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Regioselective Opening of Epoxyaldonolactones to Fluorodeoxyaldonolactones Using Tetrabutylammonium Dihydrogentrifluoride

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Abstract. A study on the hydrofluorination of epoxyaldonolactones with $Bu_4N^+H_2F_3^-$ (**1**) under solid-liquid PTC and homogeneous conditions has been performed. Unsubstituted 5,6-epoxy-hexono-1,4-lactones **2a** give the corresponding fluorohydrins in high yield using catalytic amounts of **1** and an excess of solid KHF_2, while an equimolar amount of **1** is used with 2,3-epoxyaldonolactones **2d-g** and 5,6-epoxy-hexono-1,4-lactones containing a free hydroxy group **2b,c**. In all cases the reaction is completely regio- and stereoselective affording 6-deoxy-6-fluoro-hexonolactones **3a,b** and 2-deoxy-2-fluoro-aldonolactones **3d,f**.

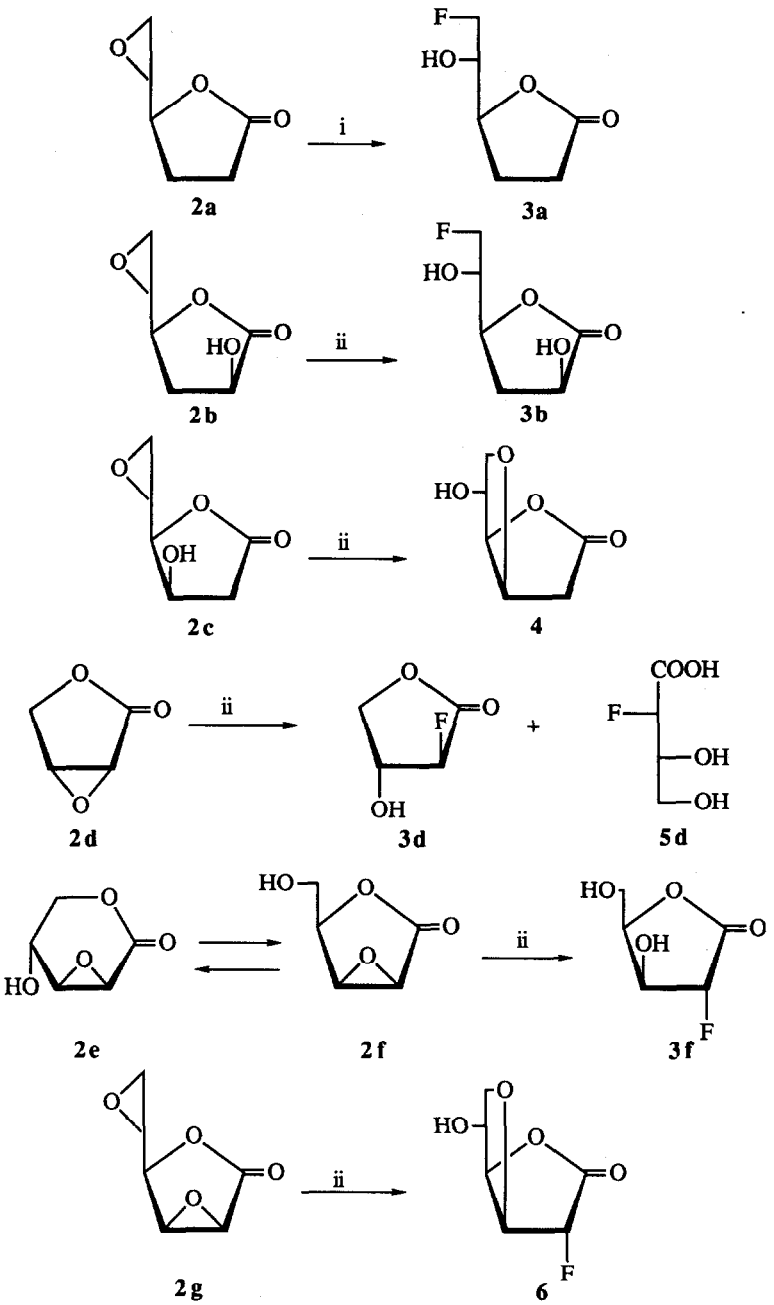
In a previous paper we have reported on the opening of 2,3-epoxy-aldonolactones with triethylamine trishydrogenfluoride to give 2-deoxy-2-fluoro-aldonolactones stereospecifically and in good yields (57-69%).[1] Long reaction times and the use of a large excess of corrosive hydrofluorinating agent represent limitations to this process. In order to overcome these drawbacks we decided to investigate the reaction of epoxy-aldonolactones with tetrabutylammonium dihydrogentrifluoride, $Bu_4N^+H_2F_3^-$ (**1**).

