Reaction of Epoxyaldonolactones with HF–Amine Complexes

Josef Jünnemann, Inge Lundt, and Joachim Thiern

Department of Organic Chemistry, The Technical University of Denmark, DK-2800 Lyngby, Denmark and Institut für Organische Chemie, Universität Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany


The opening of 2,3-epoxyaldonolactones with trialkylamine-3HF gave 2-deoxy-2-fluoroaldonolactones regio- and stereo-selectively, while collidine-3HF gave a mixture of 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-lactones in a 2:1 ratio. Pyridine 3HF and Ohali’s reagent gave complex mixtures. 5,6-Epoxyhexonolactones were opened exclusively at C-6, using the tri(hydrogen fluoride) complex of either triethylamine, collidine or pyridine. The following fluoroaldonolactones were prepared: 6-bromo-2,6-dideoxy-2-fluoro-D-glucose-1,4-lactone (5), 2,3,6-trideoxy-6-fluoro-1,4-lactone (12), 2,6-dideoxy-6-fluoro-1,4-lactone (13) and 3,6-dideoxy-6-fluoro-D-arabinohexono-1,4-lactone (14), together with the following fluoro deoxy sugars: 1,3,4,tri-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-D-glucopyranose (7), 1,2,4-tri-O-acetyl-6-bromo-3,6-dideoxy-3-fluoro-D-altropyranose (8), 1,4-di-O-acetyl-2,3,6-trideoxy-6-fluoro-D-erythro-hexopyranose (15), 1,3,4-tri-O-acetyl-2,6-dideoxy-6-fluoro-D-arabinohexopyranose (16) and 1,2,4-tri-O-acetyl-3,6-dideoxy-D-arabinohexopyranose (17).

Fluorinated carbohydrates have gained much importance for the evaluation of biochemical mechanisms, and thus the synthesis of such compounds is of great interest.1–3 The most commonly used method is the nucleophilic displacement of an activated hydroxy group,4 but, owing to the low nucleophilicity and high basicity of the fluoride ion,5 side reactions may occur. A different method is the opening of epoxides with fluoride ions.1,3,4 The regioselectivity of this reaction is dependent upon the structure and the reactivity of the sugar, as well as the type of the fluorinating reagent.

Since we have recently described a convenient method for the preparation of epoxyaldonolactones from bro-mo(oxy)aldonolactones,5 we decided to continue our study6 on the opening of such epoxyaldonolactones with HF-reagents. Previously, we have shown6 that 2,3-anhydrotetrono- and -pentono-lactones yielded 2-fluoro-2-deoxyaldonolactones when treated with triethylamine – tri(hydrogen fluoride). A similar regioselective opening of these epoxides was observed when tetrabutylammonium dihydrogenfluoride was used as the fluorinating agent.7 On the other hand, Ourari et al.8 have observed that glyceral esters, on reaction with HF–pyridine (Olali’s reagent, 70% HF) gave only β-fluoro-α-hydroxy esters. In order to investigate whether this difference in regioselectivity could be observed in epoxyaldonolactones, as a model compound, the opening of the 2,3-anhydro-1-erythro-1,4-lactone (1) with different HF–amine complexes was studied. The Et3N⋅3HF and the HF–pyridine complexes were chosen first, since they are both commercially available and easy to handle.

Results and discussion

The epoxyaldonolactone 1 was reacted with Et3N⋅3HF at 70°C as described previously,6 but this time the reaction time was determined more accurately (Scheme 1). Samples of the reaction mixture were checked at intervals by running

**Scheme 1.**

<table>
<thead>
<tr>
<th>Reaction time/temperature</th>
<th>Reagent</th>
<th>Product ratio (2:3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 d/70°C</td>
<td>Et3N⋅3HF</td>
<td>1:0</td>
</tr>
<tr>
<td>3 d/70°C</td>
<td>Oct3N⋅3HF</td>
<td>1:0</td>
</tr>
<tr>
<td>1 d/70°C</td>
<td>Olali’s reagent</td>
<td>destruction</td>
</tr>
<tr>
<td>3 d/30°C</td>
<td>Olali’s reagent</td>
<td>destruction</td>
</tr>
<tr>
<td>3 d/70°C</td>
<td>pyridine⋅3HF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>6 d/70°C</td>
<td>collidine⋅3HF</td>
<td>2:1</td>
</tr>
</tbody>
</table>

