Pergamon

Tetrahedron Letters, Vol. 37, No. 34, pp. 6115-6116, 1996
Copyright © 1996 Published by Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01305-6

Mixed Organofluorine - Organosilicon Chemistry.
6. Synthesis of gem-difluoro-*C*-glycosides and *C*-disaccharides from Acylsilanes and Trifluoromethyltrimethylsilane. An Exploratory Study.

Thierry Brigaud, Olivier Lefebvre, Richard Plantier-Royon and Charles Portella*

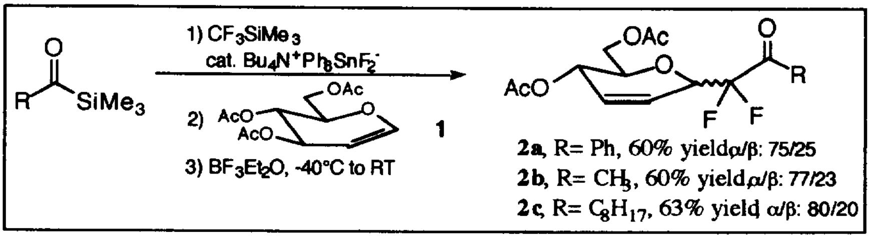
Laboratoire des Réarrangements Thermiques et Photochimiques. Associé au CNRS.
U.F.R. Sciences Exactes et Naturelles, B.P. 1039, 51687 Reims Cedex 2

Abstract: Difluoroenoxysilanes, prepared from acylsilanes and trifluoromethyltrimethylsilane under fluoride activation, were glycosylated by glucal to yield *C*-difluoroglycosides with a difluoromethylene group in place of the anomeric oxygen. Application of this methodology to a xylose-derived acylsilane led to a *C*-difluorodisaccharide. Copyright © 1996 Published by Elsevier Science Ltd

C-Glycosides are compounds of considerable interest in chemistry and biochemistry, and numerous methods have been proposed for their synthesis.[1] Moreover, the number of biologically-active, fluorine-containing compounds used in agricultural, pharmaceutical and enzyme chemistry is increasing.[2] Often, a fluorine atom or a difluoromethylene group is introduced in place of a hydroxyl group or an oxygen atom, respectively, in order to mimic the polarity as well as the hydrogen bond acceptor ability of oxygen. While many of fluorinated sugars have been reported in the literature,[3] only one research group has recently undertaken the synthesis of gem-difluoro-*C*-glycosides with the difluoromethylene group in place of the anomeric oxygen.[4] The later synthesis was achieved by radical addition on a 1-difluoromethylene sugar derived from the corresponding aldonolactone.[5]

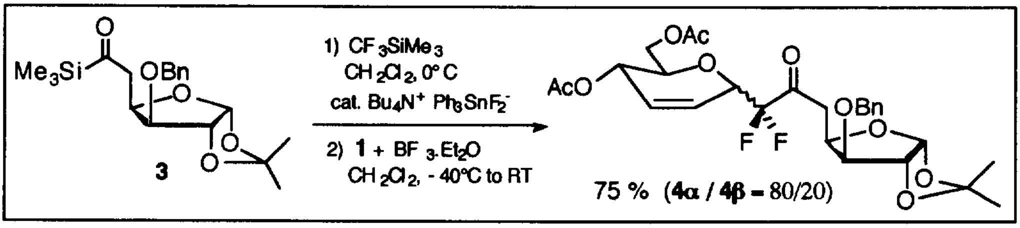
We have recently reported an effective synthesis of difluoroenoxysilanes from acylsilanes and trifluoromethyltrimethylsilane (TFMTMS) and preliminary results about their use in one-pot reactions such as alkylation or aldol reactions.[6] Since enoxysilanes can undergo C-C bond formation with activated glycosyl donors,[1] we have examined the glycosylation of difluoroenoxysilanes in order to have access to difluoro-*C*-glycosides. We report our preliminary results in this paper.

