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Synthesis of Pro-Xylane™: A new biologically active C-glycoside in aqueous media

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ABSTRACT

The scope and limitation of Lubineau's reaction were evaluated for the synthesis of C-glycosides (compounds **1–13**). Further transformation of side chain carbonyl was also achieved (compounds **16–23**). Optimization of these two steps was investigated in xylose case. Some of the compounds were shown to stimulate sulfated glycosaminoglycans (GAGs) synthesis. Compound **20** (called Pro-Xylane™) was identified as the best activator of GAGs biosynthesis. Pro-Xylane™ was developed using environmentally friendly conditions relevant to 'Green-Chemistry' principles and launched on the market in September 2006. This compound is the first example of 'Green' chemical used in cosmetic.

The importance of carbohydrates in human biology is well known.[1] For example, cell-surface carbohydrates play a key role in molecular recognition.[2] They allow the cells to communicate with their surrounding environment, and in particular they are able to interact with other sugar derivatives such as lectins,[3] glycoproteins[4] or glycolipids,[5] and thus with several hormones, enzymes, cancer cells, virus, bacteria, toxins and antibodies.

A class of carbohydrates of particular interest is represented by proteoglycans (PGs) and glycosaminoglycans (GAGs). These polysaccharides are pivotal in dermal matrix structure that embeds and sustains collagen fibers network.[6] Recent studies have shown that human aged skin contains less GAGs than young skin, which contributes to the differences in their mechanical properties.[7] These considerations raised the concept of a new class of potential skin anti-aging molecules that could help maintaining unaltered matrix structure through stimulating GAGs and PGs synthesis.

Recently, C-glycosides have received increasing interest as carbohydrate biomimetics.[8] Indeed, the substitution of an *O*-glycosidic position of native carbohydrate structures by a C-glycosidic carbon–carbon linkage makes such analogs stable against acidic or enzymatic hydrolysis. Therefore, C-glycosides have been shown to be of interest as anti-tumor agents,[9] antibiotics[10] or anti-inflammatory agents.[11]

There are several methods commonly used to synthesize C-glycoside.[12] These methods are usually based on nucleophilic attack at the anomeric position,[12a] but also on Wittig-type reaction,[13] or on glycosylidene carbene formation,[14] or substitution of the anomeric hydroxyl with halogen and subsequent chemistry (Reformatsky,[15] Grignard,[16] or radical chemistry[17]). However, most of these C–C linking reactions are burdened by the need for protecting-group installation.

In 1986, Gonzalez et al. reported the first one-step procedure to synthesize C-glycoside directly by reacting unprotected carbohydrates with barbituric acid derivatives in water.[18] Later, Lubineau et al. investigated this green reaction by reacting 1,3-diketone with unprotected carbohydrates dissolved in alkaline aqueous media.[19] In both cases, the reaction proceeded via a Knoevenagel reaction of activated methylenes with aldose (onto sugars) followed by an intramolecular Michael cyclization. Thus, the process is respectful of 'Green-Chemistry' principles[20]: it is an eco-friendly synthesis using renewable raw materials.

Here, we report the study of the scope and limitation of this reaction for the preparation of several C-glycoside derivatives and their subsequent transformation into compounds which stimulate GAGs synthesis.

The original procedure described by Lubineau is shown to be applicable to a great variety of sugars[19,21] (Scheme 1).

Thus, various sugars were transformed with penta-2,4-dione into β-keto-C-glycosides with moderate to good yields (Table 1, compounds **1**–**7**).[22] From these results, it appears that the nature of the sugar has an impact on the reaction yield (from 40% with D-arabinose up to 100% with D-glucose).