* To whom correspondence should be addressed.
Jünnemann

\[ \text{Reaction time} \quad \text{Reagent} \quad \text{Yield/product ratio} \\\n\begin{array}{ccc}
(70^\circ C) & 5 & 6 \\
3 \text{ d} & \text{Et}_3\text{N} \cdot 3\text{HF} & 68\% \quad 2:1 \\
3 \text{ d} & \text{collidine} \cdot 3\text{HF} & \\
\end{array} \]

Scheme 2.

$^{13}$C NMR spectra. After 3 days the 2-fluoro-lactone 2$^a$ was formed exclusively. With Olah’s reagent (HF--pyridine 7:3) at the same temperature, the reaction proceeded much faster, and the epoxy signals had disappeared within one day. However, the expected signals around 90 ppm in the $^{13}$C NMR spectrum, corresponding to a fluorine-substituted carbon of the minor compound, could only just be detected. More prominent signals were detected at 110–115 ppm for the major constituents, presumably arising from elimination products. Similarly, use of Olah’s reagent for 3 days at only 30°C resulted in the destruction of 1. These results were somewhat surprising when compared with the literature.$^8$

In order to use milder conditions, 1 was treated with mixtures of 3 equiv. HF and 1 equiv. of pyridine, collidine or trietylamine. With the octylamine complex only the 2-fluoro compound 2 was formed. With the aromatic amines, both hydrofluorinating agents led to a mixture of the 2-fluoro- and 3-fluoro-lactones, 2 and 3, with the 3-fluoro compound as the minor product. Varying the ratio HF:amine led in all cases to smaller yields owing to an increase in side reactions. Thus, the regioselective opening at C-2 of a 2,3-epoxy-1,4-lactone was obtained when trialkylamine 3HF complexes were used, while the 2,4,6-trimethylpyridine (collidine)-3HF complex gave a mixture of the 2-fluoro- and 3-fluoro-lactones, with the 2-fluoro-lactone as the predominant product. In no cases was the sole regioselective opening at C-3 observed.

Based on these results, the opening of the 2,3-anhydro-6-bromo-6-deoxy-D-mannono-1,4-lactone (4)$^1$ was investigated (Scheme 2). Reaction of 4 with Et$_3$N·3HF gave exclusively the 2-fluorolactone 5, isolated in 68% yield, whereas with collidine·3HF an inseparable mixture of predominantly the 2-fluorolactone 5 and the 3-fluorolactone 6 was obtained. Reduction of 5 or of the mixture 5 + 6 with bis (3-methyl-2-butyl)borane (disiamylborane)$^9$ gave the corresponding sugar derivatives. After acetylation and purification by chromatography, the structures were proved by $^1$H and $^{13}$C NMR spectroscopy to be acetylated 6-bromo-2,6-dideoxy-2-fluoro-D-glucopyranose (7) and 6-bromo-3,6-dideoxy-3-fluoro-D-altro-pyranose derivatives (8), respectively.

The regioselectivity of the opening of primary epoxy-lactones by amine-HF complexes was further investigated with the three 5,6-epoxymethylactones 9.$^9$10.$^5$ and 11.$^10$ (Scheme 3). By reaction with the tris(hydrogen fluoride) complex of either triethylamine, collidine or pyridine, in all cases the 6-fluoro-6-deoxylactones 12, 13 and 14, respectively, were obtained. With tetrabutylammonium tris(hydrogen fluoride) as the reagent, the two lactones having a deoxy function at C-3, 9 and 11, reacted similarly, whereas the 2-deoxylactone 10, gave a complex mixture, from which a 3,6-anhydrofuranose derivative was isolated in low yield.$^7$ All the reactions were complete within one day as seen by $^{13}$C NMR spectroscopy. Only the pyridine-HF reagent gave rise to considerable amounts of by-products. After purification, the fluorolactones were reduced to the sugars with disiamylborane and isolated as the acetylated 6-fluoro-6-deoxy sugar derivatives 15, 16 and 17, respectively. Reaction of the 5,6-epoxylactones with Olah’s reagent (HF--pyridine 7:3) led

Scheme 3.