We focussed our attention on tri-*O*-acetyl-D-glucal **1** as the glycosyl donor. Good yields of 2,3-unsaturated-*C*-difluoroglucosides **2**[7] were achieved in the one-pot conditions described in the Scheme 1. Regardless of starting acylsilane, a mixture of diastereomers was obtained with a similar α/β ratio (determined by ^{19}F-NMR). In glycosylation reactions with **1**, the major isomer normally has the α-configuration. This was confirmed by NMR analysis,[8] since Fraser-Reid and co-workers have shown[9] that C-5 is more shielded in the major α-diastereomer. The configurations were also checked by NOE experiments. The two isomers of compound **2a** were separated by flash chromatography and irradiation of H-1 induced an enhancement of the H-5 signal in the minor isomer (8 % NOE) whereas no effect was observed on the major isomer. These observations are in accordance with the assigned configurations.



Scheme 1

Finally, we have applied the same methodology to a sugar-derived acylsilane in order to test the feasibility of the synthesis of gem-difluoro-*C*-disaccharides. The acylsilane **3**, prepared from a selectively protected xylose derivative,[10] was converted into the corresponding difluoroenoxysilane by reaction with TFMTMS[6] in dichloromethane. This solution was added to a dichloromethane solution of **1** activated with $BF_3.OEt_2$ (Scheme 2). A high yield of the disaccharide type difluoroderivative **4** was obtained, as an 80/20 mixture of α and β isomers. Compounds **4α** and **4β** were separated by HPLC on silical gel and were fully characterized by NMR and analysis. Their relative configurations were established by analogy with compounds **2**.[8]



Scheme 2

These preliminary results provide a good illustration of the usefulness of acylsilanes and difluoroenoxysilanes in sugar chemistry. Assessment of the scope and limitations of this methodology requires further study with other acylsilanes, other glycosyl donors and different reaction conditions. The synthesis of difluoro-*C*-disaccharides will be a particular focus of this work.

Acknowledgments We thank the "Ministère de la Recherche et de l'Enseignement Supérieur" for a doctoral fellowship (O.L.).

References and Notes

1/ Postema, M.H.D. *Tetrahedron* **1992**, *48*, 8545-8599.
2/ Welch, J.T., Eswarakrishnan, S.*Fluorine in Bioorganic Chemistry*; J. Wiley and Sons, 1991.
3/ Taylor, N.F. *Fluorinated carbohydrates: Chemical and Biochemical Aspects;* A.C.S. Symposium Series N° 374, Washington D. C., 1988.
4/ Houlton, J.S.; Motherwell, W.B.; Ross, B.C. ;Tozer, M.J.; Williams, D.J.; Slawin, A.M.J. *Tetrahedron*, **1993**, *49*, 8087-8106.
5/ Herpin, T.F.; Motherwell, W.B.; Tozer, M.J. *Tetrahedron: Asymmetry*, **1994**, *5*, 2269-2282.
6/ Brigaud, T.; Doussot, P.; Portella, C. *J. Chem. Soc. Chem. Commun.*, **1994**, 2117-2118.
7/ All new compounds gave satisfactory microanalysis.
8/ Selected data: **2cα** $[\alpha]^{23}_D$ ($CHCl_3$)= + 74 (c 1.00); ^{19}F-NMR -110.4 (d, J 267 Hz), -121.6 (dd, J 267 and 22Hz); ^{13}C-NMR (glucal moiety) 71.4 (C-5), 71 (C-1). **2cβ** $[\alpha]^{23}_D$ ($CHCl_3$)= + 29 (c 0.30); ^{19}F-NMR -114.2 (d, J 261 Hz), -124.4 (dd, J 261 and 15 Hz); ^{13}C-NMR (glucal moiety) 74.1 (C-5), 74.6 (C-1). **4α** $[\alpha]^{23}_D$ ($CHCl_3$)= + 24 (c 0.36); ^{19}F-NMR -111.1 (dd, J 264 and 5 Hz), -120.7 (dd, J 264 and 21Hz); ^{13}C-NMR (glucal moiety) 71.5 (C-5), 70.9 (C-1). **4β** $[\alpha]^{23}_D$ ($CHCl_3$)= –13 (c 0.30); ^{19}F-NMR -113.9 (dd, J 263 and 5 Hz), -125.4 (dd, J 263 and 17Hz); ^{13}C-NMR (glucal moiety) 74.1 (C-5), 74.4 (C-1).
9/ Dave, D.R.; Fraser-Reid, B. *J.Org. Chem.* **1984**, *49*, 522-528.
10/ Plantier-Royon, R.; Portella, C. *Tetrahedron Lett.*, preceeding paper.

(*Received in France* 25 *March* 1996; *accepted* 1 *July* 1996)