Dipyranose Ethers

Development of a Novel Sugar Linkage: 6,6′-Ether-Connected Sugars**

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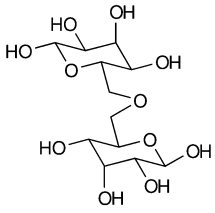
In 1997, Pérez et al. reported the structure **1** for coyolosa, a natural product isolated from the root of *Acrocomia mexicana*[1] that was shown to have a significant effect on fasting blood-glucose levels.[2] Coyolosa may well be a new candidate in the search for drugs to combat diabetes. Upon examination of the NMR spectroscopic data of Pérez et al. for this unique carbohydrate in which two pyranose groups are connected as a 6,6′-ether, we found it unlikely that coyolosa had the proposed structure **1**.[3] Although there can be no doubt that two pyranose rings linked through their 6-positions form the structure of coyolosa,[4] it is less evident that the stereochemistry of the pyranose moieties corresponds to that shown in **1**. Herein, we report a novel synthesis of 6,6′-ether-connected pyranoses and propose an absolute configuration for coyolosa based on structure–activity-relationship (SAR) studies that is different to the one originally suggested.



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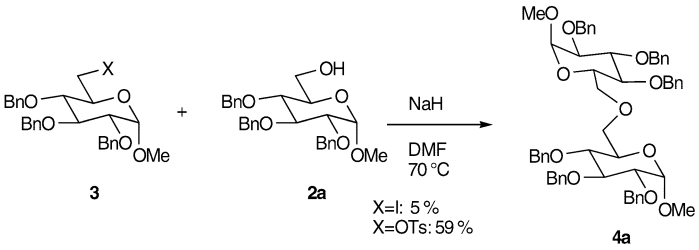
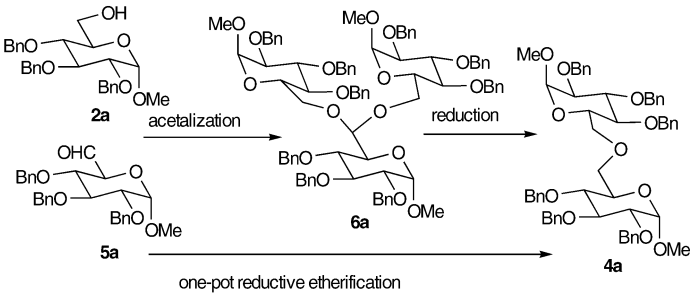
Little has been reported to date on sugars linked by ether bonds. In preliminary studies, we treated the methyl α-D-*gluco*-pyranoside **2a** with the iodide and the tosylate corresponding to **3** under basic conditions in an attempted Williamson etherification. The desired ether **4a** was only obtained in low to moderate yields (Scheme 1), as the anomeric position was unstable under the Williamson conditions, and the competing elimination could not be avoided.



Scheme 1. Synthesis of 6,6′-ether-connected pyranoses by the Williamson etherification. DMF = *N*,*N*-dimethylformamide, Tos = *p*-toluenesulfonyl.

As the Williamson etherification had proved unsuccessful in our attempt to synthesize 6,6′-ether-connected pyranoses, we instead adopted an acetalization–reduction approach, as shown in Scheme 2. In this method, a 6-aldehyde **5** is treated with a 6-alcohol **2** under mild acid-catalyzed conditions to provide an intermediate acetal derivative **6**. The treatment of



Scheme 2. Proposed synthetic routes to 6,6′-ether-connected pyranoses **4** (shown for **4a**).

6 with a reducing agent then furnishes the desired product **4**. As a two-step procedure is inconvenient, a one-pot reductive etherification,[5] which is a more reliable method for the preparation of ethers under nonbasic conditions, was also envisaged.

A large number of studies have been carried out on reductive etherification, that is, the reduction of oxocarbenium ions or acetals generated in situ to provide ethers. In particular, Lewis acid catalyzed reactions of these compounds with alkoxy silanes or hydrosilanes have proved useful for the efficient synthesis of unsymmetrical ethers.[5e–j] Although the reaction of simple carbonyl compounds (e.g. benzaldehyde) with various alcohols has already been reported, there are few methods[4j] suitable for carbonyl compounds substituted with bulky or multifunctional carbohydrates.

