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View Article Online
DOI: 10.1039/C8CC05523H

Journal Name

COMMUNICATION

Efficient and Regioselective Synthesis of γ-Lactone Glycosides Through a Novel Debenzylative Cyclization Reaction

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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An efficient and regioselective approach for the construction of synthetically important γ-lactone glycosides is reported from unprotected aldoses through a new debenzylative lactonization (DBL) reaction. The scope and limitations of this DBL reaction are described starting from a series of commercially available hexoses (L-fucose, D-galactose, D-glucose) and pentoses (D-arabinose, D-ribose, D-lyxose, D-xylose) to afford the corresponding γ-lactones in good yields and without concomitant δ-lactone formation.

Lactones are an important class of substances with applications in many fields such as polymer synthesis,[1] medicinal chemistry,[2] fuels,[3] solvents[4] and building blocks synthesis.[5, 6] Five-membered lactones, or γ-lactones, are common chemical frameworks found in many synthetic and natural products displaying a variety of biological properties (Figure 1).[7-10] In particular, carbohydrate γ-lactones are key intermediates in the synthesis of major antiviral and anticancer nucleoside analogues such as trifluridine, clofarabine, cytarabine and gemcitabine.[11, 12]

Synthetically, the preparation of protected carbohydrate γ-lactones from their corresponding commercially available sugar has been accomplished by two main methods. The first method is based on a selective anomeric oxidation of unprotected aldoses with bromine, which is frequently followed by the persilylation of the remaining alcohols.[13-17] The second method involves the multistep preparation of protected aldoses with a free anomeric hydroxyl group that can be oxidized into their corresponding aldonolactones under standard oxidation protocols. Unfortunately, these two methods are not general because their efficiency highly depends on the starting carbohydrate as well as on its protecting groups. For example, the oxidation of D-glucose with bromine predominantly gives a six-membered 1,5-pyranolactone (δ-lactone) rather than a γ-lactone, although the five-membered form is usually considered thermodynamically more stable.[13, 18-22] For these reasons, the development of new approaches to produce regioselectively γ-lactones constitutes a great challenge.

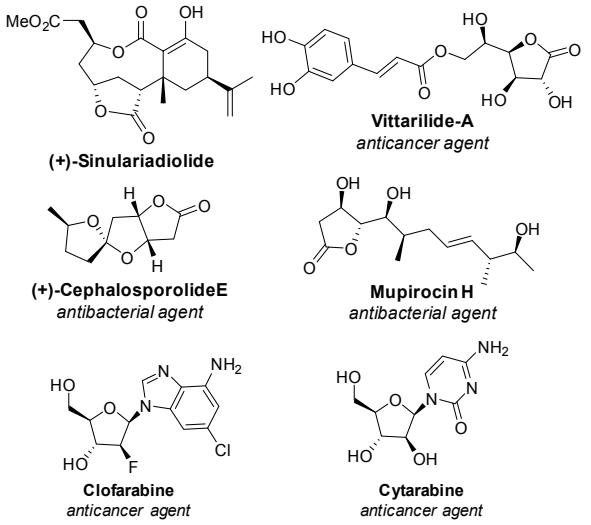

Figure 1. Bioactive γ-lactones and some nucleosides drugs synthesized from the corresponding lactones.

Recently, we have reviewed the main synthetic methodologies that have been developed to construct tetrahydrofuran moieties involving the debenzylative cycloetherification reaction (DBCE).[23-28]

This etherification occurs under slightly acidic or even neutral conditions when a benzyl ether is in δ position of an activated alcohol (sp^3 carbon). Interestingly, this reaction is regio- and stereoselective and gives exclusively tetrahydrofurans in case of a pyran/furan competition (Figure 2, top). This regioselectivity is due to a favorable conformation properly positioning the nucleophilic benzylic oxygen for a S_N reaction (Figure 2). We reasoned that if such a selective mechanism was operating with sp^2 hybridized electrophiles such as an

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Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data and copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

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DOI: 10.1039/C8CC05523H

activated carbonyl, a regioselective formation of γ-lactones could be envisioned, without the need of a protection/deprotection sequence to avoid the formation of the competing δ-lactone (Figure 2, bottom).

