SHORT COMMUNICATION

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Synthesis of Fluorinated *exo*-Glycals through Modified Julia Olefination

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An efficient synthesis of fluorinated enol ethers derived from carbohydrates is reported. A modified Julia olefination reaction of functionalized lactones with fluorine-substituted sulfones gives the corresponding monofluorinated tri- or tetrasubstituted *exo*-glycals.

Introduction

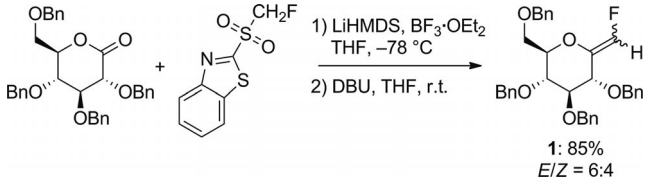
The introduction of a fluorine atom into a biologically active molecule strongly modifies the chemical and physical properties of the latter. In the specific case of fluorine-substituted enol ethers, the presence of fluorine additionally stabilizes the enol ether function and radically alters its electronic distribution.[1] In the field of carbohydrates, *exo*-glycals[2] are an important class of glycomimetics in which their monohalogenated counterparts[3] have been prepared for chemical purposes. Monofluorinated *exo*-glycals[4] have been studied as probes for glycosyl-processing enzymes, whereas 6-fluoro-5,6-anhydrocarbohydrates[5] have been investigated as inactivators of (*S*)-adenosyl-L-homocysteine hydrolase. However, these monofluoroenol ethers were prepared through stepwise methods that provide limited structural flexibility and little generality.

An original route to *exo*-glycals was recently developed in our group in Lyon[6] by using modified Julia reagents[7] on sugar-derived lactones. The reaction was further extended to the synthesis of tri- and tetrasubstituted enol ethers.[8] This methodology was used for the preparation of glycomimetics[9] and chiral ligands for catalysis[10] and for the total synthesis of bistramide A and its analogues.[11]

Julia olefination has proven to be among the more promising direct methods for the synthesis of fluoroalkenes.[12] Since a Caen's group initial work describing the one-step preparation of fluoroalkenes by a modified Julia reaction,[13] this reaction has been extended by different groups for the preparation of diversely functionalized di-, tri-, and tetrasubstituted fluoroalkenes.[14] This reaction proceeds smoothly from aldehydes or ketones to fluoroalkenes, but it has not been applied to the olefination of lactones. We report herein the synthesis of fluorinated exocyclic enol ethers through the modified Julia olefination of lactones.

Results and Discussion

Fluoroalkyl sulfones were prepared according to a literature procedure,[15] and their addition to lactones was tested to prepare *exo*-glycals. The reaction was first performed with 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone and 2-benzothiazolyl fluoromethyl sulfone (Scheme 1). Using our previous standard conditions,[11] we were gratified to learn that trisubstituted fluoroalkene **1** could be obtained in 85% isolated yield as an *E*/*Z* mixture, with a slight preference for the *E* isomer.[16]



Scheme 1. Initial attempt under our standard conditions.

This result prompted us to explore the scope of this reaction by using various fluoroalkyl sulfones and benzyl ether protected sugar lactones[17] (Table 1). 2-Benzothiazolyl fluoromethyl sulfone and 2-deoxy-3,4,6-tri-*O*-benzyl-D-gluconolactone gave the corresponding fluorinated *exo*-glycal **2** in 82% yield. In contrast to the previous result, the observed *E*/*Z* selectivity was in favor of the *Z* alkene, and