Previously, we have shown that **1** is an excellent source of hydrogen fluoride which is non-corrosive, easy to prepare and to handle, and which, avoiding moisture, can be employed in normal pyrex flasks also at relatively high temperature.[2,3] Moreover, we found that, differently from many HF/amine adducts, **1** can be used in catalytic amounts in the presence of molar excess of solid potassium hydrogendifluoride under solid-liquid phase transfer (SL-PTC) conditions,[2,3] in regioselective hydrofluorinations of many epoxyderivatives, *e.g.* *O*-protected glycidols.

In the present paper we report a systematic study of the reaction of **1** with a series of epoxylactones having 5,6- and/or a 2,3-epoxy function **2a-g**. These epoxylactones, readily prepared from bromodeoxylactones[1,4] are chiral substrates, which, by reaction with **1**, could lead to fluorodeoxylactones.

These can be converted into fluorodeoxy-sugars or alditols, compounds being highly interesting in a biological context.[5]

Scheme 1



i **2** (1 mol), **1** (0.1 mol), KHF_2 (2 mol), 75°C, 24-39h, 25-70%
ii **2** (1 mol), **1** (1 mol), 75°C, 6-63h, 10-65%

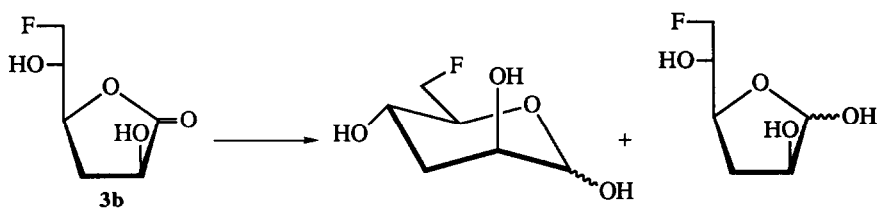
RESULTS AND DISCUSSION

Typically[3] the hydrofluorinations were performed under SL-PTC conditions, by stirring at 75°C a heterogeneous mixture of the epoxylactone **2** (1 mol), the PTC agent **1** (0.1 mol) and solid KHF_2 (2 mol) without any solvent until complete disappearance of the substrate (TLC and/or NMR analyses). Under the above conditions (Scheme 1) 2,3-dideoxy-5,6-epoxy-**D**-*erythro*-hexono-1,4-lactone (**2a**) reacted in 39h affording exclusively the 2,3,6-trideoxy-6-fluoro-**D**-*erythro*-hexono-1,4-lactone (**3a**) (70%), by regioselective attack by F^- at the less substituted epoxidic carbon atom.

