ORGANIC LETTERS

2008
Vol. 10, No. 17
3673−3676

Enantioselective Synthesis of Tetrafluorinated Glucose and Galactose

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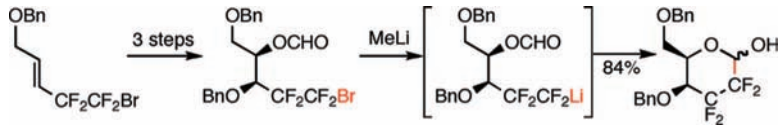
Received June 5, 2008

ABSTRACT



Polyfluorinated carbohydrates have emerged as interesting probes to investigate "polar hydrophobicity" effect(s) in protein−carbohydrate interactions. A convenient enantioselective synthesis of tetrafluorinated analogues of two of the most important monosaccharides, D-glucose and D-galactose, is reported, as well as our first results regarding the glycosylation of these sugar analogues.

Carbohydrates are central to a multitude of critical biological functions.[1] Given that carbohydrates generally do not make good drugs, research into carbohydrate mimetics is of great importance.[2]

In pioneering work, DiMagno introduced the concept of "polar hydrophobicity".[3] By extensive replacement of carbohydrate CHOH groups by CF_2 groups, binding was expected to be enhanced due to the hydrophobic effect. In addition, favorable electrostatic interactions involving the polarized C−F bond with cationic or dipolar sites in the receptor would be possible, with such interactions being negligible in aqueous medium. It was shown that the hexafluorinated pyranose **1** (Figure 1) crosses the erythrocyte membrane at an approximately 10 times higher rate than glucose itself, and it was proven that this rate increase was due to enhanced affinity to the transporter protein (and not because of simple membrane diffusion originating from increased lipophilicity).

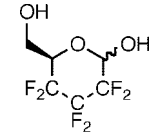


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Figure 1. DiMagno's heavily fluorinated hexapyranose.

In addition, glycosylation of natural products can significantly influence their biological activity.[4] Hence, investigations into the glycosylation of polyfluorinated sugars is also of high interest.

To enable further studies of the biological implications of these modifications, we have developed methodology for a short, convenient, and enantioselective synthesis of tetrafluorinated carbohydrates.[5] In this Letter, we report the synthesis

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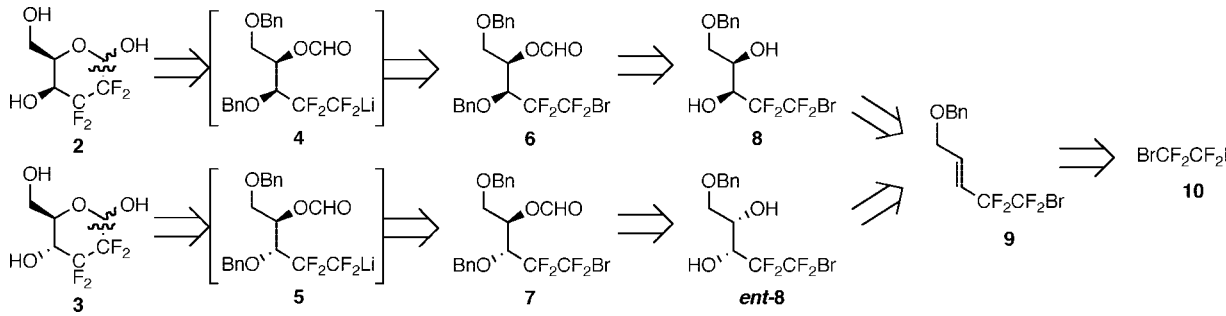
10.1021/ol801272e CCC: $40.75
Published on Web 08/01/2008

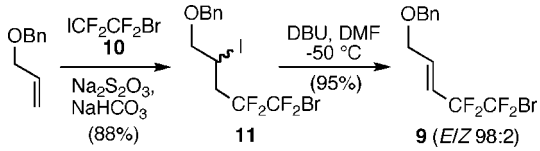
Scheme 1. Retrosynthetic Analysis



of tetrafluorinated analogues **2** and **3** of two important sugars, D-glucose and D-galactose, as well as our first results regarding their glycosylation.

