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Conversion of Glucuronic Acid Glycosides to Novel Bicyclic *β*-Lactams

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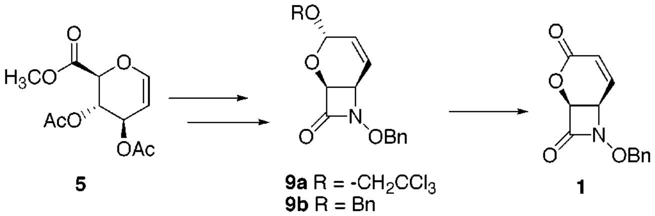
ABSTRACT



Methodology for the conversion of glucuronic acid glycosides to novel bicyclic *β*-lactams is reported. Using this strategy, we prepared two novel templates suitable for use in combinatorial chemistry strategies for the construction of a number of interesting *β*-lactam motifs. Key features of this strategy include a diastereoselective Ferrier reaction of a glucuronic acid glucal, selective *β*-lactam ring formation using a cyclic allylic alcohol, and a chemoselective benzylic oxidation.

The use of chiral pool molecules to prepare *β*-lactams has become routine.[1,2] Within this context, the use of carbohydrates as synthons is especially appealing given the density of functionality in these substrates that can ultimately be incorporated into the final targets.[3] We recognized that the carbohydrate template could be useful for the construction of a number of types of functionalized 3-hydroxy, 3,4-bicyclic, 1,4-bicyclic, and polycyclic *β*-lactams and oxamazins[4] (Scheme 1). The successful incorporation of the inherent oxygen groups and stereochemical information contained in the carbohydrates into the *β*-lactam system presents intriguing synthetic challenges, the most daunting of which is facile, differential protection of the oxygen functionalities. We felt that development of suitable chemical technologies/strategies for overcoming these obstacles would provide opportunities to expand the frontiers of *β*-lactam chemistry as well as generate new 2-azetidinone templates for biological investigations.

Our synthetic strategy using carbohydrate derivatives to prepare *β*-lactams features the N1−C4 bond closure strategy of *β*-hydroxy hydroxamates pioneered by our research group.[5] Faced with the daunting task of using such highly functionalized starting materials, we immediately recognized the necessity of masking the hydroxyl moieties that would not be directly involved in the N1−C4 cyclization step to form the *β*-lactam ring system. While a number of strategies are available to allow selective protection of the various oxygen functionalities of carbohydrate scaffolds, these strategies may require a large number of synthetic steps, especially if each functional group is to be differentiated. One goal of this research was to devise as general a strategy as possible to the targeted bicyclic intermediates, allowing access to the largest number of possible derivatives from a common core structure. In consideration of these requirements, we recognized an interesting possibility would be to mask the C2−C3 hydroxyls as an olefin moiety. This would allow additional reaction manifolds in later steps to be more readily

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(1) For two classic examples, see: (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852−853. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161−6163.

(2) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49−55.

(3) Storz, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 2380−2412.

(4) Boyd, D. B.; Eigenbrot, C.; Indelicato, J. M.; Miller, M. J.; Pasini, C. E.; Woulfe, S. R. *J. Med. Chem.* **1987**, *30*, 528−536.

(5) (a) Mattingly, P. G.; Kerwin, J. F. J.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983−3985. (b) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. K. J. *J. Am. Chem. Soc.* **1980**, *102*, 7026−7032.