In the case of the other derivatives, **2b-g**, the catalytic process gave scarse results, and therefore an equimolar amount of hydrofluorinating agent **1** was used in the absence of KHF_2. Under these reaction conditions 3-deoxy-5,6-epoxy-**D**-*arabino*-hexono-1,4 lactone (**2b**) afforded 65% of 3,6-dideoxy-6-fluoro-**D**-*arabino*-hexono-1,4 lactone (**3b**). Under SL-PTC conditions only 17% of **3b** and 8% of its C-2 epimer **3'b** (^1H, ^{13}C and ^{19}F NMR analyses)[6] were isolated from **2b** as a mixture, together with the corresponding fluoro-acids.[6]

The structure of **3b** was prooved by reduction of the lactone[7] to the corresponding sugar with bis-(3-methyl-2-butyl)-borane (disiamylborane)[8] (Scheme 2). Thus, investigating the anomeric region in the ^1H and ^{13}C NMR spectra of the sugar, consisting of the α/β-furanoses and the α/β pyranoses, it was shown

Scheme 2



that the H-2 proton was equatorially oriented in the latter.

Reaction of 2,3-anhydro-**D**-erythrono-1,4-lactone (**2d**) with stoichiometric quantity of **1** for 6h at 75°C gave the 2-deoxy-2-fluoro-**D**-threono-1,4-lactone (**3d**) in 35% yield, together with minor amounts of the open fluoroacid **5d** and some hydrolysis products.[9] Similarly, 2,3-epoxy-**D**-lyxonolactone, consisting of a mixture of the δ- and γ-lactones **2e,f**, afforded in 69h equal amounts of the 2-deoxy-2-fluoro-**D**-xylonolactone (**3f**)[1] (25%) and the fluoroacid (25%). Under the same conditions, the conversion of 2,3-5,6-diepoxy-**D**-mannono-1,4-lactone (**2g**) was complete in 7h, but only 10% of the 3,6-anhydro-2-fluoro-1,4-lactone (**6**) could be isolated from the complex reaction mixture, the remainder being polymeric materials and tars.

Treatment of 2-deoxy-5,6-epoxy-**D**-*arabino*-hexonolactone (**2c**) under both SL-PTC conditions and with equimolar amount of **1**, gave a complex mixture, from which a 3,6-anhydro-lactone **4** could be isolated in low yield. The product was not further investigated, but the ^{13}C NMR spectrum indicated the presence of a 3,6-anhydro-lactone, similar to those prepared by Jäger[10] and Vekemans.[11]

From the results above, it was shown that $Bu_4N^+H_2F_3^-$ (**1**) can open the oxirane ring in 2,3-dideoxy-5,6-epoxylactones such as **2a** regio- and stereo-selectively at the less substituted carbon atom, using only a

catalytic amount of **1**. When the lactone had a hydroxy group at C-2 (**2b**), however, an equimolar amount of **1** was needed to give the 6-deoxy-6-fluoro-lactone **3b** in good yield. Furthermore, if the lactone had a hydroxy group at C-3, a 3,6-anhydrolactone was formed. Opening of a secondary epoxide, as in the 2,3-epoxylactones, with **1**, gave the 2-deoxy-2-fluoro-lactones/acids in acceptable yields, although these were somewhat lower than we found when using triethylamine trishydrogenfluoride.[1] The reaction conditions using **1** was 75°C for about 1 day, while $Et_3N{\cdot}3HF$ afforded a reaction time at 70°C of 3 to 13 days for **2d** and **2e,f**, respectively. $Bu_4N^+H_2F_3^-$ (**1**) is probably a more acidic reagent than $Et_3N{\cdot}3HF$, which causes problems when free hydroxy groups are present in the molecules as we observed also with unprotected glycidol.[3]

Acknowledgements

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EXPERIMENTAL

The starting epoxylactones are known compounds and were prepared according to literature methods: **2a,c,g**,[4] **2b**[12] and **2d-f**.[1] Tetrabutylammonium dihydrogentrifluoride (**1**) was synthesized from the corresponding hydrogensulphate, as previously reported.[13] NMR spectra were recorded on Bruker AC-250, AC-300 and AM-500 instruments. The internal reference for spectra in $CDCl_3$ was $CDCl_3$ (δ= 76.9) for ^{13}C NMR spectra and $CHCl_3$ (δ= 7.28) for ^1H NMR spectra; for spectra in acetone-d_6 it was acetone-d_6 (δ= 29.8) for ^{13}C NMR and acetone (δ= 2.05) for ^1H NMR spectra. The external reference for ^{19}F NMR spectra was $CFCl_3$ (δ= 0.00). The coupling costants are in Hertz. Samples of the reaction mixtures were investigated directly by ^{13}C NMR spectroscopy.

