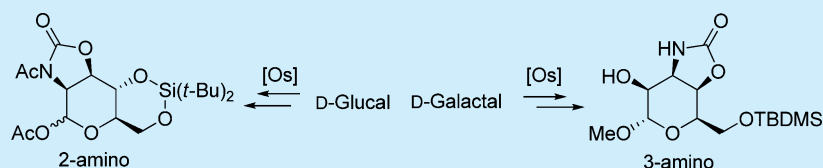


Osmium-Catalyzed Tethered Aminohydroxylation of Glycals: A Stereodirected Access to 2- and 3-Aminosugars

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S Supporting Information



ABSTRACT: The osmium-catalyzed aminohydroxylation of glycals has been achieved with complete regio- and stereocontrol by taking advantage of the Donohoe tethering approach. Glucals and galactals showed complementary reactivity in dependence of the stage at which the reaction was performed, i.e., directly or after double-bond shift consequent to a Ferrier rearrangement (that is, on the 1,2 or 2,3-unsaturated sugar), allowing access to both classes of 2-amino (mannosamine) and 3-amino (talosamine) sugar derivatives, respectively.

The importance of the 1,2-amino alcohol motif is documented by its occurrence in a wide variety of natural products and bioactive compounds, among which aminosugars and aminoglycosides are of particular relevance. In particular, 2- and 3-aminosugars are found, among the glycoconjugates, in naturally occurring antibiotics (macrolides, aminoglycosides, and anthracyclines), and SAR studies have shown the close relationship of this motif with the activity of the aminosugar-containing antibiotics.¹ Moreover, recent studies have shown that simple aminosugars exhibit antifungal and antibacterial activity.²

Extensive synthetic studies have been carried out in order to achieve the direct oxyamination of olefins,³ following the pioneering Sharpless asymmetric aminohydroxylation (AA) reaction.⁴ In order to circumvent the drawbacks of low regio- and stereoselectivity often observed in the oxidation of several classes of olefins with the Sharpless methodology, Donohoe and co-workers introduced in 2001 a variant named "tethered aminohydroxylation" (TA).⁵ This procedure guarantees full regiocontrol by tethering the nitrogen source to an allylic alcohol moiety, affording also a high level of stereoselectivity with chiral allylic substrates. The optimized protocol, recently applied in the total synthesis of valuable naturally occurring amino-hydroxylated scaffolds,⁶ employs as substrate an *O*-aryloxy carbamate, capable of directly oxidizing the used osmium(VI) catalyst to the actual osmium(VIII) active species, obviating the need of adding an external stoichiometric oxidant.⁷

Following our longstanding interest in the field of nitrogen-containing glycomimetics, particularly in iminosugars and iminodisaccharides synthesis,⁸ we turned our attention to aminosugar derivatives and envisaged that the double bond of glycal derivatives bearing a free OH group in allylic position could be manipulated to this aim. Herein we report the results of preliminary studies on the osmium-catalyzed aminohydroxylation

of glycals and 2,3-hexenopyranosides (Figure 1), taking advantage of the tethered approach to obtain, in a stereoselective

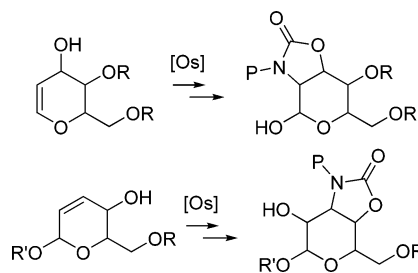


Figure 1. Aim of the work: the tethered aminohydroxylation (TA) of glycals either before or after Ferrier rearrangement.

way, suitably protected 2- and 3-aminosugars with different configurations at the new stereogenic carbon atoms.

