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Letter

De Novo Design and Asymmetric Synthesis of a *C*-1/2 Benzodioxin Fused Glycoside Analogue of Lincomycin

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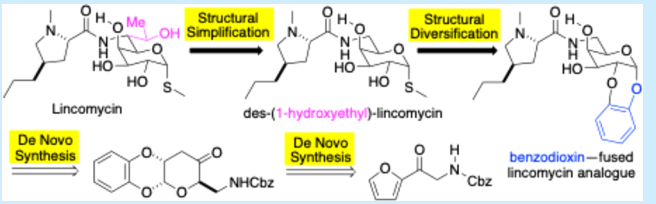
ABSTRACT: An *in silico* designed benzodioxin fused analogue of a des-(1-hydroxyethyl)-lincomycin analogue was synthesized in a *de novo* asymmetric fashion from an achiral acylfuran, a 4-(*n*-Pr)-*N*-methyl-proline, and catechol. The synthesis of the 6-amino-galactose portion of the lincomycin analogue necessitated the development of a novel stereospecific tandem Pd-glycosylation/1,4-addition reaction between catechol and an *N*-Cbz-protected 6-amino-pyranone with a Pd-π-allyl leaving group at the *C*-1 position. The desired *galacto*-stereochemistry was installed by a subsequent stereoselective ketone reduction, alcohol elimination, and diastereoselective dihydroxylation of the *C*-3/4 alkene.



The lincosamides are a class of mixed peptide/aminosugar antibiotics that have potent activity against *S. aureus*, *streptococci*, and *anaerobes*.[1] Both lincomycin and clindamycin have excellent safety profiles in humans and can be given by both oral and intravenous routes.[2] Clindamycin and to a lesser extent lincomycin have excellent activity against Gram-positive pathogens, such as *S. aureus* and *S. pyogenes*, and anaerobic pathogens, through their potent inhibition of protein synthesis.[3] However, they do not efficiently penetrate the outer membrane of Gram-negative ESKAPE pathogens, rendering these pathogens resistant to achievable drug levels.[4] When clindamycin is dosed in combination with colistin or other membrane-permeabilizing agents, Gram-negative ESKAPE pathogens are susceptible to this antibiotic.[5] This potential for Gram-negative activity has inspired the search for new, more penetrant lincosamide type antibiotics,[6] as well as other antibiotic natural products.[7,8]

Our approach to this quest is heavily influenced by recent studies from Myers et al. that first led to the discovery of iboxamycin, via an oxepane annulation on the *n*Pr-proline portion of clindamycin, and then cresomycin via an oxathiecin annulation across the *C*-1/8 position of the sugar (Figure 1).[6] Specifically, we targeted lincomycin analogues with annulation on the sugar portion of the antibiotic (Scheme 1). *In silico* analysis of a high-resolution lincosamide-ribosome cryo-EM structure (PDB 8CGK)[9] using Schrödinger Glide XP docking[10] led us to discover a pocket (Figure 2) in the structure that hypothetically could accommodate an aromatic ring connected to the *C*-1 and *C*-2 position of the lincomycin *galacto*-sugar (i.e., **1b** to **2**).

In addition to offering structural novelty for IP-protection, we hoped that the benzodioxin fusion would improve activity to compensate for the removal of the *C*-7/8 hydroxyethyl

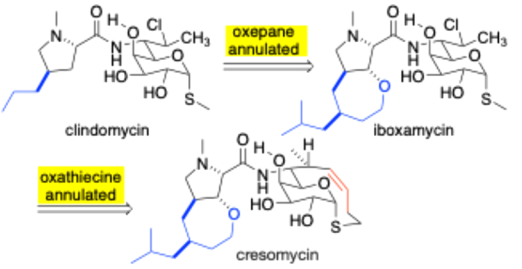
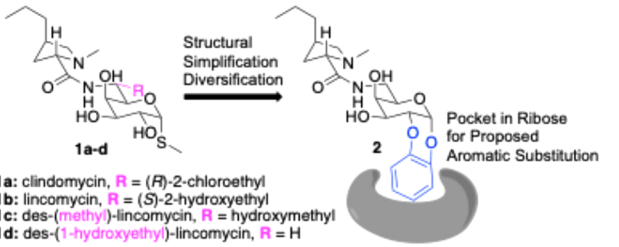


Figure 1. Design of iboxamycin and cresomycin by Myers.