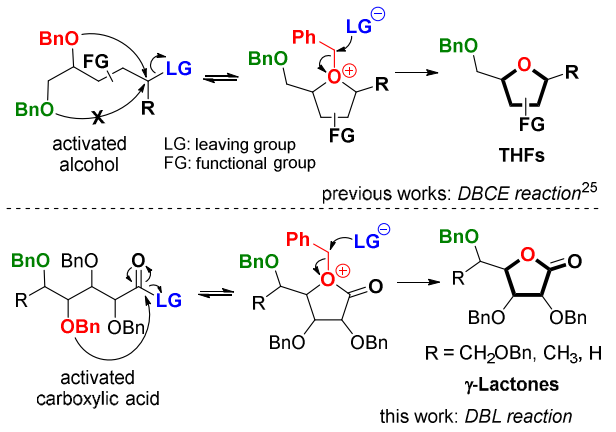


Figure 2. DBCE and DBL (DeBenzylative Lactonization) reactions.

Herein we report an efficient method to synthesize regioselectively γ-lactone glycosides in good yields through a new debenzylative lactonization (DBL) reaction. To the best of our knowledge, this type of reaction has never been exploited to prepare γ-lactones to date.

Our retrosynthetic analysis of γ-lactones type **I** is outlined in Figure 3. Carboxylic acid **II**, the key intermediate to carry out the debenzylative lactonization reaction (DBL), would be obtained by oxidation of the aldehyde generated from the deprotection of dithioacetal **III** which would be easily accessible in two steps (protection and per-benzylation) from commercially available sugars.

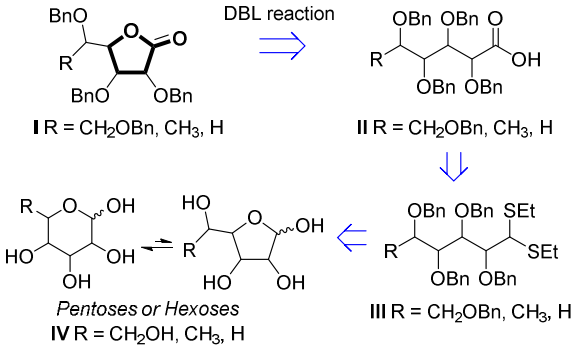
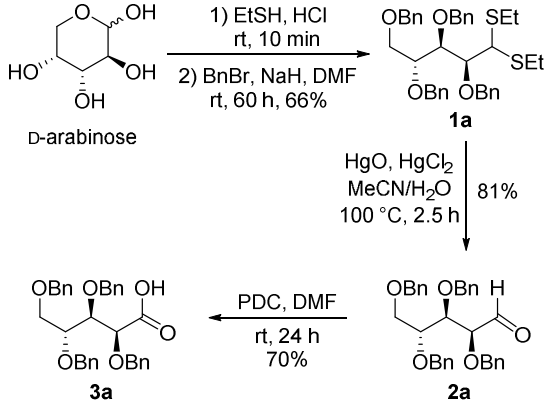


Figure 3 Retrosynthetic analysis.

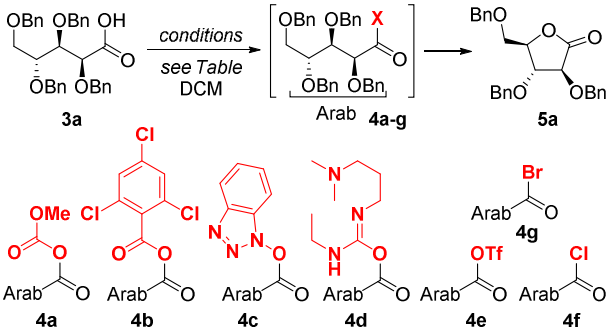
In order to screen the conditions of debenzylative lactonization, the per-benzylated acyclic carboxylic acid **3a** was selected as a model and prepared from the commercially available D-arabinose in four steps.[29] The synthesis began with protection of D-arabinose in the presence of ethanethiol under acidic conditions followed by per-benzylation of the resulting polyol to afford the masked aldehyde **1a** in 66% yield. Selective deprotection of dithioacetal **1a** with mercury salts and subsequent oxidation of aldehyde **2a** with pyridinium dichromate provided the carboxylic acid **3a** in 70% yield (Scheme 1).



Scheme 1. Synthesis of carboxylic acid **3a**.

First, the activation of **3a** either with methyl chloroformate or 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine gave only the starting material after work up (Table 1, entries 1-2).

