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Stereo- and Regioselective Glycosylations to the Bis-*C*-arylglycoside of Kidamycin

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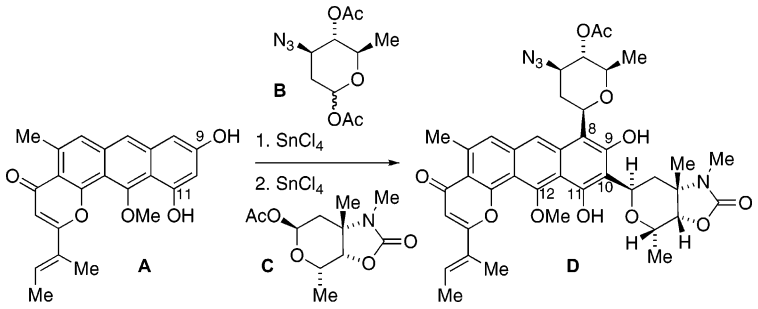
ABSTRACT



In explorations toward the total synthesis of the antitumor anthrapyran natural product kidamycin, the regioselective introduction of aminosugars angolosamine and vancosamine as *C*-arylglycosides has been accomplished onto hydroxylated anthrapyran aglycones. Specifically, the 9,11-dihydroxylated anthrapyran A undergoes sequential glycosylations with angolosamine synthon B and vancosamine synthon C to regio- and stereoselectively afford bis-*C*-glycoside D corresponding to the *C*-glycoside pattern of kidamycin.

The pluramycins are a relatively large family of antitumor antibiotic natural products containing the 4*H*-anthra[1,2-*b*]-pyran-4,7,12-trione substructure, with variations in the side chain and substitution patterns of carbohydrates on the anthrapyran core aglycone.[1] Kidamycin was isolated from *Streptomyces* soil bacteria in the early 1970s, as one of the earliest known members of the pluramycin antibiotics.[2] Kidamycin demonstrates a wide spectrum of antimicrobial activity against anaerobic bacteria, aerobic and facultative bacteria, and yeasts[3] and also has antitumor and cytotoxic properties against leukemia L-1210 as well as life-prolongation activity on mice bearing ascites tumors at single i.p. doses from just below the LD_{50} (18 mg/kg) to 1/16 of the LD_{50}.[4] The structure and conformation of kidamycin (**1**, Figure 1) was determined by NMR and X-ray crystallographic studies, exhibiting a novel *meta*-arrangement of

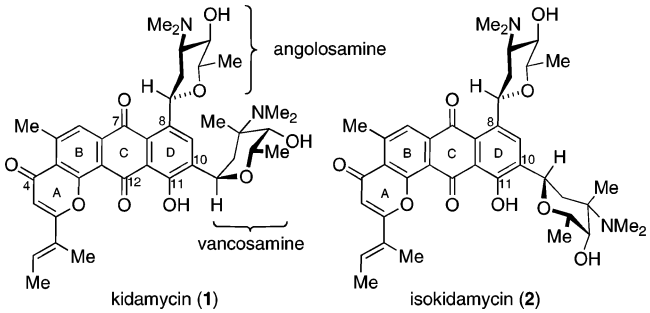


Figure 1. Structures of kidamycin and isokidamycin.

two different *C*-arylglycosidic aminosugars, with equatorially substituted angolosamine at C8 and axially substituted vancosamine at C10.[5] In the course of characterization studies, the acid sensitivity of the axial *C*-glycoside to anomerization was discovered to favor equatorially substituted vancosamine in isokidamycin (**2**), which is attributed to occur by protonation of the pyranose oxygen and elimination to a

