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Regioselective Synthesis of Difluorinated *C*-Furanosides Involving a Debenzylative Cycloetherification

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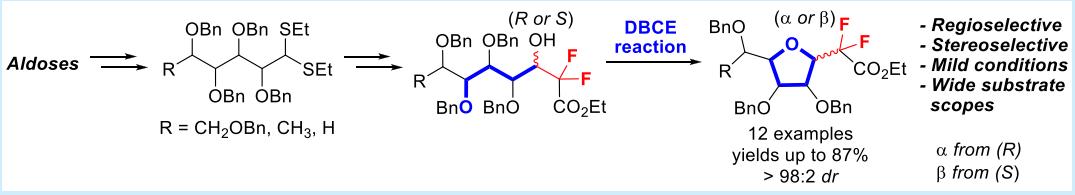
Supporting Information



ABSTRACT: A highly regioselective synthesis of valuable *gem*-difluorinated *C*-furanosides from unprotected aldoses via a debenzylative cycloetherification (DBCE) reaction induced by diethylaminosulfur trifluoride is descibed. The scope and limitations of this DBCE reaction are described using a series of commercially available pentoses and hexoses to afford, without selective protection/deprotection sequences, the corresponding *gem*-difluorinated *C*-furanosides in moderate to good yields.

Carbohydrates and their conjugates play an important role in various biological processes such as protein structure−activity modulation or cell−cell recognition.[1] These biomolecules have thus received a great deal of attention in drug research and chemical biology.[2] However, the low metabolic stability of the anomeric bond, which is easily cleaved in vivo by glycosidases, remains a major limitation for their development as drug candidates. Because of their stability toward chemical and enzymatic hydrolysis, carbohydrate analogues such as *C*-glycosides have shown improved pharmacokinetic properties compared to those of the natural saccharides.[3,4] In recent years, the fluorination of bioactive molecules has also been successfully used to improve the bioavailability and the activity of drugs or drug candidates.[5,6] As a consequence, the hydrolytic stability of *C*-glycosidic structures and the interesting properties of the fluorine atom have been combined to give rise to a new class of carbohydrate mimetics.[7,8] In particular, the introduction of CF_2 and CHF groups, as isosteres of oxygen, at the pseudoanomeric center of a *C*-glycoside can modify the pK_a of the neighboring groups and increase the lipophilicity of the entire molecule[9] compared to that of the native *O*-glycoside.[10,11]

Synthetically, although several approaches have been developed for the synthesis of *gem*-difluoromethylated pyranosides,[9,12−20] the incorporation of a CF_2 group at the anomeric position of a furanosyl ring has been described much less often. The synthesis of difluoro-*C*-furanosides was first reported by Motherwell et al. in low yields starting from difluoro-*exo*-glycals through an addition of nucleophilic or electrophilic radicals (Figure 1a).[21,22] It is noteworthy that the stereoselectivity of the radical addition is generally controlled by the configuration at C2. The second way involves a *C*-glycosylation between difluoroenoxysilanes and a glycosyl donor (Figure 1b).[23] Importantly, this *C*-glycosylation works with only 2-deoxy furanosides.

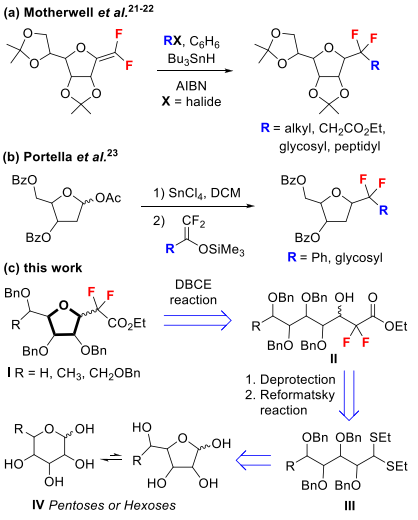


Figure 1. Known procedures for the synthesis of *exo*-CF_2-furanosides (a and b) and our retrosynthetic pathway (c).

The main synthetic approaches giving access to tetrahydrofuran derivatives through a debenzylative cycloetherification reaction (DBCE) have been reviewed recently.[24−27] Compared to classical *C*-glycosylation reactions, this cyclization is usually more efficient for the preparation of *C*-

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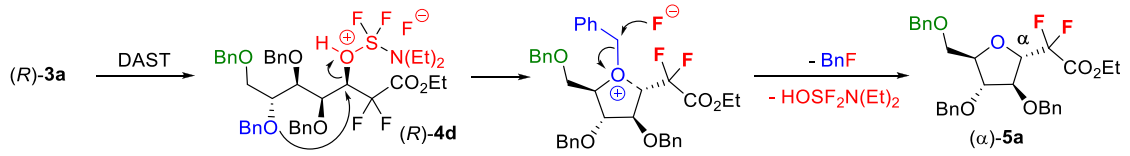


Figure 2. Proposed mechanistic pathway for DAST-induced formation of (α)-**5a**.

