ORGANIC LETTERS

2011
Vol. 13, No. 4
576–579

Highly Regio- and Stereoselective One-Pot Synthesis of Carbohydrate-Based Butyrolactones

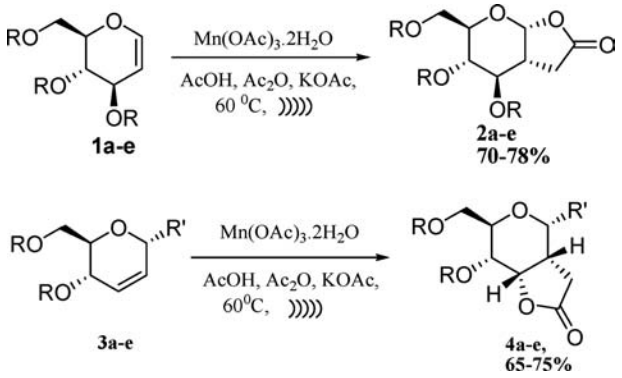
Syed Khalid Yousuf, Debaraj Mukherjee,* Mallikharjunrao L, and Subhash C. Taneja

Natural Product Chemistry Division, Indian Institute of Integrative Medicine (CSIR), Canal Road, Jammu, India 180001

dmukherjee@iiim.ac.in

Received November 10, 2010

ABSTRACT



The use of manganese(III) acetate allows the direct synthesis of diverse arrays of [4.3.0] bicyclic carbohydrate-based γ-lactone building blocks from glycals. A mechanism to explain the high regio- and stereoselectivity is proposed. The new reaction has the potential to generate libraries for biological screening.

Carbohydrate-fused γ-butyrolactone scaffolds constitute integral components of a plethora of natural products with promising bioological activities like antimicrobial,[1] cytotoxic,[2] fungicidal,[3] selective insecticidal,[4] and enzyme inhibitory[5] (due to in vivo ring-opening by biological nucleophiles). Moreover, linking the reactive heterocycles to carbohydrates improves their bioavailability.[6] In synthetic carbohydrate chemistry, the 1,2-lactone ring can be conceived as a simultaneous protecting group for anomeric and C-2 positions, offering the products which can act as precursors for the synthesis of glycosides, nucleosides, and complex natural products. Thus, under a research program directed toward the synthesis of natural product inspired new chemical entities for biological screening, we became interested in the synthesis of carbohydrate fused γ-butyrolactones.

A few approaches that are available for the construction of this kind of fused motifs include intramolecular transesterification of sugar-based esters with vicinal alcohol obtained in multiple steps,[7a−c] multicomponent Poparov reaction,[8] NIS-mediated ring-opening of 1,2-cyclopropionated

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10.1021/ol102723c
Published on Web 01/18/2011

sugar derivatives,[9] $TiCl_4$-mediated ring-opening and alcohol trapping,[10] condensation of Meldrum's acid with protected sugar lactol derivatives,[11] deglycosidation, ozonolysis of orthogonally protected 1-pentenyl sugar derivatives,[12] and radical cyclization of unsaturated carbohydrate derived acetals.[13] Recently, Linker and co-workers[6] reported the multistep synthesis of carbohydrate 1,2-lactones from glycals. Thus, there are quite a few methods in the literature for the synthesis of sugar-based lactones, but no generalized single-step method is available for such privileged systems.

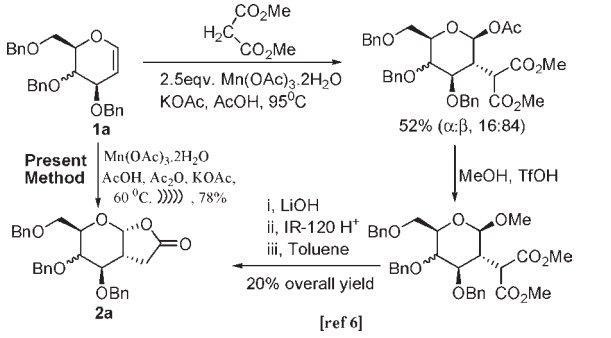
Contemporary organic synthesis demands the development of simple methods for the rapid construction of complex and biologically relevant compounds. With our recent success in the development of new synthetic strategies for the generation of new chemical entities from the carbohydrate chiral pool,[14] we envisaged to develop one-pot regio- and stereoselective generalized synthetic routes to fused lactone congeners at different positions of carbohydrate templates. For the method to be of wide applicability, certain criteria required to be fulfilled; e.g., the regio- and stereoselectivity of these reactions must be predictable.

