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Synthesis and use of new *C*-glycosyl bicyclic lactones

Arkadiusz Listkowski [†], Otman Otman [‡], Stéphane Chambert, Yves Queneau [*]

Université de Lyon, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, ICBMS, UMR5246, CNRS, Université Lyon 1, INSA-Lyon, CPE Lyon, INSA Lyon, Bât. Jules Verne, 20 Avenue A. Einstein, Villeurbanne F-69621, France

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ABSTRACT

New *C*-glycosyl bicyclic lactones have been synthesized in three steps from glycosyl bromides and used as synthons towards *C*-glycosyl derivatives which can readily be elaborated to 1,2-bisfunctionalized carbohydrate systems. The method was illustrated with several examples of pseudo conjugates prepared from the new *C*-glycosyl 1,2-fused pyrano-δ-lactonic building blocks, either with groups such as allyl or propargyl with wide subsequent reactivity, or with more elaborated moieties leading to model glycoaminoacids or pseudo nucleotide sugars.

Introduction

1,2-Annulated carbohydrate substructures are found in many natural products or serve as synthons towards very diverse complex carbohydrate-based systems.[1] Those which include a lactone function can, like carbohydrate-based lactones in general,[2] serve as building blocks towards a wide range of conjugates with applications in biological or material sciences. Several families of bicyclic systems have been reported, arising from diverse carboxylic acid containing sugars and involving or not the anomeric position (Fig. 1).[3] One advantage of the bicyclic systems is to keep the sugar backbone in its closed form while the lactone is used for connection with the other moiety of the final target by reaction with a nucleophilic species. The extension of this strategy to form *C*-glycosyl systems is however much less documented, though *C*-glycosyl variants of glycoconjugates are very interesting compounds, being insensitive to acid or enzymatic glycosidic bond cleavage and therefore attractive targets for biological or medicinal purposes.[4] *C*-Glycosyl derivatives can also show interesting properties in the field of surfactants.[5] Apart from aromatic fused systems arising from *C*-glycosyl *ortho*-carboxy arenes, such as the naturally occurring bergenin and its analogues[6] only rare examples of simple lactones with a *C*-propanoyl appendage have been previously reported,[7] though not with the idea to serve as scaffolds. Some of them have been used as intermediates towards complex structures by carbon–carbon bond formation on the carbonyl group of the lactone, either by reaction of an intermediate vinyl triflate with a

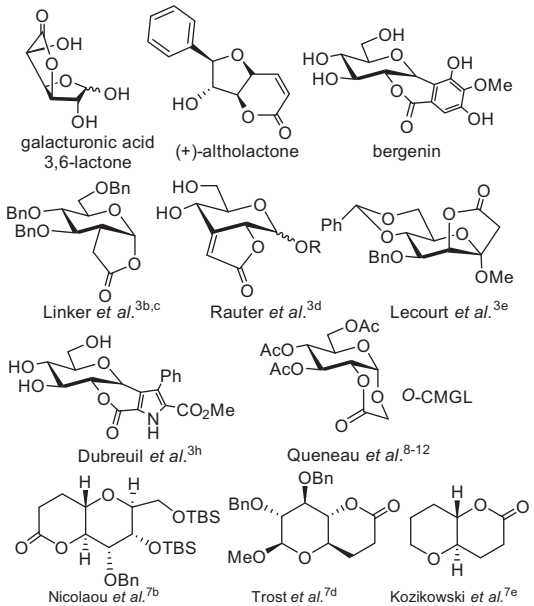

Figure 1. Examples of naturally occurring or synthetic carbohydrate-based bicyclic lactones.

* Corresponding author. Tel.: +33 47243 6169; fax: +33 47243 8896.
E-mail address: yves.queneau@insa-lyon.fr (Y. Queneau).
† Present address: Faculty of Mathematics and Natural Sciences, The Cardinal Stefan Wyszynski University, Dewajtis 5, 01-815 Warsaw, Poland.
‡ Present address: Department of Chemistry, Faculty of Science, Sebha University, PO Box: 18758, 71-Sebha, Libya.

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borane[7b] (the IJ fragment on the way to the GHIJKLMNO ring system of maitotoxin) or by reaction with a Grignard reagent.[7e]

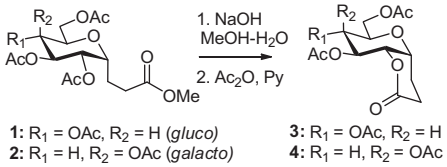
We have reported earlier that carboxymethyl glycoside lactones (*O*-CMGLs,[8] Fig. 1) are a family of bicyclolactonic synthons offering access to various types of *pseudo* conjugates such as glycoaminoacids hybrids,[9] pseudo-disaccharides,[10] pseudo-glycolipids,[11] several biologically relevant compounds[12] including non-ionic membrane imaging probes[13] and functional glycopolymers.[14] The OH-2 group of the sugar moiety, involved in the lactone function, is released upon lactone opening, and can subsequently be functionalized leading in a short sequence to 1,2-bisfunctionalized carbohydrate derivatives.[8d,11b,c,12c,14b]

Considering the readiness of the method and the importance of *C*-glycosyl derivatives in general, we have explored its extension to *C*-glycosyl targets, and we report hereafter our preliminary results on the synthesis and the reactivity of new *C*-glycosyl bicyclic lactones.