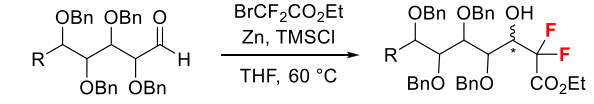
furanosides like *C*-vinylfuranosides especially because it does not require selective protection/deprotection steps, which can often be cumbersome.[28] This cyclization occurs when an activated alcohol is placed in the δ position of a benzyloxy group and gives regio- and stereoselectively tetrahydrofurans at the expense of a pyran form. This regioselectivity comes from a remarkable conformation of an acyclic substrate properly positioning the δ-benzyloxy group for an S_N reaction (Figure 2). Inspired by the unique properties of this reaction, we recently developed an efficient and regioselective strategy for the preparation of γ-lactone glycosides involving an original debenzylative lactonization (DBL).[25] To the best of our knowledge, the DBCE reaction has never previously been used to produce fluorinated *C*-glycosides. However, it is worth mentioning that the O'Hagan group described a deoxofluor-mediated DBCE reaction on an α,β,δ-trifluorinated substrate that was a undesired but high-yield (94%) transformation.[29] Continuing our research in the field of sugar mimics,[27,30−33] we report herein an efficient method for synthesizing regioselectively *gem*-difluorinated *C*-furanosides in moderate to good yields through debenzylative cycloetherifications.

Our retrosynthetic analysis of *gem*-difluorinated *C*-furanosides **I** is illustrated in Figure 1c. Alcohol **II**, the key intermediate for performing the debenzylative cycloetherification reaction (DBCE), would be generated by a Reformatsky reaction between ethyl bromodifluoroacetate and the aldehyde obtained from the deprotection of dithioacetal **III**. The latter can be easily accessed in two steps from commercially available sugars.

To explore this transformation, aldehydes **3a−h** were prepared in three steps [thioacetalation, benzylation, and thioacetal hydrolysis (see the Supporting Information)] in good yields from commercially available carbohydrates.

The Reformatsky reaction between ethyl bromodifluoroacetate and D-*arabino*-aldehyde **2a** in the presence of activated zinc dust with TMSCl, under Barbier conditions,[34,35] afforded the desired product **3a** in 53% yield with low diastereoselectivity. The configuration of the new stereogenic center in **3a** was not assigned prior to the cyclization because the DBCE reaction proceeds through an S_N2 mechanism. Thus, the (*R*,*S*) configurations of the secondary alcohol could be deduced after the assignment of the (α,β) anomeric configuration of the resulting exo-*gem*-difluorinated *C*-furanosides (α)-**5a** and (β)-**5a**, thanks to NOE NMR experiments (Figure 2). The yields of the Reformatsky couplings with the seven other aldehydes were also moderate, but they compare well with values from the literature.[36] In most cases, diastereoisomers could be separated through silica gel chromatography except for D-xylose and D-lyxose, which were used as a mixture of epimers (Table 1). We wish to outline that we did not try to optimize the diastereoselectivities of the Reformatsky couplings as our intention was to study the DBCE reactions of the two epimeric alcohols **II**, thus giving access to both α- and β-fluorinated *C*-furanosides. Indeed, an important feature of the DBCE reaction is its stereospecific (S_N2) mechanism, as will be

Table 1. Reformatsky Reactions with Aldehydes 2a−h



sugar	aldehyde	product, yield (%)	*dr* (%)
D-arabinose	**2a**	**3a**, 53	70:30
D-ribose	**2b**	**3b**, 47	75:25
D-xylose	**2c**	**3c**, 45	65:35[a]
D-lyxose	**2d**	**3d**, 50	64:36[a]
L-fucose	**2e**	**3e**, 43	43:57
D-galactose	**2f**	**3f**, 56	55:45
D-glucose	**2g**	**3g**, 60	69:31
D-mannose	**2h**	**3h**, 52	55:45

[a]Mixture that cannot be separated by silica gel chromatography.

further demonstrated below. In principle, the α/β stereoselectivity will depend on only the stereoselectivity of the Reformatsky coupling, as long as the two epimers are reactive under these conditions. Mechanistically, this approach is strikingly different from the two other methods (Figure 1a,b) that strongly depend on classical stereoelectronic effects at play in carbohydrate chemistry.