Scheme 1. Design of a Benzodioxin Fused Lincomycin



group as well as the anomeric sulfur (i.e., **1b** to **2**). It had been previously demonstrated that the lincomycin analogue **1d**

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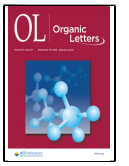


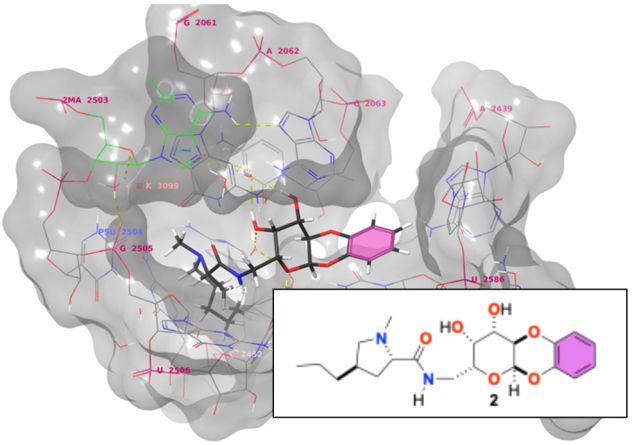
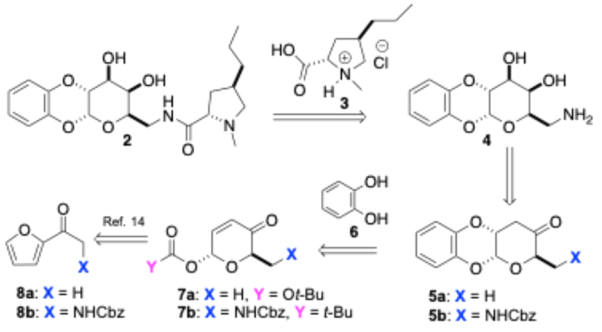


Figure 2. Docking pose of lincomycin analogue **2**. Analogue **2** (carbon black, oxygen red, and nitrogen blue) in the active site of the ribosome, using cryo-EM structure (PDB 8CGK). The benzodioxin moiety is highlighted in pink. Analogue **2** fits within the binding pocket and forms hydrogen bond interactions with a conserved water molecule, U2506 and G2505.

keeps the antibiotic profile of lincomycin (**1b**), albeit with reduced activity.[11] With this understanding, we set out to develop a novel *de novo* asymmetric synthesis of the benzodioxin fused lincomycin analogue **2** for further S-SAR studies.[12] Presumably the iterative use of a Buchwald−Hartwig type Ullmann etherification could be used to install a benzodioxin ring fusion at the *C*-1/2 of a *galacto*-sugar; however, issues associated with regio- and anomeric stereochemistry led us to consider an alternative approach.

Retrosynthetically, we envisioned the benzodioxin lincomycin analogue **2** arising from an amide coupling of the 6-aminogalactose **4** and *trans*-L-proline **3** (Scheme 2). The

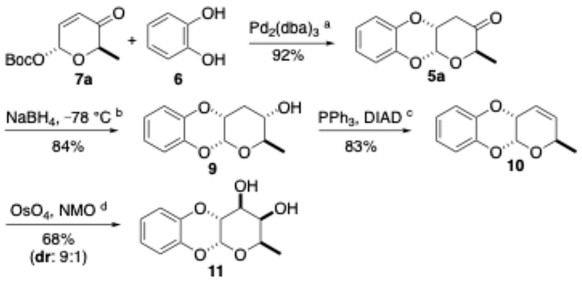
Scheme 2. Retrosynthetic Approach to Lincomycin Analogues



known substituted *trans*-L-proline **3** can be prepared from L-hydroxyproline.[13] The 6-benzodioxin fused 6-amino-*galacto*-sugar **4** could result from a Pd−π-allyl coupling and concomitant 1,4-addition between pyranone **7a**/**b** and catechol **6**. We previously disclosed a *de novo* asymmetric synthesis of pyranones **7a**/**b** with either α- or β-stereochemistry from achiral furans **8a**/**b**.[14]

As a proof of concept for this approach, we first executed the synthesis of the carbohydrate portion of the molecule with no *C*-6 substitution (Scheme 3). The synthesis began by subjecting α-D-*aculo*-pyranone donor **7a** to a Pd(0) coupling with catechol **6**,[15,16] which resulted in a stereoretentive glycosylation at *C*-1 along with a tandem oxa-Michael addition