Radical reactions constitute a path breaking area in organic synthesis.[15] In comparison to traditional methods for radical generation such as TBTH/AIBN, etc., the use of transition-metal salts and their oxides ensures remarkable regioselectivity and efficiency even with polyfunctional organic compounds. Among metal oxidants, $Mn(OAc)_3$[15] has emerged as a versatile single-electron-transfer reagent during the last two decades. However, in carbohydrate chemistry its role is limited only to a single report of malonate addition to glycals for the synthesis of 2-C glycosides.[16] The importance and requirements of the natural product based scaffolds of defined regio-/stereochemistry prompted us to probe the manganese(III) acetate mediated reaction outcomes.

Thus, initially 3,4,6-tri-*O*-benzyl-D-glucal (**1a**) was reacted with AcOH, which served both as a solvent and the source of carboxymethyl radical, in the presence of $Mn(OAc)_3 \cdot 2H_2O$ (20 mol %). However, no reaction occurred at room temperature, and the starting glycal was fully recovered after workup (Supporting Information, entry 1).

The addition of Ac_2O and use of elevated temperatures (60−100 °C) ensured the formation of the product **2a**, albeit with moderate (∼35%) yields. In order to find a suitable temperature and additive(s) for a typical radical initiation, further optimization studies were then carried out. As single-electron-transfer processes are generally favored by ultrasound,[17] irradiation of the reaction mixture with high intensity ultrasound was resorted to, which facilitated better conversion of the glycals into butyrolactone. Addition of KOAc as a radical initiator or stabilizer led to a marginal increase in yield. However, use of both Ac_2O and KOAc under sonication proved more effective, allowing the reaction to be completed in ∼6 h with an increase in yield (78%) and complete consumption of the glycal (Scheme 1).

Scheme 1. Prior Art for the Synthesis of a Butyrolactone at the 1,2-Position of a Sugar



The absence of signals for olefinic protons and occurrence of extra signals for the $-CH_2$ group at δ 2.54, 2.40 (in ^{1}H NMR), and 40.6 ppm in ^{13}C NMR confirmed the formation of the 1,2-lactone. Regioselectivity of the reaction was determined by spectroscopic analysis.[18]

Comparison of the rotation value of the product with the one reported in the literature[6] established that the reaction had proceeded with almost complete stereoselectivity. Synthesis of the same derivative **2a** previously needed four linear steps and was achieved in $<20\%$ overall yield (Scheme 1). Moreover, the route taken by Linker et al.[6] is not applicable to compounds with ester protecting groups, as the reaction sequence involves base mediated hydrolysis of methyl esters.

This encouraging observation led us to probe the generality and scope of this reaction for the construction of diverse libraries of lactone fused sugar derivatives. Thus, using optimized reaction conditions, a panel of 1,2-glycals (gluco, galacto) were subjected to $Mn(OAc)_3$-mediated radical lactonization to yield the corresponding butyrolactones in moderate to good yields (Table 1). Protecting

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(14) (a) Mukherjee, D.; Shah, B. A.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007**, *72*, 8965–8968. (b) Mukherjee, D.; Yousuf, S. K.; Taneja, S. C. *Org. Lett.* **2008**, *10*, 4831–4834. (c) Thota, N.; Mukherjee, D.; Reddy, M. V.; Yousuf, S. K.; Koul, S.; Taneja, S. C. *Org. Biomol. Chem.* **2009**, *7*, 1280–1283. (d) Yousuf, S. K.; Mukherjee, D.; Taneja, S. C. *J. Org. Chem.* **2010**, *75*, 3097–3100.
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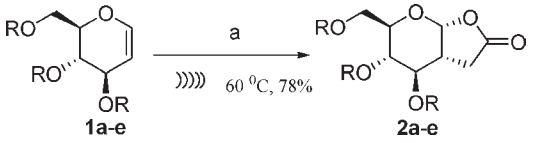
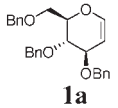
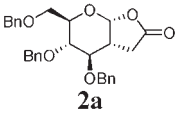
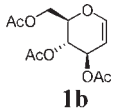
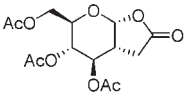
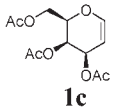
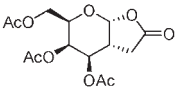
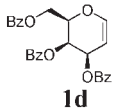
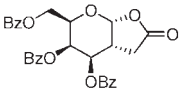
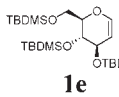
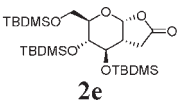
(17) Luche, J. L.; Einhorn, C.; Einhorn, J.; Sinisterra-Gago, J. V. *Tetrahedron lett.* **1993**, *49*, 10705–10714.
(18) Correlations between C-3 (δ 58.3)/H-7 (δ 2.67), H-3 (δ 4.18)/C-7 (δ 29.0), C-1 (δ 97.7)/H-7 (δ 2.67), and H-1 (δ 5.69)/C-7(δ 29.0) are in full agreement with the proposed structure. No correlation was observed between H-4 (δ 5.19) and the methylene carbon of lactone moiety, which ruled out the other regioisomer.