The retrosynthetic analysis is shown in Scheme 1. The key carbon−carbon bond disconnection as indicated corresponds to our recently established tetrafluoroethylene lithium mediated cyclization protocol,[5] featuring **4** and **5** as key intermediates. These intermediates would be obtained from the corresponding tetrafluoroalkylidene bromides **6** and **7** by a bromine−lithium exchange reaction. The absolute configuration of both **6** and **7** would be established by a Sharpless asymmetric dihydroxylation (SAD) reaction[6] of alkene **9**, with the synthesis of the *anti*-configured **7** requiring an inversion of configuration. Given S_N2 reactions in the α-position of a perfluoroalkyl group are known to be difficult,[7] it was chosen to invert the C5-OH (carbohydrate numbering), leading to enantiomeric diol ***ent*-8** as the target intermediate. Alkene **9** is not commercially available and could be obtained from bromoiodotetrafluoroethane **10** (Scheme 2).

Scheme 2. Synthesis of the *E*-Alkene Substrate **9**

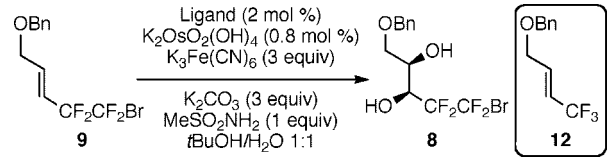


Selective radical-mediated coupling of the bifunctional building block **10** with alkenes has been reported using Fe/Cp_2TiCl_2 as the initiation system,[8] and reaction of allyl benzyl ether with **10** under these conditions afforded **11** in 80% yield. However, it was found that the yield of large-scale reactions was considerably lower, and in addition, 3.75 equiv of the relative expensive **10** had to be employed. By using sodium dithionite in basic medium as the initiator,[9] an excellent yield of **11** on a large scale was obtained despite employing a reduced excess of **10** (1.25 equiv).

Iodide elimination from β-iodoperfluoroalkanes[10] was investigated, with DBU outperforming other bases (KOH, DBN) in terms of *E*/*Z* selectivity. It was found that a low temperature (−50 °C) was necessary to achieve a very high *E*/*Z* ratio (determined by ^{1}H NMR). Despite the low temperature, the elimination reaction was very fast, and even on a large scale, complete conversion was observed after 30 min. Unfortunately, the geometric isomers were not easily separated, and most SAD reactions were executed on a mixture of isomers. The configuration of the *E*-isomer was confirmed by ^{1}H and ^{19}F NMR.[10c,e]

It is known that perfluoroalkyl-substituted alkenes have a reduced reactivity toward dihydroxylation.[11,12] The recommended modification for SAD of unreactive alkenes is to increase the OsO_4 and ligand loading.[6b] Indeed, using 0.8 mol % of OsO_4 and 2 mol % of chiral ligand, Qing reported excellent enantioselectivities (β-SAD, 99.4% ee, α-SAD, 97.5% ee, 0 °C)[12a] on a similar *E*-alkene **12** (Table 1).

Table 1. Sharpless Asymmetric Dihydroxylation of **9**



entry	ligand	*t* (°C)	time (days)	diol	yield[a] (%)	ee[b] (%)
1[c]	$(DHQD)_2PHAL$	4−6	8	**8**	77	92
2[d]	$(DHQD)_2PYR$	4−6	8	**8**	81	88
3[e]	$(DHQD)_2AQN$	0	8	**8**	67	96
4[e]	$(DHQ)_2PHAL$	5−6	10	***ent*-8**	86	86

[a] Isolated yield [b] Determined by HPLC (Chiralcel OD-H), see Supporting Information. [c] Pure *E*-**9**. [d] *E*/*Z* = 98:2. [e] *E*/*Z* = 96:4.

Using similar conditions, the enantioselectivity for the β-SAD reaction of **9** was 92% (entry 1), which is significantly lower compared to Qing's result with **12**. In addition,

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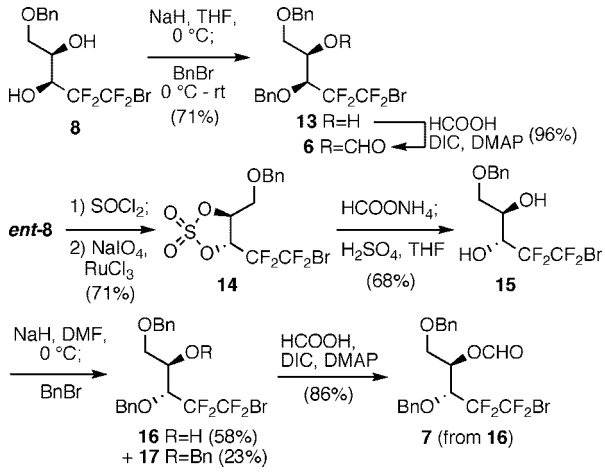
eight days at 4−6 °C were required to obtain a good yield of **8**, which is much longer than the two days at 0 °C required for **12**. However, with $(DHQD)_2AQN$, a 96% ee was obtained (entry 3). Unfortunately, the enantioselectivity for the corresponding α-SAD reaction was only 86% ee (entry 4). We did not isolate any dihydroxylation product arising from the minor *Z*-isomer.