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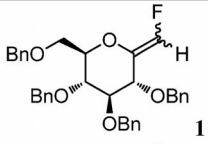
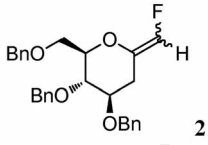
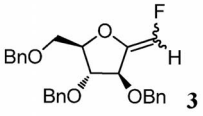
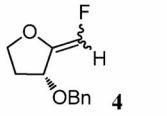
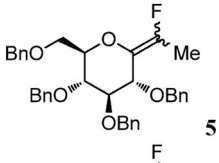
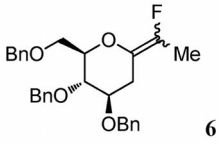
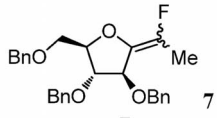
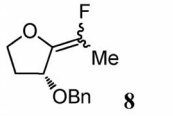
this showed the influence of the 2-alkoxy group on the relative diastereoselectivity. Furanose lactones were tested, and in these cases, products **3** and **4** were isolated in good yields. A mixture of *E*/*Z* enol ethers was obtained in a 7:3 and 6:4 ratio, respectively. 2-Benzothiazolyl fluoroethyl sulfone provided similar results, as tetrasubstituted *exo*-glycals **5**–**8** were isolated in 60–85% yield. An interesting inversion in the selectivity was observed: the *Z* isomers were preferentially obtained for 2-alkoxy-substituted derivatives **5**, **7**, and **8**, whereas the *E* isomer was favored for deoxy derivative **6**. This illustrates the opposing influences of the electronic effects of the fluorine atom and the steric effects of the methyl group.

The stereochemistry of the double bond was established in compounds **2**, **3**, **6**, and **7** by homonuclear and hetero-

Table 1. Synthesis of fluorinated *exo*-glycals from benzyl-protected sugar lactones.

Entry	Product	Yield [%]	*E*/*Z*
1	 **1**	85	6:4
2	 **2**	82	3:7
3	 **3**	77	7:3
4	 **4**	60	6:4
5	 **5**	85	4:6
6	 **6**	58	7:3
7	 **7**	70	3:7
8	 **8**	60	3:7

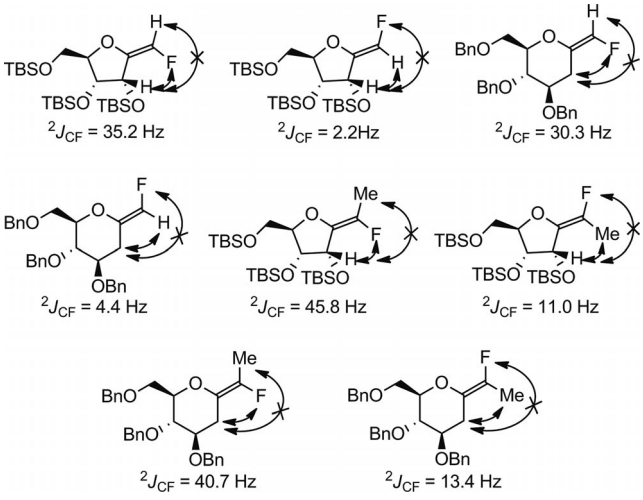
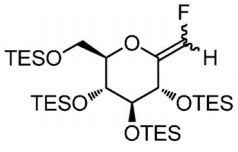
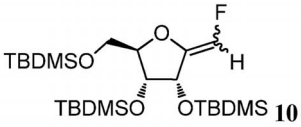
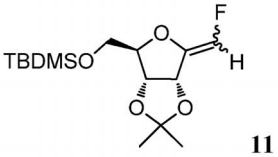
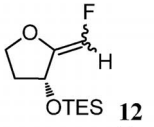
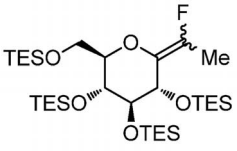
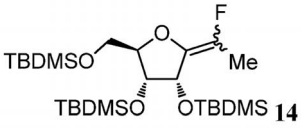
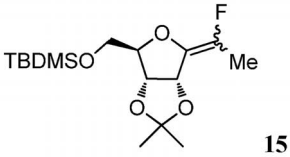
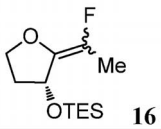


Figure 1. Observed NOEs for some fluorinated enol ethers.

