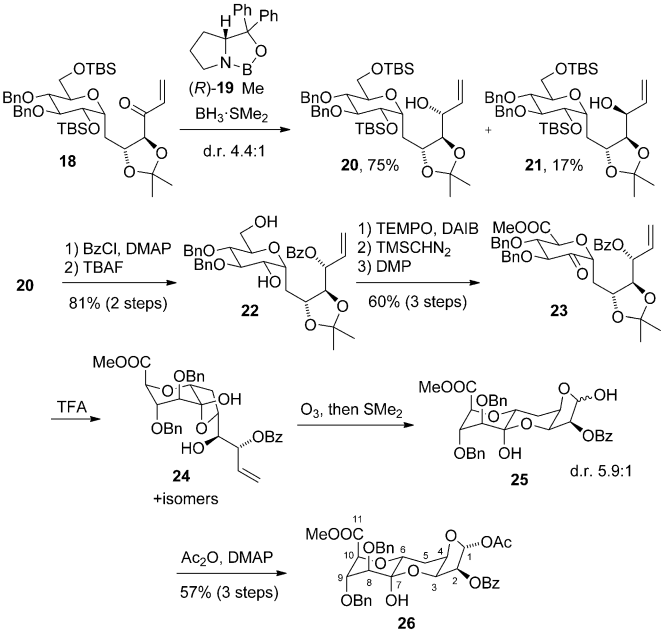


Scheme 2. Synthesis of vinyl ketone **18**. TMS = trimethylsilyl, im = imidazole, CSA = camphorsulfonic acid, CDI = *N*,*N*′-carbonyldiimide, Tf = trifluoromethanesulfonyl.

and subsequent reductive elimination to yield diol **14**.[9] Subsequent protection then yielded the twofold silyl ether **15**. Notably, this opening sequence not only installs the C-6 stereocenter (herbicidin numbering) with the correct absolute configuration but also differentiates the two desired positions toward eventual adjustment of the oxidation states.

Next, the allyl side chain of intermediate **15** was elongated through a Grubbs cross-metathesis with methyl acrylate, which gave the unsaturated ester **9** in excellent yield.[10] A highly diastereoselective Sharpless dihydroxylation and subsequent acetonide formation installed two additional stereocenters to yield methyl ester **16**. Saponification and formation of the corresponding Weinreb amide **17**, followed by reaction with vinylmagnesium bromide then provided vinyl ketone **18**, wherein the double bond is intended to later serve as a carbonyl equivalent.

Installation of the next stereocenter (C-2 in herbicidin) proved to be more challenging than anticipated. Reduction of the carbonyl group in **18** with stoichiometric amounts of the *R*-configured Corey–Bakshi–Shibata (CBS) reagent (*R*)-**19** gave a 4.4:1 mixture of separable diastereomers **20** and **21** (Scheme 3). Unfortunately, we eventually established that the undesired diastereomer **20** was formed as the major product



Scheme 3. Synthesis of an undesired diastereomer **20** and establishment of the tricyclic core **26**. TBAF = tetrabutylammonium fluoride, TEMPO = 2,2,6,6-tetramethylpiperidine 1-oxyl, DAIB = (diacetoxyiodo)-benzene, DMP = Dess–Martin periodinane, TFA = trifluoroacetic acid, DMAP = dimethylaminopyridine; Tf = trifluoromethanesulfonyl.

under these conditions (see below). This result was unexpected since the generally accepted transition-state model[11] with the (*R*)-CBS-Me reagent predicts the opposite configuration of alcohol **20**.

The structure of the major isomer **20** could only be established after further synthetic transformations, which also served as a training ground for our eventually successful synthesis. Benzoylation of alcohol **20** followed by removal of the silyl groups afforded diol **22**. This compound was subjected to a variety of oxidation conditions, most of which gave intractable mixtures with little or no desired product. Only oxidation with TEMPO and diacetoxyiodobenzene in the presence of water proved efficient. Notably, under these conditions, only the primary hydroxy group was oxidized to the corresponding carboxylic acid, whilst the secondary alcohol remained untouched. Ester formation with (trimethylsilyl)diazomethane followed by oxidation of the secondary alcohol with Dess–Martin periodinane (DMP) then provided ketone **23**. Cleavage of the acetonide with trifluoroacetic acid provided a mixture of isomeric hemiacetals. The X-ray structure[12] of the major isomer, compound **24**, which confirmed the undesired configuration at C-2, is shown in

Figure 2. Following ozonolysis and acetylation of **24**, we isolated undecose **25**, which features the furano-pyrano-pyran framework of herbicidin C (**3**). Selective acetylation of the more-accessible hemiacetal then yielded undecose **26** as single diastereomer in 72% yield over three steps.

