Fluorinated Carbohydrates

Enantioselective Synthesis of Tetrafluoroethylene-Containing Monosaccharides**

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The incorporation of fluorine or fluoroalkyl groups can have profound effects on the material characteristics or biological activity of compounds by affecting their physico-chemical and/or pharmacological properties.[1] While the incorporation of *terminal* perfluorinated moieties is common in some areas,[2] the introduction of an *internal* perfluoroalkanediyl fragment (IPF) is comparatively rare.[3] Though the incorpo-

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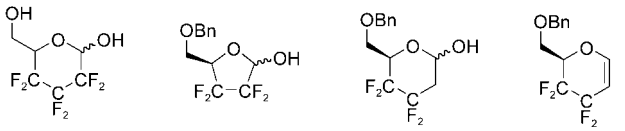
[**] We thank GlaxoSmithKline for funding. We are grateful to Prof. R. J. Whitby and Dr. Martin Swarbrick for support. Abbreviations: AQN: anthraquinone; Bn: benzyl; DCC: dicyclohexylcarbodiimide; DHQ: dihydroquininyl; DMAP: 4-dimethylaminopyridine; PHAL: phthalazine; PYR: pyrimidine.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/anie.200460746

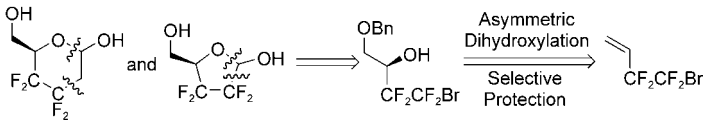
ration of fluorine is particularly well-studied for carbohydrates and nucleosides,[4] the synthesis of carbohydrates and glycosides containing IPFs and the study of the effects of the IPF introduction on their biological properties are a virtually unexplored area. Pioneering work by DiMagno proved very interesting. He proposed a general strategy for enhancing molecular recognition based on enhancing "polar hydrophobicity",[3c,d] which could be achieved by replacing polar hydrophilic groups (OH) by polar hydrophobic groups (F), with a CF_2 group as adequate substitute for CHOH. It was found that the racemic hexafluoropyranose **1** has a 10-fold increase in transport across the red blood cell membrane compared to 3-deoxy-3-fluoroglucose due to enhanced affinity for the transporter protein.



1 **2** **3** **4**

This significant study paves the way for more intensive research regarding the effect of IPF incorporation on substrate–receptor binding, especially given the abundance of carbohydrate-containing bioactive compounds and the importance of carbohydrates in cell recognition events. Hence, efficient methods to synthesize such modified monosaccharides are of importance. An enantioselective synthesis of **1** is reported by DiMagno et al.[3d] Herein we describe the first enantioselective syntheses of the tetrafluorofuranose **2**,[5] of the novel pyranose **3**, of the corresponding deprotected saccarides (see below), and of the protected glycal **4**.

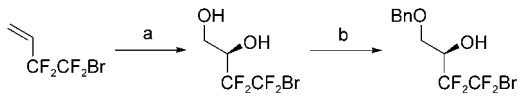
The retrosynthetic analysis for **2** and **3** is shown in Scheme 1. Given that the direct fluorination of aliphatic 1,2-diketones to α,α,β,β-tetrafluoroethylene groups is a low-yielding process,[3c,6] a fluorinated-building-block approach[7] was adopted. Cleavage of the CF_2–C and O–CH bonds as indicated were selected as the strategic disconnections. This led to **5** as a common precursor for **2** and **3**, which might be accessible from the commercially available bifunctional fluorinated building block **6**.



3 **2** **5** **6**

Scheme 1. Retrosynthetic analysis for **2** and **3**.

The synthesis of the central intermediate **5** is shown in Scheme 2. Sharpless asymmetric dihydroxylation (SAD) reactions on electron-deficient alkenes call for an increased amount of $K_2OsO_4 \cdot 2H_2O$.[8] With an in-house prepared AD-mix (0.1 M, 2 mol% $K_2OsO_4 \cdot 2H_2O$), an excellent yield (89%) was obtained after 9 days (4 °C). However, when a 1:1 ratio of K_2OsO_4:$(DHQ)_2PHAL$ was used, an *ee* value of only 54%[9] was obtained. As the standard PHAL-based ligands are not recommended for terminal alkenes,[8] we prepared AD-mix cocktails with other ligands. While with $(DHQ)_2AQN$[10] only a disappointing *ee* value of 55% was obtained, we were delighted to achieve an *ee* value of 78% (89% yield) with $(DHQ)_2PYR$[11], which is one of the highest enantioselectivities reported to date for a SAD on terminal α-perfluorinated alkenes.[11] Further investigation of the dihydroxylation is in progress.

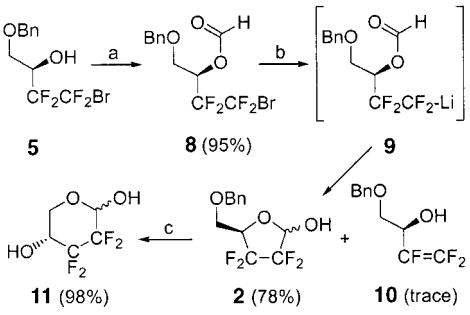


6 **7** (89%, 78%*ee*) **5** (96%)

Scheme 2. Synthesis of the central cyclization precursor **5**. a) $K_2OsO_4 \cdot 2H_2O$ (2 mol%), $(DHQ)_2PYR$ (2 mol%), $K_3[Fe(CN)_6]$, K_2CO_3, *t*BuOH, H_2O, 4 °C, 9 d; b) Bu_2SnO, toluene, reflux, 24 h, then BnBr, Bu_4NI, reflux, 16 h.

