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Catalytic Asymmetric Synthesis of All Possible Stereoisomers of 2,3,4,6-Tetradeoxy-4-aminohexopyranosides

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Abstract. We recently developed a divergent strategy for the synthesis of all eight possible 2,3,6-trideoxyhexopyranosides with three stereogenic centers. However, the diastereoselectivity for one of the three stereogenic centers was low and it was not controlled by catalysts. In this update, we described a systematic method for the first catalytic asymmetric synthesis of all eight possible 2,3,6-trideoxyhexopyranoside and all eight possible 2,3,4,6-tetradeoxy-4-aminohexopyranosides. The products derived from this strategy include the glycone of natural products grecocycline A, spinosyn A, and ossamycin. All three stereogenic centers in each product was controlled by a pair of chiral catalysts. The key to the success is the application of our recently developed dynamic kinetic stereodivergent acylation of Achmatowicz rearrangement products and chiral catalyst-directed reduction. Simple dimethylation of the 2,3,4,6-tetradeoxy-4-amino sugars afforded derivatives of naturally occurring β-D-forosaminide and β-L-ossaminide.

Keywords: deoxy sugars; amino sugars; asymmetric catalysis; carbohydrates, divergent

Deoxyamino sugars are frequently found in natural products, such as aminoglycosides, macrolides, and anthracyclines, and the sugar units are often essential to the pharmacological activities of the natural products.[1] Some examples of 2,3,4,6-tetradeoxy-4-aminopyranoside-containing natural products are shown in Figure 1. These natural products have a broad range of biological activities, such as cytotoxic agent grecocycline A,[2] protein tyrosine phosphatase 1B inhibitor grecocycline B,[2] insecticide spinosyns,[3] and oxidative phosphorylation inhibitor ossamycin.[4] Derivatives of griseusins also have potent antibiotic, antifungal, and anticancer activities.[5]

Not surprisingly, significant efforts have been devoted to the synthesis of deoxyamino sugars.[6] For example, both *O*-ethyl ossaminide and ossamine were synthesized from glucose or its derivatives in over 10 steps.[4c, 7] More recent efforts on the synthesis of ossamine and its analogues were also realized from chiral starting materials.[8]

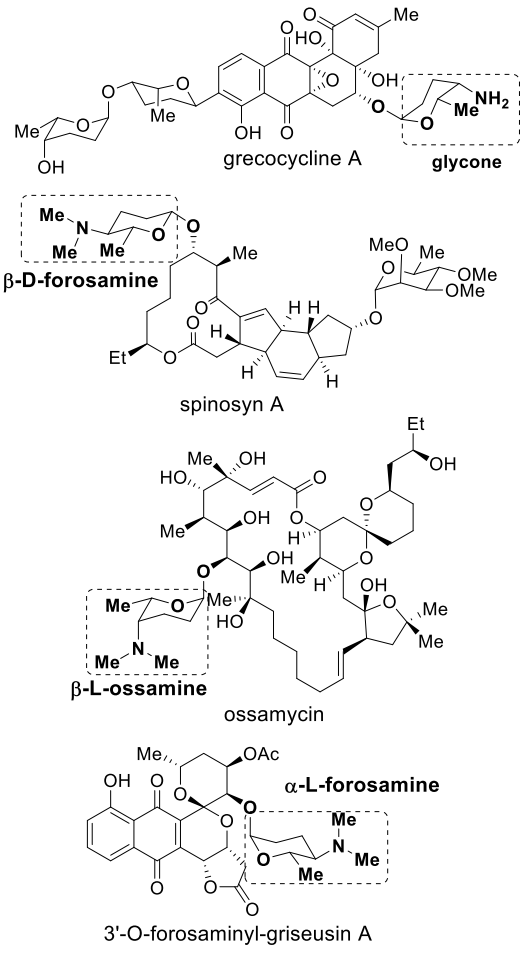

Figure 1. Natural products containing 2,3,4,6-tetradeoxy-4-amino sugars

Forosamine is a diastereoisomeric isomer of ossamine. Both α/β and D/L forms of forosamines are found in natural products as shown in Figure 1. Since