Scheme 3. Catechol Coupling and Synthesis of *galacto*-Sugars

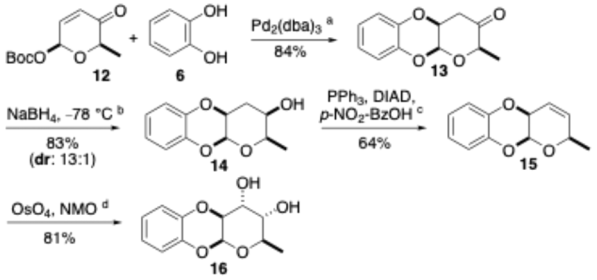


[a]$Pd_2(dba)_3$ (0.015 equiv), DPPB (0.03 equiv), CH_2Cl_2, 12 h. [b]$NaBH_4$ (2 equiv), MeOH/CH_2Cl_2 (1:1), −78 °C, 1 h. [c]PPh_3 (2.4 equiv), DIAD (2.4 equiv), CH_2Cl_2, 16 h. [d]NMO (1.5 equiv), OsO_4 (0.05 equiv), *t*-BuOH/acetone (1:1), 16 h.

to afford tricyclic compound **5a**, with the required *cis*-*C*-1/2 stereochemistry.[17] The facial selectivity of the oxa-Michael addition is governed by the tether length enforcing *cis*-ring fusion. Ketone **5a** was then stereoselectively reduced with sodium borohydride (at −78 °C) to afford equatorial alcohol **9** as a single diastereomer. This alcohol was then eliminated to alkene **10** using PPh_3/DIAD.[18] This newly formed double bond was diastereoselectively dihydroxylated under the Upjohn conditions (OsO_4/NMO)[19] to form diol **11** as the major diastereomer (9:1), with the desired *galacto*-stereochemistry stemming from the installation of the hydroxyl groups in an *anti*-relationship to the *C*-1/2 benzodioxin ring.[20]

We decided to further explore the potential for this annulation chemistry in the β-stereochemical series (Scheme 4). This would allow for the synthesis of alternative

Scheme 4. Applications to β-Pyranone to β-*altro*-Sugars



[a]$Pd_2(dba)_3$ (0.015 equiv), DPPB (0.03 equiv), CH_2Cl_2, 12 h. [b]$NaBH_4$ (2 equiv), MeOH/CH_2Cl_2 (1:1), −78 °C, 1 h. [c]PPh_3 (2 equiv), DIAD (2 equiv), *p*-NO_2-BzOH (2 equiv), CH_2Cl_2, 16 h. [d]NMO (1.5 equiv), OsO_4 (0.05 equiv), *t*-BuOH/acetone (1:1), 16 h.

carbohydrate stereoisomers by application of the same sequence on β-D-pyranone **12**. When the Pd-glycosylation was performed between β-pyranone **12** and catechol the β-benzodioxin fused ketone **13** was produced with the opposite *C*-1/2 *cis*-stereochemistry as α-benzodioxin fused ketone **5a**. The $NaBH_4$ reduction of ketone **13** resulted in *C*-4 axial alcohol **14** as the major isomer. While the stereoselectivity in the reduction of **13** with a β-benzodioxin fusion was excellent, it was slightly diminished when compared to the α-series (i.e., **5a** to **9**). The switch in the selectivity of reduction of **13** to axial alcohol **14** (compared to **5a**) results from the twist boat confirmation of **13** where the neighboring methyl group controls the stereochemistry. For the subsequent elimination

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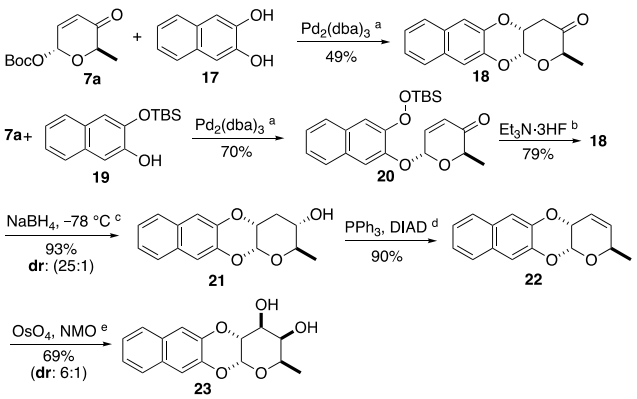
reaction of alcohol **14** to alkene **15**, it was determined that it worked most optimally using the Mitsunobu conditions (*i.e.*, PPh_3/DIAD and 4-nitrobenzoic acid).[18] This was followed by an Upjohn dihydroxylation to afford diol **16**, with *altro*-stereochemistry.[20] The stereoselectivity in the dihydroxylation of alkene **15** was even greater than that found in the α-series (**10** to **11**), which can be attributed to the *cis* relationship of the substituent at *C*-1/2/5 in **15**.

