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Synthesis of new α- and β-*gem*-difluoromethylene *C*-glycosides in the galactose and glucose series

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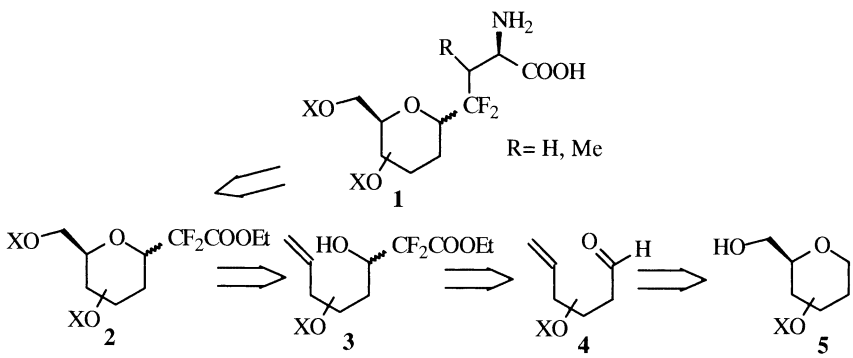
Abstract—A synthesis of *gem*-difluoromethylene *C*-glycopyranosides was efficiently achieved via a Reformatsky reaction on an aldehyde and subsequent intramolecular cyclization involving either the opening of an epoxide or an oxymercuration. © 2001 Published by Elsevier Science Ltd.

The importance of carbohydrate moiety in cellular and molecular recognition processes has stimulated intense research interest in the synthesis of modified glycoconjugates. *C*-Glycosides are synthetic compounds of considerable importance and numerous methods have been explored for their synthesis.[1,2] However, replacement of the anomeric oxygen by a methylene group may induce differences in biological functions of these hydrolytically stable derivatives. For this reason, using a difluoromethylene group in place of the anomeric oxygen bond is becoming a promising avenue for the preparation of new glycoconjugate derivatives.[3,4] Indeed, this tetrahedral and electronegative unit is considered as bioisosteric and isoplanar to oxygen.[5] However, a general synthesis of *gem*-difluoromethylene *C*-glycosides applicable to the most often encountered carbohydrates is still to discover. In this paper, we present preliminary results in glucose and galactose series related to previous studies dealing with the reactivity of ethyl bromodifluoroacetate zinc reagent.[6] We reasoned that *gem*-difluoroesters **2** would be valuable starting materials for the preparation of the corresponding amino acids **1** which can be regarded as analogues of *O*-glycoserine or *O*-glycothreonine (Scheme 1).

In a first attempt, we considered the nucleophilic attack of the ethyl bromodifluoroacetate zinc reagent on an oxonium ion generated from the corresponding functionalized carbohydrate but all our attempts failed whatever the conditions.



Scheme 1.

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We then turned our attention to a synthetic pathway involving the nucleophilic attack of the same reagent on aldehydes **4** derived from the corresponding carbohydrates **5**. The resulting olefinic alcohols **3** could then be cyclized to furnish desired products.

Synthesis of aldehyde **6** starting from methyl-D-glucoside in six steps has been previously described by Vasella.[7] The method involved a fragmentation of a 6-bromo derivative. With aldehyde **6** in hand, we then studied the attack of the ethyl bromodifluoroacetate in the presence of activated Zn dust (Scheme 2).

We obtained a 1:1 diastereomeric mixture of epimeric compounds **7a** and **7b**. We tried to enhance the stereoselectivity by making the zinc reagent at lower temperature[8] or by using difluoroenoxysilane[9] but this method failed (despite also the addition of a Lewis acid such as $BF_3{\cdot}OEt_2$). The aldehyde was in each case totally recovered. We also tried the Reformatsky-type reaction using SmI_2.[10] Addition proceeds well (yield 40%) but there was no improvement in the stereoselectivity (1:1 ratio). However, these compounds gave us an access to both α- and β-difluoromethylene *C*-glycosides. Fortunately **7a** and **7b** were easily separated by chromatography on silica gel. At this stage of our study, we were able to consider the cyclization step. We envisaged two different procedures for this purpose. The first one involved the formation of an epoxide (Scheme 3).

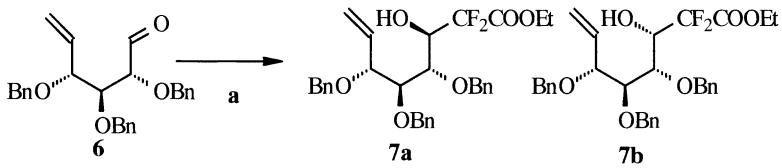
Treatment of the two ethylenic compounds **7a** and **7b** with *m*CPBA gave a 1:1 mixture of C-5 epimeric epoxides. We were unable to improve the diastereoselectivity whatever the conditions of epoxide formation. Cyclization was performed in acidic conditions (CSA, CH_2Cl_2) affording **8a** and **8b** as two 1:1 mixtures of C-5 epimeric compounds.