One major limitation of this method is the restricted availability of other activated methylenes able to react with unprotected sugars. Lubineau et al. succeeded in replacing pentane-2,4-dione by

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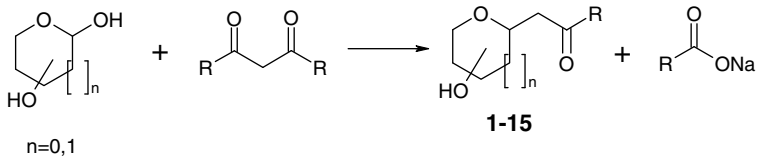


Scheme 1. Formation of C-glycoside by reacting unprotected sugar with 1,3-diketone in water. Reactions and condition: $NaHCO_3$, H_2O, 90 °C.

Table 1
Influence of the sugar or the diketone on the yield of the C-glycosides obtained using Lubineau's methodology

Compound	Starting sugar	R	Yield (%)
1	D-Glucose	Me	100[a]
2	D-Xylose	Me	87[a]
3	D-Lactose	Me	79[a]
4	D-Galactose	Me	98[a]
5	D-Fucose	Me	92[a]
6	D-Arabinose	Me	40[a]
7	3-Deoxy-D-arabinose	Me	59[a]
8	D-Glucose	Ph	58[a]
9	L-Fucose	Ph	12[a]
10	D-Xylose	Ph	6[a]
11	D-Glucose	4-OBn-Ph	37[b]
12	D-Glucose	4-OMe-Ph	52[c]
13	D-Glucose	4-OH-Ph	34c

Solvent.
[a] Water.
[b] Dioxanne/H_2O.
[c] EtOH/H_2O.

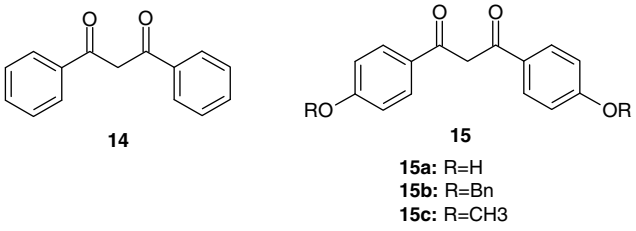


Figure 1. Other β-diketone derivatives used.

mixed diketone bearing a long alkyl chain.[23] However, yields were lower and water was replaced by a mixture of alcohol/water in order to increase the solubility of the fatty diketones. Another attempt was made in 2002 by Fessner et al. who unsuccessfully tried to react acetoacetic acid *tert*-butyl ester with sugars.[21] In our study, malonates, malonamide, malononitrile, Meldrum's acid, hexafluoroacetylaceton, 1,3-indanedione, ethyl cyanoacetate also failed to give any C-glycosides. This may be explained by the hydrolytic instability of the esters under alkaline reaction conditions.

However, it is surprising that these conditions are harsh enough to decompose *tert*-butyl esters, and a possible neighboring hydroxyl group participation should not be excluded. Indeed, the formation of furan by-products during the course of this Knoevenagel reaction is based on such mechanistic considerations[21].

Table 2
Effect of the base on Knoevenagel reaction of pentane-2,4-dione with D-xylose in water

Entry	Base	Yield	Time	Temp. (°C)
A	$NaHCO_3$	87%	18 h	90
B	$NaHCO_3$	Mixture	1 h	90
C	LiOH	56%	18 h	90
D	NaOH	88%	18 h	90
E	NaOH	90%	1 h	90
F	NaOH	97%	45 min	50

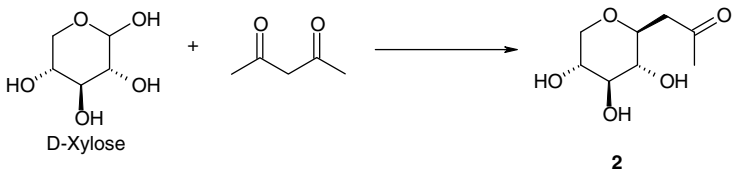
Compounds **14** and **15** (Fig. 1) were the only β-diketone derivatives that reacted with unprotected sugars to give the desired C-glycosides derivatives with low to moderate yield (Table 1, compounds **8**–**13**). Indeed, through modifying reaction conditions using co-solvents such as dioxan or EtOH, we could produce C-glycosides with acceptable yields contrary to the literature data.[21]

In order to improve the yield of the Knoevenagel reaction, the effects of various bases were investigated. Xylose was condensed with pentane-2,4-dione in water, using either sodium bicarbonate, lithium hydroxide or sodium hydroxide (Table 2 and Scheme 2).