Then, we optimized the conditions of the DBCE reaction with alcohol **3a**. First, the activation of the hydroxy group with triflic anhydride[37] gave only partial conversion, and the analysis of the ^{1}H NMR spectrum of the crude reaction mixture showed 7% cyclized product (α)-**5a** along with 41% triflate intermediate **4a** (Table 2, entry 1). Classical Mitsunobu conditions also did not efficiently promote the cyclization (entry 2), whereas the use of mesyl chloride as an activating agent gave the corresponding mesylate intermediate **4c** in 71% yield but without the formation of the expected cyclized product (entry 3). DAST[26,38] was eventually identified to be the optimal promotor of the DBCE reaction yielding the difluorinated *C*-furanoside (α)-**5a** in 62% isolated yield (entry 4). Interestingly, no traces of *C*-pyranoside isomers were observed, and only the α-furanoside could be isolated, thus showing the regioselective and stereospecific character of this cycloetherification. It is important to mention that no competitive fluorination of alcohol (*R*)-**3a** was observed with DAST.

Starting from epimeric alcohol (*S*)-**3a**, under the same conditions, the cyclization occurred efficiently, and *C*-furanoside (β)-**5a** was isolated in 74% yield (Table 2, entry 5), as expected from an inverting substitution mechanism. The anomeric configurations of both *C*-furanosides (α)-**5a** and (β)-**5a** were determined on the basis of one-dimensional NOE NMR experiments, in which H1−H3 and H1−H4 correlations were observed for the α and β isomers, respectively. These results for D-arabinoside **3a** confirmed the concerted S_N2 mechanism of the DBCE reaction because for each stereo-

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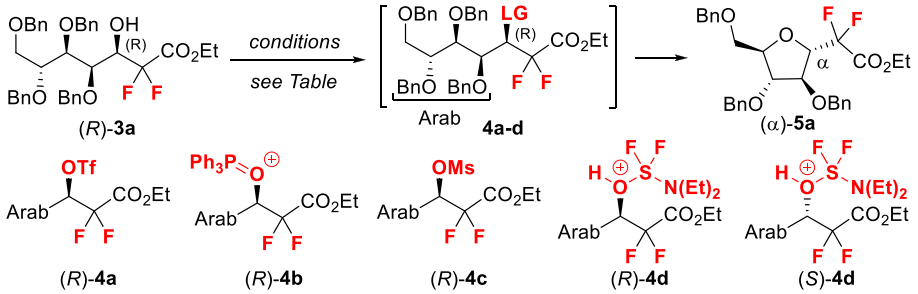
Table 2. Optimization of DBCE Reaction Conditions on Alcohol (*R*)-3a



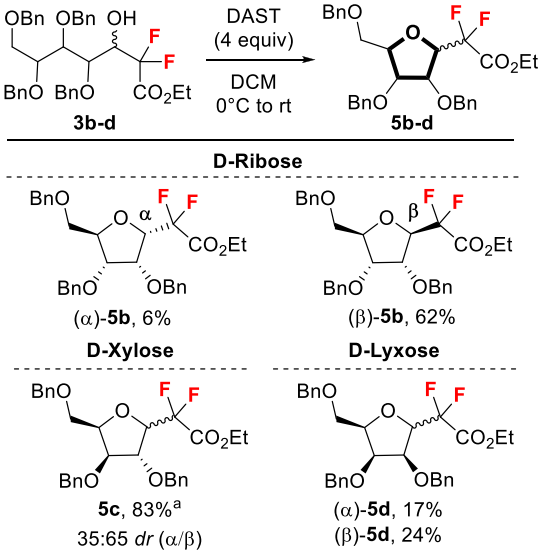
entry	reaction conditions	intermediate	conversion (%)	product, yield (%)
1	Tf_2O (1.5 equiv), 2,6-lutidine (3.0 equiv), DCM, −78 °C to rt, 12 h	(*R*)-**4a**	48[a]	(*α*)-**5a**, 7[a]
2	DIAD (1.5 equiv), PPh_3 (1.5 equiv), Et_3N (1.5 equiv), THF, rt, 17 h	(*R*)-**4b**	12	–
3	MsCl (1.5 equiv), Et_3N (1.5 equiv), DCM, rt, 17 h	(*R*)-**4c**	100	–[b]
4	DAST (2 equiv), DCM, 0 °C to rt, 24 h	(*R*)-**4d**	100	(*α*)-**5a**, 62[c]
5[d]	DAST (2 equiv), DCM, 0 °C to rt, 24 h	(*S*)-**4d**	100	(*β*)-**5a**, 74[c]