Disappointed by the absence of stereoselectivity, we then performed the cyclization using an intramolecular oxymercuration. Examples of such a reaction have been previously described in glucose series[11] and for the preparation of an azasugar.[12] When applied to compounds **7a** and **7b** this method provided single isomers **9a** and **9b**, respectively (Scheme 3). NMR studies and especially NOESY experiments clearly indicated an L-idose configuration for the two products. The conversion of the alcohol(s) **10a**[13] and **10b** was accomplished by the slow addition of an oxygenated solution of $NaBH_4$ to a solution of the organomercurial compound at 0°C in the presence of a rapid stream of oxygen.[14]

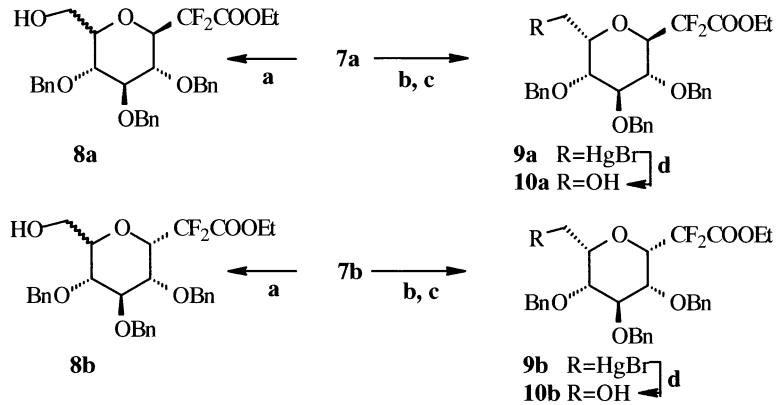
We then transposed this strategy to the galactose series (Scheme 4). Aldehyde **15** was prepared as follows. Methyl D-galactoside **11** was selectively protected as an acetal, then the two remaining hydroxyl groups were benzylated in 60% yield for the two steps. A regioselective reduction[15] of protected compound **12** (LAH, $AlCl_3$) furnished alcohol **13** in 95% yield. Mesylation of the primary alcohol followed by bromination afforded derivative **14** which was submitted to fragmentation in the presence of activated Zn dust. Key aldehyde **15** was then obtained in 77% yield from **13**.

Reaction of this aldehyde with zinc ethyl bromodifluoroacetate led to the formation of a 1:1 mixture of separable alcohols **16a** and **16b** which were submitted to oxymercuration reaction to furnish diastereoselectively isomers **17a** and **17b**, respectively (Scheme 5). NMR studies unambiguously demonstrated that the resulting products possessed the correct C-5 galactose configuration.

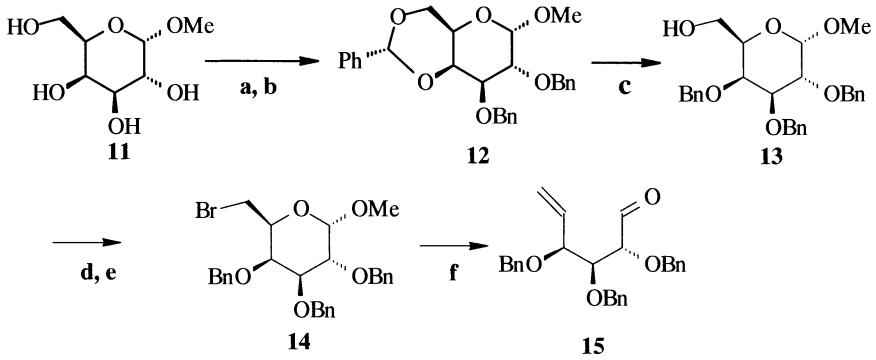
As was previously observed,[11] the stereochemistry of these intramolecular oxymercurations is highly depen-



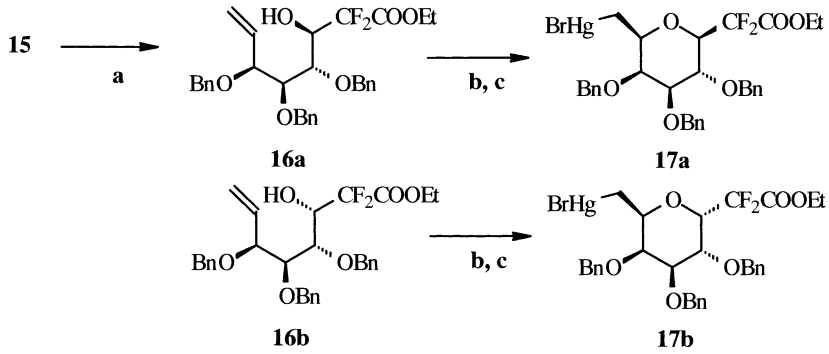
Scheme 2. *Reagents and conditions*: $BrCF_2COOEt$, Zn dust, THF, 60°C, 64%.



