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A De Novo Approach to the Synthesis of Glycosylated Methymycin Analogues with Structural and Stereochemical Diversity

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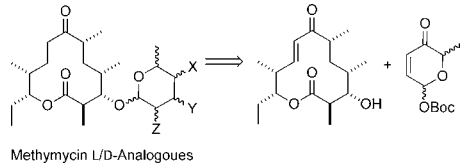
ABSTRACT



A divergent and highly stereoselective route to 11 glycosylated methymycin analogues has been developed. The key to the success of this method was the iterative use of the Pd-catalyzed glycosylation reaction and postglycosylation transformation. This unique application of Pd-catalyzed glycosylation demonstrates the breath of α/β- and D/L-glycosylation of macrolides that can be efficiently prepared using a de novo asymmetric approach to the carbohydrate portion.

Glycosylated macrolactones, known as macrolides, are an important class of polyketide antibiotics used to treat infections caused by Gram-positive bacteria.[1] *Streptomyces venezuelae* ATCC 15439 produces several 12-membered ring macrolides, including methymycin **I** and neomethymycin **II** derived from 10-deoxymethynolide **III** (Figure 1).[2] These macrolides consist of a lactone aglycon carrying a rare deoxyamino sugar, desosamine, which is important for their bioactivity. In fact, the biological activities of **I** and **II** are dramatically decreased when the sugar appendage is removed.

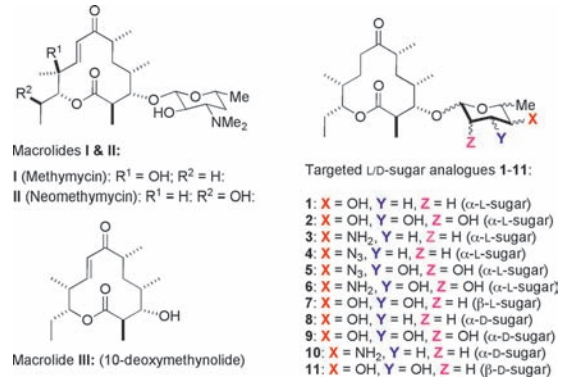


Figure 1. Macrolides (I−III) and targeted methymycin analogues **1**−**11**.

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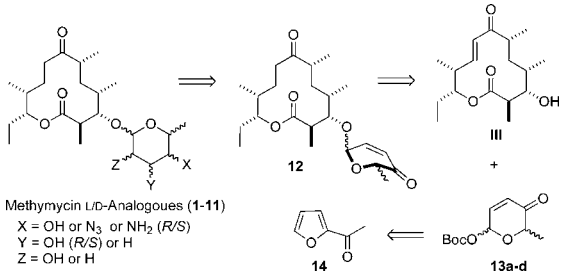
Since the deoxyamino sugar portion of macrolides is in general essential for their antimicrobial activities,[3] its modifications hold promise as a valuable approach toward preparing new macrolide antibiotics with improved and/or altered biological properties.[4] In this regard, several synthetic and biosynthetic approaches to novel glycosylated macrolides have been reported.[5] These approaches are limited in terms of the stereochemical diversity of structures that can be generated. In addition, the methods that use in vivo modified biosynthetic pathways and/or in vitro enzymatic reactions for the production of new glycosylated antibiotics[6] are limited by the availability and the lability of the sugar nucleotide glycosyl donors. Similarly, these routes often suffer from the reduced catalytic efficiency of the glycosyltransferases involved when dealing with unnatural substrates.

To address these concerns, we envisioned the development of a highly diastereoselective, yet stereodivergent, route that would allow for the mild installation of the sugar moieties onto complex antibiotic aglycons using simple achiral starting material. It is in this, as well as other, contexts that we developed a de novo asymmetric approach to carbohydrates, which we hoped would allow for the facile synthesis of various methymycin analogues for carbohydrate SAR-type studies (Figure 1). Herein, we report our successful efforts at the use of this approach for the synthesis of stereochemically (L/D- and α/β-) diverse glycosylated 8,9-dihydro-10-deoxymethymycin analogues.