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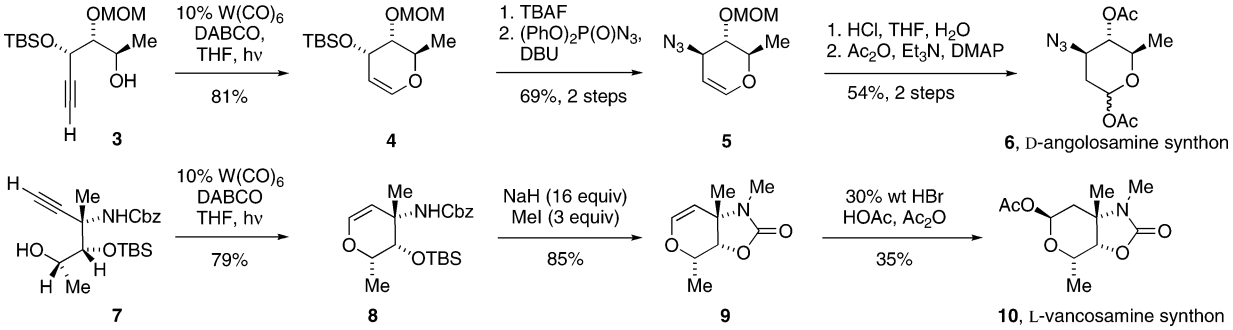
Scheme 1. Syntheses of Glycosyl Donors **6** and **10** via Alkynol Cycloisomerization



quinomethide intermediate, followed by reclosure of the pyran ring.[5a] Despite the interesting biological activity of kidamycin, this structurally complex compound has, to date, resisted total synthesis. Two syntheses of the kidamycin aglycone have been recorded,[6,7]as well as the development of several methods for the regioselective construction of *meta*-bis-*C*-arylglycosides.[8] In this report, we will disclose the first cases in which the angolosamine and vancosamine sugars have been stereo- and regioselectively introduced onto an aglycone bearing most of the features of the natural product kidamycin. Our synthetic strategy features late-stage sequential C-glycosylation at C8 of kidamycin aglycone or the related anthrapyran synthon with a suitably protected angolosamine synthon and at C10 with the vancosamine synthon.

Both carbohydrate components leading to angolosamine and vancosamine were prepared utilizing tungsten-catalyzed alkynol cycloisomerization to form pyranosyl glycal intermediates. For D-angolosamine synthon **6** (Scheme 1), cycloisomerization[9] of alkynyl alcohol **3** provided glycal **4**.[10] Removal of the silyl ether protective group allowed direct S_N2 substitution[11] to introduce an azide group with inversion of stereochemistry to produce **5**, with nonbasic nitrogen in the azide functional group.[12] Treatment of this glycal **5** with hot aqueous acid[13] effected one-pot hydrolysis of vinyl ether and cleavage of MOM ether to produce the diol, which was acylated to generate **6** as the angolosamine glycosyl donor. Likewise, the synthesis of L-vancosamine synthon **10** began with alkynol cycloisomerization of **7** to **8**.[10,14] N-Methylation of **8** was complicated by formation of bicyclic carbamate **9**,[15] which could be prevented by using exactly one equivalent of base. However, we recognized the advantages of the cyclic carbamate in avoiding carbonyl group participation of the acyclic Cbz group in glycosylations as well as the convex nature of compound **9** in stereoselective glycosylation and were able to optimize preparation of **9** by using excess base until complete conversion to the cyclic carbamate had occurred, followed by addition of iodomethane. Further derivatization of glycal **9** to glycosyl acetate **10**[16] broadened the choice of conditions for glycosylations.

In 2005, we reported the synthesis of kidamycin aglycone via the advanced intermediate **11**.[7] Friedel−Crafts-type glycosylation[17] of **11** with angolosamine synthon **5** stereo- and regioselectively provided C8-glycoside **13**, albeit with low conversion (Scheme 2). Similar results were observed with the C12-thioethyl analogue **12**.[19] The regioselectivity of these glycosylations was assigned by the disappearance of the C8 hydrogen resonance in comparing ^{1}H NMR spectra for compounds **11**−**14** and confirmed by the observation of a nuclear Overhauser effect between H7 and the anomeric hydrogen H1′ in compound **14**.[18] This glycosylation was not further optimized after we found that the *O*-methyl groups could not be removed from the aglycone nucleus in the presence of the fragile benzylic carbon−oxygen bond of the angolosamine carbohydrate, but we did demonstrate reduction of the azide of **13** to amine which was characterized as peracetylated **15**.

Introduction of vancosamine was also explored with several substrates, with C11 phenol **16** as a representative example (Scheme 2).[19,20] Initial results in $SnCl_4$-promoted glycosylation with vancosamine synthon **10** provided a mixture of C10-glycoside anomers **17** and **18**,[18] with the

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(10) See Supporting Information for details on the preparation of alkynyl alcohols **3** and **7**.