Table 1. $Mn(OAc)_3$-Mediated Synthesis of Sugar Lactones from 1,2-Glycals



S.No.	Substrate	Product	Time (h)	Yield %
1	 **1a**	 **2a**	6	78
2	 **1b**	 **2b**	6.3	70
3	 **1c**	 **2c**	6.5	70
4	 **1d**	 **2d**	6.0	75
5	 **1e**	 **2e**	6.0	73

[a] Reaction conditions: In all cases, the product was obtained by using (a) Ac_2O (17 mL), AcOH (3 mL), KOAc (15 mmol) or (b) $Mn(OAc)_3.2H_2O$ (3.7 mmol) and substrate (1.8 mmol).

linkages like ester (entries **1a**, **1b**, and **1c**), ether (entry **1d**), or silyl ether (entry **1e**) were well tolerated.

In an effort to further increase the scope of the reagent system, we next considered utilization of other unsaturated sugar derivatives in order to mimic some natural product skeleta. Gratifyingly, the reaction of the azide 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside under the optimized reaction conditions afforded **4a** in high yield (scheme 2). It is noteworthy that the known synthesis of this type of 2,3-lactone

Scheme 2. Reaction of Azide 4,6-Di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranoside

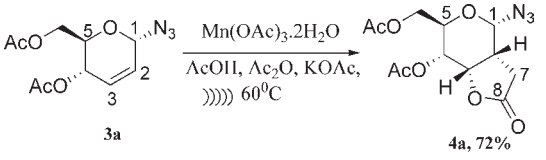
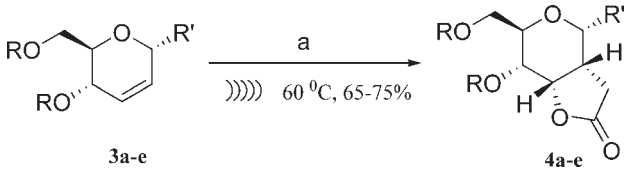
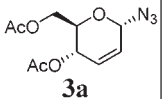
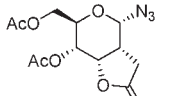
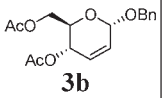
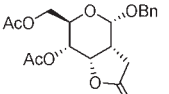
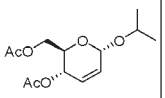
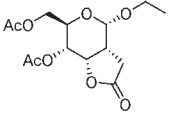
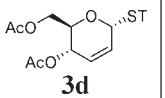
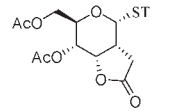
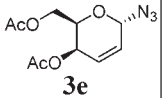
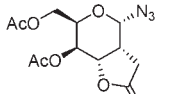


Table 2. $Mn(OAc)_3$-Mediated Synthesis of Sugar Lactones from 2,3-Glycals



S.No.	substrate	product	time (h)	yield %
1	 **3a**	 **4a**	6.3	72
2	 **3b**	 **4b**	6.5	75
3	 **3c**	 **4c**	6.3	72
4	 **3d**	 **4d**	6.3	65
5	 **3e**	 **4e**	6.5	68

[a] Reaction conditions: In all cases, the product was obtained by using (a) Ac_2O (17 mL), AcOH (3 mL), KOAc (15 mmol) or (c) $Mn(OAc)_3 \cdot 2H_2O$ (3.7 mmol), and substrate (1.8 mmol).

involved a multistep reaction sequence with poor overall yield.[10]

In order to determine the stereo- and regioselectivity of lactone formation, spectroscopic analyses were performed. The assigned regiochemistry became obvious from the HMBC spectrum.[18] The newly generated ring juncture stereochemistry, which is expected to be cis, could be either α−α or β−β in the bicyclic [4.3.0] butyrolactone system. In the MM2 energy-minimized structure of α−α isomer **4a**, the distance between H-1 and H-3 is calculated as ~3 Å, signifying that their signals should show correlation in the NOESY spectrum. This correlation indeed was clearly observed.[19]

(19) Correlations of H-1β/H-2, H-1β/H-3 in the NOESY experiments of **4a** reveal that H-1, H-2, and H-3 are cofacial, which confirms the α−α ring juncture stereochemistry of bicyclic lactone.