Table 1. Optimization of DBL reaction conditions of **3a**.



entry	reagents (equiv.)	intermediate	t(h)	Yield of **5a**[a] (%)
1	$ClCO_2Me$ (2.0), Et_3N (1.5)	**4a**	1	-b
2	$ClCOC_6H_2Cl_3$ (2.0), Et_3N (1.5)	**4b**	2.5	-b
3	HBTU (1.0), DIPEA (1.0)	**4c**	2.5	-b
4	EDC (2.0), DMAP (0.1)	**4d**	1	17
5	Tf_2O (1.5), 2,6-lutidine (3.0)	**4e**	5	78
6	$(COCl)_2$ (2.0), DMFcat	**4f**	1	84
7	$SOBr_2$ (2.0), pyridine (5.0)	**4g**	1	93

[a] Isolated yield. [b] Only starting material was recovered after work up.

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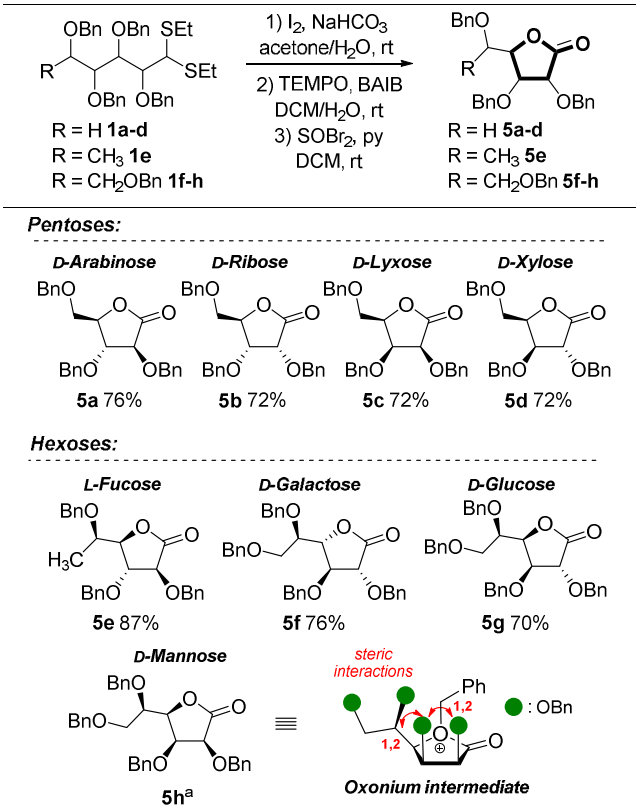
The use of classical peptide coupling reagents did not efficiently promote the cyclization. When the coupling reagent HBTU was employed, the starting material was recovered unchanged, while with carbodiimide EDC a complex mixture was obtained and the isolated yield of **5a** never exceeded 17% (entries 3-4). On the other hand, triflation of **3a** with triflic anhydride in the presence of 2,6-lutidine afforded 1,4-arabinolactone **5a** in 78% yield, while its chlorination with oxalyl chloride improved the isolated yield to 84% (entries 5-6). Formation of an acyl bromide **4g** with $SOBr_2$ was eventually found to be the best intermediate to trigger the DBL giving access to γ-lactone **5a** in 93% yield (entry 7). It is noteworthy that no trace of six membered ring (δ-lactone) was observed, thus evidencing the high regioselectivity of this reaction. The reaction conditions of this debenzylative lactonization differ from the debenzylative cycloetherifications mentioned above. The two cyclizations are mechanistically different as the etherification proceeds through a S_N2 mechanism and the lactonization through a stepwise addition-elimination on a sp^2 hybridized electrophile.

To expand the scope of the reaction and improve the generation of the starting carboxylic acid **II**, we sought to find safer and greener reagents than the highly toxic mercury and chromium salts, commonly employed for deprotection of dithioacetal **1a** and oxidation of aldehyde **2a** (Scheme 1). After a careful screening of experimental conditions, it was found that iodine and sodium bicarbonate in a mixture of acetone/H_2O promote the deprotection of **1a** while the oxidation of **2a** was achieved in the presence of TEMPO and BIAB in DCM/H_2O as a mixture (Table 2).[30, 31] Noteworthy, aldehyde **2a** and carboxylic acid **3a** do not require any purification using these protocols and they were thus used as crude materials. Therefore, under this new optimized sequence (Table 2) only two purifications by chromatography on silica gel were carried out to afford 1,4-arabinolactone **5a** starting from unprotected D-arabinose, instead of four in the previous sequence (Scheme 1). The optimization process thus dramatically improves this synthetic strategy in terms of safety, time, cost and yield.

