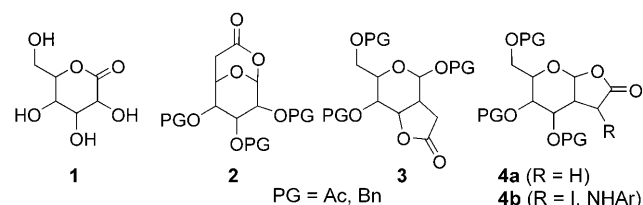


Convenient Synthesis of Bicyclic Carbohydrate 1,2-Lactones and Their Stereoselective Opening to 1-Functionalized Glucose Derivatives

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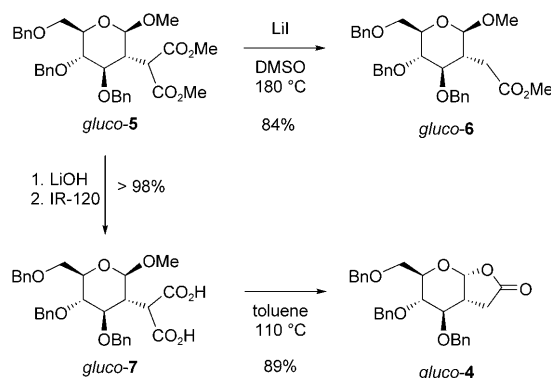
Lactones represent an important class of organic compounds, are industrial intermediates, and can be synthesized by various methods.^[1] γ -Lactones, in particular, are widespread in nature and possess promising pharmacological properties as enzyme inhibitors,^[2] due to their common ring-opening by nucleophiles. Interestingly, linking of carbohydrates to the reactive heterocycle increases water solubility, which is advantageous for the bioavailability. D-Glucono-1,5-lactone (**1**) is easily synthesized on a large scale by oxidation of the anomeric position of D-glucose and represents one of the cheapest chiral building blocks for organic chemists.^[3] On the other hand, carbohydrate-fused lactones have been less intensively studied, with some examples for 1,6-lactones **2**.^[4] Such compounds are available from uronic acids and allow stereoselective glycosylations by nucleophilic opening at the anomeric position.^[5]



In some cases, carbohydrate 2,3-lactones **3** were synthesized over many steps,^[6] but the corresponding 1,2-lactones **4** attracted less attention. Besides a few examples of higher oxidized analogues **4**,^[7] two papers on substituted lactone rings **4b** ($R=I$; $R=NHAr$) were published very recently.^[8] This is surprising, since such bicycles **4** should give easy

access to C-2 branched saccharides by reaction with nucleophiles at the anomeric center. Interestingly, unsubstituted carbohydrate 1,2-lactones **4a** ($R=H$) were not described until now. Herein we report on the convenient synthesis of such compounds and their stereoselective transformations by reactions with nucleophiles.

During the course of our studies on transition-metal-mediated radical reactions,^[9] we developed a one-step entry to 2-C-branched carbohydrates **5** by addition of dimethyl malonate to glycals.^[10] The method is applicable for unsaturated hexoses, pentoses, and disaccharides, and is characterized by high yields and stereoselectivities. More recently, we became interested in transformations of the side chain and succeeded in the cleavage to the ester *gluco-6* under drastic reaction conditions (Scheme 1).^[11] For a milder decarboxyla-



Scheme 1. Transformations of the 2-C-branched carbohydrate *gluco-5*.

tion, we saponified to the malonic acid **7** and heated only to 110 °C. Surprisingly, during thermolysis direct cyclization to lactone *gluco-4* occurred, which was isolated in high yield. Obviously, release of carbon dioxide and methanol provides the driving force of the reaction, which favors the lactonization entropically.

To further optimize the synthesis and to develop a general entry to carbohydrate 1,2-lactones **4**, we investigated differ-

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ent 2-C-branched saccharides **5**,^[11b] where the free dicarboxylic acids **7** were not isolated, but directly cyclized at 110°C after acidification with acetic acid (Table 1, Experimental Section). The method is suitable for hexoses (Table 1, en-

Table 1. Synthesis of carbohydrate 1,2-lactones **4**.^[a]

Entry	Malonate ^[11b]	Product	Yield [%] ^[b]
1	<i>gluco-5</i>	<i>gluco-4</i>	92
2	<i>galacto-5</i>	<i>galacto-4</i>	91
3	<i>xylo-5</i>	<i>xylo-4</i>	88
4	<i>arabino-5</i>	<i>arabino-4</i>	88
5	<i>malto-5</i>	<i>malto-4</i>	87
6	<i>lacto-5</i>	<i>lacto-4</i>	84

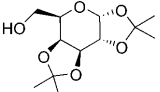
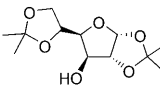
[a] Procedure and conditions see Experimental Section. [b] Yields of analytically pure products, isolated by column chromatography.

tries 1 and 2), pentoses (Table 1, entries 3 and 4) and disaccharides (entries 5 and 6), and provides the desired products in high yields. Thus, the hitherto unknown carbohydrate 1,2-lactones **4** become available in only three steps from glycals.