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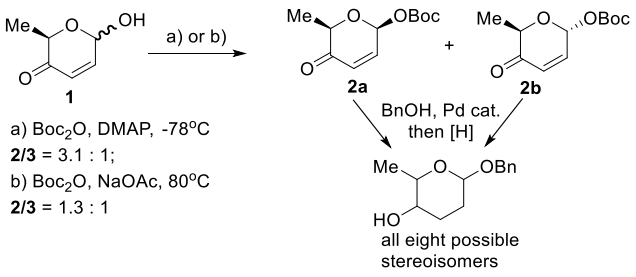
the structure and stereochemistry of forosamine was discovered in 1966 a number of synthetic routes have been developed.[7a,9] Two *de novo* syntheses of forosamine involved either the epoxidation of sorbic acid followed by kinetic resolution of the resulting acid or chemoenzymatic resolution of the epoxide derived from methyl sorbate.[10] In Evans's synthesis of lepicidin A, the L-forosamine glycone was prepared from an oxazolidinone chiral auxiliary in nearly ten steps.[11] Racemic forosamine was synthesized by Tietze's group via a domino Knoevenagel-Hetero-Diels-Alder reaction and resolved by chiral HPLC.[12] A Ru-catalyzed cycloisomerization was employed by Merck for the synthesis of L-forosamine from an acyclic chiral amino alcohol.[13] Dai's group recently accomplished a concise synthesis of spinosyn A and observed a 1:1 β/α stereoselectivity.[14] Prior to Dai's work, the undesired α-isomer was the major product[11, 15] with the exception of Roush's strategy.[16] In Roush's synthesis of spinosyn A, a deoxyamino sugar with a C2-OAc directing group was introduced to the macrocyclic aglycone with β-selectivity by Schmidt glycosylation, and the C2-OAc was later removed by deoxygenation.[16] The synthesis of Roush's glycosyl donor, however, requires more than ten steps and another five steps are necessary for the removal of the C2-OAc group after the glycosylation.

We herein report a systematic strategy for the catalytic asymmetric synthesis of all eight possible 2,3,4,6-tetradeoxy-4-aminohexopyranosides, including the glycone of natural products grecocycline A and B, spinosyn A, and ossamycin.

We previously reported a divergent strategy for the synthesis of all possible stereoisomers of 2,3,6-trideoxypyranosides (Scheme 1).[17] Lactol **1** derived from Achmatowicz rearrangement[18] was converted to carbonates **2** and **3** under two different conditions and separated by column chromatography according to O'Doherty's protocol.[19] Although the overall efficiency is very high and the palladium-catalyzed glycosidation offered complete control for the α- and β-stereoselectivity on the anomeric position,[20] the stereoselectivity for the conversion of **1** to **2a** or **2b** remained to be an unsolved problem. Recently, we[21] and others[22] reported an effective method for the dynamic kinetic stereoselective acylation of lactols derived from an Achmatowicz rearrangement[18] using chiral organocatalysts. We envision that this strategy will provide a solution for the above problem and allow us to access various deoxy and deoxyamino sugars highly stereoselectively.



Scheme 1. Previous Strategy for Divergent Synthesis of All Possible Stereoisomers of 2,3,6-trideoxypyranosides

Optically pure lactol **1** (98% *ee*) could be prepared in two steps on the gram scale from 2-acetylfuran *via* catalytic asymmetric reduction mediated by $[Cp^*RhCl]_2$/(*R*, *R*)-Ts-DPEN **L1** followed by an Achmatowicz rearrangement (Scheme 2).[17] Our chiral catalyst-directed dynamic kinetic diastereoselective acylation method provided ester products **3a** and **3b** from **1** using (*R*)- and (*S*)-BTM catalysts, respectively.[21a] These esters can be converted to the deoxyglycosides **4a** and **4b** by Pd-catalyzed allylic alkylation.[21a] Their enantiomers, ***ent*-4a** and ***ent*-4b**, can be prepared from ***ent*-1** with similar efficiency and stereoselectivity. Using $[Cp^*RhCl]_2$ and a pair of chiral ligands **L1** and **L2**, we have demonstrated that a highly diastereoselective reduction of **4a**, **4b**, ***ent*-4a**, and ***ent*-4b** can be realized.[17] All possible stereoisomers of 2,3,6-trideoxy-hexopyranosides (**5a**-**5d** and ***ent*-5a**-**5d**) can thus be prepared by the choice of two pairs of catalysts - reduction of 2-acetylfuran or enones directed by Rh(III)/**L1** or **L2** catalysts and esterification of lactols directed by (*R*)- or (*S*)-BTM catalysts. This catalytic and divergent strategy can be applied to the synthesis of numerous bioactive natural products[23] containing amicetopyranosides **5a**, **5d**, ***ent*-5a,** and ***ent*-5d** or rhodinopyranoside **5b**, **5c**, ***ent*-5b,** and ***ent*-5c** in either α/β or D/L forms.

