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Selective Synthesis of α-*C*-(Alkynyl)-galactosides by an Efficient Tandem Reaction

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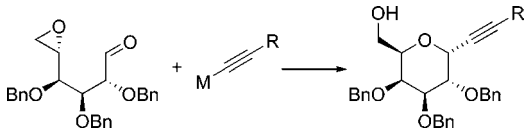

Several α-*C*-(alkynyl)-galactosides were synthesized using a tandem reaction involving the addition of a metal alkynylide to a chiral acyclic epoxyaldehyde, followed by an in situ closure of the generated alkoxide on the epoxide function.

Introduction

Carbohydrates are important constituents of glycoproteins and glycolipids that are involved in numerous biological processes.[1] Unfortunately, the use of carbohydrate-based molecules as therapeutics is limited because of the hydrolytic lability of the glycoside bond. Replacing the anomeric oxygen atom with a methylene group leads to more stable *C*-glycoside analogues with higher chemical and enzymatic stability. These compounds can be used as tools to study the role of the carbohydrate moiety in biological processes and to design potential drugs. As a result, it is not surprising that *C*-glycoside analogues have gained considerable attention in the past 2 decades, and to date numerous methods have been described for their synthesis.[2] In the literature, biological activity of *C*-glycoside analogues is generally described to be similar or lower than the parent *O*-glycoside. For example, Kishi et al. reported that the replacement of the anomeric oxygen atom with a methylene group did not significantly diminish the biological activity of the H-type II blood group trisaccharide, as a result of the similar solution conformation of the *C*-trisaccharide compared to the *O*-one.[3] To the best of our knowledge, only one example of a *C*-glycoside analogue, that of KRN 7000, has been recently described to show a biological activity better than that of the corresponding *O*-glycoside.[4]

The development of effective *C*-glycoside syntheses depends on the selective formation of only one anomer as the major reaction product in good to excellent yield. As part of an ongoing program aimed at developing the synthesis of α-*C*-glycoside analogues of complex bioactive glycosides, we report herein an efficient method to selectively access α-*C*-(alkynyl)-galactosides from an acyclic carbohydrate. Syntheses of α-*C*-(alkynyl)-galactosides have increased in the past decade because they are attractive building blocks for the synthesis of galactosides analogues.[5] To the best of our knowledge, no synthesis of α-*C*-(alkynyl)-galactosides from an acyclic carbohydrate has been previously reported.

Results and Discussion

Our strategy is based on a one-pot, two-step sequence involving the addition of a metal alkynylide to the open chain epoxyaldehyde **1**, followed by intramolecular epoxide opening

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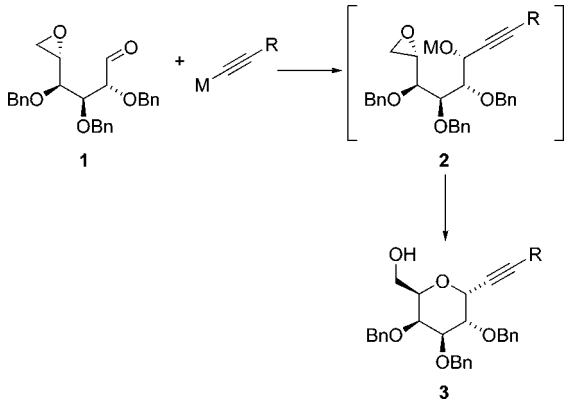
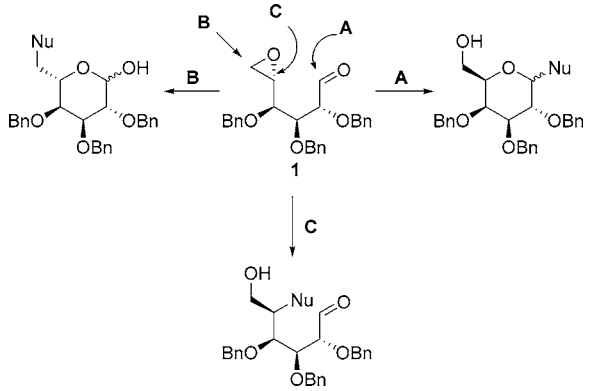
SCHEME 1. General Strategy toward α-*C*-galactosides.



SCHEME 2. Three Possible Reaction Pathways



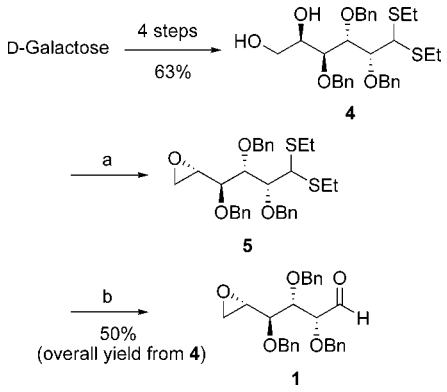
with the resulting alkoxide and exclusive formation of α-*C*-galactoside **3** (Scheme 1).

