Total Synthesis

DOI: 10.1002/anie.201104516

Total Synthesis of Sialic Acid by a Sequential Rhodium-Catalyzed Aziridination and Barbier Allylation of D-Glycal**

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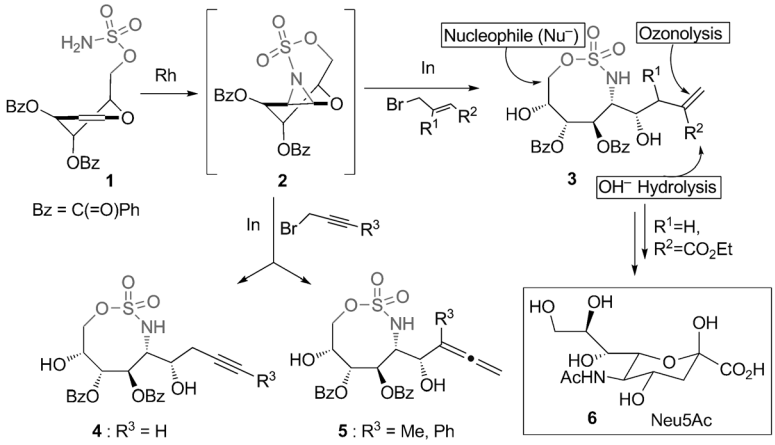
Aminoglycosides form a large class of clinically important antibiotics with a broad antibacterial spectrum, particularly against Gram-positive and Gram-negative pathogens.[1] The biologically important carbohydrates in prokaryotic and eukaryotic glycoconjugates are mainly comprised of 2-amino-2-deoxyglycopyranosides.[2] The synthesis of 2-amino-2-deoxypyranoside residues is challenging in two ways: the selective functionalization of the nitrogen moiety at the C2-position, and the formation of the glycosidic bond with appropriate glycosyl acceptors. Nowadays, glycals are often employed as versatile starting materials for such syntheses. Numerous methods have been developed for the direct introduction of a nitrogen substituent at the C2-position of glycals. These approaches involve inter- or intramolecular addition of a nitrogen atom to a glycal scaffold, which generates an aziridine intermediate, followed by ring opening with a nucleophile. These methods have been developed as general pathways to generate 2-amino sugars.[3–5]

Over the years, our research has focused on developing new synthetic methods for constructing novel frameworks on sugar molecules, and applying these methods to the synthesis of natural products.[6] We have developed an intramolecular version of a rhodium-catalyzed addition of a nitrene to a glycal scaffold. Specifically, the diastereofacial preference of the nitrogen atom transfer process is controlled by the position of a sulfamate ester moiety on the glycal molecule. This causes the glycosyl acceptor to attack the anomeric carbon atom on the opposite face of the sugar ring to the sulfamoyloxy group.[7] We have a strong interest in utilizing our protocol to synthesize the sialic acid *N*-acetylneuraminic acid (Neu5Ac; **6**) by direct C-aminoglycosylation.

We herein describe a remarkable C–C coupling reaction in the sequential rhodium-catalyzed aziridination and Barbier allylation or propargylation at the anomeric position of D-glucal (Scheme 1). The reaction proceeded selectively to form an eight-membered [1,2,3]-oxathiazocane-2,2-dioxide in a single step. Moreover, we demonstrate that a range of nucleophiles can be used with this method. The total synthesis of Neu5Ac and a protected derivative is also described.



Scheme 1. One-pot, rhodium-catalyzed aziridination and indium-mediated allylation/propargylation.

Sulfamate ester **1** was prepared from tri-*O*-acetyl glucal[7a] and treated with PhIO, MgO, and rhodium(II) trifluoroacetamide ($[Rh_2(tfacam)_4]$; 5 mol%) in CH_2Cl_2 at room temperature, under N_2. This reaction generated a nitrene in situ, which added intramolecularly to the C=C bond of the glycal. Trapping the resulting transient aziridine **2** with an appropriate carbon nucleophile was critical. Barbier allylation or propargylation has emerged as a powerful method for forming C–C bonds;[8] therefore, we applied this reaction in our synthetic system.

