Synthesis of novel sugar-lactam conjugates using the Aubé reaction†

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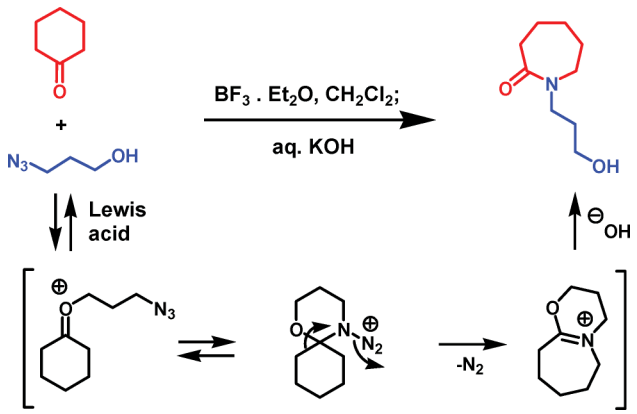
An efficient and convenient method for the synthesis of sugar-lactam conjugates is reported starting from readily available sugar azides using the Aubé reaction. Cyclic azido alcohols are used in the Aubé reaction for the first time in a carbohydrate setting. The resulting glycoconjugates could be further used to increase the chemical diversity on the sugar backbone, and may find potential applications as glycomimetics, peptidomimetics, in glycotargeting and in CNS drug delivery.

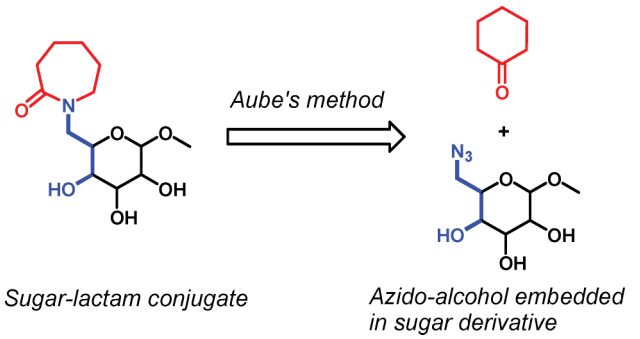
Introduction

Among the several methods available in the literature for the synthesis of lactams,[1] the method introduced by Aubé *et al.* has become more popular in recent times as an efficient and simple to use methodology.[2] This reaction continuously finds wide spread applications in organic synthesis, in particular for the synthesis of natural products. The Aubé reaction,[2] an intermolecular reaction of hydroxyalkyl azides with cyclic ketones to provide lactams, proceeds through an *in situ*-generated hemiacetal as a temporary tether that renders azide addition in an intramolecular fashion, followed by ring expansion. Interestingly, this reaction results in N-substitution of the pendant group on the azide (Scheme 1).



Scheme 1 The Aubé reaction.

The azido alcohol, a key component of the Aubé reaction, can be visualized in a readily available sugar-azide derivative and can be reacted with a variety of cyclic ketones to produce sugar-lactam conjugates (see the blue-colored portion in Scheme 2). As such, medium-sized, in particular 5–7-membered ring, lactams are of considerable interest in pharmaceutical research due to their appealing biological activities.[3] The sugar-lactam conjugates



Scheme 2 A strategy to access sugar-lactam conjugates.

resulting from the present method are expected to be important structural scaffolds in drug discovery.[4] Apart from their very different pharmacodynamic effects, these hybrid molecules often exhibit unusual pharmacokinetic properties, such as tissue permeability.[5] For example, by attaching a polar moiety like a sugar reduces the passive transport in some classes of hybrid molecule, and in other cases attachment of a carbohydrate may increase their ability to cross the Blood Brain Barrier (BBB) through active transport, resulting in a higher drug exposure in the brain. This latter technique is one of the recent approaches to CNS drug delivery.[5b,c,f,i]

Results and discussion

To start with, mannose azide **1**[6] was readily prepared from commercially available methyl-α-D-mannopyranoside and the reaction with cyclohexanone in presence of $BF_3{\cdot}Et_2O$ was attempted, followed by treatment with an aqueous KOH solution, which resulted in the desired mannose-caprolactam as a mixture of products **2** and **3**. Compound **2** is the result of 2,3-hydroxy protection as a ketal, and which can be converted into desired sugar-lactam **3** by treatment with 80% aqueous acetic acid at 80 °C (Scheme 3).[7] Interestingly, this transformation does not require protection of the hydroxyl groups on the sugar moiety. It is noteworthy to mention that the intermediate-like **2**, where the C2- and C3-hydroxy groups are protected, can be utilized for the selective manipulation at the anomeric- or C4-position of the mannose moiety. Alternatively, compound **3** can be synthesized through N-alkylation of the caprolactam using a protected mannose iodide derivative in very poor yield.[8] This route requires additional steps, and the lactams are not readily available in many cases (Scheme 4). Hence, the Aubé reaction is a superior method for accessing sugar-lactam conjugates.

