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# Chiral phosphoric acid-catalyzed desymmetrizative glycosylation of 2-deoxystreptamine and its application to aminoglycoside synthesis†

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**This work describes chiral phosphoric acid (CPA)-catalyzed desymmetrizative glycosylation of *meso*-diol derived from 2-deoxystreptamine. The chirality of CPA dictates the outcome of the glycosylation reactions, and the use of enantiomeric CPAs results in either C4-glycosylated (67 : 33 d.r.) or C6-glycosylated (86 : 14 d.r.) 2-deoxystreptamines. These glycosylated products can be converted to aminoglycosides, and the application of this strategy to the synthesis of protected iso-neamine and iso-kanamycin B with inverted connection at the C4 and C6 positions is described.**

Aminoglycosides are a group of carbohydrate-based antibiotics, which function through binding to specific sites in prokaryotic ribosomal RNA (rRNA) and affecting the fidelity of protein synthesis.[1] In addition to their antibacterial properties, aminoglycosides are potent antiviral (HIV) agents and could be employed to suppress genetic diseases.[2] While certain aminoglycosides such as paromomycin or gentamycin are FDA-approved drugs for the treatment of bacterial infections, their extensive clinical use has been curtailed by their toxicity and the rapid increase of aminoglycoside resistant strains of bacteria.[3]

Therefore, the design of new modified aminoglycosides with improved pharmacological properties represents an important challenge. Despite the extensive interest in this class of natural products, current approaches to aminoglycosides are often prohibitively long and have significant limitations in the structural modifications that can be introduced.[4] The majority of aminoglycosides contain an achiral (*meso*) 2-deoxystreptamine (2-DOS) subunit that carries glycosylation at either the C4/C5 (*i.e.* neomycin B) or C4/C6 (*i.e.* amikacin) hydroxyl groups (Fig. 1A). The possibility of desymmetrizing 2-DOS has attracted significant attention as the obtained desymmetrized derivatives can be used to provide a direct access to a wide range of functionalized aminoglycosides.[5–7] While the most concise way to desymmetrize 2-DOS is through the direct glycosylation, only enzymatically-controlled glycosylations of the C4 position of 2-DOS are known.[8] Such transformations provide powerful means for the assembly of aminoglycosides, but at the same time suffer from the limited substrate scope, and complementary non-enzymatic methods for the desymmetrizative glycosylation of 2-DOS are highly desired.

Our group has long-standing interests in developing and exploring chiral phosphoric acid (CPA)-catalysed reactions of acetals.[9,10] Recently, our group[11] along with Toshima and co-workers[12] demonstrated that CPA-catalysed acetal/glycoside formation might proceed with the recognition of alcohol chirality in racemic alcohols and carbohydrate-derived diols. Based on these observations, we surmised that CPA-catalysed glycosylation of 2-DOS derivative **1** with protected mannose donor **2** might proceed selectively and lead to desymmetrization of 2-DOS thus providing key disaccharides **α-3A** and **α-3B**. These compounds could be further used for the assembly of various aminoglycoside antibiotics and their isomeric forms with the inversed C4/C6 connectivity (Fig. 1B). This manuscript describes our studies on selective synthesis of **α-3A** and **α-3B** through CPA-controlled desymmetrizative glycosylation of *meso*-diol **1**, and further functionalization of **α-3B** to provide isomeric neamine **5** and kanmycin B derivative **10** that are not readily accessible by traditional semisynthetic methods.[4]

Our studies commenced with the synthesis of 2-DOS *meso*-derivative **1** (Scheme 1). This substrate can be obtained by direct derivatization of 2-deoxystreptamine hydrobromide salt that is readily available by degradation of neomycin B trisulfate.[13] This salt was subjected to a two-step protocol that involves protection of amines as azides (52% yield),[14] and selective TBS-protection of more reactive C5 hydroxyl group (81% yield) to provide *meso*-derivative **1**. The azide-based protection of C1 and C3 amines of **1** was selected due to the relatively small steric size and polarity of the azido group, which is beneficial for the reactivity of **1** in glycosylation reactions. While the introduction of two azides into six carbon-containing 2-DOS resulted in a shock-sensitive triol;

