Chiral phosphoric acids catalyzed regioselective and desymmetrizative glycosylation leading to the synthesis of aminoglycoside derivatives

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Medicinal Chemistry 3rd year seminar
Thursday March 9th 2017 4 pm

Clinical use of aminoglycoside antibiotics has been on the rise recently in response to increasingly limited options for the treatment of multidrug-resistant bacteria. While there is a huge necessity for developing new aminoglycosides, synthesis or modification of new aminoglycosides is challenging in that they have many amino and hydroxyl groups whose selective modification is difficult. Most aminoglycosides contain a meso-1,3-diaminocyclohexanetriol called 2-deoxystreptamine (2-DOS) in their structure. In this study, BINOL-derived chiral phosphoric acids (CPAs) were employed as catalysts to conduct a regioselective glycosylation reaction at the meso- 2-DOS. Indeed, a pair of enantiomeric chiral phosphoric acids directs the desymmetrization of 2-DOS and regioselective glycosylation by obtaining regioisomers whose connectivity is at either O-4 or O-6 positions of the 2-DOS. Considering that regioselective glycosylation has been mostly done with substrate driven control, the CPA catalyst control of regioselective glycosylation is innovative. Furthermore, the regioisomeric diglycosides formed from regioselective glycosylation catalyzed by BINOL- CPAs are subjected to another glycosylation with a designed allose derivative to afford iso- kanamycin B derivative. Particularly, this synthetic route is very beneficial in that both natural and unnatural isomers of kanamycin B are available depending on which isomers of diglycoside to begin with. This is significant because a synthesis of an isomeric form (unnatural) of any aminoglycosides has not been reported up to date. As a result, the BINOL- CPA catalyzed regioselective synthesis of aminoglycoside will extend the variety of aminoglycoside antibiotics and possibly contribute to the development of novel aminoglycoside antibiotics.