Monoalkylation of terminal 1,2-diols flanked by a perfluoroalkyl group under basic conditions was reported to result exclusively in the protection of the secondary alcohol, testimony to its increased acidity.[12] We found that monobenzylation via the corresponding 1,2-stannylene acetal[13] proceeded with the *opposite* regioselectivity. The reactivity of this hitherto undescribed type of stannylene acetal appears to be fully controlled by steric factors, with no observable electronic influence of the perfluoroalkyl group.

The synthesis of furanose **2** (Scheme 3) began with the formylation of **5** (78% *ee*). At this stage, an anionic cyclization was envisaged. Though perfluoroalkyl lithium species are known to be unstable, the main decay pathway being fluoride elimination,[14] in situ trapping of such species by aldehydes, ketones, and esters is known.[15] Such a process has not yet been demonstrated in an intramolecular fashion, and we hoped that the rate of cyclization would outstrip that of elimination. Reaction of **8** with several alkyl lithium reagents was investigated to effect the initial lithiation (all reactions at −78 °C in THF). Reaction with 1 equiv of *n*BuLi for 1 h resulted in the isolation of the desired furanose **2** as an inseparable anomeric mixture in 43% yield. Also isolated were **10** (11%) and **5** (17%), produced by the expected β-fluoride elimination and/or by nucleophilic attack of *n*BuLi



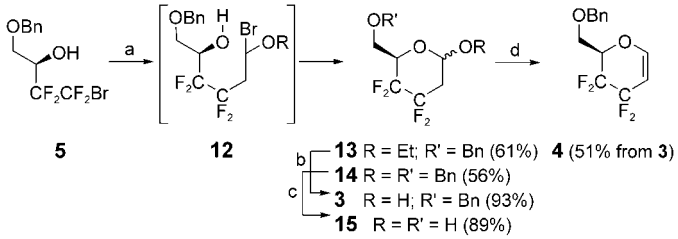
5 **8** (95%) **9**

11 (98%) **2** (78%) **10** (trace)

Scheme 3. Synthesis of fluorinated pentose **2**. a) DCC, DMAP, HCOOH, CH_2Cl_2, RT, 16 h; b) MeLi (1 equiv), THF, −78 °C, 3 h; c) $Pd(OH)_2/C$, H_2, RT, 16 h.

on the formate ester. Reaction with 2 equiv of *t*BuLi under the same conditions resulted in the same product mixture: **2** (43%), **10** (22%), and **5** (15%). However, with MeLi (1 equiv), 78% of **2** was obtained with only trace amounts of **10** present, and with no **5** observed at all. Finally, the deprotected pentose was obtained by hydrogenolysis of the benzyl group, and was isolated as the pyranose **11** as evidenced by ^{1}H NMR spectroscopy (DMSO) and HMBC NMR experiments (see the Supporting Information). An anomeric ratio of 2.6:1 was observed.

The synthesis of tetrafluoropyranose **3** and glycal **4** is shown in Scheme 4. The ring formation was envisaged to



Scheme 4. Synthesis of fluorinated pyranose **3** and glycal **4**. a) $Na_2S_2O_4$, $NaHCO_3$, DMSO, H_2C=CHOR, RT, 16 h. b) H_2SO_4 (25% aq.), dioxane, reflux, 4 h. c) $Pd(OH)_2$/C, EtOAc, RT, 12 h. d) *o*-$NO_2C_6H_4$-SeCN, PBu_3, THF, RT, 1 h, then H_2O_2 (30% aq.), $NaHCO_3$, RT, 1.5 h.

occur by a domino sequence as follows: perfluoroalkyl radical generation to initiate intermolecular addition onto ethyl vinyl ether, followed by atom transfer to give the α-bromoether **12**, which would cyclize, in an S_N2- or S_N1-type process, to yield the ethyl glycoside **13**. For this transformation the solvent proved to be of importance. With MeCN/H_2O mixtures, typically used for dithionite-mediated perfluoroalkyl radical generation,[16] the reaction proved quite capricious, with a maximum yield of 44% of **13** (after 16 h at reflux). Conversely, the reaction in DMSO[17] proved much faster, even at room temperature, and reliably afforded **13** in significantly better yields.

Using benzyl vinyl ether, the dibenzyl-protected **14** was synthesized in good yield under identical reaction conditions. The fully deprotected pyranose **15** could now be obtained in a single step by hydrogenolysis (1.4:1 mixture of anomers). Anomeric deprotection of **13** gave the 6-*O*-benzyl pyranose **3**, and subsequent subjection to Grieco elimination conditions[18] resulted in the formation of glycal **4**.

In summary we have reported a short enantioselective synthesis of a tetrafluorinated pentose and hexose, and of a tetrafluorinated glycal. A fluorinated-building-block approach was followed, using a SAD reaction on a terminal α-perfluorinated alkene to introduce chirality. A very high *ee* value for this class of alkenes (78%) was obtained. The key operation in the synthesis of **2** and **3** was the ring formation. We report the first cyclization involving perfluoroalkyl lithium species and demonstrate that the rate of *5-exo* cyclization is faster than that of the competing fluoride elimination under the conditions used. We have also established a novel domino perfluoroalkyl radical addition/atom transfer/nucleophilic cyclization approach to obtain a pyranose structure. Finally, we have achieved a fully regioselective, high-yielding monoalkylation protocol for terminal 1,2-diols substituted by a perfluoroalkyl chain, with complementary selectivity to existing methods. The short, high-yielding sequence for the synthesis of **2** and **3** should make such IPF-modified monosaccharides easily accessible building blocks. Further research on the reactivity of the monosaccharides/glycal in glycosylation reactions is in progress.

Received: May 21, 2004

Keywords: asymmetric dihydroxylation · carbohydrates · fluorine · perfluoro compounds · synthetic methods

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