Scheme 3. *Reagents and conditions*: (a) *m*CPBA, then CSA, CH_2Cl_2, 71% (**8a**), 63% (**8b**); (b) $Hg(OTFA)_2$, THF; (c) $NaHCO_3$, then KBr, 85% (**9a**), 79% (**9b**); (d) $NaBH_4$, O_2, DMF, 0°C, 50% (**10a**), 46% (**10b**).



Scheme 4. *Reagents and conditions*: (a) PhCHO, $ZnCl_2$; (b) BnBr, NaH, DMF, 60% from **11**; (c) $LiAlH_4$, $AlCl_3$, ether, CH_2Cl_2, 95%; (d) MsCl, NEt_3, CH_2Cl_2; (e) LiBr, butan-2-one, 95% from **13**; (f) Zn, $CeCl_3$, MeOH, 81%.



Scheme 5. *Reagents and conditions*: (a) $BrCF_2COOEt$, Zn dust, THF, 60°C, 98%; (b) $Hg(OTFA)_2$, THF; (c) $NaHCO_3$, then KBr, 95% (**17a**), 72% (**17b**, 4:1 mixture of C-5 epimers).

dent on the C-4 configuration. The influence of an oxygen on this position has been well studied and explained.[16] It proceeds via an intramolecular attack on a π complex; the conformer where the oxygen is in the plane of the double bond is favored (Fig. 1). Thereby, the internal nucleophile is constrained to attack on the *Re* face for **17a** or on the *Si* face for **9a.**

In conclusion, an access to the α- and β-*gem*-difluoromethylene *C*-glycosides has been developed. A diastereoselective ring formation via an intramolecular oxymercuration was the key step. Currently, experiments are underway to prepare compound **1**. Our present work deals with functional transformation of the carboxylic ester to obtain the desired amino acids. We are also studying new methods of cyclization to avoid the use of mercury salts and the application of this strategy to other biologically interesting carbohydrates.

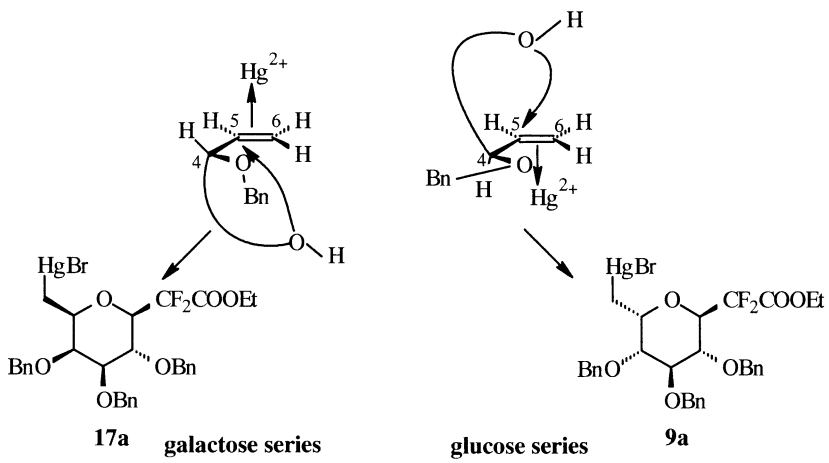


Figure 1. Favored π complex and intramolecular attack in the glucose and galactose series.

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13. Compound **10a**: ^{1}H NMR ($CDCl_3$): δ 1.27 (t, $J=7.17$, 3H), 3.7–4.0 (m, 5H), 4.10–4.22 (m, 4H), 4.51–4.9 (m, 6H), 7.2–7.4 (15H); ^{19}F NMR ($CDCl_3$): δ −113.73 (d, $J=263$), −121.06 (d, $J=263$); ^{13}C NMR ($CDCl_3$): δ 12.58, 57.57 (C-6), 62.05, 68.09 (t, $J=26$), 72.48, 73.59, 73.70, 74.22 (t, $J=26$), 74.31, 75.48, 77.25, 80.89, 126.59, 126.78, 126.94, 127.12, 127.25, 127.38, 136.19, 136.33, 136.87, 163.2 (t, $J=32$) (CF_2 signal is too small). IR (neat): 3445, 2928, 1769; $[\alpha]_D^{20}=+10.2$ (*c* 0.4, $CHCl_3$).
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