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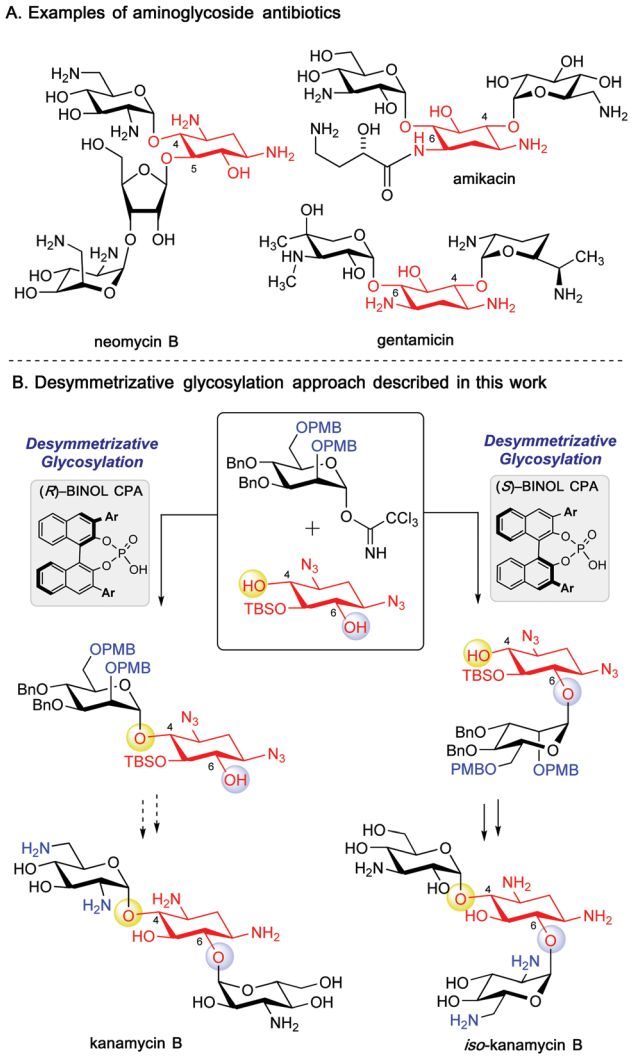
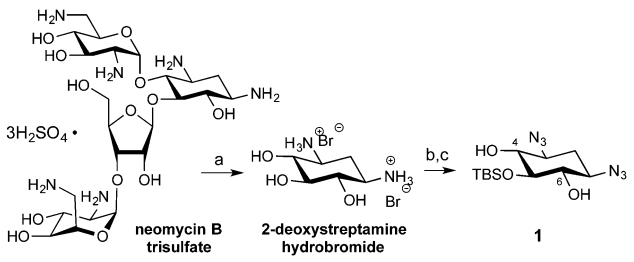



Fig. 1 Application of desymmetrizative glycosylation to synthesis of aminoglycosides.



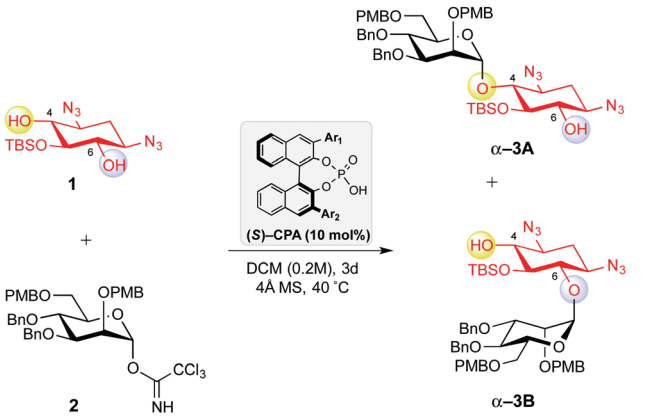

Scheme 1 Preparation of 2-deoxystreptamine derivative **1**. [a]Conditions: (a) HBr (conc.), reflux; (b) 1*H*-imidazole-1-sulfonyl azide·$H_2SO_4$, $CuSO_4$, $K_2CO_3$, 52% yield; (c) TBSOTf, 2,6-lutidine, THF, r.t., 81% yield.

the C5 TBS-protected derivative **1** was found to be stable to detonation by heat or shock (refer to SI for further details).