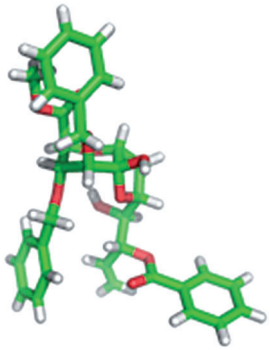
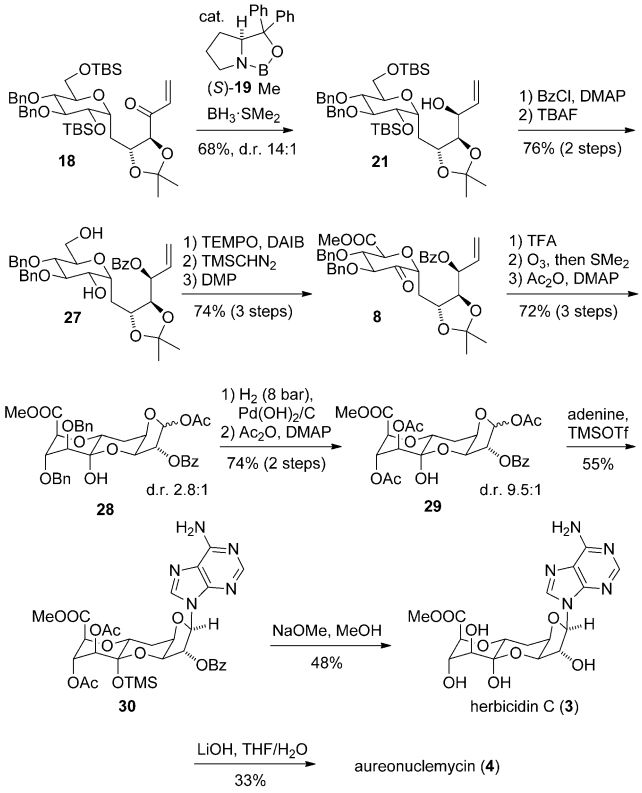


Figure 2. X-ray structure of hemiacetal **24**.

To correct the stereochemistry at C-2 we revisited the diastereoselective reduction of ketone **18** (Scheme 4). Simple reduction with $BH_3{\cdot}SMe_2$ gave a 1.4:1 mixture of diastereomers in favor of the desired diastereomer **21**. However, use of the *S*-configured CBS-Me enantiomer (*S*)-**19**, again in stoichiometric amounts, provided the desired alcohol **21** in d.r = 14:1. These results suggest a matched case of substrate **18** and the (*S*)-CBS-Me reagent. Notably, the amount of (*S*)-**19** could be reduced to catalytic quantities (10 mol%) whilst keeping the d.r. value at 14:1.



Scheme 4. Total syntheses of herbicidin C (**3**) and aureonuclemycin (**4**).

With our stereochemical problem surmounted, we could proceed with the total synthesis (Scheme 4). First, a benzoyl group was installed at C-2 to assist the late-stage glycosylation. Subsequent deprotection with TBAF yielded diol **27**, which was converted into ketoester **8** by using the previously established oxidation/esterification sequence. Reiteration of our cyclization conditions (TFA, O_3, Ac_2O) provided undecose **28** as a mixture of diastereomers in 72% yield over three steps. Since debenzylation was found to be impossible at the end of the synthesis, the two remaining benzyl protecting groups in **28** had to be swapped for acetyl groups at this stage, which yielded tricyclic intermediate **29**.

With compound **29** in hand, we proceeded to investigate the crucial late-stage glycosylation. Much to our satisfaction, this proved to be possible by using a modification of the Hilbert–Johnson–Vorbrüggen protocol.[13] Under these conditions, glycoside **30** was isolated in 55% yield as a single diastereomer. The correct stereo- and regiochemical outcome of the glycosylation was confirmed by NMR spectroscopy and ultimately proven by our successful total synthesis. This was achieved by global deprotection under Zemplén conditions, which gave herbicidin C (**3**) as a colorless solid. The identity of our synthetic material was confirmed by detailed spectroscopic studies, including NMR titration with an authentic sample of the natural product (see Supporting Information). Saponification of the base-labile herbicidin C (**3**) under mild conditions yielded aureonuclemycin (**4**), the third member of the herbicidin class accessible by total synthesis.

In summary, we have achieved the first total synthesis of two complex undecose nucleoside antibiotics, namely herbicidin C (**3**) and aureonuclemycin (**4**). Our route integrates a stereoselective C-glycosylation with several reagent-controlled stereoselective transformations and a surprisingly facile and highly diastereoselective late-stage N-glycosylation. Our synthetic strategy could give rise to several other members of the class. Investigations in this regard are well underway and will be reported in due course.

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[12] **24**: $C_{34}H_{36}O_{10}$, $M_r = 604.644\ g\,mol^{-1}$, colorless rod, $0.38 \times 0.14 \times 0.12\ mm^3$, tetragonal, *P*43, $a = 13.3203(3)$, $b = 13.3203(3)$, $c = 18.4658(3)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 3276.39(11)$ Å^3, $Z = 4$, $\rho = 1.22580(4)\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.090\ mm^{-1}$, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 173(2)$ K, 2θmax 50.64°, 20777 reflections, 5911 independent, 4680 with $I \geq 2\sigma(I)$, $R_{int} = 0.0395$, mean $\sigma(I)/I = 0.0338$, 360 parameters, $R(F_{obs}) = 0.0606$, $R_w(F^2) = 0.1727$, $S = 1.021$, min./max. residual electron density: $-0.205/0.309\ e\,Å^{-3}$; data collection by means of a Nonius KappaCCD diffractometer equipped with a rotating anode generator (ϕ and ω scans), structure solution by direct methods with SIR97, structure refinement with SHELXL-97, disorder of the phenyl rings and ethyl groups has been handled by split models; crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 859056 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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