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COMMUNICATION

Lewis acid-catalyzed stereoselective lactonization and subsequent glycosidation of 2-*C*-malonyl carbohydrates†‡

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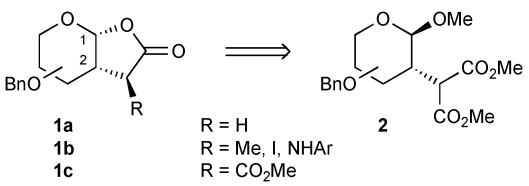
Gold(III) bromide is a suitable catalyst for the stereoselective cyclization of 2-*C*-malonyl carbohydrates to the anomeric center under retention of one ester group. Reopening of the lactones with alcohols in the presence of TMSOTf affords allyl, propargyl and benzyl glycosides with high α-selectivity.

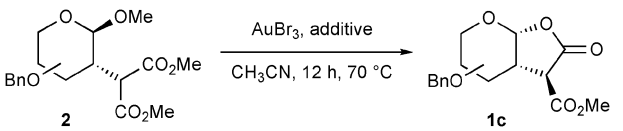
Lactones **1**‡ represent interesting analogs of naturally occurring carbohydrates, due to their 2-*C*-functionalization and fixed conformation (Scheme 1). We synthesized unsubstituted derivatives **1a** (R = H) from malonates **2**, which are easily available by radical addition of dimethyl malonate to glycals,[1] in few steps.[2] Very recently, Mukherjee *et al.* published a direct entry to lactone **1a** by reaction of glycals with acetic acid in the presence of manganese(III) acetate.[3] Substituted lactones **1b** are available in high stereoselectivities by alkylation of lactone **1a**,[4] cyclopropane opening[5] or through a four-component reaction.[6] However, lactones **1c** (R = CO_2Me) were hitherto unknown, since all attempts to cyclize malonates **2** in the presence of stronger Brønsted or Lewis acids failed, due to decarboxylations. Herein we describe the convenient synthesis of such carbohydrate 1,2-lactones **1c** in one step from malonates **2** in the presence of gold(III) bromide and their subsequent reaction with alcohols.

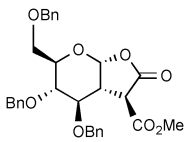
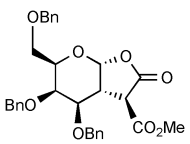
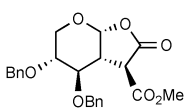
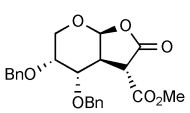


Scheme 1 Lactones **1** and possible synthesis from malonates **2**.

During our studies on gold-catalyzed glycosidations,[7] we investigated 2-*C*-nitromethyl carbohydrates as substrates very recently.[8] However, reactions of the corresponding 2-*C*-malonyl derivative *gluco*-**2** with various alcohols in the presence of gold(III) bromide afforded low yields of trans-glycosylated products besides some lactone *gluco*-**1c**. To further optimize this reaction and to establish a general entry to carbohydrate 1,2-lactones, we investigated the gold-catalysis in the less-nucleophilic solvent acetonitrile (Table 1). Without any additive we found no conversion of the starting material *gluco*-**2** (entry 1). However, the simple addition of two equivalents of water afforded the lactone *gluco*-**1c** in 75% yield in analytically pure form (entry 2) (ESI†).[9] The *galacto*-configured 2-*C*-malonyl carbohydrate **2** reacted under

Table 1 Synthesis of carbohydrate 1,2-lactones **1c**[a]



Entry	Config.[b]	Additive	Product	Yield[c] (%)
1	*gluco*	None	—	0
2	*gluco*	H_2O		75
3	*galacto*	H_2O		58
4	*xylo*	H_2O		67
5	*arabino*	H_2O		68

[a] For procedure see ESI.† [b] Configuration of starting material **2**. [c] Yield of analytically pure products, isolated by column chromatography.