Our basic retrosynthetic analysis for the preparation of the stereochemically diverse methymycin analogues is shown in Scheme 1. The plan was that various amino- and/or deoxy-

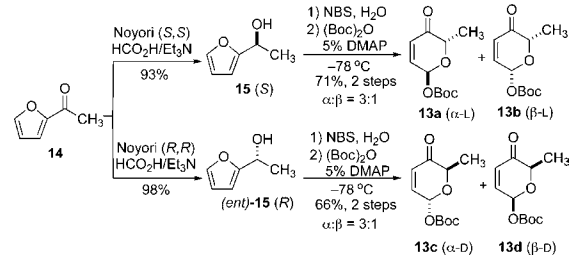
Scheme 1. Retrosynthetic Analysis of Methymycin Analogues



sugar glycosylated macrolide analogues could be prepared from macrolides like **12** with the desired pyranone stereochemistry. The macrolides **12**, in turn, could be prepared by a stereospecific Pd-catalyzed coupling of macrolactone **III** and **13a**−**d**.[7,8] The required pyranone stereoisomers **13a**−**d** can be stereoselectively prepared from the achiral acetyl furan **14** via our de novo asymmetric synthesis approach.[9]

Accordingly, our synthetic effort began with the isolation of 10-deoxymethynolide **III**[4d] and preparation of the required D/L- and α/β-Boc-pyranones **13a**−**d** for coupling.[8] As previously described, the Pd-glycosyl donors **13a**−**d** were synthesized from the achiral acetyl furan **14** by a very practical three-step sequence, employing an enantioselective Noyori reduction (**14** to **15**/*ent*-**15**), an Achmatowicz oxidation, and a stereodivergent *tert*-butyl carbonate formation (see Scheme 2).[10]

Scheme 2. Synthesis of D/L- and α/β-Boc-Pyranones **13a**−**d**



The double bond of 10-deoxymethynolide **III**[4d] was then selectively reduced by treatment with excess diimide (NBSH, Et_3N)[11] to give the desired 8,9-dihydro-10-deoxymethynolide (**16**) in 95% yield (Scheme 3). The resulting macrolactone **16** was subjected to the diastereoselective Pd-catalyzed glycosylation with α-L-Boc-pyranone **13a**, producing α-L-glycoside **12** as a single diastereomer in good yield (86%). A $NaBH_4$ reduction[12] of enone **12** gave the equatorial allylic alcohol **17** in 82% yield. Diimide reduction of **17** with an excess triethylamine and *O*-nitrophenylsulfonyl hydrazide led to the 2,3-dideoxy analogue **1** in excellent yield (90%). Preparation of the *rhamno*-sugar analogue **2** was accomplished by diastereoselective dihydroxylation of **17** under Upjohn conditions[13] (OsO_4/NMO) in 85% yield.

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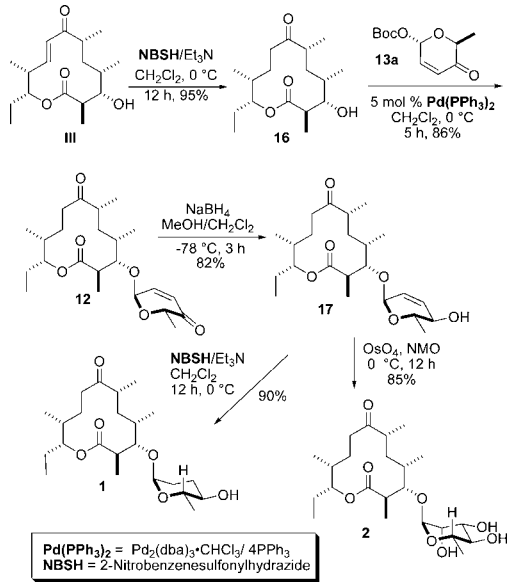
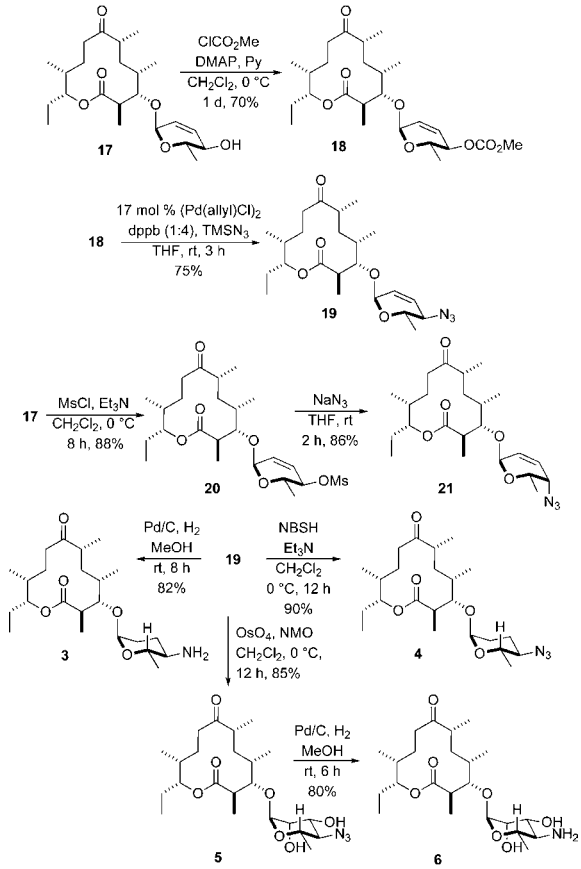
Scheme 3. Syntheses of α-L-Sugar Analogues **1** and **2**