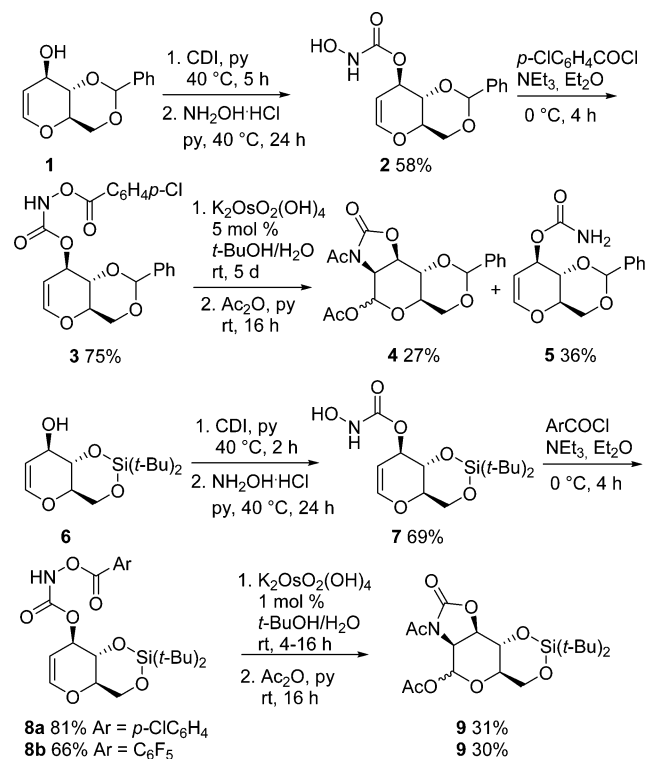
Glycals offer a viable choice for accessing aminosugars.^{9–11} However, these compounds present inherent challenges associated with specific carbohydrate features. Several procedures for the introduction of an amino group at C-2 of glycals have been reported. Among the metal-free procedures, Lemieux and co-workers were able to introduce an oxime¹² or an azido¹³ group at C-2 of galactal, and Danishefsky proposed a sulfonamidoglycosylation of glycals,¹⁴ while a direct [4 + 2] cycloaddition of dibenzyl azodicarboxylate with glycals allowed the preparation of 2-amino-2-deoxycarbohydrates and more complex aminoglycosides.¹⁵ A one-pot acetamidoglycosylation with glycal donors was also described.¹⁶ Carreira proposed a direct transition-metal-promoted amination of glycals using

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manganese nitrido complexes which afforded *N*-trifluoroacetamido derivatives.¹⁷ Intramolecular nitrogen atom delivery strategies, either metal-free or promoted by Rh(II) and copper salts, were also described by Rojas and co-workers.¹⁸ These reactions, efficient on allal derivatives, were not completely chemoselective with glucals, resulting in lower yields. In contrast, only a few synthetic efforts have been documented for obtaining 3-aminosugars from unsaturated carbohydrates, and these often require lengthy and not very efficient synthetic routes.¹⁹ Nicolaou and co-workers employed a tethered reaction for the introduction of a *N*-phenylamino functionality at C-2 or C-3 of glucal derivatives with IBX.²⁰ Recently, a direct tandem hydroamination–glycosylation of glycals was described.²¹

We initially investigated the TA reaction on the benzylidene-protected glucal **1**, synthesized from 3,4,6-tri-*O*-acetyl-D-glucal according to the literature.²² The required precursor **3** was prepared by reaction of allyl alcohol **1** with *N,N'*-carbonyldiimidazole (CDI) followed by hydroxylamine hydrochloride in pyridine, which afforded **2** (58%) followed by aroylation with *p*-chlorobenzoyl chloride (Scheme 1). The TA reaction was then

Scheme 1. TA Reaction on Glucals

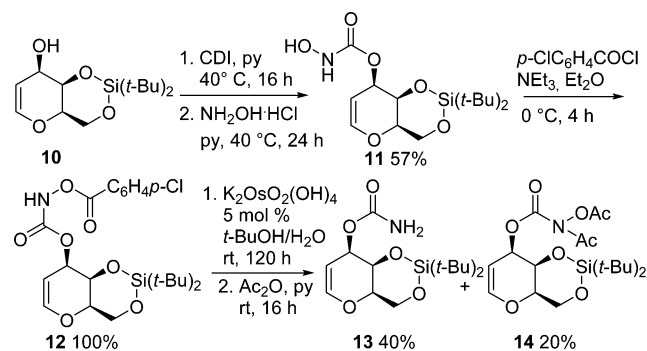


performed on the *O*-aroyloxy carbamate **3** with 5 mol % of K₂OsO₂(OH)₄ for 5 days.²³ Direct acetylation of the crude reaction mixture with an excess of acetic anhydride in pyridine gave a mixture of two compounds, that were identified as carbamate **5** (36%) and an anomeric mixture ($\alpha/\beta = 0.8:1$, as determined by ¹H NMR integration) of the desired oxazolidinone **4** (27%), acetylated at both the anomeric oxygen and at the oxazolidinone nitrogen. The scarce chemoselectivity obtained in the aminohydroxylation of **3** prompted us to consider a differently protected glucal. The di-*tert*-butylsilylene glucal **6**, obtained from 3,4,6-tri-*O*-acetyl-D-glucal as previously reported,²⁴ was reacted with CDI followed by the addition of hydroxylamine to afford the hydroxycarbamate **7** (69%),^{18c}