(11) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

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(18) See Supporting Information for more details on the positional and stereochemical assignments for C-glycosylation products.

(19) Compound **12** arose from an unsuccessful attempt to remove methyl ethers from **11** with $AlCl_3$/EtSH (ref 20).

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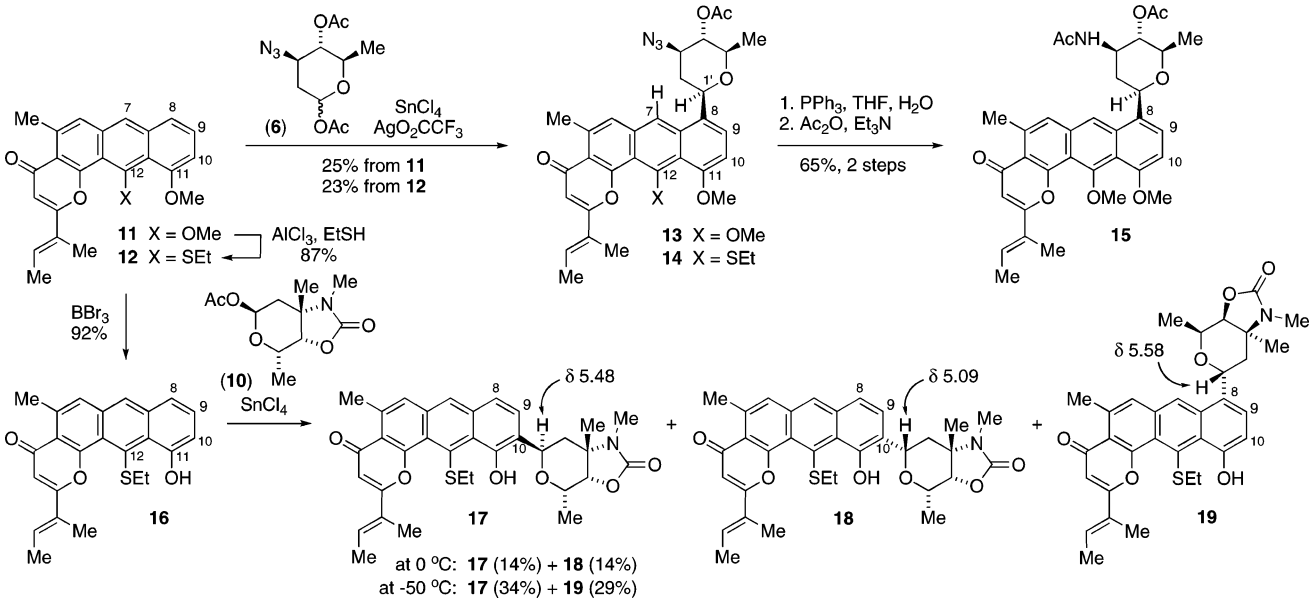
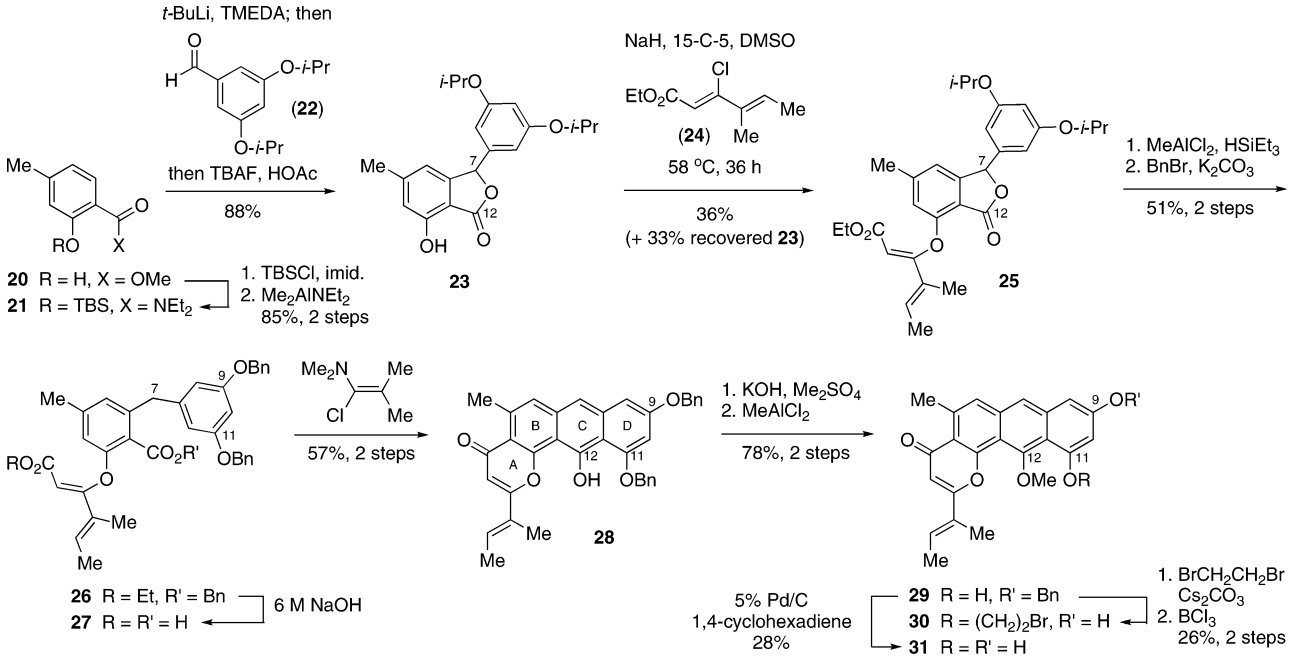
Scheme 2. Glycosylations of Anthrapyrans **11**, **12**, and **16**