We next investigated methods for the construction of various *C*-4-amino/azido sugar analogues (Scheme 4). Toward this goal, a methyl carbonate leaving group was installed on the allylic alcohol by reaction of **17** with methyl chloroformate to form the *C*-4-carbonate **18** in 70% yield. Exposing carbonate **18** to the Sinou conditions[14] ($TMSN_3$, $(Pd(allyl)Cl)_2$/1,4-bis(diphenylphosphino)butane) afforded a single regio- and stereoisomeric allylic azide **19** in 75% yield. However, when alcohol **17** was subjected to Mitsunobu conditions using TMS azide as the nucleophile, no desired *C*-4-azido compound **21** was formed. Therefore, a two-step S_N2 reaction route was employed, in which the allylic alcohol **17** was converted into mesylate **20** (MsCl/Et_3N) in an excellent yield (88%), followed by treatment of **20** with NaN_3/THF to afford the inverted *C*-4-azido isomer **21** in 86% yield.

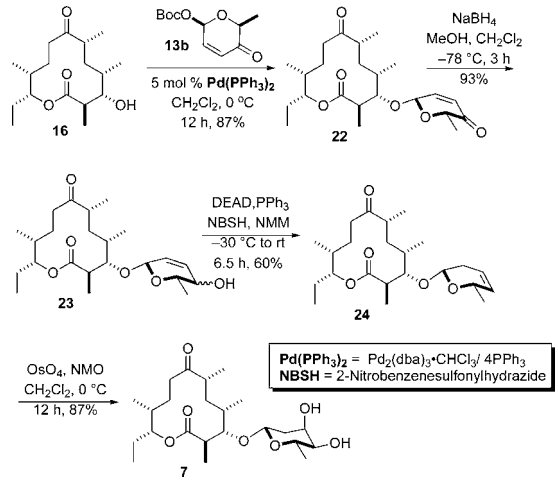
Scheme 4. Syntheses of α-L-Amino Sugar Analogues **3**−**6**



These azide intermediates can now be converted to different amino sugar analogues. As depicted in Scheme 4, hydrogenolysis (Pd/C, H_2, MeOH) of allylic azide **19** via a one-pot reduction of both azide and the allylic double bond gave the dideoxyamino sugar analogue **3** in 82% yield. As before, diimide reduction of the allylic azide **19** gave 2,3-dideoxy analogue **4** in 90% yield. Alternatively, diastereoselective dihydroxylation (OsO_4/NMO) of **19**, followed by reduction of azide (Pd/C, H_2, MeOH) produced the aminorhamnose analogue **6** via a *rhamno*-azidosugar **5** intermediate.

We next investigated the synthesis of the 2,6-dideoxy *β*-L-*allo*-sugar analogue **7** of methymycin (Scheme 5), which builds on our digitoxin work.[15] Thus, macrolactone **16** and *β*-L-pyranone **13b** were subjected to Pd-catalyzed glycosylation to give *β*-L-glycoside **22** as a single diastereomer in good yield (87%). A $NaBH_4$ reduction of ketone **22** provided a mixture of diastereomeric allylic alcohols **23** in 93% yield. Exposing the mixture of allylic alcohols **23** to the Myers' reductive rearrangement conditions[16] (NBSH/PPh_3/DEAD, NMM, −30 °C to rt) provided olefin **24** in a moderate yield (60%). Finally, Upjohn dihydroxylation of olefin **24** (OsO_4/NMO) gave exclusively the 2,6-dideoxy *allo*-sugar analogue **7** in 87% yield.

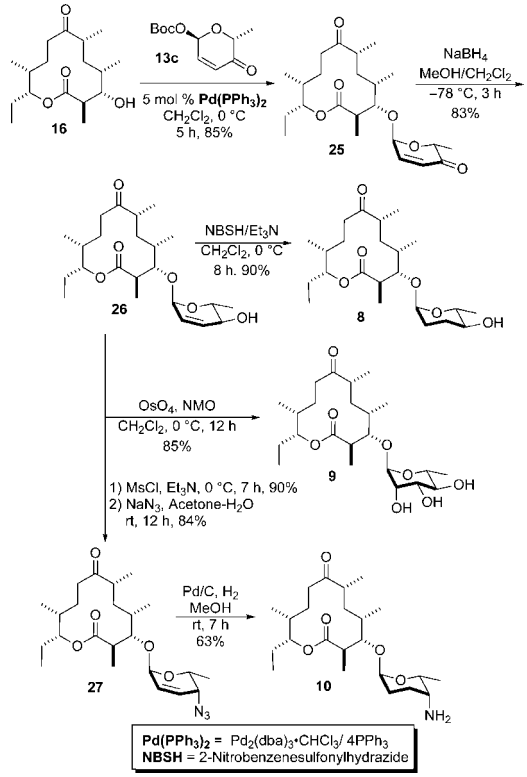
Scheme 5. Synthesis of *β*-L-Sugar Analogue **7**