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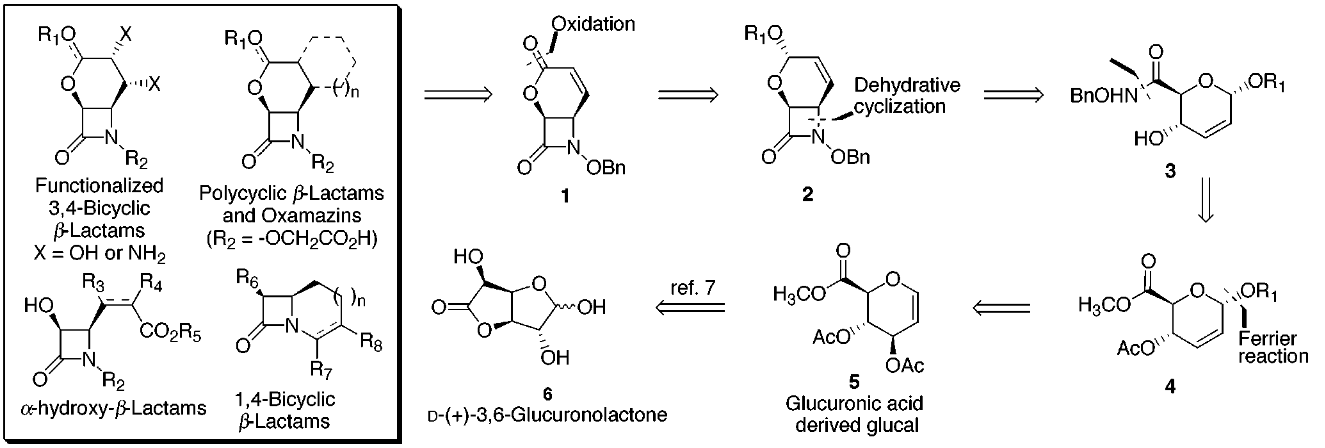
Scheme 1. Retrosynthetic Analysis of Targets **1** and **2**

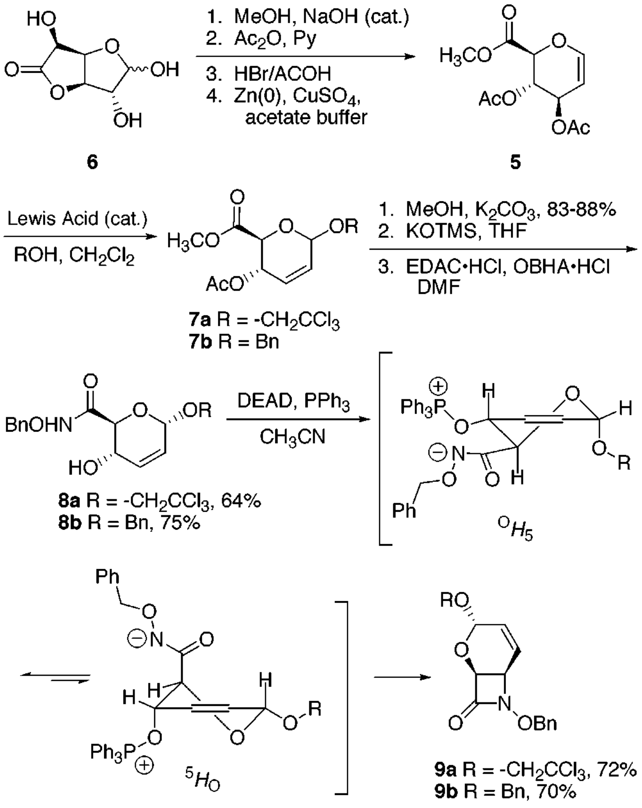


accessed and the preparation of additional derivatives unavailable from the diol directly. This strategy also raised an opportunity to further test the scope of our N1−C4 ring closure protocol with allylic alcohol systems. While previous attempts to use acyclic allylic alcohols in this fashion have been successful,[6] we recognized that the proposed cyclic system contained additional steric demands not present in the previous systems that could make the ring closure difficult or impossible. In this letter, we report the successful application of our synthetic strategy to the preparation of two novel bicyclic β-lactam systems suitable for use in combinatorial chemistry strategies from a common carbohydrate precursor.

