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Addition of amines and carbon nucleophiles to vinyl sulfone-modified 6-deoxy-hex-3-enopyranoside: a case of nucleophile dependent diastereoselectivity

Rahul Bhattacharya, Tanmaya Pathak *

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721 302, India

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ABSTRACT

Reactions of amines and carbon nucleophiles with 4-sulfonyl-hex-3-enopyranoside generate a range of C-3 amino- and C-3 branched-chain sugars, which are analogues of 3-amino-3,6-dideoxy sugars and 3-C-branched-chain-3,6-dideoxy sugars. The diastereoselectivity of addition reaction is nucleophile dependent; while both nitrogen and carbon nucleophiles added in cis-fashion, amines generated C3-C4 trans-diaxial products (*gulo*-derivatives), and carbon nucleophiles afforded C3–C4 trans-diequatorial products (*gluco*-analogues).

1. Introduction

Aminosugars and branched-chain sugars are important classes of modified carbohydrates.[1,2] Several 3-amino-3,6-dideoxy sugars and 3-C-branched-chain-3,6-dideoxy sugars which belong to special classes of amino- and branched-chain sugars are reported in the literature. Some of these aminosugars such as ristosamine,[3,4] daunosamine,[3–6] ravidosamine,[7,8] desosamine,[9–12] and mycosamine[13,14] are the structural components of either macrolide antibiotics such as methamycine, pikromycine,[13] and amphotericin B[14] or tetracyclins such as ravidomycine[7,8] and daunomycin[15] (Fig. 1).

Although there are a limited number of reports on the natural occurrence of C-3-substituted-branched-chain sugars, D-aldgarose is the best known example of this kind.[16] However, a 3,6-dideoxy branched-chain sugar,[17] namely, methyl 2-*O*-benzoyl-3,6-dideoxy-3-*C*-methyl-α-D-altropyranoside was used for the construction of the complex molecule rifamycin W. Yet another related sugar reportedly exists as a component of a complex molecule callipeltoside A, a novel class of antitumor agent (Fig. 2).[18]

In spite of the noted importance of C-3 functionalized 3,6-dideoxysugars, synthesis of this class of compounds remains a challenging task. Sugar triflates,[12–14] epoxide,[11] and ketones[19,20] are the commonly used intermediates for the incorporation of nitrogen functionality at C-3 of 6-deoxy-hexopyranosides. 4,6-Dichloro derivatives have also been used frequently for the synthesis of 3-amino-3,6-dideoxysugars.[11,20–22] 3-Amino-3-deoxy*gluco*-derivatives were generated in a regioselective fashion from 6-deoxy analogues of 2,3-anhydro *allo*-pyranosides.[11] However because of the nonselective regiochemical outcome,[21] the 3,4-anhydro *allo*- and *galacto*-pyranosides are not the substrates of choice.[23] On the other hand, use of C-3-ulopyranosides for the synthesis of C-3-*N* aminosugars are notably interesting compared to the other methods,[13,20,21] although the reduction of such sugar-derived oxime and hydrazone derivatives using common reducing agents afforded a mixture of aminosugars.[8,19] In the case of C–C bond formation, nucleophilic displacement of C-3-O-sulfonylated carbohydrates by carbon nucleophiles are of negligible interest because of the secondary nature of the C-3 hydroxyl groups. Although ring-opening reactions of sugar-derived epoxides by carbon nucleophiles are known to be less efficient,[23] limited number of 3-functionalized-3,6-dideoxysugars were synthesized by reacting the corresponding oxiranes with carbon nucleophiles.[24–27] A minor method using cyanopropionaldehyde diethylacetal and (*S*)-propyleneoxide generated a mixture of four methyl glycosides of 3-cyano-2,3,4-6-tetradeoxysugars.[28]

2. Results and discussion

Vinyl sulfone-modified pyranosides and furanosides function as efficient Michael acceptors capable of generating a wide range of products by reaction with several nucleophiles in a diastereoselec-

* Corresponding author.
E-mail address: tpathak@chem.iitkgp.ernet.in (T. Pathak).

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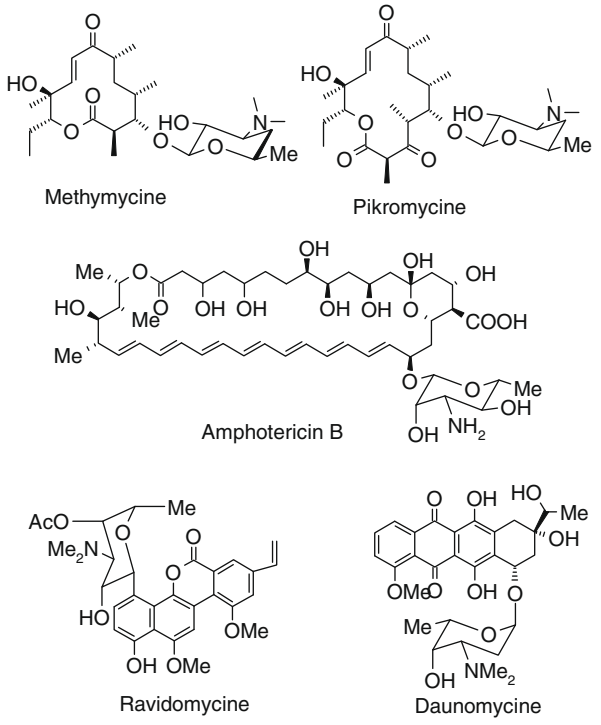


Figure 1. 3-Amino-3,6-dideoxysugars as components of macrolide antibiotics and tetracyclins.