which was converted into the corresponding *p*-chlorobenzoyl derivative **8a** in 81% yield. Compound **8a** was reacted under the standard TA conditions (*t*-BuOH/H₂O = 3/1) with a reduced amount of catalyst (1 mol %) and selectively provided an anomeric mixture ($\alpha/\beta = 2:1$) of the desired oxazolidinone **9** in 31% yield (36% based on converted **8a**) after acetylation of the crude reaction mixture. To our delight, the silylene **8a** had undergone a clean TA exclusively, albeit leading only to a moderately increased yield. Encouraged by these preliminary results, the hydroxycarbamate **7** was reacted with a different acid chloride, namely pentafluorobenzoyl chloride, reported as a superior reoxidant for the TA reaction (Scheme 1).⁷ Unfortunately, no improvement was achieved, since the TA conditions (1 mol % catalyst), applied to the *O*-aroyl hydroxycarbamate **8b**, obtained as above, provided the desired oxazolidinone **9** (as a 2:1 α/β anomeric mixture) in 30% yield, again with complete chemoselectivity.

In order to extend the study of the scope and limitations of the TA reaction to other glycals, the same protocol was applied to 3,4,6-tri-*O*-acetyl-D-galactal. The di-*tert*-butylsilylene galactal **10** was prepared in two steps as reported.²⁵ The required *O*-aroyloxy carbamate **12** was readily accessed in 57% overall yield by sequential reaction of **10** with CDI and hydroxylamine hydrochloride and subsequent aroylation (Scheme 2). Com-

Scheme 2. TA Reaction on Galactal



pound **12**, when subjected to the TA conditions (5 mol % catalyst) followed by acetylation, failed to cyclize to the desired oxazolidinone. Instead, on purification by FCC over silica gel, the carbamate **13** and the acetyl acetyloxy carbamate **14** were recovered in 40% and 20% yield, respectively.

Rationalization of the substrate dependent behavior (glucal vs galactal) in the above TA reactions relies on the mechanism proposed by Donohoe.⁵ On this basis, the intermediate trioxoimido osmium(VIII) complex **A** in the glucal series (from **3** or **8a,b**) is well suited for the intramolecular [3 + 2] cycloaddition in its preferred half-chair ⁴H₅ conformation to generate the cyclic oxazolidinone **4** or **9** after hydrolysis and acetylation (Figure 2a). With galactal **12**, the opposite configuration at C-4 places the silyloxy group in the axial position in complex **B**, thus hampering the cyclization. Accordingly, the formation of **13** may be ascribed to hydrolysis of this intermediate (Figure 2b).²⁶

Following these observations, it was expected that 2,3-hexenopyranosides, obtained upon Ferrier rearrangement,²⁷ would undergo a TA process to give 3-aminosugars. One such derivative, the gluco *O*-aroyloxy carbamate **17**, was prepared in good yield from the 6-*O*-protected α -methyl glucoside **15**, obtained from 3,4,6-tri-*O*-acetyl-D-glucal in three steps and 74%

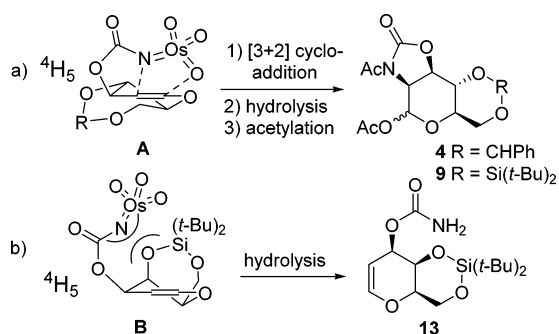
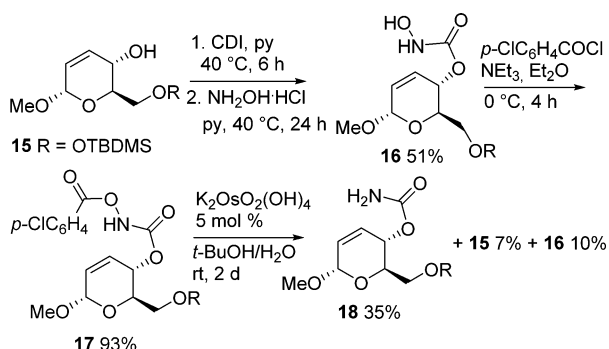


Figure 2. Likely intermediates in the TA reaction with glucal and galactal derivatives.