This strategy is chemically challenging in terms of regioselectivity. Indeed, aldehyde **1** possess three electrophilic sites and the reaction of **1** with nucleophiles could potentially give three different products following pathways A, B, or C (Scheme 2). Since alkyne addition to 1,2-epoxyaldehydes has been described to be highly regioselective[6] (i.e., addition only at the aldehyde function), we were confident with the outcome of our strategy (pathway A).

Aldehyde **1** was synthesized from the known diol **4**,[7] which was available from D-galactose in four steps (Scheme 3). Reaction of diol **4** with pivaloyl chloride under classical conditions furnished the monoprotected primary pivalate ester. Epoxide **5**, contaminated with a small amount (<10%) of an unidentified compound, was then formed by treatment of the secondary alcohol with mesyl chloride, followed by ester deprotection and mesylate elimination with potassium hydroxide. Finally, deprotection of the dithioacetal group afforded aldehyde **1** in a 50% overall yield from diol **4**.

To obtain the desired α-*C*-galactosides, alkyne addition to aldehyde **1** must be highly selective in favor of the 1,2-*syn* alkoxide **2** (Scheme 1). Very recently, we described a 1,2-*syn* selective coupling of a chiral trialkoxyaldehyde and various alkynes in which the best selectivity was obtained with the use of a zinc alkynilide.[8] The necessary alkynylzinc reagents were

SCHEME 3. Synthesis of Aldehyde 1[a]



[a] Reagents and conditions: (a) (i) *t*BuCOCl, pyridine, CH_2Cl_2, (ii) MsCl, DMAP, CH_2Cl_2, (iii) KOH, MeOH; (b) I_2, $CaCO_3$, THF/H_2O.

prepared by reaction of the corresponding alkynylithium derivative with 2 equiv of freshly prepared zinc chloride.[9] Since the ring opening of an epoxide with a nucleophile requires activation with a Lewis acid, we expected that this excess of zinc chloride could play the role of the subsequent epoxide activator. The addition of the zinc phenylacetylide to aldehyde **1** in diethyl ether at 0 °C in the presence of zinc chloride was then performed. TLC analysis of the reaction after 2 h at 0 °C showed the almost exclusive formation of a more polar compound, the intermediate **2** that had been previously isolated (with a minor amount of 1,2-*anti* alcohol). The reaction mixture was then allowed to stir at room temperature for 24 h, allowing formation of the desired α-*C*-galactoside, isolated in 55% yield as the major reaction product. The ^{1}H NMR spectrum of compound **3** showed a doublet at 5.07 ppm with a coupling constant of $^3J_{1-2} = 5.6$ Hz, which is characteristic for the α configuration of *C*-galactosides.[5f] The formation of **3** and the absence of any detectable *β*-*C*-galactoside both showed that the first step of our procedure was highly regio- and stereoselective. Unfortunately, the cyclization step of this tandem process was not complete and a mixture of unreacted 1,2-*syn* and 1,2-*anti* alcohols **2** was obtained in 14% yield (in a ratio 2:1). It is important to note that when unpurified zinc chloride was used, alcohol **2** was the *only* isolated product with no traces of the cyclized derivative **3**.

To accelerate the second step of this tandem process, further experiments were then carried out. First of all, the reaction mixture was slightly heated to 35 °C for 24 h, but no improvement in the yield was observed. Several additives were then tested to further activate the epoxide ring opening (1 M $ZnCl_2$/THF solution, $Ti(OiPr)_4$, LiBr). The best result was obtained with an excess of lithium bromide, and α-*C*-galactoside **3** was isolated in 73% yield with no trace of the *β*-isomer.

The optimized reaction conditions were then selected to extend our strategy to various alkynes. These results are reported in Table 1. Reaction of alkynes containing an alkyl chain led to the formation of only one compound, the corresponding α-*C*-galactoside in similar yields (entries 2 and 3). With trimethylsilylacetylene, the first step of the process was less selective than previously observed in our model study.[8] Indeed, the α-*C*-

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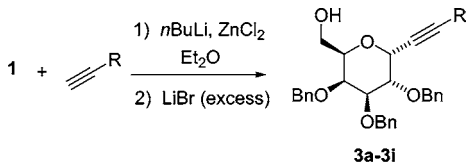
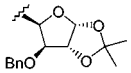
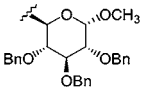
(9) $ZnCl_2$ (10 g) was refluxed in 1,4-dioxane (80 mL) in the presence of with zinc dust (1 g). After hot filtration and cooling to precipitate $ZnCl_2$, it was recrystallized from 1,4-dioxane and stored in a desiccator over P_2O_5.