The initial investigation was focused on optimizing the metal-mediated allylation[9] of **2**. The results are summarized in Table 1. Allylmagnesium bromide was very reactive with **2**; however, no coupled products were obtained (Table 1, entry 1). Other metal–allyl reagents prepared from In, Sn, and Zn were examined under the same reaction conditions. Indeed, when **2** was treated with allyl bromide in the presence of In metal in THF, a coupling reaction occurred and oxathiazocane **7** was obtained in 72% yield (Table 1, entry 2). Attempts were made to optimize the reaction

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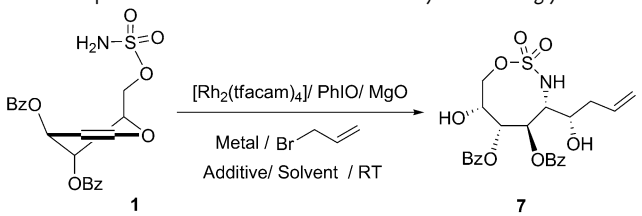
[**] We thank Prof. Francois Mathey and Prof. Koichi Narasaka for fruitful discussions. We also thank Dr. Yong Xin Li for X-ray analyses and gratefully acknowledge Nanyang Technological University (NTU; RG 50/08) and the Ministry of Health (MOH; NMRC/H1N1R/001/2009) Singapore for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104516.

Table 1: Optimization of the metal-mediated allylation of D-glycal **1**[a].



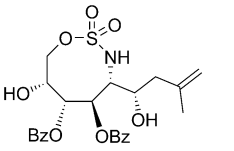
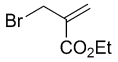
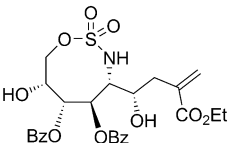
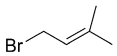
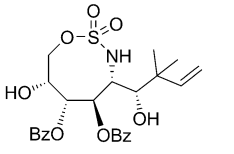
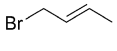
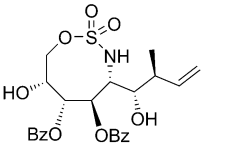
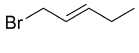
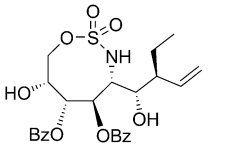
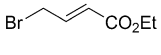
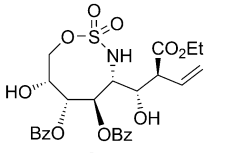
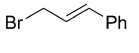
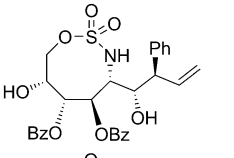
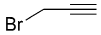
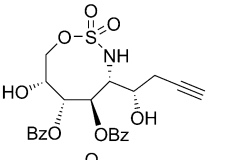
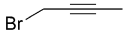
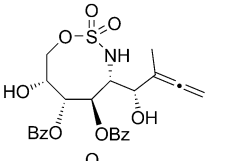
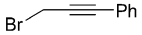
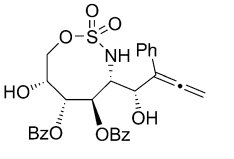
Entry	Metal	Additive	Solvent	Yield [%]
1	Mg	–	THF	–
2	In	–	THF	72
3	In	InF_3	THF	40
4	In	$InBr_3$	THF	30
5	In	NaI	THF	35
6	In	KI	THF	85
7	In	KI	CH_2Cl_2	50
8	In	KI	DMF	–
9	Sn	KI	THF	–
10	Zn	KI	THF	39
11	Zn	KI	CH_2Cl_2	–
12	Zn	KI	DMF	–