Spots were visualized on TLC either by charring with H_2SO_4 or by the NH_2OH/Fe^{3+} reagent.[14] Column chromatography was performed on silica gel (40-63mm, Merck 9385) using the flash technique. Evaporations were performed *in vacuo* at 40°C. Microanalyses were performed by Leo Microanalytical Laboratory. Optical rotations were measured with a Perkin-Elmer 241 instrument.

General Method for the Preparation of Fluorohydrins

Method A: a mixture of the epoxylactone **2** (1 mmol) and tetrabutylammonium dihydrogentrifluoride (**1**) (1 mmol) was stirred at 75°C until the starting material was no longer detectable (NMR and/or TLC analyses). The fluorohydrins were purified by column chromatography.

Method B: The epoxylactone **2** (1 mmol) was treated with a catalytic amount of **1** (0.1 mmol) in the presence of an excess of solid KHF_2 (2 mmol) until no more starting material could be detected. After cooling, the reaction mixture was diluted with acetone (20 ml), filtered on celite and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography. Starting epoxylactone, reaction time, chromatographic eluant, yield and spectroscopic and analytical data of fluorohydrins are given below.

2,3,6-Trideoxy-6-fluoro-D-erythro-*hexono-1,4-lactone (3 a)*. 5,6-Anhydro-2,3-dideoxy-D-*erythro*-hexono-1,4-lactone (**2a**);[4] method B; 39h; EtOAc-hexane, 2:1; 70%; $[\alpha]_D$= +11.3° (c. 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$): δ, 5.03 (ddd, 1H, $J_{5,6}$ 4.4, $J_{6,6'}$ 9,8, $J_{6,F}$ 47.0, H-6), 4.52 (m, 1H, H-4), 4.48 (ddd, 1H, $J_{5,6'}$ 5.0, $J_{6,F}$ 47.0, H-6) , 4.04 (dq, 1H, $J_{5,F}$ 19.2, $J_{H,H}$ 4.8, H-5), 3.16 (bs, 1H, OH), 2.54 (m, 2H, H-3, H-3'), 2.28 (m, 2H, H-2, H-2'). ^{13}C NMR ($CDCl_3$): δ, 177.5 (s, C-1), 83.2 (d, C-6, $J_{6,F}$ 170.0), 79.1 (d, C-4, $J_{4,F}$ 5.9), 70.4 (d, C-5, $J_{5,F}$ 19.6), 28.1 (s, C-2), 22.4 (s, C-3); ^{19}F NMR ($CDCl_3$): δ -230.62 (dt, $^2J_{H,F}$ 47.6, $^3J_{HF}$ 16.8). *Anal. Calc.* for $C_6H_9FO_3$: C, 48.65; H, 6.12; *Anal. Found* : C, 48.75; H, 6.23.

3,6-Dideoxy-6-fluoro-D-arabino-*hexono-1,4-lactone (3b).* 5,6-Anhydro-3-deoxy-D-*arabino*-hexono-1,4-lactone (**2b**);[12] method A; 24h; EtOAc-hexane, 4:1; 65%; $[\alpha]_D$= -4.6° (c. 2.5, acetone). ^1H NMR (acetone-d_6): δ, 4.98 (d, 1H, J_{HH} 5.4, OH), 4.85 (d, 1H, J_{HH} 5.4, OH), 4.7-4.3 (m, 4H), 4.04 (dq, 1H, J_{HH} 4.6, $J_{5,F}$ 21.6, H-5), 2.63 (m, 1H), 2.18 (m, 1H); ^{13}C NMR (acetone-d_6): δ, 176.8 (s, C-1), 84.6 (d, C-6, $J_{6,F}$ 169.5), 75.7 (d, C-4, $J_{4,F}$ 7.4), 71.1 (d, C-5, $J_{5,F}$ 19.0), 68.5 (s, C-2), 33.2 (s, C-3); ^{19}F NMR (acetone-d_6): δ, -225.10 (dt, $^2J_{H,F}$ 46.0, $^3J_{H,F}$ 22.9). *Anal. Calc.* for $C_6H_9FO_4$: C, 43.90; H, 5.54; *Anal. Found* : C, 43.62; H, 5.60.