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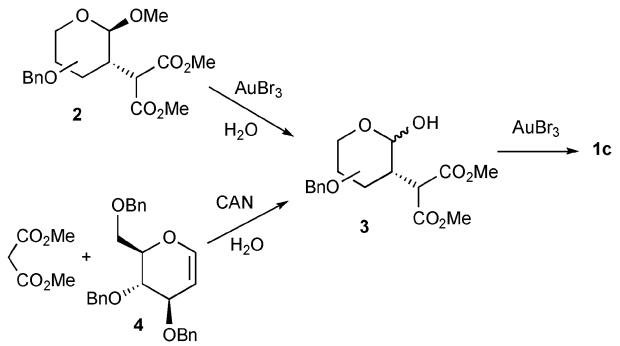
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all compounds. Determination of the configuration of the lactones by NOE measurements. See DOI: 10.1039/c1cc13425f

‡ This article is part of the *ChemComm* 'Glycochemistry and glycobiology' web themed issue.



Scheme 2 Proposed intermediate **3** in the formation of lactones **1c**.

the same conditions in somewhat lower yield (entry 3). Furthermore, pentoses *xylo*-**2** and *arabino*-**2** are suitable substrates for the lactonization as well (entries 4 and 5). Thus, gold(III) bromide is a mild catalyst for the convenient synthesis of the hitherto unknown carbohydrate 1,2-lactones **1c** from easily available malonates **2** in only one step.

From the mechanistic point of view, the addition of water is essential for the lactonizations (Table 1, entries 1 and 2). Therefore, we propose the formation of hemi acetals **3** as intermediates by cleavage of the methyl glycoside in the first step (Scheme 2). Subsequent cyclization affords lactones **1c**, and thus both steps are catalyzed by gold(III) bromide. To further prove this hypothesis, we synthesized hemi acetals **3** independently by radical addition of dimethyl malonate to glucal **4** in the presence of cerium ammonium nitrate (CAN) and water (Scheme 2). Indeed, reaction of intermediate **3** with gold(III) bromide or zinc(II) chloride afforded the same lactone **1c**. The influence of water became obvious in a one-pot synthesis of glycoside **6b** from malonate *gluco*-**2** (see below and ESI†).

Interestingly, products **1c** are formed as single stereoisomers. Obviously, the annelated ring to the γ-lactone is always 1,2-*cis*-configured, which is predetermined by the preset stereocenter of the starting materials **2**. Thus, the lactone ring is located above the sugar plane for *arabino*-**1c** (entry 5), but below the plane for all other products (entries 2–4). On the other hand, the ester group might occupy the *exo* or *endo*-position at the lactone ring, but a sole product is formed. We determined the configurations of these new stereocenters by detailed 500 MHz NOE measurements (ESI†). Thus, cross-peaks between 1-H and 2-H prove the *cis*-orientation of all γ-lactones **1c**. More importantly, an NOE effect between 3-H and the proton at the lactone ring indicates the *exo*-orientation of the ester group (Fig. 1).

The preferred formation of the *exo*-isomer **1c** for all lactonizations can be explained by steric interactions of the ester group with the sugar ring, which is minimized in the *exo*-configuration. This stereochemistry is in complete accordance to our previous studies on the alkylation of lactones **1a**[4] and corresponds nicely to literature-known cyclopropane openings.[5]

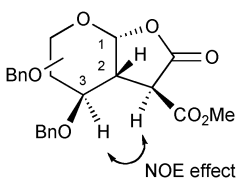


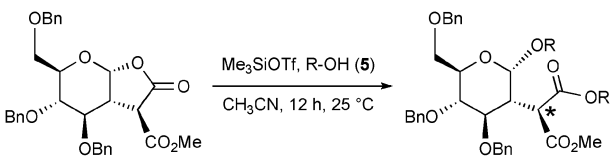
Fig. 1 NOE effect in lactones **1c**.

To demonstrate the potential of lactones **1c** as glycosyl donors, we investigated the opening of the lactone ring with nucleophiles next. In our previous studies we had found that scandium(III) triflate is a suitable Lewis acid to catalyze reactions of unsubstituted derivatives **1a**.[4] However, this Lewis acid was too reactive and gave decomposition products. Therefore, we employed trimethylsilyl triflate (TMSOTf) as an activator for the opening of lactone *gluco*-**1c**. Now the reaction proceeded smoothly with various alcohols **5**, and the glycosides **6** were isolated in good yields (Table 2, ESI†).[10] Only the hexinol **5e** required longer reaction time and gave somewhat lower yield (entry 5).