[a] For generation of the aziridine intermediate **2**: Glycal **1** (30 mg, 1 equiv.) was treated with $[Rh_2(tfacam)_4]$ (5 mol%), PhIO (1.5 equiv), MgO (5 equiv), and 4 Å molecular sieves in dry CH_2Cl_2 (3 mL) at RT. For preparation of allyl nucleophiles: A mixture of metal powder (2 equiv), allyl bromide (3 equiv), and additive (1 equiv) was stirred in THF (1 mL) at RT for 1 h. OBz = OC(=O)Ph.

conditions by adding InF_3, $InBr_3$, NaI, or KI in conjunction with In and THF (Table 1, entries 3–6). Interestingly, adding KI to the reaction significantly improved the yield of the product to 85%. Furthermore, the stereochemical outcome of the reaction was maintained. Changing the solvent to CH_2Cl_2 or *N*,*N*-dimethylformamide (DMF) dramatically reduced the yield of product to 50% and 0%, respectively (Table 1, entries 7 and 8). Using allyltin in THF or allylzinc in various solvents did not improve the yield of product (Table 1, entries 9–12). The reaction with In/KI/THF was definitively the best, giving a high yield of pure oxathiazocane **7**.

A variety of allyl bromides were coupled with **2** under our optimized conditions. In all cases, the C–C coupled oxathiazocane derivatives were obtained in moderate to good yields (Table 2, entries 1–7). The high resolution mass spectrum showed clear *m/z* $[M+Na]^+$ signals corresponding to the chemical formulas of the oxathiazocane products. Moreover, NOE experiments showed no correlation between H2 and H6 (counting the carbon atom at CH_2OSO_2NH as C1). The configuration at the stereogenic centers was assigned on the basis of the small coupling constants between the *cis*-oriented protons ($J_{2,3}$ and $J_{5,6} < 1$ Hz) in the NMR spectrum, as well as the large coupling constants between the *trans*-oriented protons ($J_{4,5} = 9.4$–9.8 Hz). The allylation reaction was also regioselective. Allylic rearrangement generated a terminal alkene, thereby resulting in the more highly functionalized carbon atoms from the substituted allyl bromides occupying the α position of the newly formed C–C bond (Table 2, entries 3–7). The ^{1}H NMR spectra acquired for compounds **11** and **12** were consistent with these two products being obtained as a mixture of two diastereomers. We were unable to separate the diastereomeric mixtures by column chromatography; however, the stereochemistry of the major diastereomer of **12** was unambiguously elucidated by single-crystal X-ray analysis (Figure 1).

Table 2: Barbier allylation and propargylation of D-glycal **1**.

Entry	Nucleophile	Product[c]		Yield [%]
1			**8**	86
2			**9**	93
3			**10**	87
4			**11**	80 (1:1.6)[a]
5			**12**	72 (1.5:1)[a]
6[b]			**13**	53
7			**14**	74
8			**15**	90
9			**16**	89
10			**17**	77

[a] The number in parenthesis is the diastereomeric ratio. [b] 0.1 equiv of $InBr_3$ was used. [c] OBz = OC(=O)Ph.