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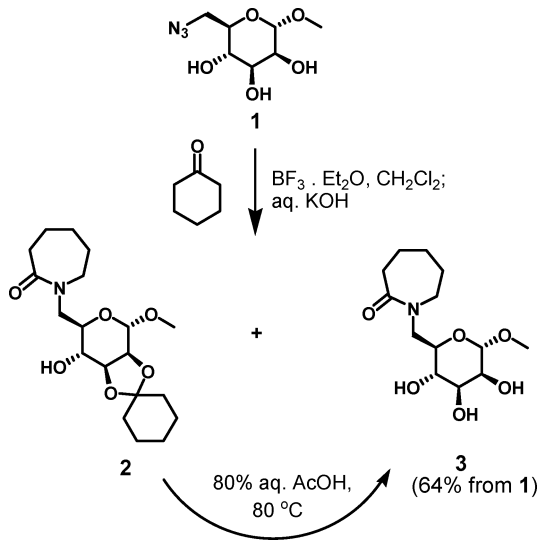
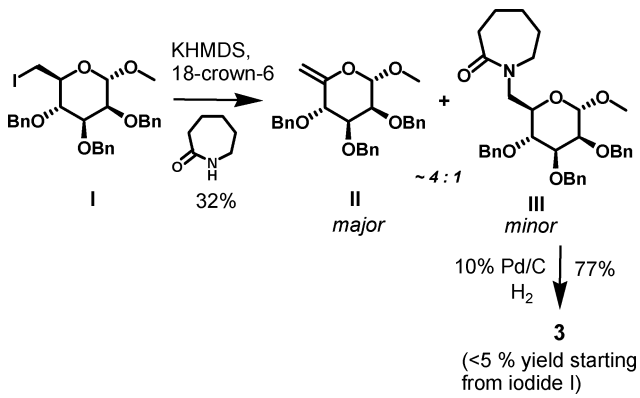
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC reference number 783639. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob00719f



Scheme 3 The synthetic route for accessing sugar-lactam conjugates.



Scheme 4 An alternative attempted route to sugar-lactam conjugates.

Having the protocol in hand, we tested the scope of this methodology with different ketones; the results are outlined in Chart 1. The reaction of mannose azide **1** with cyclobutanone and cyclopentanone resulted in products **4** and **5**, respectively, in good yields. Pyranone and its corresponding sulfur analogue produced sugar-lactam conjugates **6** and **7**, respectively. Next, we looked at the effect of 4-substitution on cyclohexanone and found that 4-phenyl cyclohexanone and 4-*t*-butyl cyclohexanone gave desired lactams **8** and **9**, respectively, in a highly diastereoselective manner.[9] The stereochemistry of the newly formed center was determined to be of *R*-configuration (as drawn) using X-ray crystallographic data† from the tetraacetate of sugar-lactam **8** (see Fig. 1).[10] This phenomenon can be utilized for the synthesis of chiral lactams and their derivatives using readily available sugar-based hydroxy azides, and this method could be complimentary to those already existing.[2c,e] As many drug-like compounds possess the diazepinone moiety in their core structure,[11] gaining access to related scaffolds with sugar hybrids would be rewarding. Accordingly, N-protected 4-piperidone was reacted with **1** to yield **10** in moderate yield. Under the same reaction conditions, 2-indanone produced corresponding bicyclic lactam **11** in poor yield.