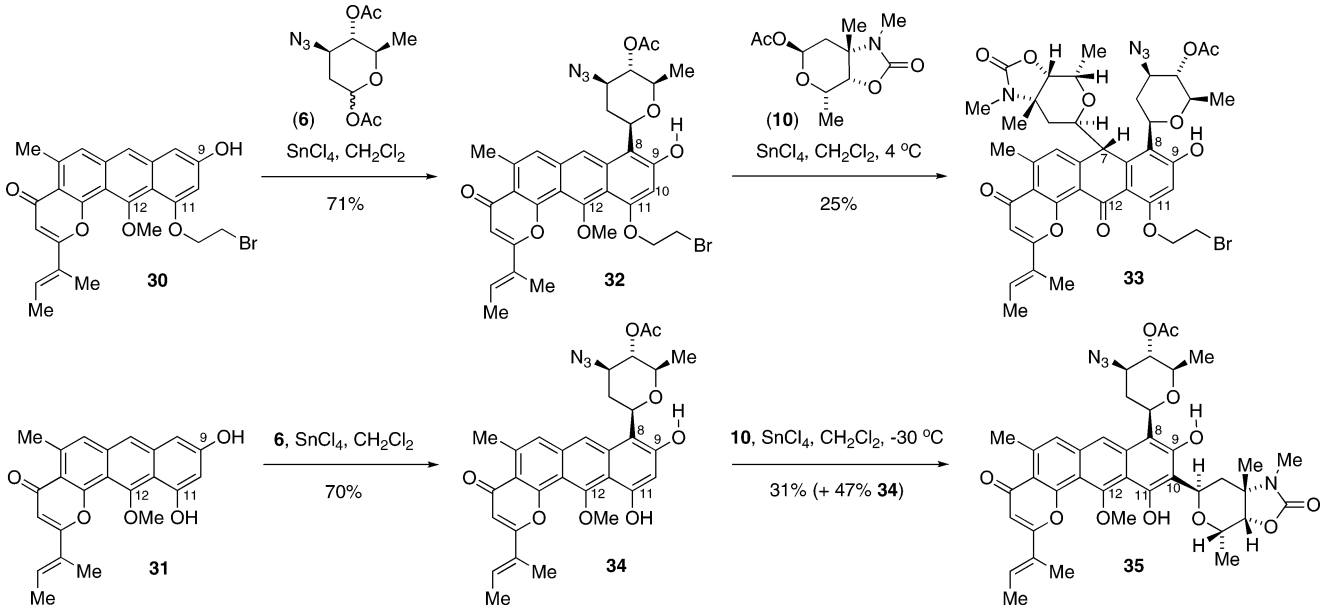
formation of equatorially substituted **18** attributed to Lewis acid catalyzed anomerization in a mechanism analogous to that proposed for the isomerization of kidamycin (**1**) to isokidamycin (**2**). The positional selectivity for this glycosylation at C10 was evident by the disappearance of the C10 hydrogen resonance in the formation of compounds **17** and **18**, and the anomeric stereochemistry was assigned in analogy with kidamycin (**1**) and isokidamycin (**2**), with the anomeric ^{1}H resonance of δ 5.48 for **17** consistent with a pseudoequatorial hydrogen, relative to the shielded pseudoaxial anomeric hydrogen of **18** at δ 5.09. Lowering the reaction temperature increased stereoselectivity as well as the isolated yield for production of **17**,[21] but under these conditions, we also observed formation of the *para*-C8-glycoside isomer **19**, characterized by the absence of the C8 hydrogen and the presence of the C10 hydrogen in comparison with compounds **16**−**18**.[18]

