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Carbasugars

Optimized and Scalable Synthesis of Carba-α-D-Glucosamine

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Abstract: An efficient, high-yielding synthesis of carba-α-D-glucosamine is reported. Key features of this optimized route include an innovative protecting group strategy and an unusual, stereoconvergent Ferrier carbocyclization of a hindered substrate. The sequence enables the synthesis of larger amounts of this structurally novel antibiotic to allow more detailed biological evaluations of its unique mode of action.

Carbapyranosides constitute an important class of natural products[1] and present key subunits of a variety of elaborated metabolites.[2] Several of these glycopyranoside analogs demonstrate attractive biological profiles as some enzymes cannot distinguish these stabilized carbocyclic derivatives from the authentic carbohydrates.[2,3] Prominent examples include cyclophellitol (**1**, Figure 1) which is a β-glucosidase inhibitor or the herbicidal agent carbapyranose MK7067 (**2**).[2,4,5] Due to higher stability, carba sugars are often used in drugs to substitute the more labile glycopyranosides.[6–8]

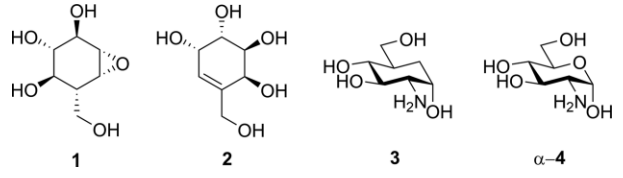

Figure 1. Structures of cyclophellitol (**1**), MK7067 (**2**), α-D-glucosamine (GlcN, α-**4**), and its carbocyclic analog carba-α-D-glucosamine (CGlcN, **3**).

Carba-α-D-glucosamine (CGlcN, **3**) the carbocyclic analog of α-D-glucosamine (GlcN, α-**4**) shows interesting antibiotic activity against various pathogenic bacteria, including *Bacillus subtilis* and *Staphylococcus aureus*.[9] After cellular uptake and C-6 phosphorylation, it effectively activates the glutamine-fructose-6-phosphate amidotransferase (GlmS) riboswitch in vitro to a similar extent as the natural substrate α-**4**. The result is down-regulation of the GlmS expression.[9] In addition to a mere conformational change as observed for other riboswitches, this ribozyme then also catalyzes mRNA self-cleavage,[9,10] which adds to a unique mode of action. Usually, this mechanism is necessary for regulation in the process of cell wall biosynthesis.[11] The intracellular concentration of GlcN (α-**4**), a precursor of peptidoglycan is regulated by this allosteric inhibition.[12] If the GlmS riboswitch is activated by CGlcN (**3**) the cell-wall biosynthesis is inhibited because the production of peptidoglycan is not possible anymore due to a lack of GlcN (α-**4**). The result is cell death. Unfortunately, a more detailed analysis of this unique mode of action as well as further development is severely hampered by supply issues.[9,13,14,15] There are several synthetic strategies towards carbapyranosides reported in the literature, using both carbohydrates as starting material[16–20] and non-carbohydrate approaches.[19,21–25] However, most of these previous synthetic research does not treat carba analogs of amino sugars like GlcN (α-**4**). Consequently, a more efficient synthetic route to carbasugar **3** is desirable.

Herein, we report the design and implementation of an improved, efficient total synthesis of CGlcN (**3**), which allows for reliable and scalable access to this promising antibacterial agent. Key features of this concise route include a beneficial uniform protective group strategy and a challenging stereoconvergent Ferrier carbocyclization of a hindered epimeric substrate.