To amplify the scope of this method and also to understand the structural requirements of the sugar moiety, different sugar azides were reacted using cyclopentanone under the same conditions;

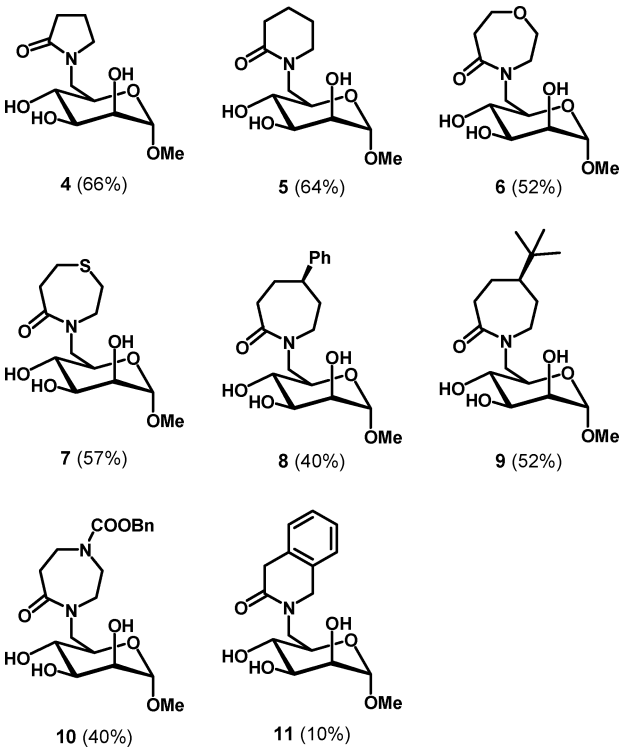


Chart 1 Products obtained from the reactions of **1** with various ketones under Aubé reaction conditions.

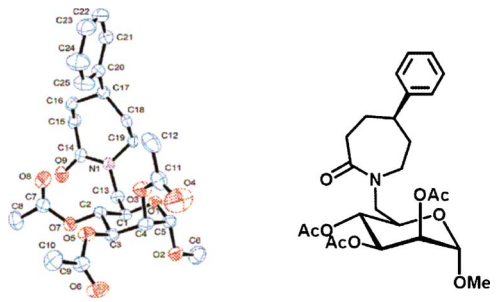


Fig. 1 An ORTEP diagram of the triacetate of **8** (hydrogens are omitted for clarity).

the results are compiled in Chart 2. The reaction on glucose derivative **12**[12] proceeded smoothly and furnished desired sugar-lactam **20** in 66% isolated yield. In this case, no intermediate such as **2** was observed as the C2- and C3-hydroxy groups were *trans* to each other on the pyranose moiety. Deoxy sugar azides **13** and **14**, prepared from D-glucal,[13] resulted in **21** and **22**, respectively. The reaction of furanose sugar azide derivative **15**[14] with cyclopentanone also produced desired lactam **23**[15] in good yield. As expected in the Aubé reaction on 4-deoxy glucose azide derivative **16** using cyclopentanone, no ring expansion took place and no trace of compound **24** was observed. In the case of galactose azide derivative **17**,[16] forcing conditions were required to correspondingly yield **25**. Compound **18**,[17] being a secondary azide, also reacted with cyclopentanone to produce corresponding sugar-lactam conjugate **26**[15] in 52% yield. It is interesting to note that in examples **15** and **18**, a 1,2-azido alcohol moiety is present, unlike the 1,3-azido alcohol moiety found in the rest of the examples. To understand the role of the free hydroxy group in the