With the *meso*-derivative **1** in hand, the catalyst-controlled glycosylation of **1** with trichloroacetimidate **2** was investigated next (Table 1). The mannose-derived trichloroacetimidates undergo α-selective glycosylations, which is required for the synthesis of natural aminoglycosides such as kanamycin B.[15] To test the inherent selectivity of the glycosylation reaction, the mixture of **1** and **2** was subjected to catalytic quantities of TMSOTf. While the formation of ~1 : 1 mixture of disaccharides **α-3A** and **α-3B** was indeed observed, the substantial quantities of other isomeric disaccharides inseparable from **α-3A** and **α-3B** complicated further analysis.

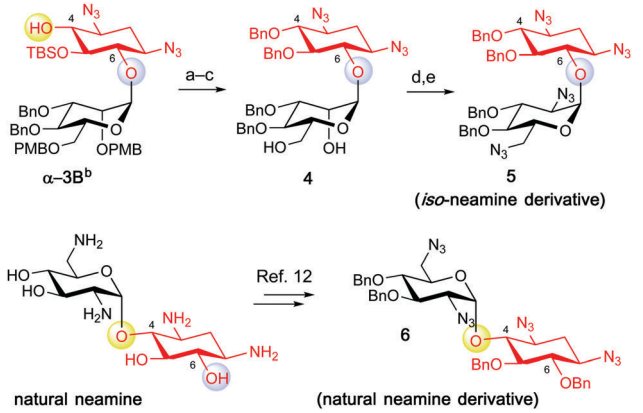
Similarly, the attempts to promote the reaction by using diphenylphosphoric acid as the catalyst (Table 1, entry 1), did not result in clean formation of **α-3A** or **α-3B**, but rather led to decomposition of the starting materials. To our delight, BINOL-backbone-containing CPAs[16] were found to be significantly better catalysts of this glycosylation;[11,12,17,18] however, strong dependence of the catalytic activity on the nature of the 3,3′-aryl substituents was observed. Thus, CPAs without electron withdrawing group on their backbones (entry 2) failed to promote the glycosylation reaction at all. However, more acidic catalysts with electron withdrawing 3,3′-aryl groups did promote the formation of inseparable mixtures of **α-3A** and **α-3B** with variable selectivities (entries 3–15). Remarkably, the use of (*S*)-CPA with Ar = 3,5-$(SF_5)_2C_6H_3$ resulted in **α-3B** as the main product (86 : 14 d.r., 74% yield, entry 14). Finally, the use of enantiomeric

Table 1 Optimization of desymmetrizative glycosylation of protected 2-deoxystreptamine **1** and functionalized mannose **2**[a]