3,6-Anhydro-2-deoxy-D-arabino-*hexono-1,4-lactone (4).* 2-Deoxy-5,6-epoxy-D-*arabino*-hexonolactone (**2c**); method B; 21h: EtOAc:hexane, 2:1; 10%; ^{13}C NMR ($CDCl_3$): δ, 175.8 (s, C-1), 88.2 (s, C-4), 76.8 (s, C-3), 74.3 (s, C-6), 73.4 (s, C-5), 35.7 (s, C-2).

2-Deoxy-2-fluoro-D-threono-1,4-lactone (3d) and -threonic acid (5d). 2,3-Anhydro-D-erythronolactone (**2d**);[1] method A; 6h; EtOAc:hexane, 4:1; 35%; ^1H and ^{13}C NMR spectra were in accordance with those published.[1] ^{19}F NMR of **3d** ($CDCl_3$): δ, -198.05 (dd, $^2J_{H,F}$ 51.1, $^3J_{H,F}$ 16.9).

2-Deoxy-2-fluoro-D-xylono-1,4-lactone (3f). 2,3-Anhydro-D-lyxono-1,5 (**2e**) and -1,4-lactone (**2f**); method A; 63h; 25%; EtOAc:hexane, 4:1; ^1H and ^{13}C NMR spectra were in accordance with those published.[1] ^{19}F NMR (acetone-d_6): δ, -190.14 (dd, $^2J_{H,F}$ 53.9, $^3J_{H,F}$ 20.9).

3,6-Anhydro-2-deoxy-2-fluoro-D-glucono-1,4-lactone (6). 2,3:5,6-Dianhydro-D-mannono-1,4-lactone (**2g**); method A; 8h; EtOAc-hexane, 4:1; 10%. ^1H NMR (acetone-d_6): δ, 5.36 (dd, 1H, $^2J_{H,F}$ 50.9, $J_{H,H}$ 4.13), 5.33 (dd, 1H, $J_{H,H}$ 7.81, $J_{H,H}$ 4.44), 4.97 (ddd, 1H, $^3J_{H,F}$ 20.5, $J_{H,H}$ 7.82, $J_{H,H}$ 4.14), 4.59 (m, 1H), 4.13 (m, 2H); ^{13}C NMR (acetone-d_6): δ, 170.8 (d, C-1, $J_{1,F}$ 27.0), 91.3 (d, C-2, $J_{2,F}$ 191.0), 80.9 (d, C-3, $J_{3,F}$ 24.6), 80.6 (d, C-4, $J_{4,F}$ 5.8), 74.8 (s, C-6), 69.2 (s, C-5); ^{19}F NMR (acetone-d_6): δ, -189.30 (dd, $^2J_{HF}$ 50.0, $^3J_{HF}$ 19.8).