[a]The ratio [41:7 (*R*)-**4a**:(*α*)-**5a**] was calculated from the crude ^{1}H NMR spectrum. [b]Mesylate (*R*)-**4c** was isolated in 71% yield. [c]Isolated yield. [d](*S*)-**3a** was used as the starting material instead of (*R*)-**3a**.

isomeric alcohol (*R*)- or (*S*)-**3a** a single *C*-furanoside was isolated (Figure 2).

The scope of this transformation was then examined with various aldoses to study the influence of the substrate on the DBCE process. First, a series of pentose derivatives (Scheme 1) were subjected to the optimal DBCE reaction conditions. D-*xylo* derivative **3c** used as a 35:65 *R*/*S* epimeric mixture was converted into fluorinated *C*-furanosides **5c** in 83% yield with the same ratio (35:65 *α*:*β*), as anticipated from an S_N2 mechanism. Interestingly, the two diastereoisomers derived from D-ribose, (*R*)-**3b** and (*S*)-**3b**, reacted differently in the presence of DAST. While the conversion of the DBCE reaction with epimer (*R*)-**3b** was only 6% to yield *α*-configured product (*α*)-**5b**, its diastereoisomer, (*S*)-**3b**, afforded *C*-furanoside (*β*)-**5b** in 62% yield (Scheme 1). Increasing the reaction time and the amount of reagent did not improve the isolated yield of (*α*)-**5b**. This significant difference in reactivity can be explained by the steric repulsions between the two benzyloxy groups at positions C-2 and C-3, and the CF_2CO_2Et group, which are all-*cis* in (*α*)-**5b** and *trans* in the transition state generating (*β*)-**5b**.

Scheme 1. Synthesis of Various Fluorinated *C*-Furanosides from Pentoses



[a]Two equivalents of DAST was used.

With regard to the D-lyxo substrates (*R*,*S*)-**3d**, engaged as a mixture in DBCE reaction, the respective *C*-furanosides (*α*)-**5d** and (*β*)-**5d** were isolated in 17% and 24% yields (i.e., 41% overall), respectively. Here again, only a partial conversion of diastereoisomer (*S*)-**3d** was observed while its epimer (*R*)-**3d** was fully consumed. The steric repulsions existing at the transition state can also be invoked to explain the difference in reactivity. Indeed, to access molecule (*β*)-**5d**, all of the substituents at positions C-1−C-4 of the furanose ring are in a *cis* relationship that can strongly increase the energy of the transition state.

The scope of the DBCE reaction was then expanded to a series of hexoses (Scheme 2). D-Galactose and L-fucose derivatives showed similar reactivities under the optimized DBCE conditions. Indeed, alcohols (*R*)-**3f** and (*S*)-**3f** derived from D-galactose were successfully converted to the corresponding *C*-furanosides (*α*)-**5f** and (*β*)-**5f** in 58% and 54% yields, respectively. When fucoside (*R*)-**3e** was activated by DAST, the cyclization occurred in 53% yield, whereas its epimer, (*S*)-**3e**, gave the desired product (*β*)-**5e** in only 25% yield accompanied by (*β*)-**6e** as a byproduct, increasing the yield of cyclization to 61% (Scheme 2). The formation of (*β*)-**6e** could be explained by a selective debenzylation at C-5 under slightly acidic conditions in the presence of the excess of DAST (Figure 2).

The DAST-induced DBCE reaction of the D-*gluco* derivatives **3g** proceeded efficiently starting from the *S*-epimer as *C*-furanoside (*β*)-**5g** was isolated in 87% yield. However, the cyclization of epimer (*R*)-**3g** failed, thus showing again that the relative configuration of the CF_2CO_2Et and the benzyl group at C-2 strongly influences the reactivity of the starting alcohol. As expected,[25] both diastereoisomers of D-mannose (*R*)-**3h** and (*S*)-**3h** did not undergo DBCE reaction. Indeed, this lack of reactivity has been explained by an unfavorable "*cis*" relationship between all substituents of the furan ring, in the oxonium intermediates. The specific behavior of D-mannose derivatives toward debenzylative cyclizations has already been observed by Nicotra and our group.[25,39] The structures of **5a**−**g** have been