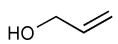
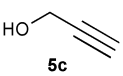
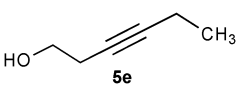
Interestingly, the methyl ester group remains intact in the products **6**, whereas the former lactone is converted into a new ester group. Furthermore, the stereocenter at the 7-position is conserved during the lactone opening, giving access to unsymmetric 2-*C*-malonyl carbohydrates **6** in diastereomerically pure form. This can be rationalized by a selective attack of trimethylsilyl triflate at the lactone carbonyl group and subsequent esterification with alcohols **5**. The carbenium ion at the 1-position is trapped by the alcohols in the same step. The anomeric mixture for methyl glycoside **6a** (entry 1) and the very high α-selectivity for all other products **6b–e** (entries 2–5) are in accordance to our openings of lactone *gluco*-**1a**[4b] and can be explained by an anomerization during the Lewis acid catalyzed reaction.[8] Thus, all stereocenters of starting material *gluco*-**1c** are conserved during lactone opening and the products **6** might be suitable precursors for further transformations.

In conclusion, we have synthesized bicyclic carbohydrate 1,2-lactones with an ester substituent for the first time.

Table 2 Reaction of lactone *gluco*-**1c** with alcohols **5**[a]



gluco-**1c** **6**

Entry	Alcohol **5**	Product **6**	Time/h	Yield[b] (%)
1	HO–Me **5a**	**6a**	4	90[c]
2	 **5b**	**6b**	2	78
3	 **5c**	**6c**	2	81
4	HO–Bn **5d**	**6d**	2	72
5	 **5e**	**6e**	12	61

[a] For procedure see ESI.† [b] Yield of analytically pure products, isolated by column chromatography. [c] 0.8 : 1.0 mixture of α- and β-anomer.

The cyclization of 2-*C*-malonyl carbohydrates proceeds under gold-catalysis under mild conditions and affords only one stereoisomer. Subsequent glycosidations with alcohols were realized in the presence of trimethylsilyl triflate with high stereoselectivities. Thus, the two Lewis acids complement each other in reactivity and can be employed for selective lactonizations or glycosidations respectively. Overall, the newly synthesized bicyclic carbohydrate 1,2-lactones might be attractive chiral building blocks in carbohydrate chemistry. Their opening at the anomeric center with carbon nucleophiles would give access to carbohydrate 1,2-bis-*C*-analogs. Additionally, the two different ester groups in products **6** can be transformed chemoselectively (*e.g.* cleavage of the benzyl ester in the presence of the methyl ester) under conversion of the stereogenic center. In addition, hydrolysis followed by Curtius rearrangement would give access to *C*-2 amino acid appended glycosides. The unsaturated glycosides **6b** and **6c** are interesting precursors for ring closing metathesis. Studies for such further chemical transformations are currently in progress.

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Notes and references

‡ The name "carbohydrate 1,2-lactone" is used in this communication for simplicity, although "2-oxo-hexahydro-furo[2,3-b]pyran" would be the correct IUPAC nomenclature.

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8 S. R. Vidadala, T. K. Pimpalpalle, T. Linker and S. Hotha, *Eur. J. Org. Chem*., 2011, 2426 An alternative explanation for the high α-selectivities might be the intermediary formation of a labile β-triflate and subsequent S_N2 reaction with the alcohols. We thank a reviewer for this suggestion.

9 *General procedure for $AuBr_3$-catalyzed lactonizations*: to a solution of methyl glycoside **2** (112 mg, 0.2 mmol) in acetonitrile (3 mL) was added water (0.4 mmol) and 8 mol% of $AuBr_3$ at room temperature. The resulting mixture was heated to 70 °C and stirred until TLC showed complete conversion. The reaction mixture was concentrated *in vacuo* to obtain a crude residue which was purified by silica gel column chromatography (ethyl acetate–petroleum ether) to give lactones **1c** in analytically pure form.

10 *General procedure for lactone openings:* to a solution of lactone *gluco*-**1c** (106 mg, 0.2 mmol) in acetonitrile (3 mL) was added nucleophile **5a** (0.6 mmol) and TMSOTf (45 mg, 0.2 mmol) at room temperature. The mixture was stirred at this temperature until TLC showed complete conversion. After dilution with water (5 mL), the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by silica gel column chromatography (ethyl acetate–petroleum ether) to afford the products **6**.