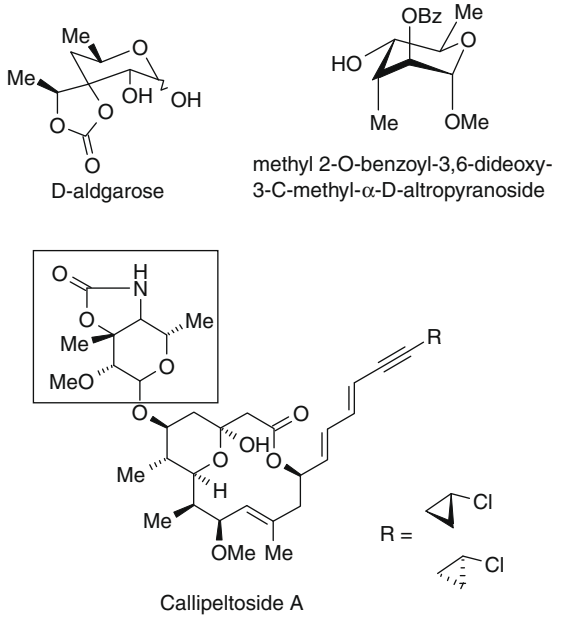
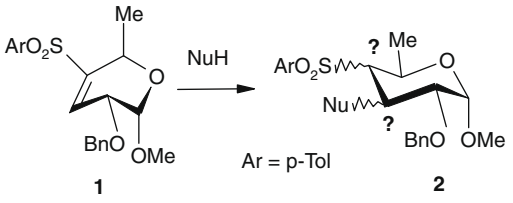


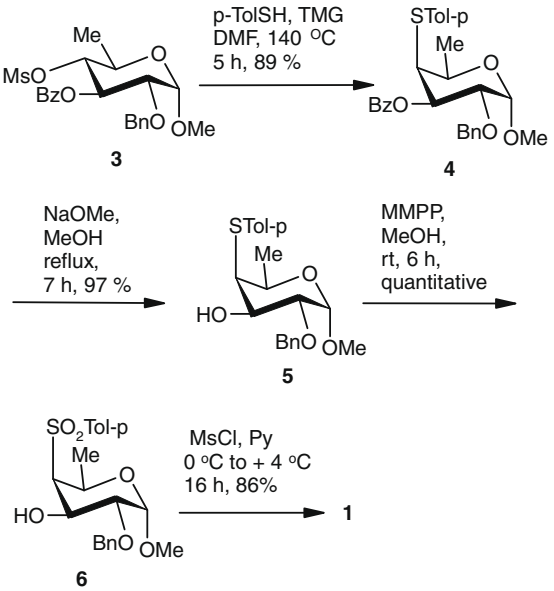
Figure 2. Selected examples of C-3-branched-3,6-dideoxysugars.

tive fashion.[29,30] This strategy would also be useful for producing a number of 3-deoxy-3-modified carbohydrates. Barring a report on the use of 2-sulfonyl-hex-2-enopyranoside as a Michael acceptor and another describing the use of 4-sulfonyl-hex-3-enopyranoside as a partner in a cycloaddition reaction, this strategy for the functionalization of the C-3 carbon of a vinyl sulfone-modified carbohydrate remains unexplored.[29,30] In the light of the above discussion and in order to study the scope of C-3 functionalization we intended to synthesize and study the reaction patterns of a 4-sulfonyl-hex-3-enopyranoside **1** derived from D-glucose. We opined that a Michael acceptor like **1** is highly capable of generating both amino- and branched-chain sugars represented by the general structure **2** (Scheme 1).

A retrosynthetic analysis of the route to **1** necessitated the introduction of the tolylthio group at the C-4 position of a hexopyranosyl sugar. One of the easiest ways of forming a C–S bond would be the displacement of suitably oriented and protected sugar-sulfonates or the regioselective ring opening of epoxy-sugars with sulfur nucleophiles. The use of any 3,4-anhydro sugars as starting materials was ruled out because of the ambiguity of the ring-opening reaction in terms of regioselectivity discussed above.[21,23] Moreover, retrosynthetic analysis indicated that a higher number of reaction steps would be required for the synthesis of suitably substituted 3,4-anhydro sugar (*gluco*- and *galacto*-) compared to the synthesis of *gluco*-mesylate **3**. Thus, the sugar-derived mesylate **3**[31] was reacted with *p*-tolylthiol in DMF in the presence of TMG at about 150–160 °C to afford **4** in 89% yield within 5 h (Scheme 2). The regio- and stereospecificities of attack of *p*-tolylthiolate to C-4 position of **3** was a foregone conclusion because of its inbuilt structural features. Thus, the α-*gluco*-mesylate **3** produced *galacto*-derivative **4** as expected. Treatment of compound **4** with methanolic NaOMe at reflux temperature for 7 h afforded compound **5** in excellent yield. The corresponding sulfone derivative **6** was generated in quantitative yield at room temperature within 6 h by oxidizing **5** with magnesium monoperoxyphthalate hexahydrate (MMPP) in MeOH. Compound **6** was subjected to elimination reaction using MsCl in pyridine at +4 °C to afford **1** in 86% yield (Scheme 2). The identity of vinyl sulfone **1** was established on the basis of spectroscopic and analytical data, the vinyl proton appearing at δ 6.85.



Scheme 1. Proposed reaction pattern of vinyl sulfone-modified carbohydrate **1**.



Scheme 2. Synthesis of methyl 2-*O*-benzyl-3,4,6-trideoxy-4-(4-methylphenyl)-sulfonyl-α-D-*erythro*-hex-3-enopyranoside **1**.