Results and discussion

The *C*-glycosyl lactones were prepared in three steps from peracetylated glucosyl or galactosyl bromides. Intermediate *C*-glycosyl propanoates **1** and **2** [methyl 3-(3,4,6-tri-*O*-acetyl-α-D-gluco- and galactopyranosyl)-propanoate][15] were obtained in 88% and 74% yields, respectively, by anomeric radical addition to methyl acrylate using Giese–Praly conditions.[16] Applying a saponification-acetylation sequence led to the desired new *C*-CMGLs **3** (*gluco*) and **4** (*galacto*) in 70% and 68% yields, respectively (Scheme 1). The carboxylate group released in the intermediate *C*-glycosyl is first to undergo acylation forming a mixed anhydride (not isolated) which is readily transformed into a lactone ring by intramolecular reaction with OH-2, while OH-3, 4 and 6 are also acetylated. The new lactones **3** and **4** were fully characterized,[17,18] and exhibited a very typical 18 Hz geminal coupling constant for the two hydrogen atoms of the CH_2 next to the lactone function indicating a rather rigid bicyclic lactone ring conformation, as previously found in the *O*-glycosyl systems.[8]

A short preliminary investigation of the ability of the new *C*-glycosyl lactones to serve as carbohydrate ligation synthons was then performed by studying their reaction with three simple amines, benzylamine, allylamine, propargylamine, these two latter offering wide potential subsequent uses.[19] The expected amides **5**–**10**, having OH-2 free and all three other positions acetylated were obtained in 88–94% yields (Fig. 2). The resulting amides exhibited NMR shifts and coupling constants which suggest a close conformational similarity with their *O*-glycoside counterparts previously reported.[8,9] Notably, clear evidence for the unprotected OH-2 is



Scheme 1. Synthesis of the new *C*-glycosyl lactones.

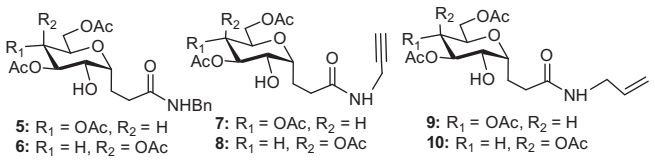


Figure 2. *C*-Glycosyl amides from lactones benzyl, propargyl and allyl-amines.

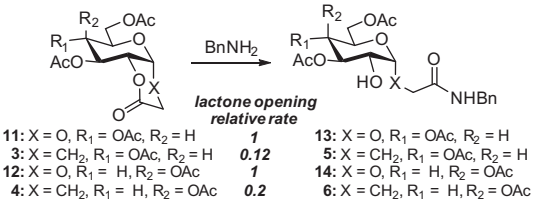


Figure 3. Compared rates for the opening of *C*-glycosyl versus *O*-glycosyl lactones with benzylamine in the *gluco* and *galacto* series.

given by ^1H chemical shifts of H-2 in the range of 4 ppm or lower, whereas acetylated ones are over 4.2 ppm.

The case of benzylamine was used for comparing the reactivity of the *C*- and the *O*-glycosyl lactones. The rate of the lactone opening reaction was measured by ^1H NMR spectroscopy, following the disappearance of the H-3 signal of the starting lactone **3** and the appearance of H-3 in amide **5**. By comparing with the same reaction using the *O*-glycosyl lactone **11**, it was found that the opening of the *C*-glycosyl lactones was ca. 8-fold slower (full data shown in Supplementary material). The same measurements performed in the *galacto* series (rate of formation of benzylamides **6** and **14** from lactones **4** and **12**) showed consistent results, though with a narrower difference (5-fold) in the rates (Fig. 3). These rate differences are difficult to fully interpret being possibly related to several parameters (inductive effect of the oxygen atom versus its involvement in the anomeric linkage, chair or partially twisted conformation of the lactone cycle), however these results suggest that, even though less reactive than their *O*-glycosyl counterparts, the *C*-glycosyl lactones exhibited sufficient reactivity to serve as promising scaffolds.

The interest of the method for accessing more elaborated targets is illustrated in Figure 4, first with the preparation of conjugates by reaction of the new lactones with aspartic acid and aminodeoxyuridine, leading to *C*-glycosyl glycoaminoacid hybrids **15** and **16** in 84 and 90% yields respectively, and *C*-glycosyl nucleotide-sugar analogue **17**. Aminodeoxyuridine, having two unprotected OH groups, could also be used, leading to amide **18** in 63% yield. In these cases, although no side product was clearly identified, we can hypothesise that the lower yields are due to competitive transamidification of the 6-OAc group of the starting lactone, as observed in the reaction of the *O*-glycosyl lactone with an aminosugar.[10] Finally, the ability for the *C*-glycosyl adducts to be further functionalized at OH-2 was illustrated by the transformation of the *galacto* allylamide **10** and the *gluco* allylamide **9** to the corresponding 2-carbamates, using octyl or dodecyl isocyanate,