The alternative cis structure ($\beta-\beta$) having H-1 and H-3 distance of ~4 Å in the energy-minimized structure is not expected to show a NOESY relationship between the two signals. Therefore, the formation of the ($\beta-\beta$) structure could be ruled out.

We subsequently studied a series of 2,3-glycals having different anomeric protections to synthesize the corresponding lactones. In all cases, moderate to good yields were observed (Table 2) without the formation of byproducts.

Understandably, all these reactions proceeded via a radical reaction mechanism with the formation of a C−C bond, followed by a lactonization step. The regioselectivity is determined at the level of formation of the C−C bond. Possibly, the key interactions are between the SOMO of the electron-deficient acetoxy radical and the HOMO of the glucal double bond, which determines the site of initial attack of the acetoxy radical.

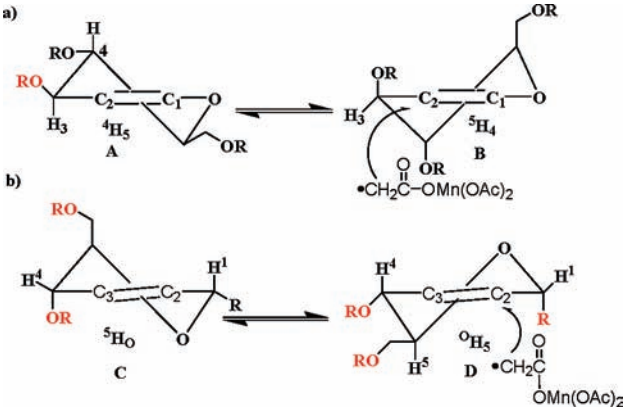


Figure 1. Conformational preference for (a) 1,2-glucal and (b) 2,3-glucal.

The high stereoselectivities of the lactonization may be rationalized by considering the ground-state conformational distribution of glycals. The glycals are known to be conformationally flexible, and their conformational preference is sensitive to hydroxyl protection. In the case of 1,2-glycals, the ratio of normal half chair $^4H_5$ (A) and conformationally inverted isomer $^5H_4$ (B) (Figure 1) can affect the stereoselectivity of lactonization. It is well recognized that the electron-withdrawing substituents at C-6 including benzyl favors the $^5H_4$ (B) conformation and the best stereoselectivity comes from the glycals existing preferably in conformation.[20] The two faces of the conformer (B) are well differentiated, the upper (β) face being hindered by two pseudoaxial substituents, while the bottom (α) face is shielded by only one axial C(4)-OR group. The latter is therefore the favored face for the free radical attack. It explains the α-selectivity of lactonistaion of 1,2-glycals.

Similarly, 2,3-glycals also exist in two different conformations, ^5H_O and $^OH_5$.[21] Small anomeric substituents generally favor the $^OH_5$ conformation. Assignment of conformation was accomplished by NMR spectroscopy of compound **3c** where $^3J_{3,4}$ = 2.3 Hz is indicative of the $^OH_5$ conformation.[21] In this situation, the upper face is hindered by ring oxygen, driving the reaction to exclusive α−α lactone formation.[22]

In summary, a regio- and stereoselective one-pot synthesis of carbohydrate based butyrolactones has been accomplished. The method is applicable in the construction of natural product based libraries for biological screening. A plausible mechanism has also been given to explain the high regio- and stereoselectivity of the SET reaction.

Acknowledgment. We are thankful to Dr. R. A. Vishwakarma, Director, IIIM Jammu, for encouragement and support and Mrs. Basant Purnima for 2D NMR spectroscopy. S.K.Y. acknowledges DST (GAP-1145), New Delhi, for the fellowship.

Supporting Information Available. Experimental procedures; spectral and analytical data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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(22) The attack of the carboxy methylene radical bonded to the manganese, which may also coordinate with α-disposed anomeric substitutents, could be an alternative explanation for the exclusive α C−C bond formation leading to α−α lactonization as suggested by one of the reviewers.