Surprisingly, the nature of the base had a tremendous effect on reaction yield (Table 2, entries A, C and D). The base also impacted reaction time, since the same yields were obtained with ($NaHCO_3$, 18 h) and (NaOH, 1 h), whereas ($NaHCO_3$, 1 h) led to a mixture of C-glycoside diastereoisomers and starting materials (Table 2, entries A, B and E). The best yield was obtained with NaOH at 50 °C for 45 min (Table 2, entry F). Decreasing reaction time and temperature are indeed two key points in green chemistry.

Some of the keto C-glycosides described in Table 1 were then subjected to further transformation. Reduction to alcohols **16–23** using aqueous sodium borohydride ($NaBH_4$) yielded a mixture of two diastereoisomers in good yield (Table 3 and Scheme 3).[24]

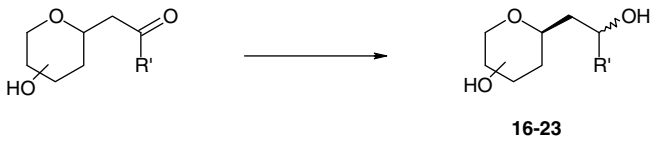
We noticed that reduction of C-xyloside **2** gave a slight diastereomeric excess when performed in isopropanol (*i*-PrOH) compared to water or methanol (Table 4, entries G–I and Scheme 4). Adding acid could further improve the selectivity of reduction step (Table 4, entries J and K). The reduction with $NaBH_4$ in *i*-PrOH/AcOH (9/2)[25] yielded the most pure diastereoisomer with de ca. 90% as a crystalline product. Whereas all other conditions produced a sticky oily mixture of diastereoisomers. As shown in Figure 2, the structure of pure diastereoisomer obtained after re-crystallization was unambiguously determined by X-ray diffraction as the S diastereoisomer.[26]



Scheme 2. Formation of the keto C-xyloside **2**. Reagents and condition: base, time, temperature, H_2O.

Table 3
C-glycosides from keto derivative reduction with $NaBH_4$

Compound	Starting sugar	R′	Yield (%)
16	D-Glucose	Me	88
17	D-Fucose	Me	65
18	D-Arabinose	Me	90
19	D-Lactose	Me	65
20	D-Xylose	Me	98
21	L-Fucose	Me	86
22	D-Glucose	4-OMe-Ph	100
23	D-Glucose	4-OH-Ph	75



16-23

Scheme 3. Reduction of keto C-glycosides: $NaBH_4$, H_2O or alcohol.

Table 4
Effect of solvent, acid and reducing agent on the diastereoselectivity of the reduction of compound **2**

Entry	Reducing agent	Solvent	Acid	Yield (%)	de (%)
G	$NaBH_4$	H_2O	None	99	6
H	$NaBH_4$	MeOH	None	78	0
I	$NaBH_4$	*i*-PrOH	None	95	20
J	$NaBH_4$	*i*-PrOH	HClaq	98	44
K	$NaBH_4$	*i*-PrOH	AcOH	98	90
L	$NaBH(OAc)_3$	*i*-PrOH	None	90	92
M	$NaBH_4/ZnCl_2$	*i*-PrOH	None	0	na[a]
N	$NaBH_4/CeCl_3$	*i*-PrOH	None	100	40
O	Ru/C	H_2O	None	82	0

[a] na, not applicable.

