A Convenient Method for Replacement of the Anomeric Hydroxy Group in Carbohydrates by Difluoromethyl Functionality

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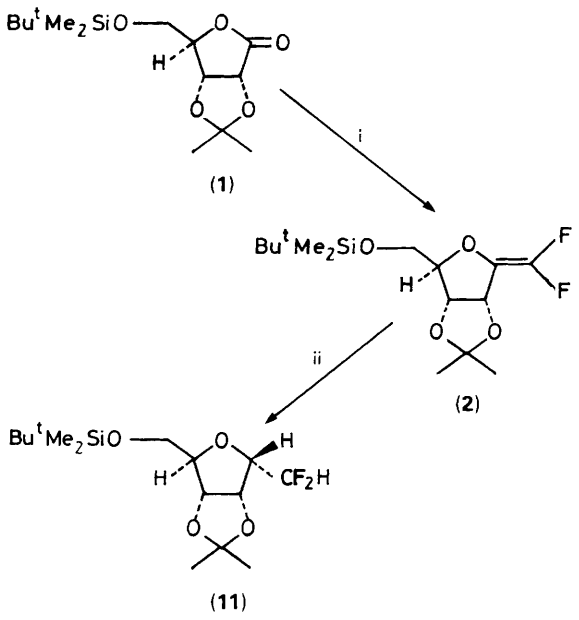
Difluoromethylenation of carbohydrate lactones followed by catalytic hydrogenation provides a concise sequence for the title transformation.

The enhancement of biological activity in many natural product classes by the selective introduction of one or more fluorine atoms is a proven cornerstone strategy of the pharmaceutical industry.[1] We were intrigued, however, by the possibility in *C*-glycoside chemistry that site specific replacement of an oxygen atom, possessing stereochemically significant lone pairs,[2] by the larger difluoromethylene unit would provide compounds which still retained hydrogen bonding potential. Although such a replacement is rarely considered, the principle has been exemplified in the case of difluoro-



Scheme 1. *Reagents*: i, $(Me_2N)_3P/CF_2Br_2/Zn$; ii, H_2/10% Pd–C.

methylene diphosphonic acids and related congeners as analogues of biological phosphoryl species.[3] Herein, we report the implementation of this concept with particular reference to regiospecific replacement of the anomeric hydroxy group in carbohydrates by the difluoromethyl moiety.

The synthetic sequence, as outlined in Scheme 1, for the particular case of the D-ribose derivative (**1**), required hydrogenation of an intermediate difluoroenol ether (**2**), which was in turn to be derived by difluoromethylenation of an inexpensive sugar lactone. To the best of our knowledge, with the single exception of a report describing the photochemistry of a difluoroenol ether prepared from a formate ester,[4] the preparation and chemistry of this functional array has been little studied. Moreover, the proven utility of methyl-1-ene sugars as versatile intermediates in a range of transformations leading to *C*-glycosides,[5] and the existence of chiral tetrahydrofuran units possessing a methyl group adjacent to the ring oxygen atom in a range of natural products, such as muscarines,[6] furanomycin,[7] and boromycin,[8] provided additional impetus for such an approach.

In the event, difluoromethylenation was smoothly accomplished by reaction of the lactone with five equivalents of the reagent formed by the reaction of tris(dimethylamino)phosphine with dibromodifluoromethane and zinc in refluxing anhydrous tetrahydrofuran.[9] The results obtained with a selection of typically protected carbohydrate lactone derivatives are given in Table 1, and reveal that preparatively useful yields may be obtained from a range of γ-lactones. The successful conversion from the inherently less reactive δ-lactone of the D-gluconolactone (**9**) derivative is particularly noteworthy, indicating not only the tolerance of the readily removed silyl ether protection, but also demonstrating that the presence of an isopropylidene group is not required in order to maintain the closed lactol structure in the initial intermediate formed by nucleophilic attack.[10] The mechanism of the difluoromethylenation sequence proceeds in all probability by a non-ylid type mechanism.[11]

The transformation of the difluoroenol ether group into the difluoromethyl group was cleanly achieved by hydrogenation using a 10% palladium on carbon catalyst in ethanol or ethyl

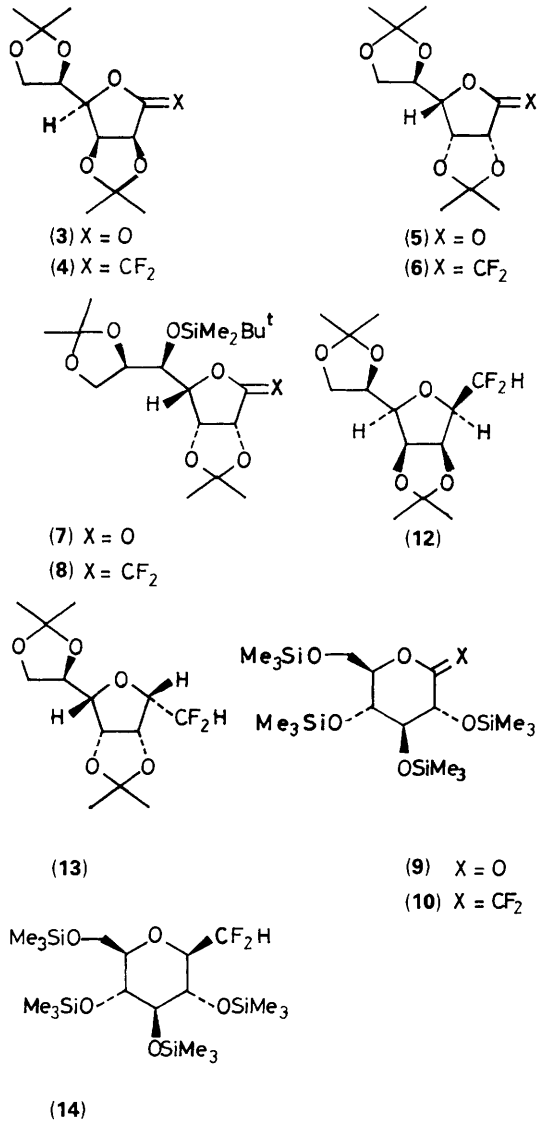


Table 1. Difluoromethylenation of carbohydrate lactones.

Starting material	Product	Yield[a] /%
(**1**)	(**2**)	56
(**3**)	(**4**)	64
(**5**)	(**6**)	67
(**7**)	(**8**)	57
(**9**)	(**10**)	66

[a] All compounds were fully characterised by ^1H, ^{13}C and ^{19}F n.m.r. and i.r. spectroscopy.

Table 2. Hydrogenation of 1-difluoromethylene carbohydrates.

Starting material	Product	Yield /%
(**2**)	(**11**)	95
(**4**)	(**12**)	98
(**6**)	(**13**)	98
(**10**)	(**14**)	78[b]

[b] Hydrogenation in ethanol led to loss of trimethylsilyl protecting groups. Quoted yield includes subsequent reprotection.

acetate, (Table 2) with the stereospecific delivery occurring exclusively from the convex face of the isopropylidene derivatives. The anomeric stereochemistry was proven by the typical *cis*-coupling constant (4—6 Hz) between the anomeric proton and its vicinal neighbour. Similarly, reduction of (**10**) gave predominantly (**14**), which was assigned as the β-anomer from the typical diaxial coupling constant (9 Hz) between the anomeric proton and its vicinal neighbour, in accordance with literature precedent.[5]

The present reaction therefore provides ready access to a series of synthetically versatile difluoromethyl-1-ene sugars as precursors for a range of biological analogues as illustrated in the present context by reduction to the difluoromethyl *C*-glycosides.

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