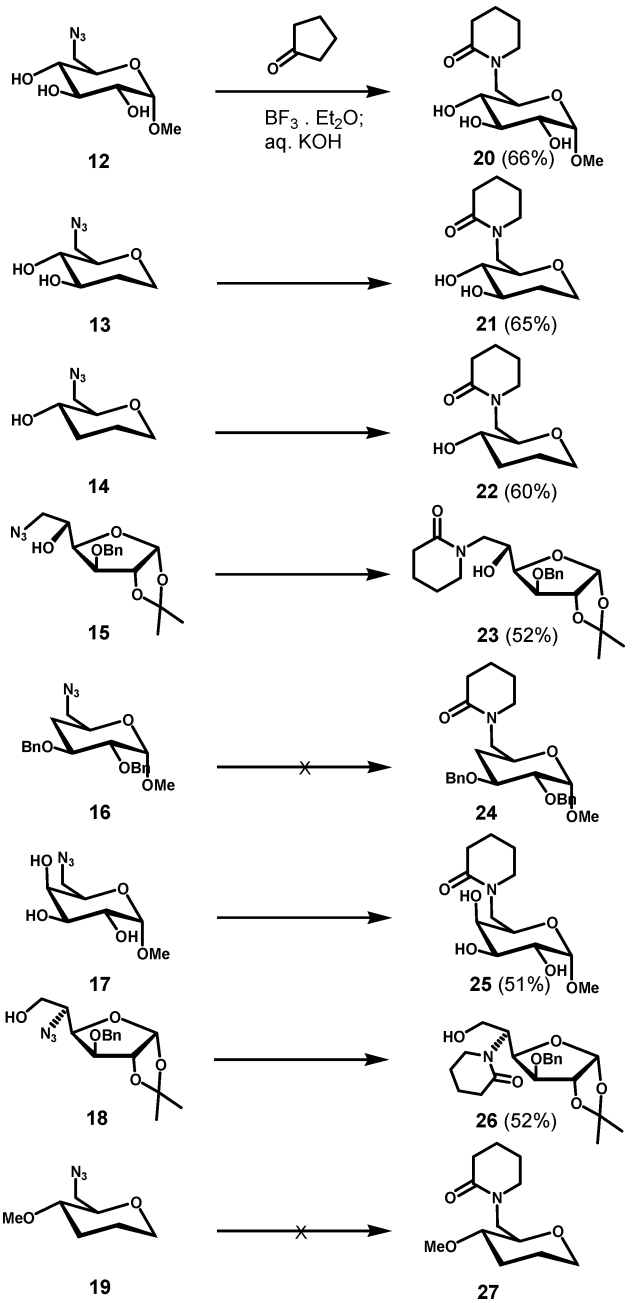


Chart 2 The products obtained from the reactions of **1** with various ketones under Aubé reaction conditions.

sugar azide, we prepared sugar azide **19**, where the hydroxy group is protected as a methyl ether, and reacted it with cyclopentanone under the same conditions. As anticipated, the reaction did not take place to produce **27**. Based on these observations, we propose that the presence of a free 4-hydoxy group is necessary on the pyranonse moiety. The *trans* stereochemistry of 4-hydroxy group with respect to the azidomethyl group may facilitate the reaction. A plausible intermediate for the reaction of glucose azide **12** with cyclopentanone is shown in Fig. 2. To the best of our knowledge, no methods for the synthesis of sugar-lactam conjugates exist in the literature. The present protocol has the potential to expedite, or at least provide a valuable alternative route, to the others already known. The observed diastereoselectivity during the reaction with

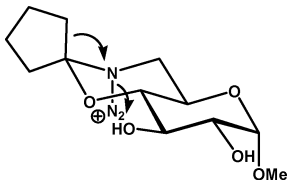


Fig. 2 A plausible intermediate for the reaction of glucose azide **12** with cyclopentanone.

substituted cyclohexanones could be explored further to generate enantiopure lactams and their derivatives. We have also shown in this paper for the first time that cyclic azido alcohols can be used in Aubé reactions, in particular, in a carbohydrate setting.

Conclusions

In summary, we have developed a new method to access sugar-lactam conjugates using the Aubé reaction. We have studied this reaction using various ketones and sugar azides to increase the scope of the method and also to understand the structural requirements of the sugar moiety. These multifunctional compounds could be used to increase the diversity of sugar frameworks and may find applications as potential glycomimetics, peptidomimetics or as building blocks for the synthesis of novel glycoconjugates and molecular receptors. Biological screening of these compounds and further exploration of the chemistry of cyclic azido alcohols will be the subject of future work.

Experimental

General methods

All reagents, starting materials and solvents (including dry solvents) were obtained from commercial suppliers and used as such without further purification. Reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise specified. Column chromatography was performed on silica gel (Rankem, 100–200 mesh). Deuterated solvents (Cambridge Isotope Laboratories) for NMR spectroscopic analyses were used as received. All NMR spectra were recorded on a Varian 400 MHz spectrometer. Coupling constants are measured in Hz. All chemical shifts are quoted in ppm relative to tetramethylsilane using the residual solvent peak as a reference standard. Optical rotations were recorded using a Rudolph Autopol-V polarimeter at 589 nm (sodium D-line). Mass spectra were measured with ESI ionization. Mass spectroscopy was carried out on an Agilent MSD/VL spectrometer, an API QStar Pulsar (Hybrid Quadrupole-TOF LC/MS/MS) spectrometer or a JMS-T100LC, Accu TOF (DARTMS) instrument. Infrared (IR) spectra were recorded on a Perkin-Elmer 100 FT-IR spectrometer. Melting points were measured (uncorrected) using BUCHI melting point B-545.