The subsequent conversion to the cyclization precursors **6** and **7** is shown in Scheme 3. Regioselective benzylation

Scheme 3. Synthesis of the Cyclization Precursors



was achieved by exploiting the increased acidity of the hydroxyl group adjacent to the fluoroalkyl substituent.[13] With NaH as base, excellent regioselectivity was obtained leading to **13** in 71% yield, with the dibenzylated product (not shown) only isolated in 4.5% yield. Subsequent formylation led to **6** in excellent yield.

The initial approach for the synthesis of the tetrafluorinated glucose precursor **7** involved analogous benzylation of ***ent*-8** to give ***ent*-13**, but all attempts to achieve subsequent formate formation with inversion of C5-OH configuration failed completely (not shown). Hence, ***ent*-8** was converted to the corresponding cyclic sulfate **14**, followed by regioselective opening[12a,b] with ammonium formate. Unfortunately, despite using mild conditions for the subsequent residual sulfate hydrolysis,[14] concomitant formate hydrolysis could not be avoided, leading mainly to the *anti*-diol **15**. Hence, **7** was then obtained by regioselective benzylation of **15** as described above. We were surprised to observe that in this case the desired benzyl ether **16** was isolated in only 58% yield, next to an unexpectedly large amount of the dibenzyl ether **17**. DIC-mediated formylation then gave **7**.

Next, the anionic cyclization reaction was investigated (Scheme 4). Bromine−lithium exchange was initiated with 1 equiv of MeLi,[5] leading to the lithiated derivatives **4** and **5**. We were pleased to observe that, in addition to the formation of furanoses reported earlier,[5] the cyclization to give the pyranose derivatives **18** and **22** also proceeded in excellent yield. Scaling up of the reaction was uneventful and allowed the isolation of a set of minor byproducts, all arising from the lithiated intermediate. Expected byproducts were the β-fluoride elimination products **19** and **23**, assigned via the characteristic trifluorovinyl signals (^{19}F NMR) as well as the characteristic $CF{=}CF_2$ band (IR),[15] and the protonated products **20** and **24**, easily assigned by the large $^2J_{F-H}$ coupling constant for $-CF_2H$ (≈53 Hz). To our surprise, the corresponding methylated compounds **21** and **25** were also obtained, which are thought to arise from reaction of **4** and **5** with the byproduct of the Br−Li exchange reaction (CH_3Br). Key spectroscopic data for **21** and **25** ($-CF_2CF_2CH_3$) include a *tt* ($\delta \approx 1.8$ ppm, ^1H NMR) showing a characteristic $^3J_{H-F}$ and $^4J_{H-F}$ coupling.

Finally, hydrogenolysis of **18** and **22** led to the deprotected tetrafluorinated D-glucose and D-galactose as an inseparable mixture of anomers (Scheme 5).

At this stage, our attention turned to the glycosylation of these polyfluorinated sugars. Because a cation is destabilized when adjacent to a perfluoroalkyl group,[16] formation of an oxocarbenium ion intermediate, typical for most conventional glycosylation methods, is difficult. For the same reason, glycosidic bonds are expected to be very stable when 2,2-difluoro substitution is present. Glycosylation of (protected) **1** by nucleophilic substitution of a corresponding triflate was reported to be slow, though solvolysis was successful.[3b] However, glycosylation by anomeric alkylation[17] has proven to be possible for related (di)fluorinated systems,[18,19] and this method was selected for further study.