In a similar fashion, aglycon **16** was subjected to a diastereoselective Pd-catalyzed glycosylation with α-D-Boc-pyranone **13c** producing α-D-glycoside **25** as a single diastereomer in

good yield (85%) (Scheme 6). A $NaBH_4$ reduction of enone **25** afforded the equatorial allylic alcohol **26** in 83% yield.

Scheme 6. Syntheses of α-D-Sugar Analogues **8**−**10**

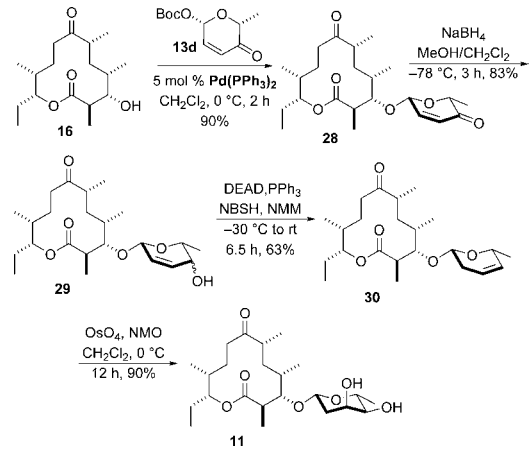


Diimide reduction of the allylic alcohol **26** (NBSH/Et_3N) as described above led to the dideoxy analogue **8** in an excellent yield (90%). The final conversion of **26** to the *rhamno*-sugar analogue **9** was achieved by diastereoselective dihydroxylation using the Upjohn conditions (OsO_4/NMO). The desired product was obtained in 85% yield.

Via a similar two-step S_N2 reaction route, allylic alcohol **26** was converted into the inverted *C*-4-azido compound **27** in 76% overall yield by mesylation (MsCl/Et_3N; 90%) followed by treatment with NaN_3/$Acetone_{(aq)}$ (84%). Reduction of the *C*-4-azido group and allylic double bond in compound **27** under hydrogenolysis conditions (Pd/C, H_2, MeOH) gave the *C*-4-deoxyamino analogue of methymycin **10**. The desired compound was isolated in a modest yield (63%) through reverse-phase chromatography.

The synthesis of the 2,6-dideoxy β-D-*allo*-sugar analogue **11** of methymycin was performed according to an analogous sequence as described above for the synthesis of **7** (Scheme 7). Namely,

Scheme 7. Synthesis of β-D-Sugar Analogue **11**



Pd-catalyzed glycosylation of macrolactone **16** using β-D-pyranone **13d** gave β-D-glycoside **28** as a single diastereomer in good yield (90%). A $NaBH_4$ reduction of ketone **28** afforded a mixture of diastereomeric allylic alcohols **29** that was converted to olefin **30** under the Myers' reductive rearrangement conditions (NBSH/PPh_3/DEAD, NMM, −30 °C to rt) in moderate yield (63%). Finally, Upjohn dihydroxylation of olefin **30** gave exclusively the 2,6-dideoxy *allose*-sugar analogue **11** in 90% yield.

In conclusion, a divergent yet highly stereoselective route to 11 variously substituted (amino/azido/dideoxy) methymycin analogues has been developed. The key to the success of this method is the iterative use of the Pd-catalyzed glycosylation reaction, ketone reduction/Myers' reductive rearrangement, diastereoselective dihydroxylation, and regioselective reductions. This unique application of the established Pd-catalyzed glycosylation strategy allows for efficient preparation of challenging and stereochemically diverse glycoside macrolide targets. While some postglycosylation transformations were not compatible with the macrolide double bond, there was no need for ketone protection.[17] The testing of these macrolide analogues will be reported in due course as well as the use of this methodology toward other biologically important aglycons.

Acknowledgment. We are grateful to NIH (GM054346 and GM035906 to H.-w.L., and GM088839 to G.A.O.) and NSF (CHE-0749451 to G.A.O.) for the support of our research.

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

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