Next, we investigated the lactone opening with various nucleophiles **8** and selected *gluco-4* as substrate, since this configuration is widespread in nature, and we expected interesting products would arise. Lewis acids have proven to be suitable catalysts for such openings,^[12] and the functionalization of 1,6-lactones **2** at the anomeric center was accomplished with silylated nucleophiles in the presence of trimethylsilyl triflate^[5a,b] or tin tetrachloride.^[5c,e] However, lactone *gluco-4* afforded no conversion (TMSOTf) or cleavage of the *O*-benzyl protecting groups (SnCl₄). Evidently, the reactivity of the Lewis acid had to be carefully tuned. Finally, the best conditions were found with Sc(OTf)₃,^[12] which was previously applied for the opening of substituted lactones **4b**.^[8a] Thus, a broad variety of nucleophiles **8** afforded the ring-opening products **9** in good yields (Table 2).

Initially, we investigated the addition of alcohols **8a–e** (Table 2, entries 1–5), where the free carboxylic acid was directly esterified under the reaction conditions after opening at the anomeric center. Interestingly, α/β selectivities strongly depend on the nucleophile and the reaction times. Thus, methanol (**8a**) afforded the β -methyl glucoside **9a** after 30 min in excellent yield, whereas an epimerization to the α -anomer occurred after 4 h. 2-Propanol (**8b**) furnished an anomeric mixture (Table 2, entry 2), however with alcohols **8c–e** α -glucosides **9c–e** were isolated selectively after longer reaction times. Such an anomerization is in accordance with the recently published opening of 1,6-lactones **2**^[5e] and is very important for further transformations of the products (vide infra). Even *tert*-butyl alcohol (**8c**) reacted as a nucleophile with this method (Table 2, entry 3). Due to the two long alkyl chains, octyl glucoside **9e** was an interesting product (Table 2, entry 5), which resembles a carbohydrate analogue of phospholipids.^[13] Finally, carbohydrates with a free OH group were suitable nucleophiles **8f,g**, although disaccharides **9f,g** were isolated in only moderate yields (Table 2, entries 6 and 7). The lability of the glycosidic bond in the

Table 2. Opening of the lactone *gluco-4* with nucleophiles **8a–k**.^[a]

Entry	Nucleophile 8	Product 9 (%) ^[b]
1	MeOH	9a (92)
2	<i>i</i> PrOH	9b (78)
3	<i>t</i> BuOH	9c (65)
4		9d (78)
5	OctOH	9e (60)
6		9f (53)
7		9g (30)
8	25 % NH ₃ /H ₂ O	9h (95)
9	Me ₃ SiN ₃	9i (75)
10	EtSH	9j (82)
11	Et ₃ SiH	9k (78)

[a] Procedure and conditions see Experimental Section. [b] Yields of analytically pure products (see the Supporting Information).

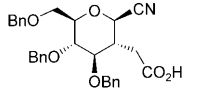
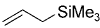
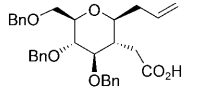
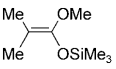
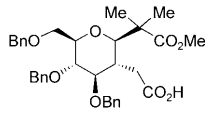
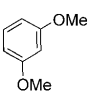
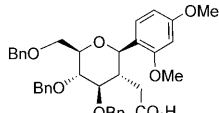
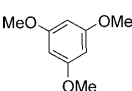
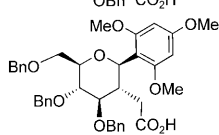
presence of scandium triflate required short reaction times, which explains the selective formation of β -anomers and the absence of esterification of the carboxylic acid.

We were able to introduce heteroatoms at the anomeric center of lactone *gluco-4* as well (Table 2, entries 8–10). The reaction with aqueous ammonia is especially attractive, since it opens simple access to bicyclic lactam **9h** in excellent yield. Glucosyl azide **9i** was formed with trimethylsilyl azide (**8i**) as nucleophile, which can be applied in click chemistry^[14] or as a precursor for dendrimers,^[15] whereas ethanethiol (**8j**) afforded ethyl thioglucoside **9j** as a potential glycosyl donor^[16] in good yield. Both reactions gave selectively β -anomers, but with **9i** the intermediary silyl ester was hydrolyzed during workup (Table 2, entry 9), whereas **9j** was isolated as stable thioester (Table 2, entry 10). Final-

ly, we succeeded in synthesizing the 1-deoxy derivative **9k** in 78 % yield by hydride opening (Table 2, entry 11).