To further explore the potential of this chemistry to install different aromatic groups, we wanted to assess the applicability to other aryl diols (Scheme 5). As a test case, we decided to try

Scheme 5. Synthesis of a Naphthodioxin Fused *galacto*-Sugar

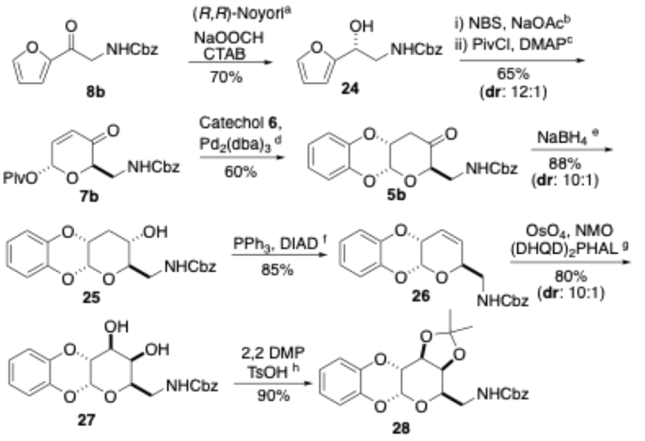


[a]$Pd_2(dba)_3$ (0.02 equiv), DPPB (0.04 equiv), CH_2Cl_2, 12 h. [b]$Et_3N{\cdot}3HF$ (3 equiv), THF, 12 h. [c]$NaBH_4$ (2 equiv), CH_2Cl_2/MeOH (2:1), −78 °C, 1 h. [d]PPh_3 (2.4 equiv), DIAD (2.4 equiv), CH_2Cl_2, 16 h. [e]NMO (1.5 equiv), OsO_4 (0.1 equiv), *t*-BuOH/acetone (1:1), 16 h.

the glycosylation of α-pyranone **7a** with 2,3-dihydroxynaphthalene **17** to form the *C*-1/2 napthodioxin fused product **18**. The resulting annulation reaction with 2,3-dihydroxynaphthalene to form **18** proceeded in poor to moderate yields when compared to the analogous reaction with catechol **6**. To further optimize this process, we explored the Pd-glycosylation between pyranone **7a** and the known 2-OTBS-3-hydroxynaphthalene **19**,[21] which resulted in aryl glycoside **20**. This glycosylation product **20** was then subjected to TBS-deprotection-mediated cyclization to afford **18** in a moderate 55% yield over two steps. While the overall yield to **18** was similar, we found the 2-step procedure was more reliable. The subsequent reduction of ketone **18** to alcohol **21** followed by dehydration to alkene **22** proceeded with good yields and selectivities. Dihydroxylation of the alkene **22** to diol **23** also proceeded in good yield. The dihydroxylation occurred with the same facial preference as **10** to **11**, to give *galacto*-stereochemistry, albeit with diminished selectivity.

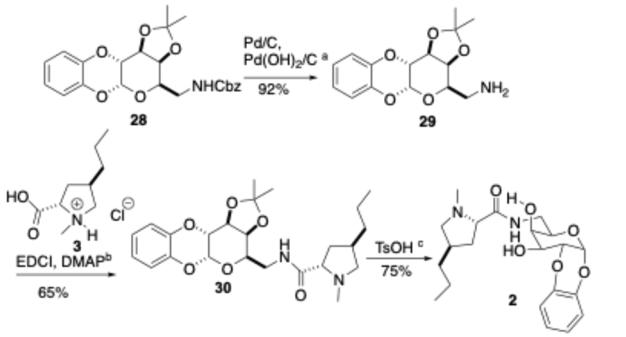
We sought to apply this methodology to *C*-6 aminated pyranone **7b** to achieve des-(1-hydroxyethyl)-lincomycin analogue **2** (Scheme 6 and 7). Previously, we demonstrated the enantioselective synthesis of *C*-6 *N*-Cbz-protected pyranone **7b** from achiral *N*-Cbz-protected α-aminoacetylfuran **8b**.[14b] The *de novo* asymmetric approach involved a Noyori reduction of ketone **8b** provided amino alcohol **24**. An Achmatowicz rearrangement followed by pivalate protection was used to diastereoselectively convert **24** to pyranone **7b**. Pd-glycosylation of pyranone **7b** with catechol **6** afforded ketone **5b** with diminished efficiency but equivalent diastereoselectivity to the *C*-6 methyl series (enone **7a** to ketone **5a**).