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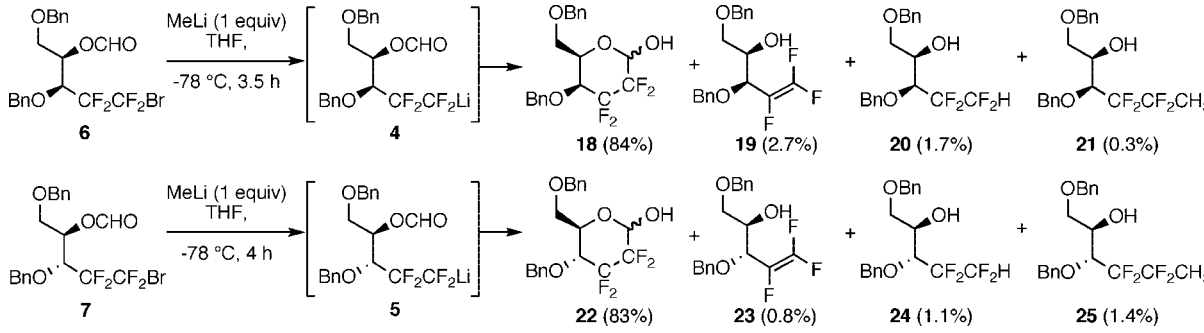
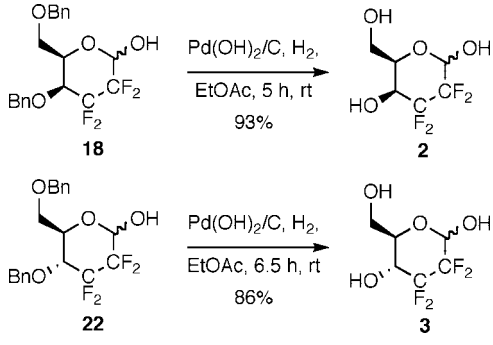
Scheme 4. Anionic Cyclization to the Tetrafluorinated Galactose and Glucose Derivatives

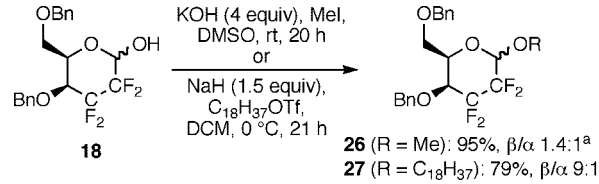


Our first investigations into the glycosylation of **18** by anomeric alkylation are shown in Scheme 6. The use of Fried conditions[19a] led to **26** in high yield, but with a modest anomeric selectivity. Interestingly, reducing the amount of KOH (1.3 equiv) results in a slight excess of the α-anomer ($\beta/\alpha = 1{:}1.1$). More encouraging results in terms of anomeric selectivity were obtained with NaH as a base, while still obtaining a good yield. Separation of α- and β-anomers of **26** and **27** was successfully achieved by chromatography. The anomeric configuration was tentatively assigned based on the chemical shift of the anomeric proton, with the equatorial anomeric proton (α-anomer) downfield compared to an axial anomeric proton (β-anomer), and on the $^2J_{F2-C1}$ coupling constants. The magnitude of $^2J_{F2-C1}$ is dependent on the orientation of an electronegative substituent on the coupled carbon atom, with an increase in magnitude going from a *gauche* to a *trans* orientation of the substituent with respect to the fluorine involved in the coupling.[20] In this respect, the anomeric substituent outweighs the ring oxygen in importance. Hence, for **26**, the anomer with the higher chemical shift for the anomeric proton also displays $^2J_{F2-C1}$ values of 37.7 and 25.1 Hz, which are consistent for **26α**. The large value is the coupling of F_{ax} with the anomeric carbon atom. For **26*β***, both $^2J_{F2-C1}$ values are 23.2 Hz.[21] Interestingly, for **26α**, both $^2J_{F3-C4}$ coupling constants (30.0 and 17.4 Hz) confirm that the 4-OBn is in the axial position. Similar values were found for **26*β***, suggesting both anomers **26** exist in a $^4C_1$ chair conformation.

Scheme 5. Final Deprotection Step



Scheme 6. Anomeric Glycosylation



[a]Based on isolated yield of the pure anomers. [b]Determined by ^{19}F NMR on the crude reaction mixture.

In summary, 2,3-dideoxy-2,2,3,3-tetrafluoro-D-galactose **2** and 2,3-dideoxy-2,2,3,3-tetrafluoro-D-glucose **3** were successully synthesized via our perfluoroalkylidene lithium mediated cyclization strategy. Glycosylation was successfully achieved using an anomeric alkylation protocol. Further research into the identification of conditions to achieve highly α- and β-selective glycosylations is in progress.

Acknowledgment. R.S.T. thanks the Overseas Research Students award scheme for funding. We wish to acknowledge the use of the EPSRC's Chemical database service at Daresbury.[22]

Supporting Information Available: Experimental procedures and spectral data, including copies of ^1H and ^{13}C NMR spectra, and determination of the enantioselectivity of the SAD reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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