As shown in Figure 2, the carbocyclic core **5** of target carbasugar **3** was envisioned to arise from a Ferrier rearrangement of a suitably functionalized pyranoside α/β-**6**, in analogy to the described route.[9,13,15] However, in contrast to this report, a

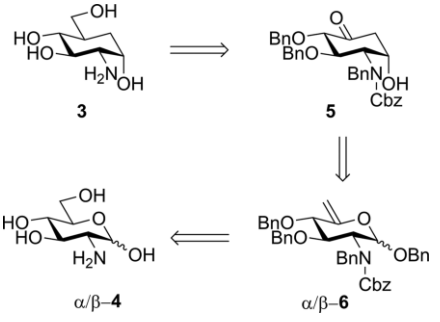

Figure 2. Retrosynthetic analysis of CGlcN (**3**).

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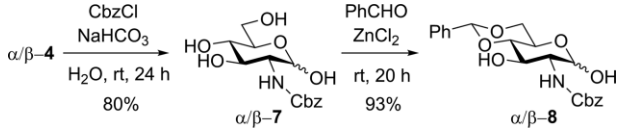
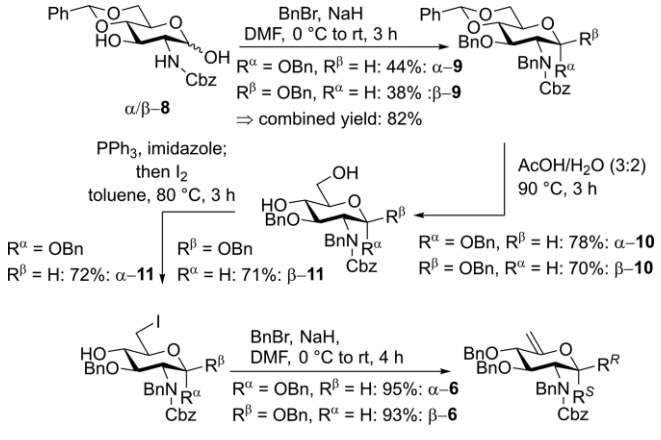
more bulky substrate bearing a benzyl residue at the anomeric oxygen was chosen. This would allow for a more convenient and uniform protective group strategy. It was hoped that fully benzylated precursor α/β-**6** would be more easily accessible from GlcN (α/β-**4**) as cheap and readily available starting material, in contrast to the previous report utilizing a methyl ether at the anomeric hydroxyl, which had proved to be difficult to install.[14,26]

As shown in Scheme 1, the implementation of this synthetic design was initiated by Cbz-protection of α/β-**4**, which efficiently proceeded in aqueous solution with benzyl chloroformate (80 %).[27] Derived α/β-**7** was then elaborated as benzylidene acetal using benzaldehyde and zinc chloride to access α/β-**8**,[13] likewise in high yield (93 %). Importantly, both steps were readily scalable (25 g), without the need for chromatographic purification. Both derivatives resided as inseparable, rapidly equilibrating mixtures of the α- and the β-anomer, similar to parent compound α/β-**4**.



Scheme 1. Protection of GlcN (α/β-**4**).

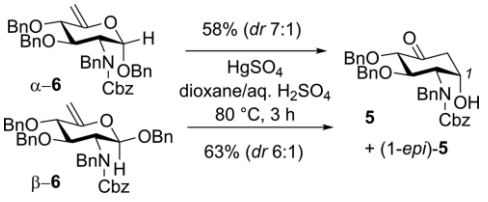
As shown in Scheme 2 the anomeric position of α/β-**8** was then benzylated using benzyl bromide with NaH in an efficient and scalable manner (82 %), confirming our synthetic design and resolving one of the key limitations of the reported route.[14] Almost identical amounts of the two anomers were obtained, which can be separated by column chromatography. After cleavage of the benzylidene acetal of α/β-**9**, the resulting diol α/β-**10** was selectively converted to monoiodide α/β-**11** by an Appel reaction. The primary hydroxyl function of α/β-**10** reacted much faster[28] and using one equivalent of iodine gave mono iodinated sugar α/β-**11** exclusively. The remaining free secondary hydroxyl group was then protected with benzyl bromide under strong basic conditions (NaH), which also led to the elimination of HI to obtain vinyl ether α/β-**6**, in agreement with an earlier observation for a related substrate.[13] Again, all four steps proceeded with improved yields.[13] Furthermore, we



Scheme 2. Further synthetic elaboration towards vinyl ether α/β-**6**.