Reduction of 3b. A THF solution of borane-dimethyl sulfide complex (3.25 mmol, 1.63 ml) was cooled in ice and stirred under argon while 2-methyl-2-butene/THF (6.5 mmol, 3.25 ml) was added and then kept for 5h at room temperature. The resulting solution of disiamylborane[7,8] was cooled in ice and stirred, and a

solution of **3b** (0.65 mmol, 107 mg) in THF (1 ml) was added and the solution was kept at room temperature for 16h. Water (5 ml) was added and the mixture was boiled under reflux for 1h, and then reduced to half volume. More water was added and the mixture was extracted three times with dichloromethane to remove borinic acids. The acqueous phase was concentrated to give 73 mg of a mixture of pyranoses and furanoses in the ratio *ca* 3:1. Analysis of the anomeric region was as follows: ^{1}H NMR (D_2O): δ, 5.23 (H-1, $J_{1,2}$ 0.5, β-fu), 4.98 (H-1, $J_{1,2}$ 0.5, α-py), 4.86 (H-1, $J_{1,2}$ 1.0, β-py). ^{13}C NMR (D_2O): δ, 101.7 (C-1, J_{CH} 172.6, β-fu), 94.9 (C-1, J_{CH} 171.8, α-fu), 94.3 (C-1, J_{CH} 160.8, β-py), 92.4 (C-1, J_{CH} 169.4, α-py).[15]

REFERENCES AND NOTES

1. Bols, M.; Lundt, I. *Acta Chem. Scand.* **1990**, *44*, 252-256.
2. Landini, D.; Penso, M. *Tetrahedron Lett.* **1990**, *31*, 7209-7212.
3. Landini, D.; Albanese, D.; Penso, M. *Tetrahedron* **1992**, *48*, 4163-4170.
4. Lundt, I.; Pedersen, C. *Synthesis* **1992**, 669-672.
5. (a) Welch, J.T. *Tetrahedron* **1987**, *43*, 3123-3197. (b) Mann, J. *Chem. Soc. Rev.* **1987**, *16*, 381-436. (c) Card, P.J. *J. Carbohydr. Chem.* **1985**, *4*, 451-487.
6. The mixture of fluoroacids was not separated but identified by NMR analysis. **3'b**: ^{1}H NMR (acetone-d_6): δ, 5.0 (d, 1H, J_{HH} 5.3, OH), 4.9 (d, 1H, J_{HH} 5.5, OH), 4.7-4.4 (m, 4H, $J_{6,F}$ 47.6, H-2, H-4, H-6, H-6'), 4.0 (dq, 1H, J_{HH} 5.1, $J_{5,F}$ 19.9), 2.6 (ddd, 1H, J_{HH} 3.2, 8.5, 13.1, H-3), 2.2 (dt, 1H, J_{HH} 8.0, 8.0, 13.1, H-3'). ^{13}C NMR (acetone-d_6): δ, 177.4 (s, C-1), 84.7 (d, C-6, $J_{6,F}$ 169.1), 77.2 (d, C-4, $J_{4,F}$ 6.3), 71.4 (d, C-5, $J_{5,F}$ 19.0), 67.2 (s, C-2), 32.2 (s, C-3). ^{19}F NMR (acetone-d_6): δ, -224.5 (dt, $^2J_{HF}$ 46.6, $^3J_{HF}$ 19.1).
7. Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1981**, *90*, 7-16.
8. Brown, H.C.; Mandal, A.K.; Kulharni, S.U. *J. Org. Chem.* **1977**, *42*, 1392-1398.
9. Previously we have treated the enantiomer of **2d** with triethylamine trishydrogenfluoride to give 2-deoxy-2-fluoro- L-threono-lactone (**L-2d**) in 57% yield after 3 days.[1]
10. Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108-1118.
11. Vekemans, J.A.J.M.; Dapperns, C.W.M.; Classen, R.; Koten, A.M.J.; Godefroi, E.F.; Chittenden, G.J.F. *J. Org. Chem.* **1990**, *55*, 5336-5344.
12. Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand.* **1986**, *B 40*, 163-171.
13. Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953-955.
14. (a) Stahl, E. Thin Layer Chromatography, Springer Verlag, Berlin 1969. (b) Whittaker, V.P. and Wijesundera, S. *Biochem. J.* **1952**, *51*, 348-357.
15. Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans.2* **1974**, 293-297.