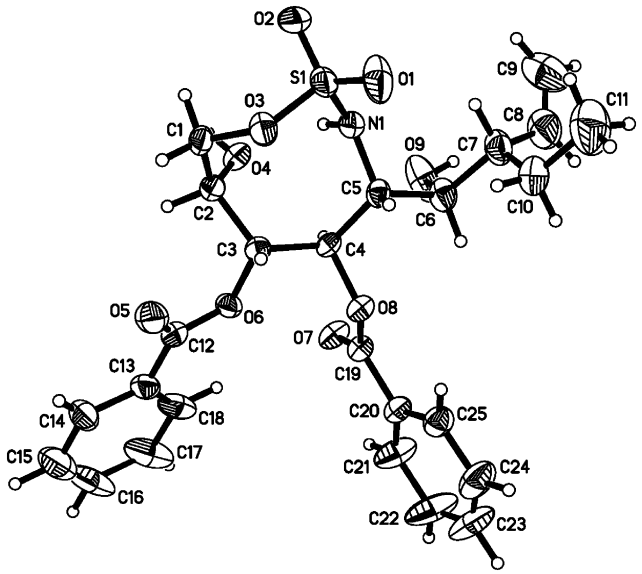
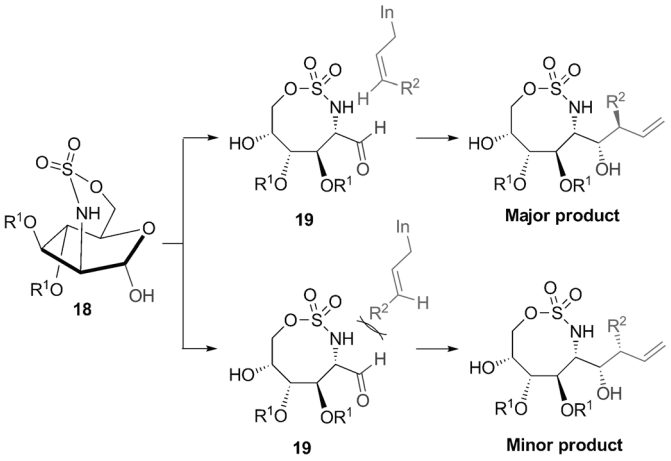


Figure 1. X-ray crystallographic analysis of the major diastereomer of oxathiazocane **12**. The X-ray analysis was done with 50% probability of ellipsoids.[17]



Scheme 2. A plausible mechanism for the formation of the oxathiazocane ring.

The coupling reaction of **1** and propargyl bromide proceeded under the optimized reaction conditions to give oxathiazocane **15** in 90% yield (Table 2, entry 8). In contrast, substituted propargyl bromides, such as 1-methyl and 1-phenyl propargyl bromide, formed the allene products **16** and **17**, respectively (entries 9 and 10). The presence of the allene moieties was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The resonances of the methylene protons of **16** and **17** appeared as multiplets between 5.30 and 5.42 ppm, and the resonances of the central carbon atom of the allene groups appeared at 205.1 ppm and 207.4 ppm, respectively.

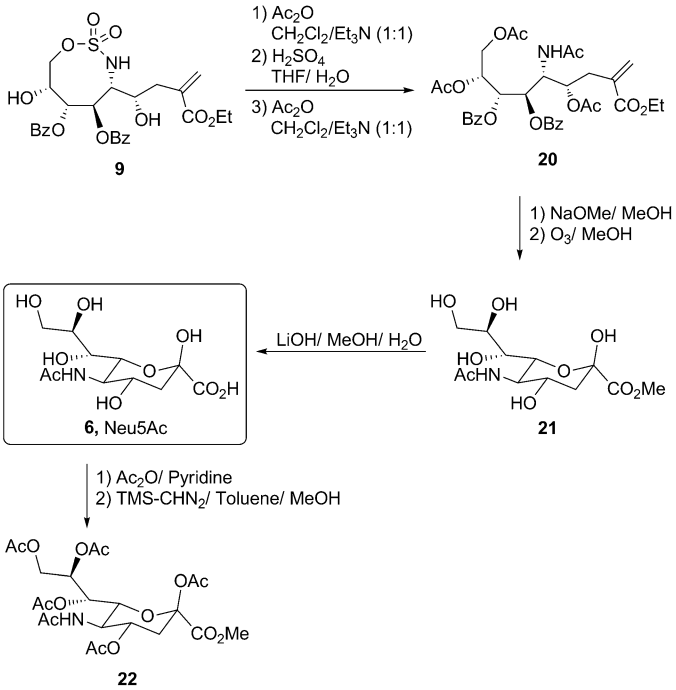
The formation of oxathiazocane derivatives involved two sequential steps: expansion of sugar ring followed by C-glycosylation. We propose that a water molecule plays a significant role in these particular steps. Although we attempted to generate the allylindium reagent under N_2 in anhydrous THF, we could not exclude water completely. Therefore, a water molecule could possibly attack the anomeric carbon atom before or after allylation or propargylation.