Toward the goal of preparing a common novel core structure containing a endocyclic olefin suitable for late stage functionalizations, our initial focus was the preparation of bicyclic β-lactam **1** (Scheme 1). We envisioned that β-lactam **1** could be derived through an oxidation of the allylic acetal moiety of β-lactam **2**. Retrosynthetic cleavage of the N1−C4 bond provided the allylic alcohol *O*-benzyl hydroxamate **3**, which could be accessed from the differentiated diester **4**. We envisioned that diester **4** could be derived through a diastereoselective Ferrier reaction[7] of glucuronic acid derived glucal **5**. Glucal **5** can be easily prepared from D-(+)-3,6-glucuronolactone according to a reported literature procedure.[8]

In the synthetic direction, using the literature procedure of Wyss et al., we were able to prepare multigram quantities of the starting glucuronic acid glucal **5** (Scheme 2).[8] Next, we investigated the possibility of developing a diastereoselective Ferrier reaction[7] for this compound. Ferrier reactions of glucal **5** have been previously investigated by Wieczorek and Thiem.[9] Unfortunately, none of the reported aglycons were suitable for our purposes since we hoped to be able to incorporate an alcohol bearing a group amenable to selective manipulation later in the synthesis. However, given the harsh Lewis acid conditions needed to carry out Ferrier reactions[7,9] and the need to differentiate other protected oxygen functionalities later in our synthetic strategy, we were left with few viable options. Two potentially useful candidate nucleophiles for the proposed Ferrier reaction were trichloroethanol (TCE) and benzyl alcohol. Our hope was that the resulting

Scheme 2. Synthesis of β-Lactams **9a**−**b**



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(6) (a) Zercher, C. K.; Miller, M. J. *Tetrahedron Lett.* **1989**, *30*, 7009−7012. (b) Sheppard, A.; Miller, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2519−2525. (c) Farouz, F.; Miller, M. J. *Tetrahedron Lett.* **1991**, *32*, 3305−3308.

(7) For discussion and lead references, see: (a) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1965**, *20*, 67−137. (b) Ferrier, R. J. *Adv. Carbohydr. Chem.* **1969**, *24*, 199−266.

(8) Wyss, P. C.; Kiss, J.; Arnold, W. *Helv. Chim. Acta* **1975**, *58*, 1847−1864.

acetal could eventually be deprotected via acid-catalyzed hydrolysis,[10] a Zn-mediated reduction protocol (TCE),[11] or a selective oxidation or reduction (benzyl group). Toward this end, glucal **5** was separately reacted with TCE and benzyl alcohol under a variety of conditions[9,12] to give glycosides **7a**−**b** (Scheme 2). These experiments led to optimized reaction conditions allowing moderate yields of both glycosides (Table 1). Of note was the isolation of a single anomer of the benzyl glycoside using a catalytic amount of $BF_3{\cdot}OEt_2$ at −10 °C (entry 4, Table 1). This procedure proved to be especially appealing since the product could be isolated directly from the reaction mixture via recrystallization!

Table 1. Conditions for Ferrier Reaction of Glucal **5**

entry	ROH	Lewis acid	temp./time	α/β^a	yield^b
1	TCE^c	$BF_3{\cdot}OEt_2$	0 °C/4 h	5:1	53%
2	TCE	$BF_3{\cdot}OEt_2$	−78 °C/12 h	5:1	69%
3	BnOH	$InCl_3$	room temp./30 min	4:1	39%
4	BnOH	$BF_3{\cdot}OEt_2$	−10 °C/4 days	>99:1	53%

^{a} Determined by ^{1}H NMR. ^{b} Isolated. ^{c} TCE = Trichloroethanol.