Scheme 6. Application to C-6 Amino *galacto*-Sugars



[a](*R*,*R*)-Noyori catalyst (0.005 equiv), CTAB (0.1 equiv), NaOOCH (5 equiv). [b]NBS (1.1 equiv), NaOAc (2 equiv). [c]PivCl (1.1 equiv), DMAP (1.2 equiv). [d]$Pd_2(dba)_3$ (0.05 equiv), PPh_3 (0.1 equiv), CH_2Cl_2, 30 min. [e]$NaBH_4$ (2 equiv), MeOH/CH_2Cl_2 (1:1), 0 °C to RT, 5 h. [f]PPh_3 (2 equiv), DIAD (2 equiv), THF, 16 h. [g]NMO (1.5 equiv), OsO_4 (0.02 equiv), $(DHQD)_2PHAL$ (0.08 equiv), *t*-BuOH/acetone (1:1), 16 h. [h]2,2-Dimethoxypropane (10 equiv), TsOH (0.1 equiv), acetone, 5 h.

Scheme 7. Synthesis of a Benzodioxin Fused Analogue



[a]Pd/C (10% w.r.t. 28), $Pd(OH)_2$/C (10% w.r.t. 28), H_2, EtOH, 16 h. [b]EDCI (1.5 equiv), DMAP (1.5 equiv), DMF, 16 h. [c]TsOH (1.2 equiv), MeOH, 60 °C, 4 h.

Ketone **5b** was then reduced with sodium borohydride at 0 °C to obtain a major diastereomer **25** without the need for cryogenic conditions. Next, Mitsunobu conditions transformed alcohol **25** to alkene **26**. The double bond was dihydroxylated using Sharpless asymmetric dihydroxylation conditions[22] to afford **27** with increased facial selectivity for the *galacto*-stereochemisry compared to the Upjohn conditions previously employed.[14] Diol **27** was subsequently protected as an acetonide to give the fully protected sugar **28**.

Next, the *N*-Cbz-group in **28** was cleanly deprotected under hydrogenolysis conditions using a combination of Pd/C and $Pd(OH)_2$, affording the primary amine **29** (Scheme 7). An EDCI promoted amide bond coupling of the known 4-propyl L-proline carboxylic acid[13] **3** with amine **29** gave an acetonide protected form of the target molecule **30**, which was deprotected with TsOH in methanol to provide the desired des-(1-hydroxyethyl)-lincomycin analogue **2**.

The newly designed lincomycin analogue **2** was screened for antibiotic activity against *S. aureus,* and either a wild-type *E. coli* K-12 strain or *E. coli* strains with increased permeability

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characteristics (Δ*tolC* and *lptD4213* mutants).[23] Unfortunately, no activity was found (minimal inhibitory concentration, MIC > 128 μM) compared with the potent activity of clindamycin for *S. aureus* (MIC = 0.25 μM) and *E. coli tolC* and *lptD* mutant strains (MIC = 4 μM) (see SI). This disappointing result made us reevaluate our interpretation of the reported activity for des-hydroxyethyl analogue **1d**.[12] Bannister had previously reported that analogue **1d** retained weak activity but with the same spectrum of activity as lincomycin, whereas we were unable to detect any activity against clinically relevant pathogens.

In conclusion, we have developed a *de novo* asymmetric synthesis of a novel benzodioxin fused analogue of a des-(1-hydroxyethyl)-lincomycin **2** from achiral acylfuran **25**. The synthesis of **2** occurred in 10 steps and 7% overall yield. In support of this synthetic effort, a new one-pot, two-step Pd–π-allyl coupling and concomitant 1,4-addition between pyranones and catechols was developed. The initial annulation products can be diastereoselectively converted into *galacto*-sugars via a three-step reduction, elimination and dihydroxylation sequence. The resulting annulation reaction occurred in good overall yields and stereoselectivity for both α- and β-pyranones. In the β-series, sugars with *altro*-stereochemistry are selectively formed. Analogue **2** was designed *in silico* based on Schrödinger Glide XP docking to a cryo-EM lincosamide-ribosome structure. Unfortunately, no antibacterial activity was found for lincomycin, analogue **2**. In our analogue design, we underestimated the importance of the *C*-7/8 hydroxy-ethyl portion of lincomycin to its overall activity. In retrospect, we could have been more cognizant of the qualitative nature of the reported activity for lincomycin analogue **1d**. Consequently, we underestimated the impact of the removal of the hydroxyethyl group on lincomycin (i.e., **1a** to **1d**). However, it should be noted that this new Pd-annulation reaction expands the asymmetric Achmatowicz approach to unnatural carbohydrate motifs. The further application of this approach in synthesis will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c03402.

Complete experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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