Experimental observations and computational results provided strong evidence that the glycosyl acceptor attacked the positively charged, anomeric carbon atom on the opposite face of the oxathiazocane ring to the sulfamoyloxy group.[7a] The proposed mechanism for the expansion of the sugar via a hemiacetal intermediate is shown in Scheme 2. After forming the unstable intermediate **2**, water acts as a nucleophile to give hemiacetal **18**, which is transformed into aldehyde **19**. Steric factors then determine that the preferred approach for the allylindium reagent to **19** is on the *R*-face, with the R_1 substituent directed away from the bulky oxathiazocane moiety.[10]

We have developed a new strategy to construct a backbone of nine carbon atoms, which is potentially very useful for synthesizing a library of biologically active sialic acids. Sialic acids are a diverse family of naturally occurring 2-keto-3-deoxynanonic acids. Such compounds are common in cell-surface glycoconjugates, in which they are found as the terminal sugar, linked through α-ketosides. Sialic acids are abundant in mammalian systems,[11] and the most ubiquitous derivatives are those formed from Neu5Ac. Various therapeutic agents and diagnostic tools for infectious diseases have been developed through understanding the biological roles of Neu5Ac. This insight has further advanced the discovery of anti-influenza drugs such as Relenza and Tamiflu.[12] Since the first chemical synthesis of Neu5Ac by Cornforth et al in 1958,[13] numerous researchers studies towards the synthesis of Neu5Ac and its derivatives have been reported.[14,15]

To obtain **6**, the sulfamoyloxy moiety of oxathiazocane **9** was removed to access an acyclic methylene compound. Subsequent deprotection and ozonolysis allowed the pyranose ring of **6** to re-form.[15] From a synthetic standpoint, the nucleophilic displacement of SO_3, especially from a large oxathiazocane, can be promoted by protecting the nitrogen atom with an electron-withdrawing group. Thus, oxathiazocane **9** was treated with acetic anhydride in a mixture of CH_2Cl_2 and Et_3N to give a reactive triacetate.[16] Cleavage of the sulfamoyloxy group was achieved under acidic conditions, and the resulting crude product was acetylated to afford a 74% yield of stable tetraacetate **20** (Scheme 3). Following the deprotection of **20** with NaOMe in MeOH, and subsequent ozonolysis, crude pyranoside **21** was treated with one equivalent of LiOH in aqueous MeOH to form **6.** After ion-exchange chromatography (Dowex 1X8-100 resin, formate form), the yield of isolated **6** was 60%. The conversion of **6** into its protected derivative **22** was achieved by acetylation and methylation in a one-pot reaction (Scheme 3). The analytical data obtained for **22** was consistent with that previously reported in the literature.[14i,j,m]

In summary, a rhodium-catalyzed, intramolecular addition of a nitrene to a glycal, followed by Barbier allylation or propargylation, provides a high degree of stereocontrol in the synthesis of substituted [1,2,3]-oxathiazocane-2,2-dioxides. We used this method to synthesize Neu5Ac, and designed a common strategy to synthesize its analogues. The use of other



Scheme 3. Synthetic route to Neu5Ac and its protected derivative **22**. TMS = trimethylsilyl

nucleophiles to open the sulfamate ring or starting from different sugar substrates may afford new synthetic routes to common and uncommon sialic acids.

Received: June 30, 2011
Revised: September 9, 2011
Published online: October 18, 2011

Keywords: Barbier allylation · glycosylation · propargylation · sialic acids · total synthesis

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[10] See the Supporting Information. An alternative mechanism is proposed to explain the regio and stereoselectivity of aziridination and indium-mediated allylation or propargylation. A DFT calculation supports the proposed mechanism.

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[17] CCDC 846689 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