With the two glycosides in hand, we set out to determine the set of conditions necessary for the formation of the requisite β-hydroxy hydroxamates **8a**−**b**. While the transformation of esters **7a**−**b** to the hydroxamates **8a**−**b** would seem to be straightforward, we discovered that it was actually quite challenging and required the development of a novel strategy. For instance, after removal of the acetate group, attempts to saponify the methyl ester with LiOH followed by an aqueous EDAC·HCl coupling with *O*-benzylhydroxylamine hydrochloride (OBHA·HCl)[5] proved to be disastrous and provided only decomposition products. This and related attempts showed that these glycosides appear to be highly sensitive to the reaction conditions. We were, therefore, pressed to develop a strategy to access hydroxamates **8a**−**b** using neutral or near-neutral reaction conditions. To our delight, we found that deprotection of the methyl ester could be carried out effectively using KOTMS in THF.[13] After removal of the solvent and dissolution of the salt in dry DMF, a mixture of EDAC·HCl and OBHA·HCl was added resulting in the formation of the hydroxamates **8a**−**b**, which in the case of **8b** could be isolated directly from the reaction mixture by recrystallization.

We next focused our attention on the formation of the β-lactam ring. As mentioned earlier, this transformation represented an interesting test of our N1−C4 ring closure methodology. The allylic nature of the activated alcohol provided the possibility of forming either the desired four-membered or an undesired six-membered heterocycle. While our group has shown that open chain allylic alcohols can be successfully used as β-lactam precursors,[6] the cyclic nature of allylic alcohols **8a**−**b** imposes additional steric demands on the proposed cyclization reaction. For example, to allow the formation of the β-lactam ring via an S_N process requires the reactive intermediate to adopt a ^5H_O conformation (Scheme 2) in which the ester and alcohol functionalities are in *pseudo*-axial positions and the aglycon is in a *pseudo*-equitorial position preventing anomeric and allylic stabilization.[14] One would expect that such a conformation would be higher in energy than the corresponding $^OH_5$ conformation (Scheme 2). This hypothesis is supported by NMR studies of 2,3-unsaturated pyranosides.[14,15] These studies have found that α-*erythro*-2,3-unsaturated glycosides prefer the $^OH_5$ conformation displaying $J_{4,5}$ coupling constants of ~9 Hz, while the corresponding β-anomers display $J_{4,5}$ coupling constants of ~2−3 Hz indicating the adoption of a ^5H_O conformation.[14,15] The observation of a $J_{4,5}$ coupling constant of 9.50 Hz for α-**7b** suggests the preference for this system to also adopt a $^OH_5$ conformation.

Given these considerations, our success in this endeavor seemed far from certain. Therefore, we were delighted to find that subjection of hydroxamates **8a**−**b** to Mitsunobu reaction conditions[5] provided the desired novel bicyclic β-lactams **9a**−**b** as stable crystalline solids in good yields. This result serves to further underscore the robustness of our N1−C4 ring closure strategy toward the construction of β-lactams. The structure and absolute stereochemistry of β-lactam **9b** were confirmed by X-ray diffraction.

With the successful preparation of β-lactams **9a**−**b**, we targeted the selective deprotection of the acetal moiety as the next synthetic goal. For β-lactam **9a**, we were disappointed to find that a number of conditions failed to provide the desired hemiacetal[10,11,16] or lactone.[17] However, we hypothesized that the two benzyl moieties of β-lactam **9b** should have differing reactivities. We were encouraged by a report in which a benzyl aglycon had been successfully oxidized to a benzoate ester using in situ generated Collin's reagent.[18] Model studies using diester **7b** showed that these conditions did indeed provide the targeted benzoyl aglycon product **10** (Scheme 3). Further, treatment of a model *N*1-*O*-benzyl-β-lactam under the same conditions showed that no oxidation occurred at the hydroxamate benzyl group. Encouraged by these results, we subjected β-lactam **9b** to the same conditions hoping to receive the benzoyl aglycon. To our surprise, under these conditions, β-lactam **9b** showed

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(9) Wieczorek, E.; Thiem, J. *Synth. Lett.* **1998**, *5*, 467−468.

(10) (a) Isidor, J. L.; Carlson, R. M. *J. Org. Chem.* **1973**, *38*, 554−556. (b) Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 979−980. (c) Oku, A.; Kinugasa, M.; Kamada, T. *Chem. Lett.* **1993**, 165−168.