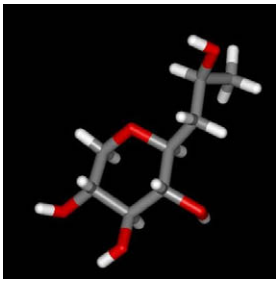


Figure 2. X-ray diffraction of the C-xyloside diastereoisomer obtained from selective reduction.

Since *i*-PrOH and acetic acid were crucial for diastereoselection leading to S diastereoisomer, two transition states could be proposed (Fig. 3). The first one is based on a Meerwein–Porndorf [27] type reduction, the second one is not.

It is to note that we tried to directly use $NaBH(OAc)_3$ that is likely formed in situ.[28] This reducing agent indeed gave the highest purity of diastereoisomer (Table 4, entry L). On the other hand, using other reported reagent combination gave either a far lower rate (e.g., with $NaBH_4/CeCl_3$[29]) or almost no reaction (e.g., with $NaBH_4/ZnCl_2$[30]): Table 4, entries M and N.

Although these reactions were performed in water and/or alcohols, the E-factor was not acceptable from an ecological viewpoint due to a tedious procedure for borate salts removal.[31] The E-factor was much diminished using catalytic hydrogenation with Ru/C for the reduction step.[32] The reaction product was then a 50/50 diastereoisomer mixture (de = 0) (Table 4, entry O).

The biological activities of some synthesized C-glycosides were then studied on human fibroblast cultures in order to select the best compound able to stimulate GAG synthesis and thereby have potential anti-aging properties (Table 5). The best results were obtained with compound **20**, a C-xyloside (50/50 mixture of diastereoisomers). Sulfated GAG synthesis is often initiated by the same monosaccharide, xylose.[33] The GAG chains could then be linked to a protein core via a β-O-glycosidic bond between xylose and the hydroxyl group of a serine aminoacid of protein sequence. The mechanism of GAGs synthesis stimulation by our C-xylosides is still under investigation in our laboratory.

Some stereochemical features of compound **20** were important for biological activity. Indeed, further studies indicated that the β-C-glycosidic bond was essential to maintain activity compared to the α-C-glycosidic. Furthermore, the stereochemistry of the hydroxyl group in the aglycon moiety has an impact on the activity level of GAG synthesis, since different diastereomeric ratios led to different activity level (Fig. 4).

In summary, we explored the scope and limitations of a very powerful method to synthesize C-glycosides using environmentally friendly conditions relevant to 'Green-Chemistry' principles. The C-glycosides were further functionalized and tested for biological activity of potential interest in skin anti-aging applications in cosmetic. Some of these compounds were shown to exhibit stimulating properties on GAGs synthesis. Further applications of these compounds and more functionalizations are still under study in our laboratories. For example, aldol condensation, reductive alkylation and oxime formation were achieved in good yields in the same spirit of optimization of 'Green-Chemistry' conditions.

Compound **20** was identified as the best inducer of sulfated GAGs synthesis in vitro and was also proved active in vivo in a clinical trial. It was developed in cosmetic skincare products as Pro-Xylane™.[35] This compound is the first example of "Green" chemical in cosmetic. It is made from a renewable feedstock (xylose is extracted from beechwood), in only 2 steps in water and using a catalytic reduction (E-factor 36). Furthermore, Pro-Xylane™ is an eco-friendly compound. It is biodegradable (software BIOWIN[36] + experiments),

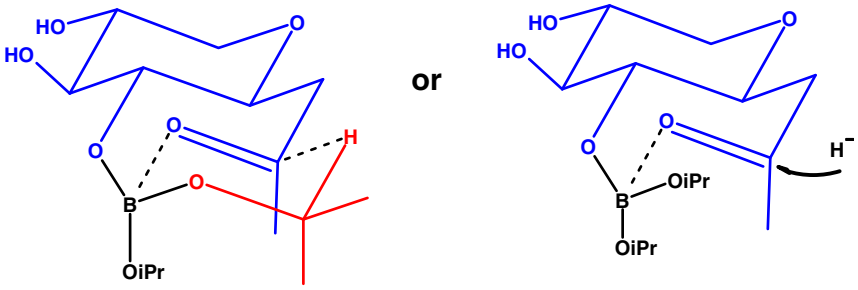
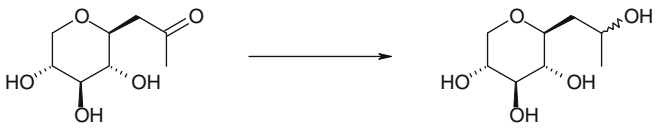