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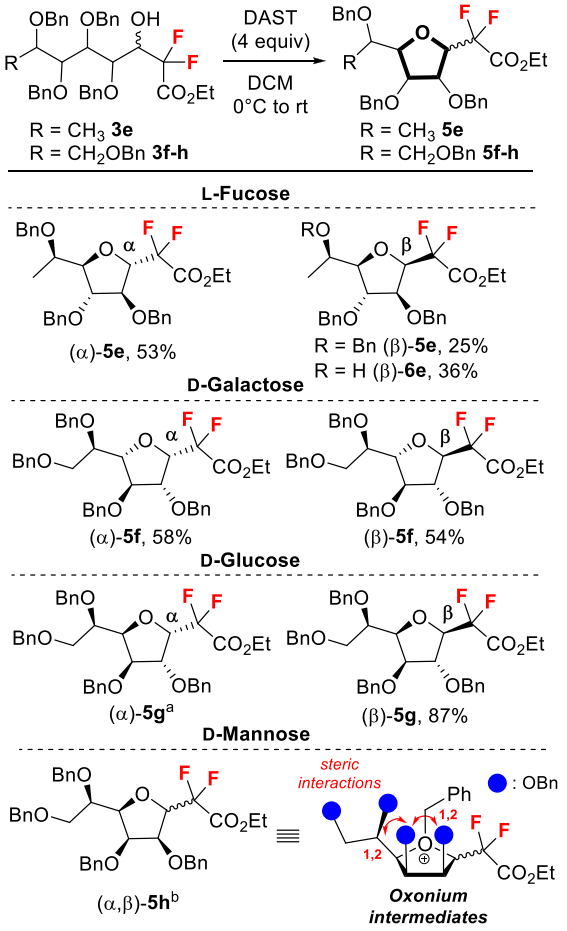
Scheme 2. Synthesis of Various Fluorinated *C*-Furanosides from Hexoses



[a]A 15% conversion was calculated, and no trace of (α)-**5g** was observed. [b]A complex mixture was obtained starting from both isomers of **3h**.

fully demonstrated using literature data analysis and NMR spectroscopy (^{1}H, ^{13}C, ^{19}F, COSY, HSQC, and HMBC). The pyran structure has been ruled out by HMBC NMR experiments in which a spatial coupling could be observed between H-5 and a benzylic carbon. On the other hand, the absence of coupling between the benzylic carbons and H-4 is in good accordance with the furanoside ring. In all cases, regardless of the starting acyclic sugar, only *C*-furanosides were formed, showing the highly regioselective character of the DBCE process. Additionally, all reactions described in this study are stereospecific because each diastereoisomer provided a distinct *C*-furanoside.

To summarize, the stereochemical pattern of the sugar moiety showed an important effect on the efficiency of the DBCE process. Similar observations had been reported by Barker and co-workers during their pioneering work on the anchimeric assistance of the benzyloxy group.[40] While D-arabinose, D-xylose, L-fucose, and D-galactose showed no difference in reactivity between the two isomers with respect to cyclization, D-ribose, D-lyxose, D-glucose, and D-mannose have difficulty undergoing cyclization for at least one of the two diastereoisomers.

In conclusion, a DAST-induced regio- and stereoselective debenzylative cycloetherification reaction was developed starting from perbenzylated acyclic aldoses bearing a *gem*-difluoromethyl ester moiety, giving access to various difluorinated *C*-furanosides. The scope and limitations of this reaction have been described on various substrates derived from widely used commercially available pentoses (D-ribose, D-arabinose, D-xylose, and D-lyxose) and hexoses (D-glucose, D-galactose, and L-fucose) and to give a series of difluorinated *C*-furanosides in moderate to good yields without the requirement of a selective protection/deprotection strategy of the starting polyol.

Moreover, because of its stereoinverting S_N2 mechanism, this DBCE reaction could be an important alternative for the future design of natural or artificial bioactive molecules containing a furanoside ring. Indeed, the α/β stereoselectivity that is often difficult to control in most of the known approaches is not problematic in this case because the cyclization is stereospecific. Thus, as a direct perspective, it can be envisioned to exploit novel methodologies for the introduction of the CF_2CO_2R moiety such as Honda's Rh-catalyzed Reformatsky reaction.[41] Additionally, the ester moiety present in each final molecule can be easily modified and transformed in many other functional groups or heterocyclic structures that are biologically relevant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01878.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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