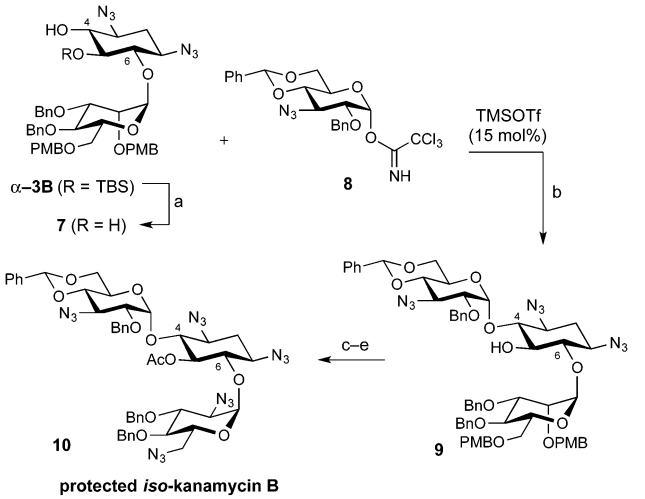



| Entry | Catalyst $Ar_1$, $Ar_2$ = | Conversion, % (yield, %) | Diastereoselectivity (**α-3A** : **α-3B**) |
|---|---|---|---|
| 1 | $(PhO)_2PO_2H$ | Decomposition | N/A |
| 2 | (*S*)-2,4,6-$(iPr)_3$-$C_6H_2$ | No rxn | N/A |
| 3 | (*S*)-3,5-$Cl_2$-$C_6H_3$ | <25 | 50 : 50 |
| 4 | (*S*)-2,5-$(CF_3)_2$-$C_6H_3$ | <25 | 26 : 74 |
| 5 | (*S*)-3,5-$(CN)_2$-$C_6H_3$ | <25 | 50 : 50 |
| 6 | (*S*)-3,5-$F_2$-$C_6H_3$ | 37 | 33 : 67 |
| 7 | (*S*)-(1*H*)-(4-Ph)-1,2,3-triazolyl | <25 | 42 : 58 |
| 8 | (*R*)-3,5-$(CF_3)_2$-$C_6H_3$ | 52 | 60 : 40 |
| 9 | (*S*)-3,5-$(CF_3)_2$-$C_6H_3$ | 25 | 30 : 70 |
| 10 | (*R*)-$Ar_1$ = $C_6F_5$, $Ar_2$ = H | <25 | 50 : 50 |
| 11 | (*S*)-$Ar_1$ = $C_6F_5$, $Ar_2$ = H | 34 | 26 : 74 |
| 12 | (*R*)-$C_6F_5$ | 30 | 58 : 42 |
| 13 | (*S*)-$C_6F_5$ | 61 | 25 : 75 |
| **14** | **(*S*)-3,5-$(SF_5)_2$-$C_6H_3$** | **88 (74)** | **14 : 86** |
| **15** | **(*R*)-3,5-$(SF_5)_2$-$C_6H_3$** | **62 (51)** | **67 : 33** |

[a] Conditions: donor **2** (1.5 equiv.), acceptor **1** (1 equiv.), catalyst (10 mol%), DCM (0.2 M) 4 Å MS, 40 °C for 3 days; d.r. was determined by NMR analysis of the crude mixture.




Scheme 2 Stereochemical assignment of products **3** and synthesis of protected iso-neamine **5**[a]. [a]Conditions: (a) TBAF, THF, 4 Å MS, 82% yield; (b) NaH, BnBr, DMF, 40 °C, 84% yield; (c) DDQ, DCM/$H_2O$, (10 : 1), 0 °C to r.t. overnight, 67% yield; (d) $Tf_2O$, pyridine, DCM, −15 °C; (e) $NaN_3$, DMF, 40 °C, 30% yield (2 steps). [b]Transformations a–e were carried on 86 : 14 mixture of **α-3B** : **α-3A** the mixture was separated after the first step (a) and only deprotected **α-3B** was advanced to **5**.




Scheme 3 Application to the synthesis of isomeric kanamycin B derivative **10**[a]. [a]Conditions: (a) TBAF, THF, Å MS, 82% yield; (b) **4** (1 equiv.), **8** (1.5 equiv.) TMSOTf (15 mol%), DCM/$Et_2O$ (1 : 1, 0.25 M), 0 °C, 66% yield; (c) $Ac_2O$, DMAP (10 mol%), pyridine, r.t., 89% yield; (d) DDQ, DCM/$H_2O$ (10 : 1), 0 °C to r.t. overnight, 86% yield; (e) $Tf_2O$, 2,6-lutidine, DCM, −78 °C, 1 h, then $NaN_3$ (20 equiv.) in DMSO, 90 °C, overnight, 16% yield.

(*R*)-CPA overturned the selectivity and favoured **α-3A** product (67 : 33 d.r., 51% yield, entry 15).

The α-C1 configuration of **3A** and **3B** could be conveniently confirmed by observing the $J(C_1–H)$ to be 173 and 169 Hz (*cf.* ESI†), which is consistent with the values typically observed for the α-mannosides (∼170 Hz) and inconsistent with the $J(C_1–H)$ for the β-mannosides (∼160 Hz). However, the proposed connectivity (*i.e.* C4- *vs.* C6) required further validation (Scheme 2). This was achieved by converting the 86 : 14 mixture of **α-3B** and **α-3A** into molecule **5** and comparing it with the known neamine derivative **6**. The synthesis of **5** from **α-3B** commenced with subjecting **α-3B** to TBAF to remove C5-TBS group (82% yield), reprotecting the resultant diol as a benzyl ether (84% yield), and removing of the PMB protecting groups on mannose subunit by DDQ (67% yield) to provide disaccharide **4**. Diol **4** was subjected to a two-step protocol that included converting the mannose subunit to 2,6-bis-triflate, which was subjected to nucleophilic substitution with sodium azide in DMF to provide desired derivative **5** in 30% yield (2 steps). The $^1H$ and $^{13}C$ NMR spectra for the synthetic derivative **5** were distinctly different from the corresponding spectra of known natural neamine derivative **6**[13] supporting the glycosylation at the C6 position of 2-DOS in **α-3B**.