At this stage, we modified our aglycone synthesis to introduce an additional hydroxyl substituent at C9, which might be advantageous in more easily forming *C*-glycosides at C8 as well as C10. *Ortho*-lithiation[22] of amide **21** and addition to the aldehyde **22**, followed by desilylation,

Scheme 3. Synthesis of Anthrapyrans Bearing a 9-Hydroxyl Substituent



Scheme 4. Bisglycosylations of 9-Hydroxyl-Substituted Anthrapyrans **30** and **31**



provided the lactone **23**. The phenol of **23** underwent addition−elimination[23] with β-chlorodienoate (**24**)[7,24] to form compound **25**, although forcing conditions were required as phenolate reactivity was diminished due to conjugation with the ester carbonyl. Reductive opening of the doubly benzylic C7 lactone also resulted in removal of the isopropyl ethers, but global O-benzylation of both phenols and the carboxylic acid provided **26**, which was easily purified. After saponification of both esters to dicarboxylic acid **27**, double Friedel−Crafts cyclization[25] provided the anthrapyran **28**, which was converted into a variety of O-protected congeners **29**−**31** (Scheme 3).

Glycosylation was first conducted with the bromoethyl ether protected **30** bearing a single phenol at C9, which was anticipated to direct *ortho*-C-glycosylation[26] at both C8 and C10. Introduction of angolosamine synthon **6** proceeded in good yield and with apparent complete stereo- and regioselectivity for C8-glycosylation[17,18] in product **32** (Scheme 4). However, the attempted introduction of vancosamine via the C9-hydroxyl group instead provided the surprising result of C7-glycosylation to provide the anthrone **33**, which was characterized by observation of ^{1}H−^{1}H coupling between the C7 hydrogen and the anomeric hydrogen of the vancosamine unit,[18] as well as the white color of product **33**, consistent with interruption of conjugation in the C ring at C7. Thus, the aglycone substrate **31** without protective groups at either C9 or C11 phenols was subjected to glycosylation with angolosamine donor **6**, providing C8-glycoside **34** in good yield, which in turn underwent regio- and stereoselective glycosylation with vancosamine synthon **10** to provide the C10-glycoside **35**,[18] possessing a *meta*-bisglycosylated anthrapyran with considerable structural similarity to kidamycin (**1**).

Although we have not yet completed the synthesis of kidamycin, we have demonstrated a number of interesting and informative glycosylation transformations which have culminated in the successful preparation of the bis-*C*-arylglycoside **35** closely corresponding to most of the structural features of kidamycin. Continuing efforts will focus on completing the total synthesis either from the doubly glycosylated intermediate **35** or, less aggressively, by removing the C9 oxygen from intermediate **34** prior to the second glycosylation to introduce the *C*-vancosamine glycoside.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The *C*-vancosamine glycosylation product **17** undergoes partial anomerization to a mixture of **17** and **18** upon the prolonged reaction time or higher temperature required for complete conversion of starting materials.

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