Acetal formation was investigated first. An equimolar amount of the methyl α-D-*gluco*-pyranoside **2a** reacted with the aldehyde **5a** very slowly to give the acetal derivative **6a** in poor yield. However, when an excess of **2a** was used in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 0°C, **6a** was isolated in 91% yield. It had been anticipated that the acetal derivative, which contains three bulky pyranosides, would be relatively unstable. However, we found that **6a** was so stable that it could be purified without difficulty by silica-gel column chromatography. The structure of this acetal derivative is unusual and has many features that remain to be investigated.[6]

The reactions of the D-*gluco*-, D-*galacto*-, D-*manno*-, and D-*allo*-pyranosides **2a, 2b, 2c**, and **2d**, respectively, with the

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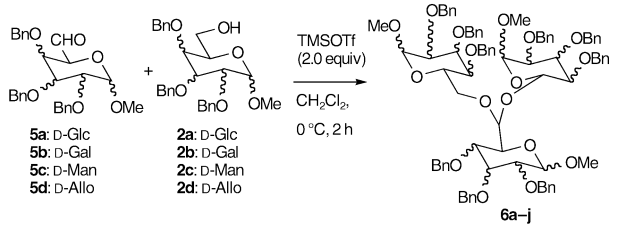
aldehyde derivatives **5a–d**[7] under similar conditions afforded the corresponding acetal derivatives **6a–j** (Table 1). The excess of the pyranoside **2** was recovered quantitatively in each case and reused in other reactions.

Table 1: Acetalization of aldehydes **5** with alcohols **2** catalyzed by TMSOTf.[a]

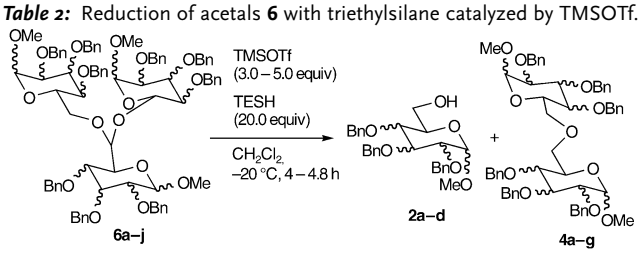


Entry	5	2 (6-OH)	6	Yield [%][b]
1	**a** (Glc)	**a** (Glc)	**a** (Glc-Glc-Glc)	91
2	**a** (Glc)	**b** (Gal)	**b** (Gal-Glc-Gal)	81
3	**a** (Glc)	**c** (Man)	**c** (Man-Glc-Man)	93
4	**b** (Gal)	**a** (Glc)	**d** (Glc-Gal-Glc)	93
5	**b** (Gal)	**b** (Gal)	**e** (Gal-Gal-Gal)	76
6	**b** (Gal)	**c** (Man)	**f** (Man-Gal-Man)	84
7	**c** (Man)	**a** (Glc)	**g** (Glc-Man-Glc)	75
8	**c** (Man)	**b** (Gal)	**h** (Gal-Man-Gal)	76
9	**c** (Man)	**c** (Man)	**i** (Man-Man-Man)	80
10	**d** (All)	**d** (All)	**j** (All-All-All)	69

[a] Reactions were conducted with 10 equivalents of **2**. [b] Yield of isolated product.

With the desired intermediates **6** in hand, we then investigated the reduction step with triethylsilane (TESH) as the reducing agent. It was found that TMSOTf accelerated the reduction of **6** with TESH efficiently to give the desired 6,6′-ether-connected pyranosides **4**. The acetals **6a–j** were successfully converted into the corresponding pyranosides **4a–g** and the excess of the alcohol **2** could be recovered quantitatively and reused (Table 2). This is the first example

Table 2: Reduction of acetals **6** with triethylsilane catalyzed by TMSOTf.