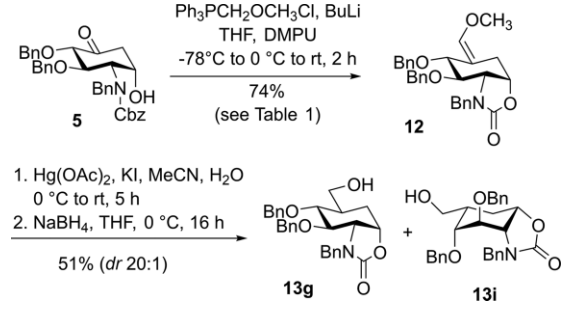
could explicitly show, that either anomer reacts with essentially identical yield and selectivity, which opens up the valuable option of carrying out the sequence with epimeric mixtures, as these converge into the desired epimer at a later step of the route (see below).

Gratifyingly, the key Ferrier carbocyclization[13,29,30] of hindered vinyl ether α/β-**6** towards the desired 5-oxo-carbaglucosamine **5** could then be implemented. Optimal results were obtained with mercuric(II) sulfate in a mixture of dioxane and 5 mM aqueous sulfuric acid (Scheme 3). Again, the influence of either C-1 configuration was studied, resulting in a similar yield (58 % and 63 %) and selectivity (7:1 and 6:1), confirming that the outcome is not affected by the anomeric form of the starting material. In both cases, desired (*S*)-isomer **5** was obtained as the major product, regardless of whether the α- the β- or the mixture of α/β-**6** was used.



Scheme 3. Stereoconvergent Ferrier carbocyclization of anomeric vinyl ethers α- and β-**6** towards 5-oxo-carbaglucosamine **5**.

The keto function of 5-oxo-carbaglucosamine **5** was then homologated by an enol ether Wittig reaction towards enol ether **12** (Scheme 4). As shown in Table 1, different reaction conditions were evaluated for optimization of a reported process (entry 1),[13] involving solvents DME (entries 2, 3) and THF (entries 4, 5) with or without co-solvent *N*,*N*′-dimethylpropyleneurea (DMPU). Optimal results were obtained in THF and DMPU, resulting in an improved yield (74 %, entry 5 vs. originally reported 60 %, entry 1). The reaction proceeded with high selecti-



Scheme 4. Homologation of 5-oxocarbaglucosamine **5** and subsequent oxymercuration-reduction of the full carbocyclic backbone **12**.

Table 1. Influence of the solvent and DMPU as additive on the yield of vinyl ether **12**.

Entry	Solvent	Cosolvent	Yield
1[13]	DME	–	60 %
2	DME	–	57 %
3	DME	DMPU (10 equiv)	61 %
4	THF	–	54 %
5	**THF**	**DMPU (10 equiv.)**	**74 %**

vity, giving the (*E*)-product exclusively. Overall, the procedure towards **12** was reliable, also on a larger scale, and more than 3 g could be readily obtained in the first batch.

Further elaboration of **12** towards protected carbasugar **13** then involved oxymercuration and subsequent reduction of the organomercury intermediate,[31] giving D-*gluco*-**13g** together with minor amount of the L-*ido* configuration **13i** (Scheme 4). The original protocol[13] was again optimized giving the desired D-*gluco* isomer with improved selectivity (20:1 vs. 7:1). At this stage, the configurations of **13g** and **13i** were confirmed by NOESY-NMR analysis (Figure 3), in combination with key coupling constants. The rather larger values of 5.1 Hz (**13g**) and 4.6 Hz (**13i**) for the $J_{H\text{-}3,\ H\text{-}4}$ coupling indicated *trans* configurations for **13g** and **13i**. Additionally, the value of 8.1 Hz for the $J_{H\text{-}4,\ H\text{-}5}$ coupling constant of **13g** confirmed the *trans* configuration between H-4 and H-5, while no coupling constant could be determined for the *cis* coupling of H-4 and H-5 in **13i**, due to unsatisfactory resolution. The transformation of a related compound of cyclohexanone **5** to the desired D-*gluco* configured carbon skeleton has also been described in the literature but with more steps to be carried out.[17] So the method used here was considered to be more efficient.