Figure 3. Transition states proposed for the diastereoselective reduction of the C-xyloside.



2 20

Scheme 4. Reduction condition of compound **2**: reducing agent, acid, solvent.

Table 5
Effect of C-glycosides on the D-[6-H3]-glucosamine incorporation in the GAG fraction by human fibroblasts[34]

Compound	[C]	%	*P*
None	—	100	—
Transforming growth factor-β (TGF-β) (positive control)	10 ng/mL	348	<0.01
Xylose	0.5 mM	52	<0.01
	0.1 mM	85	>0.05
	0.02 mM	106	>0.05
Lyxose	2.0 mM	86	>0.05
	0.4 mM	102	>0.05
	0.08 mM	90	>0.05
Compound **2**	10.0 mM	161	<0.01
	2.0 mM	141	<0.01
	0.4 mM	110	>0.05
Compound **4**	10.0 mM	99	>0.05
	3.0 mM	119	>0.05
	1.0 mM	136	<0.01
Compound **20**	3.0 mM	218	<0.01
	1.0 mM	169	<0.01
	0.3 mM	139	>0.05
Compound **10**	1.0 mM	95	>0.05
	0.3 mM	102	>0.05
	0.1 mM	120	>0.05

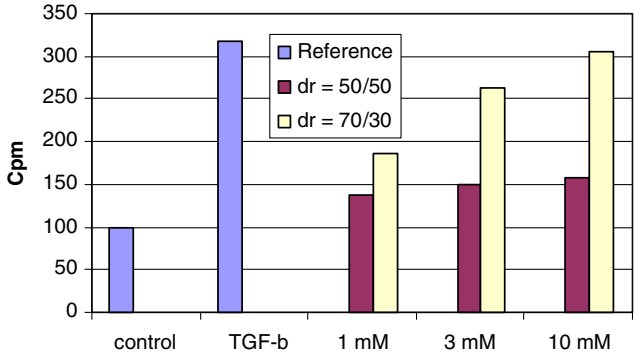


Figure 4. Effect of the diastereomeric ratio of compound **28** on the D-[6-H3]-glucosamine incorporation in the GAG fraction by human fibroblasts (dr, diastereomeric ratio; cpm, count per minute).

and has no bioaccumulation (software KOWWIN[37]) and no ecotoxicity (software ECOSAR[38] + experiments).[39]

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22. *General procedure:* Monosaccharide (1 equiv), acetylaceton (1.2 equiv) and sodium bicarbonate (1.5 equiv) were refluxed in water for 12 h. The aqueous phase was cooled down to room temperature, washed with ethyl acetate, acidified with the resin Dowex 50X-200, filtered and concentrated in vacuo, to afford the pure product as a brown oil. The structures of the C-glycosides were confirmed by NMR and mass spectroscopy.
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34. *General experiment procedures:* Normal human dermal fibroblast (NHDF) monolayers were cultured in control medium *with or without* TGF-β (10 ng/mL) or compounds X–Y for 72 h at 37 °C in humid atmosphere of 95% air and

5% CO_2 and labeled with ^{35}S-sulfur during the final 24 h. The GAG fraction was isolated from both the medium and the fibroblast layer (soluble and insoluble GAGs) and purified by anion exchange chromatography. ^{35}S-radioactivity incorporated into the GAGs was then measured. Experimental tested doses were selected as maximal non-toxic doses.

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