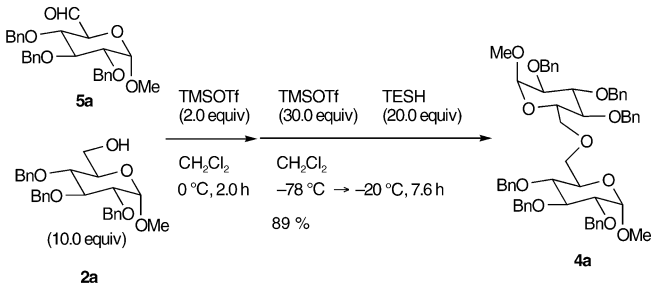


Entry	6	4	Yield [%][a]
1	**a** (Glc-Glc-Glc)	**a** (Glc-Glc)	96
2	**b** (Gal-Glc-Gal)	**b** (Glc-Gal)	79
3	**c** (Man-Glc-Man)	**c** (Glc-Man)	95
4	**d** (Glc-Gal-Glc)	**b** (Gal-Glc)	75
5	**e** (Gal-Gal-Gal)	**d** (Gal-Gal)	82
6	**f** (Man-Gal-Man)	**e** (Gal-Man)	73
7	**g** (Glc-Man-Glc)	**c** (Man-Glc)	73
8	**h** (Gal-Man-Gal)	**e** (Man-Gal)	69
9	**i** (Man-Man-Man)	**f** (Man-Man)	64
10	**j** (All-All-All)	**g** (All-All)	56

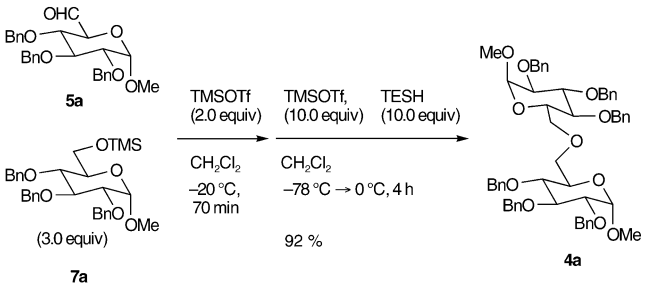
[a] Yield of isolated product.

of the synthesis of these types of carbohydrates, which are connected through the 6,6′-positions by an ether linkage rather than by the usual glycoside linkage.[8]

Having established the required acetalization–reduction procedures, we next turned our attention to the development of a more convenient, one-pot synthesis. First, the one-pot etherification of **2a** with **5a** was investigated. Their acetalization in the presence of TMSOTf was carried out at 0 °C for 2 h, and subsequent addition of TMSOTf and TESH to this system led to the conversion of the acetal into **4a** in 89 % yield (Scheme 3). However, in this case an excess of **2a** and the other reagents was required for the reaction to reach completion. To establish a more efficient synthetic method, we examined the possibility of decreasing the amount of **2a** required by substituting it in the reaction with its 6-OTMS derivative **7a**. After surveying a variety of conditions, we found that 3 equivalents of **7a** were sufficient to provide **4a** in 92 % yield (Scheme 4). The 6-OTMS group may play a role in decreasing the degree of coordination between **7a** and TMSOTf or TESH.



Scheme 3. One-pot acetalization–reduction reaction of **2a** and **5a** with triethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate.

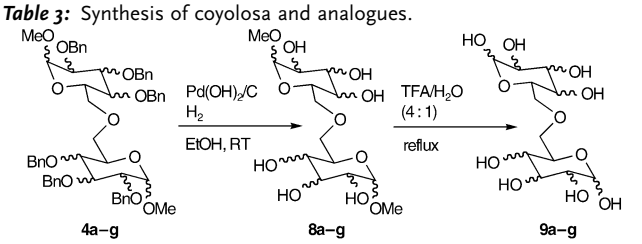


Scheme 4. One-pot acetalization–reduction of **5a** and **7a** with triethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate. TMS = trimethylsilyl.

To complete the synthesis of coyolosa and its analogues we still needed to unmask the hydroxy groups in **4**. Removal of the benzyl groups of **4a–g** by hydrogenolysis furnished the corresponding pyranosides **8a–g**. Treatment of **8a–g** with trifluoroacetic acid then gave the desired 6,6′-ether-connected pyranoses **9a–g** in moderate to good yields (Table 3).

We inspected the spectral data[9] of **9a–g** for confirmation of their structure and reconsidered the possibility of the proposed structure **1** of coyolosa based on structure–activity-relationship (SAR) studies. According to the procedure reported,[1] the biological activity of all synthetic 6,6′-ether-

Table 3: Synthesis of coyolosa and analogues.