The stereoselective synthesis of disaccharide **α-3B** offered an intriguing possibility of converting this substrate to isomeric kanamycin B with reverse connectivity of the sugars at the C4 and C6 position (Scheme 3). The direct functionalization of kanamycin B to form this derivative represents a significant challenge, while the desymmetrizative functionalization of 2-DOS would provide a more straightforward access to aminoglycosides of this type.[4] Thus, the synthesis of iso-kanamycin B commenced with the cleavage of the C5 TBS group of **α-3B** that resulted in diol **7** (70% yield) along with the regioisomeric product arising from the deprotection of **α-3A** (12% yield). This deprotection was necessary as the TBS group obstructed the glycosylation of the C4 position. The product **7** was subjected to glycosylation with trichloroacetimidate **8** to provide trisaccharide **9** as a single diastereomer and regioisomer in 66% yield, and the observed $J(H_1–H_2)$ = 3 Hz for the new anomeric stereocenter of **9** was consistent with the α-configuration.

The formation of protected iso-kanamycin B (**10**) was completed by oxidizing the trisaccharide with DDQ to remove the PMB groups in the mannose subunit (86% yield). The resultant diol was subjected to bis-triflation and azide substitution to yield compound **10**. While the bis-triflation proceeded smoothly, the displacement of the C2-triflate of mannose subunit with sodium azide[19] was found to be sluggish and provided the desired protected iso-kanamycin B in only 16% yield (2 steps).

The plausible reaction intermediates for the formation of **α-3A** and **α-3B** are proposed in Fig. 2. Our prior mechanistic and theoretical studies of CPA-catalyzed regioselective glycosylation of 6-dEB and oleandomycin-derived macrolactones[20] identified covalently linked anomeric phosphates such as **11A** as viable reaction intermediates. However, considering that the exclusive formation of **α-3A** and **α-3B** from **α-2** is observed in these studies, the formation of an oxocarbenium-based ion pair **11B** cannot be ruled out.

In conclusion, we were able to demonstrate that chiral phosphoric acids catalyze desymmetrizative glycosylation of 2-deoxystreptamine-derived *meso*-diol **1** with mannose trichloroacetimidate donor **2**. While the evaluated achiral acids could not promote this glycosylation selectively, the (*S*)-enantiomer of CPA (Ar = 3,5-$(SF_5)_2$-$C_6H_3$) catalysed diastereoselective formation of the C6 glycosylated product **α-3B** in 86 : 14 d.r. This transformation was accomplished on significant scale (0.3 g of **α-3B**), and is of utility for the preparation of functionalized aminoglycosides. Thus, intermediate **α-3B** was converted into the isomeric protected aminoglycosides neamine and kanamycin B with reversed

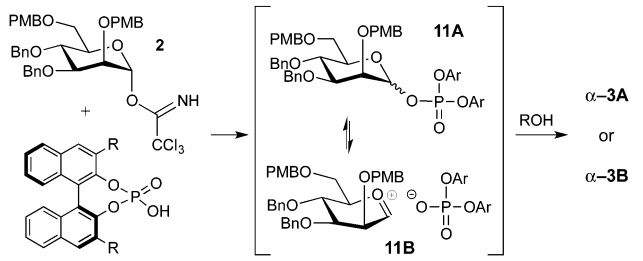



Fig. 2 Plausible mechanism of glycosylation.



connectivity at the C4 and C6 positions of 2-DOS. Further applications of this transformation as well the investigation of the reaction mechanism are the subjects of ongoing studies by our laboratory.

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