To further examine the scope of this strategy, we also prepared dihydropyranone **6a** efficiently and stereoselectively using secondary alcohol cyclohexanol as the nucleophile for the Pd-catalyzed allylic alkylation. The reduction of **6a** was highly diastereoselective and yielded 2,3,6-trideoxy hexapyranoside **6b**.

Having all eight stereoisomers **5a**-**5d** and ***ent*-5a**-**5d** in hand, we then turned our attention to the synthesis of their corresponding deoxyamino sugars by introducing the amino group through a Mitsunobu reaction and subsequent reduction (Scheme 3). All eight 2,3,4,6-tetradeoxy-4-aminohexopyranosides **8a**-**8d** and ***ent*-8a**-**8d** were prepared in high yields. Deoxyamino sugar **8e** bearing a secondary alcohol was also prepared by the same sequence in a good overall yield.

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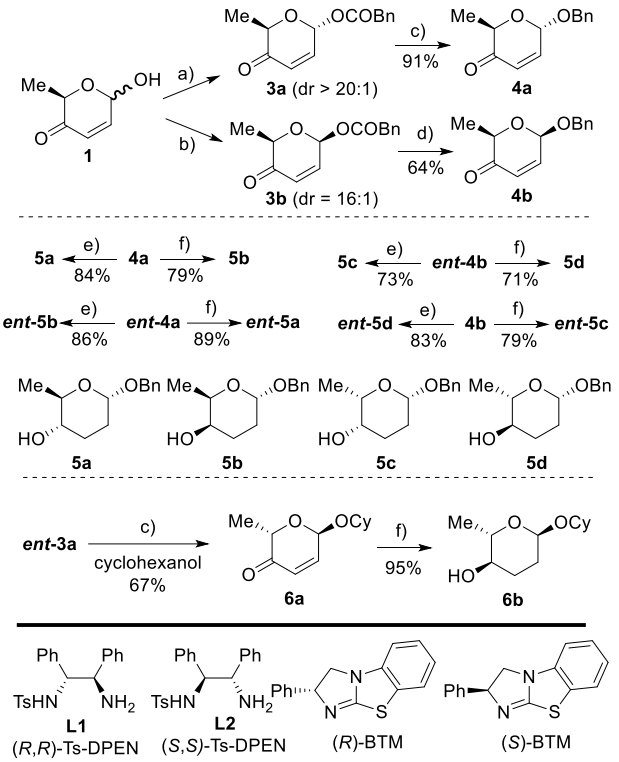
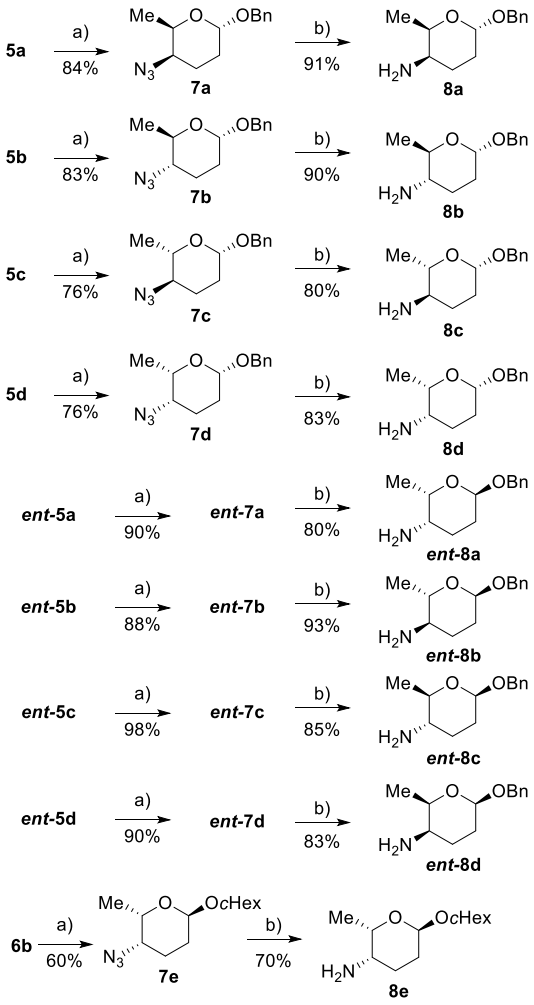