Entry	4	9	Yield [%][a]
1	**a** (Glc-Glc)	**a**	78
2	**b** (Glc-Gal)	**b**	50
3	**c** (Glc-Man)	**c**	72
4	**d** (Gal-Gal)	**d**	59
5	**e** (Gal-Man)	**e**	76
6	**f** (Man-Man)	**f**	37
7	**g** (All-All)	**g**	59

[a] Yield from **4**.

connected pyranoses **9a**–**g** on glucose tolerance in alloxane-induced diabetic rats was investigated. Surprisingly, **9f** demonstrated the most favorable effect on fasting blood-glucose levels, which was similar to that of coyolosa, as reported by Pérez et al.[1,10] We therefore tentatively propose that the structure of coyolosa might be the mannose-derived isomer **9f**, if this natural product is indeed a 6,6′-ether-connected carbohydrate.

In conclusion, we have developed a novel synthesis of 6,6′-ether-connected pyranoses through an acetalization–reduction procedure. For convenience, a one-pot synthesis was also established. Based on an SAR study, we suggest that the structure of coyolosa might be the 6,6′-ether-connected mannose. Additional synthetic and biological studies on ether-connected carbohydrates are currently underway in our laboratory.

Experimental Section

General procedure for acetalization: TMSOTf (46 μL, 0.25 mmol) was added to a mixture of **5a** (58.9 mg, 0.13 mmol) and **2a** (592 mg, 1.30 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was stirred for 2 h then poured into a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was subjected to silica-gel column chromatography (toluene/AcOEt 2:1), and the excess of **2a** was recovered quantitatively. Silica-gel column-chromatographic purification (hexane/Et_2O 1:1) of the remaining material afforded **6a** (159.7 mg, 0.12 mmol, 91 %) as an oil.

General procedure for acetal reduction: TMSOTf (21 μL, 0.12 mmol) and triethylsilane (123 μL, 0.77 mmol) were added successively to a solution of **6a** (52.8 mg, 0.038 mmol) in CH_2Cl_2 (0.4 mL) at −78 °C. The reaction mixture was stirred at −20 °C for 4 h then poured into a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was subjected to silica-gel column chromatography (toluene/AcOEt 2:1), and the excess of **2a** was recovered quantitatively. Silica-gel column-chromatographic purification (hexane/AcOEt 4:1) of the remaining material afforded the desired product **4a** (33.5 mg, 0.037 mmol, 96 %) as a colorless solid.

One-pot procedure for the synthesis of 4: TMSOTf (79 μL, 0.44 mmol) was added to a solution of **5a** (20.3 mg, 0.044 mmol) and **7a** (70.7 mg, 0.13 mmol) in CH_2Cl_2 (0.2 mL) at −78 °C. The reaction mixture was stirred at −20 °C for 70 min, then triethylsilane (70 μL, 0.44 mmol) was added at −20 °C. The reaction mixture was stirred at 0 °C for 4 h then poured into a saturated solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica-gel column chromatography (toluene/AcOEt 2:1), and the excess of **2a** was recovered quantitatively. Silica-gel column-chromatographic purification (hexane/AcOEt = 4:1) of the remaining material afforded the desired product **4a** (36.8 mg, 0.042 mmol, 92 %) as a colorless solid.

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[2] It was reported that coyolosa showed a significant blood-sugar-lowering effect on normal and alloxane-induced diabetic mice when administered at doses of 2.5–40 mg kg^{-1} i.p. (intraperitoneal); see reference [1].
[3] It was reported by Pérez et al. that the NMR spectrum of coyolosa was measured as a solution in $CDCl_3$; however, it is impossible to dissolve unprotected pyranoses in $CDCl_3$. Therefore, we believe there may be an error in the description given in the report. We were unsuccessful in our attempts to contact the authors and were therefore unable to obtain a sample of the natural product from them.
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[6] Further investigations are in progress.
[7] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165 – 168.
[8] No nomenclature has been established as yet by the IUPAC for these types of pyranoses connected by ether bonds. Hence, we hesitate to assign them names.
[9] Spectral (^{1}H NMR, ^{13}C NMR) and analytical (HRMS) data showed **9a**–**g** to be the 6,6′-ether-connected pyranoses. See Supporting Information.
[10] A dosage of 60 mg kg^{-1} of **9f** caused a maximum blood-sugar lowering of 26 % in 2 h in alloxane-induced diabetic rats.