(11) (a) Just, G.; Grozinger, K. *Synthesis* **1976**, 457−458. (b) Doboszewski, B.; Zamojski, A. *Carbohydr. Res.* **1984**, *132*, 29−38.

(12) Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **2000**, *41*, 1271−1274.

(13) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.

(14) Angerbauer, R.; Schmidt, R. R. *Carbohydr. Res.* **1981**, *89*, 193−201.

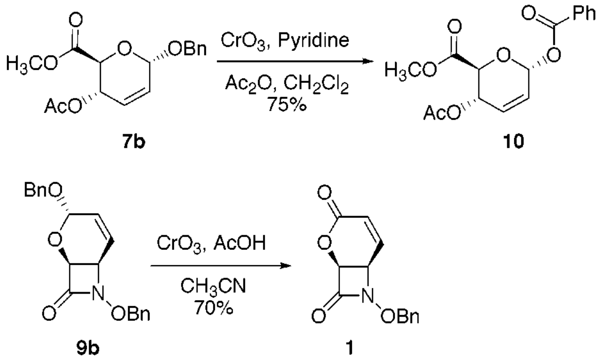
(15) Dyong, I.; Schulte, G.; Lam-Chi, Q.; Friege, H. *Carbohydr. Res.* **1979**, *68*, 257−273.

(16) (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Markó, I. E. *Tetrahedron Lett.* **1999**, *40*, 1799−1802. (b) Nair, V.; Nair, L. G.; Balagopal, L.; Rajan, R. *Indian J. Chem., Sect. B* **1999**, *38B*, 1234−1236.

(17) Grieco, P. A.; Oguri, T.; Yokoyama, Y. *Tetrahedron Lett.* **1978**, 419−420.

(18) Hasegawa, A.; Seki, E.; Hioki, Y.; Kiso, M.; Azuma, I. *Carbohydr. Res.* **1984**, *131*, 61−9.

Scheme 3. Selective Aglycon Oxidation



no reaction. Anticipating that the reduced reativity of the CrO$_3$ was attributable to the pyridine ligands, we subjected β-lactam **9b** to CrO$_3$ and acetic acid.[19] We hypothesized that under these reaction conditions, not only would the benzylic oxidation occur but trace amounts of water in the reaction would set the stage for an acid-catalyzed anomeric exchange to provide the hemiacetal, which would then be oxidized to the desired lactone. To our delight, we found that subjection of **9b** to these reaction conditions provided lactone **1** in good overall yield (Scheme 3).

The synthesis of bicyclic β-lactams **9a**−**b** and **1** represents the enantioselective synthesis of two novel β-lactam templates suitable for transformation to a plethora of unique substrate classes. The robustness of the developed chemistry is exemplified by the fact that the conversion of glucal **5** to β-lactam **9b** requires only one chromatographic separation and that the sequence can be carried out on a multigram scale. The future directions of this research involve targeting specific β-lactam structures accessible from the highly functionalized intermediates **9a**−**b** and **1** and carrying out investigations into the chemical reactivity of these unusual substrates. Also of current interest is the possibility of unmasking the C3 hydroxyl, which would allow the preparation of unusual α-amino acids via *N*-carboxy anhydrides.[20] The results of these and other studies will be published as appropriate.

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Supporting Information Available: Experimental procedures and characterization for all new compounds reported, including copies of ^{1}H and ^{13}C NMR spectra as well as X-ray data for compound **9b.** This material is available free of charge via the Internet at http://pubs.acs.org.

OL017026V

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(19) Araki, K.; Kawa, M.; Saito, Y.; Hashimoto, H.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3137−3143.

(20) Palomo, C.; Oiarbide, M.; Landa, A.; Esnal, A.; Linden, A. *J. Org. Chem.* **2001**, *66*, 4180−4186.