Table 2. Influence of the protecting group.[a]

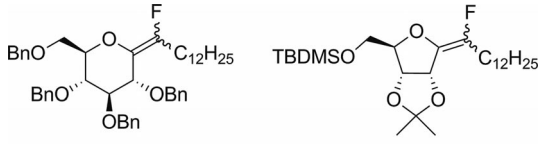
Entry	Product	Yield [%][b]		*E*/*Z*[b]	
		A	B	A	B
1	 **9**	–	94	–	8:2
2	 **10**	46	43	7:3	7:3
3	 **11**	70	–	6:4	–
4	 **12**	20	68	4:6	5:5
5	 **13**	–	93	–	4:6
6	 **14**	37	27	3:7	2:8
7	 **15**	83	40	3:7	3:7
8	 **16**	29	68	2:8	3:7

[a] TES = triethylsilyl, TBDMS = *tert*-butyldimethylsilyl. [b] Procedure A: reaction performed with $BF_3{\cdot}OEt_2$; procedure b: reaction performed without $BF_3{\cdot}OEt_2$.

nuclear NOE measurements (Figure 1). The stereochemistry of the remaining compounds could be assigned by ^{1}H–^{1}H NOESY experiments or by the combination of the relative chemical shifts of the signals in the ^{19}F NMR spectra and the magnitudes of the $^2J_{CF}$ and $^3J_{CF}$ coupling constants (see the Supporting Information).[18]

We next focused on the influence of the protecting groups on the course of the olefination reaction (Table 2). Both isopropylidene and silyl ether protecting groups were tolerated on the lactone, and trisubstituted and tetrasubstituted glycals **9**–**16** were obtained in moderate to good yields. In the case of triethylsilyl ethers **9**, **12**, **13**, and **16**,[19] better yields were obtained without the addition of a Lewis acid.[20] As in the non-fluorine-substituted case, we noticed that a *tert*-butyldimethylsilyl protecting group on the C-2 hydroxy group of the γ-lactone derivative negatively influenced the course of the reaction, and significantly lower yields were observed for **10** and **14**. The stereoselectivity of the formation of the double bond improved when the reaction was conducted with a silyl ether protecting group, as in the case of glucopyranose **9** when compared to benzyl-protected **1**. However, the opposite effect was observed for furanoses **12** and **16**, as the selectivity shifted towards the *Z* isomer.

Having a straightforward method in hand to access alkylated *exo*-glycal derivatives, we investigated the synthesis of fluorinated neoglycolipid skeletons. The reaction of tetrabenzylgluconolactone with a benzothiazolyl sulfone containing a fatty acid like hydrocarbon chain gave corresponding fluoroalkene **17** in 53% yield (Figure 2). Better results were observed when the olefination was performed with a protected D-ribonolactone; in that case, tetrasubstituted fluorinated enol ether **18** was obtained in 83% yield. Again, the steric demand of the alkyl chain appeared to be significant, as improved *Z* selectivity was observed in both cases.



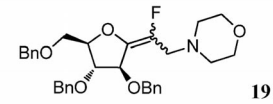
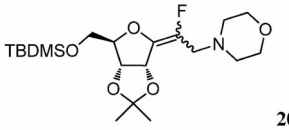
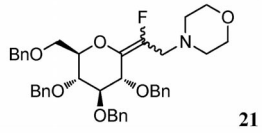
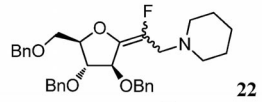
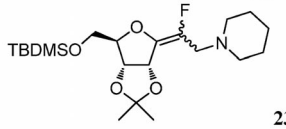
17: 53%
E/*Z* = 3:7

18: 83%
E/*Z* = 2:8

Figure 2. Introduction of long alkyl chains.

To extend the panel of fluorinated *exo*-glycals, Julia olefination was attempted with amino-substituted sulfones derived from morpholine and piperidine. The amino group was found to be compatible with the reaction. Indeed, fluoroallylamines **19**–**23** were obtained in modest to good yields (Table 3). As observed previously, the *Z* alkenes were formed preferentially, as the steric demand of the amino group directed the selectivity of the formation of the double bond. Low yields were observed in some cases because of difficulties during the separation of the products on silica gel.