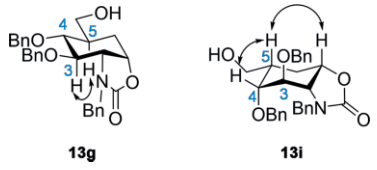
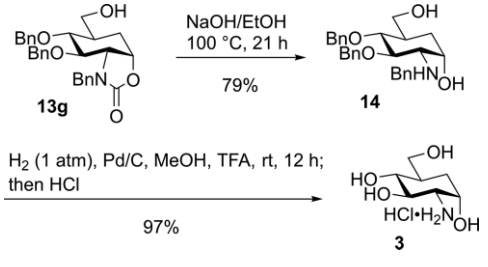


Figure 3. Stererochemical confirmation of D-*gluco*-**13g** and the L-*ido* **13i** by NOESY-correlations.

The cyclic carbamate of carbasugar **13g** was then saponified with aqueous NaOH in ethanol to obtain partially deprotected carbasugar **14** in good yield (79 %, Scheme 5). After initial attempts to effectuate final removal of all benzyl ethers following a reported procedure (1 atm hydrogen pressure of a solution of benzylated carbasugar in methanol with 10 % Pd/C as a catalyst) failed in our hands,[9] it was realized that the desired conversion could be carried out in an effective and reliable manner upon addition of trifluoroacetic acid (10 equiv.) giving target carbasugar **3** as its trifluoroacetate salt. The counterion may then be exchanged against chloride by addition of 0.2 M aqueous HCl and subsequent lyophilization, giving hydrochloride salt of CGlcN (**3**) in a yield of > 95 % from **14**.



Scheme 5. Completion of the total synthesis of CGlcN (**3**).

In summary, an efficient synthetic route towards carba-α-D-glucosamine (**3**) has been reported. The stereoselective sequence allows access to the target compound in 11 steps and 5.3 % overall yield, which compares favorably to a previous route.[9,13,26] Key features of this improved approach include an innovative protecting group strategy, an unusual Ferrier carbocyclization of a hindered substrate, and optimization of several previously reported procedures. This new synthetic route proved to be well-scalable and more than 3 g of the fully functionalized carbocyclic core **12** were obtained in the first batch. Furthermore, the anomeric influence on the selectivity and yield of each conversion was studied in detail, demonstrating that the sequence may be carried out with anomeric mixtures, as they efficiently converge into the desired epimer in the course of a beneficial, stereoconvergent Ferrier rearrangement. This will be important for future scale-up. Following this sequence, larger quantities of this novel antibacterial agent may now be prepared to enable more detailed evaluations of its unique biological profile and unusual mode of action. Also, the strategies developed herein may be applicable for the preparation of designed analogs as well as related carbocycles.

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Keywords: Carbasugars · Ferrier carbocyclization · Natural products · Synthetic methods · Total synthesis

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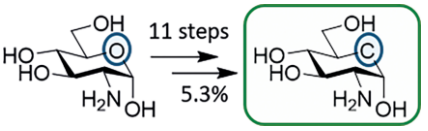

A scalable route to carba-α-D-glucosamine involves a stereoconvergent Ferrier rearrangement of hindered substrates in combination with a uniform protective group strategy and will enable more detailed biological studies of the unique mode of action of this potent novel antibiotic.

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