Methyl 6-deoxy-6-*N*-azepan-2-one-α-D-mannopyranoside (3). To a mixture of 6-azido-6-deoxy-methyl-α-D-mannopyranoside (**1**)[6] (0.25 g, 1.14 mmol) and cyclohexanone (0.18 mL, 3.50 mmol) in dichloromethane (5 mL) was added $BF_3{\cdot}Et_2O$ (0.57 mL, 4.57 mmol) drop-wise under an argon atmosphere at 0 °C. The reaction mixture was allowed to warm up to room temperature, and stirring was continued for 24 h. The reaction mixture was diluted with diethyl ether (5 mL) and 50% aqueous KOH (1 mL)

was added. After stirring for an additional 1 h, the reaction mixture was evaporated to dryness and purified by column chromatography using 30% ethyl acetate : hexane to neat ethyl acetate to obtain **2** and **3** in 230 and 36 mg quantities, respectively.

Compound **2**: mp = 89–91 °C; $[\alpha]_D^{25}$ = −15.6° (*c* 1, CH_3OH); IR ($CHCl_3$): 1071, 1099, 1623 and 3368 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.34–1.79 (series of m, 15H), 2.51–2.61 (m, 2H), 3.33 (d, J = 3.6 Hz, 1H), 3.36 (s, 3H), 3.49 (d, J = 2.4 Hz, 1H), 3.52–3.55 (m, 1H), 3.58–3.64 (m, 2H), 3.85 (d, J = 4.80 Hz, 1H), 3.88 (d, J = 4.80 Hz, 1H), 4.00 (dd, J = 5.6, 7.6 Hz, 1H), 4.09 (d, J = 5.6 Hz, 1H) and 4.87 (s, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 179.9, 110.9, 99.6, 78.5, 76.5, 71.5, 70.6, 55.3, 53.1, 50.7, 39.2, 37.5, 36.4, 30.7, 28.7, 26.0, 25.0, 24.7 and 24.5; LCMS = 370.2 (M + 1); HRMS (ESI) m/z calc. for $C_{19}H_{31}NO_6Na$ $[M + Na]^+$: 392.2049, found: 392.2096.

Compound **3**: $[\alpha]_D^{25}$ = +24.4° (*c* 1, CH_3OH); IR ($CHCl_3$): 1610 and 3392 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.64–1.82 (m, 6H), 2.55–2.58 (m, 2H), 3.34 (s, 3H), 3.47 (t, J = 10 Hz, 1H), 3.55–3.62 (m, 4H), 3.66 (dd, J = 3.6, 9.2 Hz, 1H), 3.76–3.81 (m, 2H) and 4.58 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100.6 MHz, CD_3OD) δ 179.7, 102.9, 73.3, 71.8, 71.7, 69.6, 55.3, 53.1, 51.0, 37.6, 30.8, 28.7 and 24.4; MS = 290 (M + 1); HRMS (ESI) m/z calc. for $C_{13}H_{24}NO_6$ $[M + H]^+$: 290.1603, found: 290.1586.

Conversion of compound 2 to compound 3. Compound **2** (230 mg) was dissolved in 80% aqueous acetic acid (5 mL) and stirred at 80 °C. After 24 h, the reaction mixture was evaporated to dryness to furnish the crude product. The crude compound was purified by column chromatography using silica gel and eluted with 50% ethyl acetate : hexane to neat ethyl acetate to obtain 170 mg of title product **3**; overall yield: 205 mg (64%). Experimental compounds **4–11** were prepared using an analogous procedure to that described for the synthesis of **3**. See the ESI for experimental details for all the compounds.†

Acknowledgements

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7 See the ESI for detailed experimental information†.

8 During the alkylation step, unwanted olefin **II** was obtained as a major compound. The spectral data of compound **3** prepared *via* this route was compared with that of **3** obtained by the Aubé reaction and found to be identical. Experimental details and all other unsuccessful attempts to prepare sugar-lactam conjugate **3** are available in the ESI†.

9 HPLC analysis of the reaction mixture showed a >95 : 5 diastereoselectivity. Only the major isomer was isolated.

10 The stereochemistry of the newly formed chiral center in compound **9** is assumed to be as drawn based on the X-ray structure of the triacetate of **8**†.

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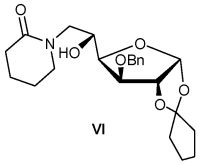
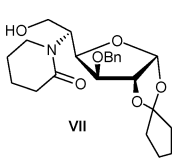
15 Along with **23** and **26**, small amounts of corresponding cyclopentanone ketals **VI** (13%) and **VII** (21%) were also isolated, respectively. Their tentative structures are shown below: .





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