Table 3. Reaction with aminosulfones.[a]

Entry	Product	Yield [%]	*E*/*Z*
1	 **19**	61	2:8
2	 **20**	91	2:8
3	 **21**	54	2:8
4	 **22**	41	0:1
5	 **23**	39	0.5:9.5

[a] TBDMS = *tert*-butyldimethylsilyl.

Conclusions

In conclusion, we have developed a fluoroenol ether synthesis by using modified Julia reagents for the preparation of tri- and tetrasubstituted fluorinated exocyclic enol ethers from lactones. This general route offers original and convenient access to the synthesis of fluoro *C*-glycoside and nucleoside analogues. This series of compounds constitutes a new family of glycomimetics with, for example, potential biological activities as glycosidase inhibitors.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of all reported compounds.

Acknowledgments

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[16] Typical procedure for the synthesis of fluorinated enol ethers: In a 5 mL round-bottomed flask under an atmosphere of argon, 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone (96 mg, 0.178 mmol, 1.5 equiv.) and 2-(fluoromethylsulfonyl)benzothiazole (27 mg, 0.117 mmol, 1.0 equiv.) were dissolved in freshly distilled THF (480 μL) at –78 °C. Then, $BF_3{\cdot}OEt_2$ (22 μL, 1.5 equiv.) and a solution of LiHMDS (1 M in THF, 240 μL, 2.0 equiv.) were added dropwise over 5 min. Stirring was maintained for 45 min, and then the mixture was hydrolyzed at –78 °C, diluted with dichloromethane, stirred at room temperature for 15 min, and extracted with dichloromethane (2×). The organic layers were combined and washed with brine, dried with sodium sulfate, and concentrated. The residue was dissolved in dry THF (1.2 mL) and DBU (37 μL, 2.0 equiv.) was added. Stirring was maintained for 1 h, and then the mixture was concentrated by rotary evaporation and purified by flash chromatography to afford the desired product (56 mg, 0.100 mmol, 85% yield).

[17] Benzylated lactones were prepared by using a DMSO/acetic anhydride mixture, see: H. S. Overkleeft, J. Van Wiltenburg, U. K. Pandit, *Tetrahedron* **1994**, *50*, 4215–4224.

[18] In agreement with previous observations in the case of fluorine-substituted enol ethers,[2,3] the ^{19}F NMR chemical shift is found to be on average 14.4 ppm more negative in the *E* isomer than in the *Z* isomer; The $^2J_{CF}$ coupling constants were found to be consistently lower in the *Z* isomer than in the *E* isomer, whereas the $^3J_{CF}$ coupling constant was found to be ca. 2.5 Hz in the *Z* isomer and near zero in the *E* isomer.[3c] These correlations will be addressed in more detail in an upcoming paper.

[19] Silylated lactones were prepared by silylation of the corresponding hydroxy lactones, see: P. V. Murphy, C. McDonnell, L. Hämig, D. Paterson, R. J. K. Taylor, *Tetrahedron: Asymmetry* **2003**, *14*, 79–85.

[20] Typical procedure for the synthesis of fluorinated enol ethers without $BF_3{\cdot}OEt_2$: In a 5 mL round-bottomed flask under an atmosphere of argon, 2,3,4,6-tetra-*O*-triethylsilyl-D-gluconolactone (104 mg, 0.164 mmol, 1.5 equiv.) and 2-(fluoromethylsulfonyl)benzothiazole (25 mg, 0.109 mmol, 1.0 equiv.) were dissolved in freshly distilled THF (440 μL) at –78 °C. Then, a solution of LiHMDS (1 M in THF, 220 μL, 2.0 equiv.) was added dropwise over 5 min. Stirring was maintained for 45 min, and then the mixture was hydrolyzed at –78 °C, diluted with dichloromethane, stirred at room temperature for 15 min, and extracted with dichloromethane (2×). The organic layers were combined and washed with brine, dried with sodium sulfate, and concentrated. The residue was dissolved in dry THF (1.1 mL) and DBU (34 μL, 2.0 equiv.) was added. Stirring was maintained for 1 h, and then the mixture was concentrated by rotary evaporation and purified by flash chromatography to afford the desired product (66 mg, 0.102 mmol, 94% yield).

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