Having established the optimal conditions for γ-lactone synthesis, the scope of this strategy was examined with various aldoses (Table 2). All dithioacetals **1b-h** were prepared from the corresponding aldoses as previously described for D-arabinose (Scheme 1) (see SI). The results gathered in Table 2 show that four pentoses **1a-d** and three hexoses **1e-g** were converted into their per-benzylated γ-lactones in good yields (70-87%) over three steps and only one purification. Gratifyingly, in all cases, the regioselectivity of the process is once again demonstrated since, only five-membered lactones were isolated whatever the initial length of the carbon skeleton. The structures of **5a-g** were fully ascertained by NMR spectroscopy, using ^1H, ^{13}C, $^1H/^1H$ correlations, and $^1H/^{13}C$ correlations (HSQC, HMBC). Structural proof of γ-lactones has been accomplished by HMBC NMR experiments and literature data analysis. First, the coupling between H-5 and a benzylic carbon indicates that a benzyloxy group is attached to C-5 carbon, which is inconsistent with a six-membered lactone. On the other hand, H-4 does not show coupling with any benzylic carbon, which is in a good agreement with γ-lactone structures.

Within this series, the only limitation that we found was the formation of the more challenging γ-mannonolactone **5h**. The reaction yielded a complex mixture of products from which the desired lactone **5h** could not be isolated pure. This particular problematic reactivity likely arises from the steric repulsions between the two benzyloxy groups of the ring and the C5-C6 chain, which are all-*cis*, in the oxonium intermediate (Table 2). A similar observation was previously reported by Nicotra for the iodocycloetherification of benzylated hept-1-enitols.[32] However, the debenzylative lactonization worked very satisfayingly with the gluco derivative **1g** in which a single 1,2-*cis* relationship is present (molecule **5g**, Table 2).

Table 2. Synthesis of various γ-lactones.



[a] Complex mixture was obtained.

In addition, the γ-lyxonolactone **5c** was synthesized efficiently despite the *cis*-relationship between all the substituents of the pentose (Table 2). These results show that in all-*cis* structures, the additional steric hindrance of the primary CH_2-OBn group of the precursor of **5h** is responsible of the differential reactivity compared to **5c**.

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Globally, all these results highlight the advantages of the DBL reaction in term of regioselectivity and efficiency allowing an easy and general access to a broad range of per-benzylated γ-sugar lactones from their commercial aldoses.

In conclusion, we have developed a new, efficient and regioselective debenzylative lactonization reaction starting from per-benzylated acyclic aldoses bearing a carboxylic acid giving access to various γ-lactone glycosides. This reaction could be applied to the substrates derived from widely used commercially available hexoses (L-fucose, D-galactose, D-glucose) and pentoses (D-arabinose, D-ribose, D-lyxose, D-xylose), to produce the corresponding γ-lactones in good yields without the need of a protection/deprotection sequence of the starting polyol. Furthermore, the findings described herein represent a significant advance in regioselective synthesis of γ-lactone glycosides and will create new opportunities for the generation of original nucleosides and natural compounds.

Conflicts of interest

There are no conflicts to declare.

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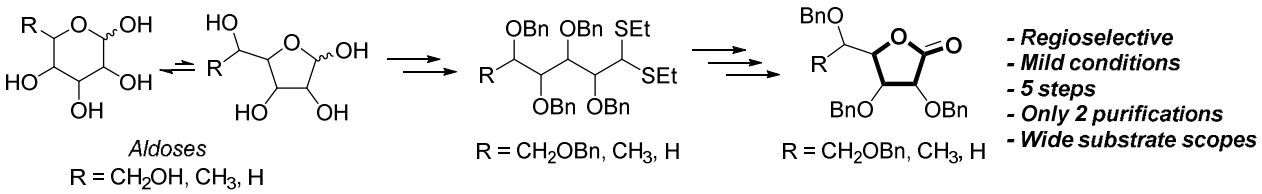
Graphical abstract:



Aldoses
R = CH_2OH, CH_3, H

R = CH_2OBn, CH_3, H

R = CH_2OBn, CH_3, H