TABLE 1. Alkynylation of Aldehyde 1 with Various Zinc Alkynilides



3a-3i

Entry	R	Product	Yield (%)
1	Ph	**3a**	73
2	*n*-C_3H_7	**3b**	69
3	*n*-C_5H_{11}	**3c**	63
4	$SiMe_3$	**3d**	62
5	$CH_2OTBDMS$	**3e**	69
6	$C(=CH_2)CH_3$	**3f**	73
7		**3g**	70
8		**3h**	55
9		**3i**	48

glycoside was accompanied with a small amount (12%) of a more polar compound (entry 4). The ^{1}H NMR spectrum of the latter product showed a $^3J_{1-2} = 9.5$ Hz, which is characteristic of a β configuration for *C*-glycosides.[5c] This was the only case in which the presence of a β-*C*-galactoside was detected. Two functionalized alkynylides were also tested and the corresponding α-*C*-galactosides were obtained in good yields (entries 5 and 6). Our strategy worked equally well with more elaborate alkynes containing a carbohydrate or amino alcohol chain. These alkynes were prepared following known procedures from the corresponding aldehydes.[10−12] Reaction with the xylose-derived alkyne was complete after 6 h at room temperature and gave the (1→5)-α-*C*-disaccharide as a single compound in 70% yield (entry 7). Reaction with the glucose-derived alkyne was less efficient, and the corresponding α-*C*-galactoside was obtained in only 55% yield (entry 8). Finally, reaction with an amino acid derived alkynilide was examined, and we were pleased to isolate the α-*C*-galacto-amino alcohol in 48% yield (entry 9), showing that nitrogen-containing compounds can be obtained with this new method.

In summary, we have developped an efficient strategy to selectively synthesize simple as well as complex α-*C*-galactosides using a one-pot, two-step sequence involving the addition of a metal alkynylide to a chiral acyclic epoxyaldehyde, followed by an in situ closure of the generated alkoxide on the epoxide function. This process was highly regio- and stereoselective. Further investigations are currently in progress in order to obtain α-*C*-galactoside analogues of bioactive molecules.

Experimental Section

Typical Procedure for Synthesis of α-*C*-Galactosides. Freshly purified zinc chloride (1 mmol) was fused under vacuum (0.1 mmHg). After cooling, diethyl ether (1.5 mL) was then introduced under argon. To this solution was added a solution of lithium alkynyl derivative (prepared from alkyne (0.55 mmol) and *n*-BuLi (0.2 mL, 0.5 mmol, 2.5 M solution in hexanes) in diethyl ether (2 mL)) at 0 °C. The solution was stirred for 45 min at 0 °C before the addition of a solution of freshly purified aldehyde **1** in diethyl ether (1 mL). The solution was stirred at 0 °C until starting material was consumed, and solid lithium bromide (0.25−0.3 mmol) was then added to the reaction mixture. The solution was allowed to stir at room temperature for 24 h, diluted with diethyl ether, and quenched with a saturated NH_4Cl solution. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The resulting crude oil was purified by silica gel column chromatography.

3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-6-*C*-(2,3,4-tri-*O*-benzyl-α-D-galactopyranosyl)-α-D-*xylo*-hex-5-ynofuranoside (3g). Yield: 70%. Colorless oil. $[\alpha]^{25}_D$ +67.2° (*c* 1.0, $CHCl_3$). IR (film, cm^{-1}): 3474, 3063, 3030, 2988, 2933, 1497, 1454, 1077. ^{1}H NMR ($CDCl_3$) δ: 7.40−7.23 (m, 20H, H arom), 5.97 (d, 1H, J = 3.6 Hz), 4.96−4.78 (m, 4H), 4.77−4.64 (m, 5H), 4.56−4.48 (m, 2 H), 4.10 (dd, 1H, J = 5.5, 9.7 Hz), 4.00 (br d, 1H, J = 2.5 Hz), 3.96−3.78 (m, 3H), 3.63 (dd, 1H, J = 6.2, 11.5 Hz), 3.40−3.34 (m, 1H), 1.48 (s, 3H), 1.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 138.6, 138.2, 138.1, 137.5, 128.4, 128.3, 128.2, 127.8, 127.6, 127.5, 127.4, 112.4, 104.5, 83.3, 82.9, 82.6, 82.2, 75.3, 74.7, 74.4, 73.7, 73.3, 73.0, 72.5, 70.8, 67.5, 62.1, 26.8, 26.1. HRMS (ESI) *m*/*z* calcd for $C_{43}H_{46}O_9Na$ (M + Na) 729.3040, found 729.3061.

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Supporting Information Available: General experimental methods and characterization data for all new compounds **1**, **3a**−**3i**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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