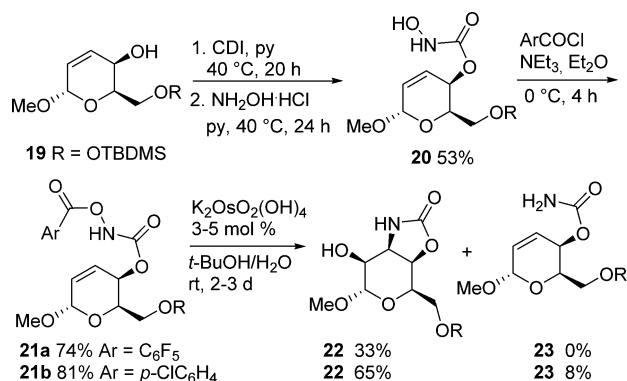
overall yield as previously described.²⁸ However, when reacted under TA conditions with 5 mol % of catalyst, **17** failed to undergo cyclization (Scheme 3), and the carbamate **18** was isolated as the major product (35%), together with minor amounts of **15** (7%) and **16** (10%), probably formed on hydrolysis of **17**.

Scheme 3. TA Reaction on D-Gluco-2,3-hexenopyranoside



The same synthetic strategy was then attempted with 3,4,5-tri-*O*-acetyl-D-galactal (Scheme 4). The required unsaturated

Scheme 4. TA Reaction on D-Galacto-2,3-hexenopyranoside



galacto derivative **19** was prepared in 60% overall yield by Ferrier rearrangement of 3,4,5-tri-*O*-acetyl-D-galactal followed by acetyl deprotection and TBDMS protection at the primary alcohol as reported.²⁹ Application of a synthetic sequence similar to that reported above for **15** but using pentafluorobenzoyl chloride provided the pentafluoroaroyl carbamate **21a** (Scheme 4). To our delight, the TA reaction on **21a** using 3 mol % of Os catalyst provided the desired oxazolidinone **22** in 33% yield.

Notably, when the reaction was repeated with *p*-chlorobenzoyl carbamate **21b**, synthesized in even higher yield (81%) from **20**, and with portionwise addition of the catalyst (5 mol %) over 3 days, the yield of **22** increased to a remarkable 65% (Scheme 4).

As discussed before, the observed substrate selectivity in the aminohydroxylation reaction on substrates **17** and **21a,b** may be rationalized according to the intermediates depicted in Figure 3.

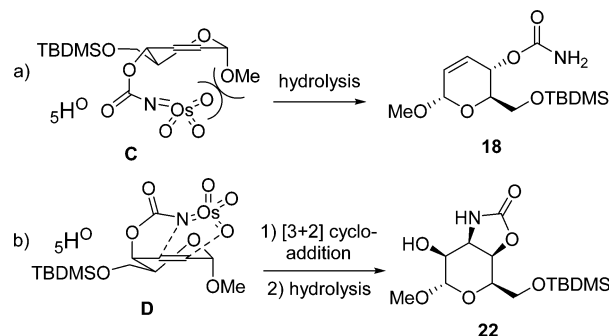
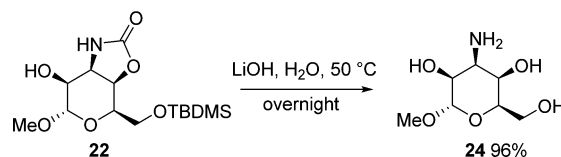


Figure 3. Likely intermediates in the TA reaction with D-gluco- and D-galacto-2,3-hexenopyranosides.

Thus, the [3 + 2] cycloaddition of the gluco complex **C** is hampered by the anomeric methoxy group, with consequent failure of cyclization and reductive cleavage to give the carbamate **18** (Figure 3a). In contrast, the cycloaddition of galacto complex **D** meets with success, allowing formation of the desired oxazolidinone **22** (Figure 3b).

Finally, the conversion of the product oxazolidinones into the free aminosugars was demonstrated by hydrolysis of **22** to the corresponding 3-aminotaloside **24** (Scheme 5) with LiOH in H₂O at 50 °C overnight. This also caused concomitant deprotection of the TBDMS group, affording methyl-3-amino-3-deoxy- α -D-pyranoside (**24**)³⁰ in excellent yield.

Scheme 5. Synthesis of Methyl 3-Amino-3-deoxy- α -D-pyranoside (**24**)



In summary, straightforward access to 2- and 3-aminosugar derivatives by means of the osmium-catalyzed tethered aminohydroxylation (TA) reaction on 1,2- or 2,3-hexenopyranosides showed complementary substrate selectivity in the gluco and galacto series, with glucals yielding the desired 2-aminosugars while galactals failed. By way of contrast, D-galacto 2,3-enopyranosides afforded 3-aminosugars. Work is underway in our laboratory to expand the scope of the reaction and exploit this strategy for the synthesis of relevant aminosugar targets.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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