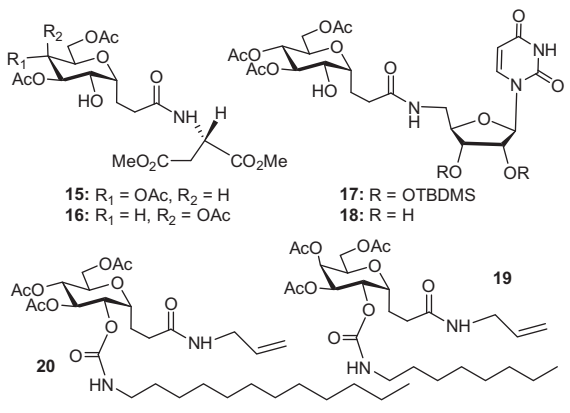


Figure 4. Examples of *C*-glycosyl pseudoglycoconjugates and disubstituted systems from *C*-glycosyl lactones.

respectively. Thus, the 1,2-disubstituted derivatives **19** and **20**, bearing unsaturated and hydrophobic groups as functional appendages, were obtained in 58% and 60% yields, respectively.

In conclusion, we have described the synthesis and the use of new *C*-glycosyl 1,2 annulated lactones which can serve as carbohydrate donating systems for the preparation, under mild conditions and in fair to good yields, of mono or disubstituted *C*-glycosyl pseudo-conjugates. The method offers straightforward access to derivatives with relevance to biological or materials sciences.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, ^{1}H and ^{13}C NMR data and spectra of all compounds, lactone opening reaction rates measurements) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.07.017.

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17. Lactone **3** (*gluco*); $[\alpha]_D$ +45 (c = 1.05, $CHCl_3$); HRMS (CI) *m*/*z* calcd for $C_{15}H_{21}O_9$ $(M+H)^+$ 345.1186, found 345.1183; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.22 (t, 1H, *J* = 4.61 Hz, H-3), 4.85 (t, 1H, *J* = 4.52 Hz, H-4), 4.62 (dd, 1H, *J* = 6.96 Hz, *J* = 11.2 Hz H-6a), 4.29–4.38 (m, 2H, H-1 and H-2), 4.01–4.15 (m, 2H, H-5 and H-6b), 2.81 (ddd, 1H, *J* = 6.8 Hz, *J* = 9.8 Hz, *J* = 18.1 Hz, H-8a), 2.53 (ddd, 1H, *J* = 5.1 Hz, *J* = 6.78 Hz, H-8b), 1.90–2.25 (m, 11 H, H-7a, H-7b and 3s × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 169.9, 168.9, 168.7 (4 × C=O), 75.2 (C-2), 72.9 (C-5), 68.3 (C-3), 66.1 (C-4), 62.1 (C-1), 60.7 (C-6), 25.9 (C-8), 23.6 (C-7), 20.8, 20.78, 20.75 (3 × CH_3).
18. Lactone **4** (*galacto*): $[\alpha]_D$ +76 (c = 1.29, $CHCl_3$); MS (ESI) *m*/*z* = 344.9 $[C_{15}H_{21}O_9$ $(M+H)^+]$; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.44 (dd, 1H, *J* = 3.3 Hz, *J* = 5.7 Hz, H-4), 5.27 (dd, 1H, *J* = 5.2 Hz, *J* = 3.3 Hz, H-3), 4.68 (dd, 1H, *J* = 9.1 Hz, *J* = 12.3 Hz, H-6a), 4.44 (dd, 1H, *J* = 2.9 Hz, H-2), 4.38–4.25 (m, 2H, H-1, H-5), 4.02 (dd, 1H, *J* = 3.9 Hz, *J* = 12.3 Hz, H-6b), 2.73 (ddd, 1H, *J* = 7.2 Hz, *J* = 9.4 Hz, *J* = 17.7 Hz, H-8A), 2.48 (ddd, broad, 1H, *J* = 5.8 Hz, *J* = 6.0 Hz, H-8b), 2.00–2.15 (m, 11 H, H-7a, H-7b and 3s × CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0 (COO), 169.5, 169.4, 169.1 (3 × C=O), 77.0 (C-2), 71.8 (C-5), 69.0 (C-3), 65.8 (C-4), 61.9 (C-1), 59.7 (C-6), 26.0 (C-8), 23.7 (C-7), 20.97, 20.96, 20.76 (3 × CH_3). Anal. Calcd. for $C_{15}H_{20}O_9$: C, 52.32; H, 5.85. Found: C, 52.21; H, 5.98.
19. Typical procedure for lactone opening: a mixture of lactone **3** (100 mg, 0.29 mmol) and allylamine (22 μL, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was stirred for 72 h at room temperature. After evaporation of the solvent under reduced pressure, the residue was purified over silica gel (EtOAc–pentane 4/1) to give amide **7** in 94% yield. Other examples: see the Supplementary material.