The last topic of our studies was the reaction of lactone *gluco-4* with *C*-nucleophiles **8l–p** in the presence of scandium triflate (Table 3). This should give easy access to inter-

Table 3. Opening of the lactone *gluco-4* with *C*-nucleophiles **8l–p**.^[a]

Entry	Nucleophile 8 ^[b]	Product 9 (%) ^[c]
1	Me ₃ SiCN 8l	 9l (90)
2	 8m	 9m (83)
3	 8n	 9n (85)
4	 8o	 9o (67)
5	 8p	 9p (77)

[a] Procedure and conditions see Experimental Section. [b] Yields of analytically pure products (see the Supporting Information).

esting *C*-glycosides,^[17] which was already demonstrated with other Lewis acids and 1,6-lactones **2**.^[5a,b] Indeed, we were able to isolate 1,2-*bis-C*-branched glucose derivatives **9l–n** with the silylated nucleophiles **8l–n** in high yields (Table 2, entries 1–3). Additionally, electron-rich arenes enabled the simple synthesis of *C*-aryl glycosides **9o,p** (Table 3, entries 4 and 5). The opening proceeds for all reactions stereoselectively to β -anomers, since subsequent epimerization is not possible.

Finally, we present interesting applications of the synthesized ring-opening products with two examples (Scheme 2). Nitrile **9l** was smoothly converted into the diester **10** in 86 % yield. Such 1,2-*bis-C*-branched glucose derivatives with a methyl ester group at the 1-position are suitable intermedi-

ates in total synthesis.^[18] On the other hand, allyl ester **9d** is predestined for ring-closing metathesis,^[19] since due to the selective α -anomerization during the lactone opening, both double bonds occupy the same side of the carbohydrate. Indeed, we were able to synthesize macrolide **11**, which, flanked by the saccharide, might possess interesting biological properties.^[20]

In conclusion, we developed a convenient and general entry to bicyclic carbohydrate 1,2-lactones in only three steps from glycals. Opening of the *gluco*-configured lactone was demonstrated with various nucleophiles, which enabled the introduction of hetero and carbon substituents at the anomeric position. The reactions proceed with good yields and high stereoselectivities, and the products allow further interesting transformations.

Experimental Section

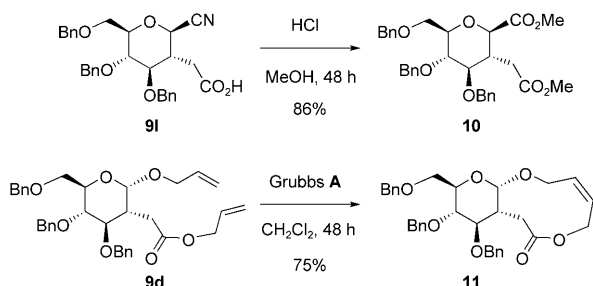
General procedure for the synthesis of carbohydrate 1,2-lactones **4:** A solution of the 2-*C*-branched carbohydrate **5** (2.0 mmol) and LiOH·H₂O (210 mg, 5.0 mmol) in MeOH/H₂O (4/1, 20 mL) was heated under reflux for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was dissolved in toluene, and the pH value was adjusted to 3 with acetic acid. The solution was heated under reflux for 1 h. After the solvents were evaporated, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate 7:1).

General procedure for the ring opening with nucleophiles: A solution of lactone *gluco-4* (475 mg, 1.0 mmol), Sc(OTf)₃ (740 mg, 1.5 mmol), and Drierite (20–40 mesh) (680 mg, 5.0 mmol) in dry dichloromethane (20 mL) was stirred at 0 °C under an argon atmosphere. After 30 min the nucleophile **8** (5.0 mmol, 5.0 equiv) was added to the mixture. The solution was stirred at room temperature until TLC showed complete conversion. The reaction was quenched with saturated NaHCO₃ solution (30 mL), and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated, and the products **9** were isolated by flash chromatography. All products **4** and **9** were completely characterized (see Supporting Information).

Acknowledgements

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Keywords: carbohydrates • lactones • nucleophilic addition • ring-opening • synthetic methods



Scheme 2. Transformations of ring-opening products **9l** and **d**.

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