a) (*R*)-BTM (10 mol%), Piv_2O (1.3 eq), $PhCH_2CO_2H$ (1.3 eq), *i*Pr_2NEt (2.5 eq), $CHCl_3$, 76% yield; b) (*S*)-BTM (10 mol%), Piv_2O (1.3 eq), $PhCH_2CO_2H$ (1.3 eq), *i*Pr_2NEt (2.5 eq), $CHCl_3$, 73% yield; c) $Pd_2(dba)_3$ (2.5 mol %), PPh_3 (10 mol%), ROH (1.5 eq); d) $Pd_2(dba)_3$ (2.5 mol %), PPh_3 (10 mol%), ROH (1.5 eq), *i*Pr_2NEt (1.5 eq); e) $[Cp^*RhCl_2]_2$ (0.5 mol%), (*S,S*)-Ts-DPEN (1.2 mol%), HCO_2Na, 40 °C; f) $[Cp^*RhCl_2]_2$ (0.5 mol%), (*R,R*)-Ts-DPEN (1.2 mol%), HCO_2Na, 40 °C;

Scheme 2. Dynamic Kinetic Stereoselective Acylation of Lactols Followed by Pd-catalyzed Stereospecific Allylic Alkylation and Chiral Catalyst-Directed Reduction



a) PPh_3 (3 eq), DIAD(2.5 eq), DPPA(2.5 eq), THF, -20 °C-rt;
b) PPh_3 (2.5 eq), H_2O, reflux, THF.

Scheme 3. Preparation of all possible 2,3,4,6-tetradeoxy-4-aminohexopyranosides

Among the deoxyamino glycosides in Scheme 3, ***ent*-8a** is the glycone in natural product grecocyclines A and B. To further demonstrate the utility of this strategy, we next prepared *O*-benzyl-β-D-forosaminide **9**, *O*-benzyl-β-L-ossaminide **10**, and *O*-benzyl-α-D-forosaminide **11** by introducing the *N*,*N*-dimethyl group *via* reductive amination following a known protocol (Scheme 3).[24] Deoxyamino glycoside **9** and **10** are the glycones in natural products spinosyn A and ossamycin.

In summary, we have developed a catalytic asymmetric synthesis of all eight possible stereoisomers of 2,3,4,6-tetradeoxy-4-aminopyranosides in 7 steps starting from 2-acetylfuran with approximately a 20% overall yield for each isomer. The three stereogenic centers are dictated by two pairs of chiral catalysts. The synthesis of ossaminide and forosaminide were also realized efficiently. We anticipate that this systematic synthetic strategy can be extended to the divergent synthesis of other aminoglycosides and their analogues and applied to the synthesis of complex natural products with a high level of control for each stereogenic center.

Experimental Section

Procedure for the synthesis of 8a from 5a:

To a solution of compound **5a** (62 mg, 0.3 mmol, 1 equiv) in THF (15–20 mL per mmol) was added PPh_3 (236 mg, 0.9 mmol, 3 equiv) at -20 °C. To this mixture was added a solution of DIAD (152 mg, 0.75 mmol, 2.5 equiv) and DPPA (207 mg, 0.75 mmol, 2.5 equiv) in THF (5–7 mL per mmol) at -20 °C. The reaction mixture was then allowed to warm to room temperature and monitored by TLC (~12 h). The resulting solution was then diluted with Et_2O, washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield the crude product, which was purified by column chromatography to give product **7a** (57 mg, 0.23 mmol, 84%) as a colorless oil.

To a solution of azide **7a** (42 mg, 0.17 mmol, 1.0 equiv) in THF (30–40 mL per mmol) and H_2O (183 mg) was added PPh_3 (2.5 equiv), and the reaction was stirred under reflux and monitored by TLC (~10 h). After evaporation, the residue was purified by column chromatography to yield compound **8a** (33.8 mg, 0.15 mmol, 90%) as a colorless oil.

Acknowledgements

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UPDATE

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Each stereogenic center is controlled by a chiral catalyst.