266
to complex mixtures, from which no fluoro-substituted lactones could be isolated.

Having shown that Et$_3$N·3HF opens both a 2,3- and 5,6-epoxy function in hexono-1,4-lactones regioselectively at C-2 and C-6, respectively, its behaviour towards 2,3-5,6-dianhydro-D-manno-1,4-lactone was investigated. The course of the reaction was monitored by $^{13}$C NMR spectroscopy and the signals from the exocyclic oxirane were seen to disappear first. However, no distinct fluoro-lactone could be obtained at any time and the final result was a complex mixture.

It may be assumed that the different behaviour of amine HF mixtures towards oxiranes is dependent upon the content of ‘free’ HF. Et$_3$N·3HF is a distillable complex with no excess of HF capable of acting as a source of nucleophilic fluoride, in contrast with the acidic Ohl’s reagent. The difference in the regioselectivity of trihydrogenflouride complexes of the aliphatic and aromatic amines cannot be interpreted at the moment.

In summary, it was shown that both Et$_3$N·3HF and Oct$_3$N·3HF regioselectively open 5,6-anhydrohexono-1,4-lactones to give 6-fluoro-6-deoxy-1,4-lactones, whereas 2,3-anhydrolactones yield 2-fluoro-2-deoxy-1,4-lactones exclusively. Attempts to obtain 3-fluoro-3-deoxy-1,4-lactones by opening the 2,3-lactones using Ohl’s reagent as described by Ourari for simple epoxy esters, led to complex mixtures. With milder reagents, such as aromatic amine·3HF, no regioselectivity was observed and mixtures of 2- and 3-fluoro-1,4-lactones were obtained.

**Experimental**

**General methods.** Optical rotations were determined on a Perkin Elmer 241 polarimeter. $^1$H NMR spectra were measured on Bruker M 270 and AC 250 spectrometers with SiMe$_4$ as an internal standard. Column chromatography was performed on silica gel (230–400 mesh, Merck 9835) using the flash technique. Spots were visualized on TLC by charring with H$_2$SO$_4$. Evaporations were performed in vacuo at 30°C.

3-Deoxy-3-fluoro-D-threono-1,4-lactone (3). 2,3-Anhydro-L-erythronolactone (1)$^9$ (1.0 g, 10.0 mmol) in trimethylpyridine–tris(hydrogen fluoride) (5 ml) was heated to 70°C in a polyethylene tube. After 3 days the mixture was cooled to room temperature, diluted with acetone (25 ml), filtered through silica, and concentrated. Purification by column chromatography yielded a mixture of 2 and 3. $^{13}$C NMR (CDCl$_3$): $\delta$ 170.5 (d, C-1, $J_{CF}$ 22.5 Hz), 90.9 (d, C-2, $J_{CF}$ 194 Hz), 70.8 (d, C-3, $J_{CF}$ 20.2 Hz), 69.0 (d, C-4, $J_{CF}$ 11.2 Hz). The spectrum was identical with that described.$^9$ 3: 169.5 (s, C-1), 89.4 (d, C-3, $J_{CF}$ 186.6 Hz), 78.4 (d, C-2, $J_{CF}$ 23.1 Hz), 67.4 (d, C-4, $J_{CF}$ 19.5 Hz).

6-Bromo-2,6-dideoxy-2-fluoro-D-glucono-1,4-lactone (5). A solution of 4$^2$ (1.0 g, 4.48 mmol) in Et$_3$N·3HF (5 ml) was heated to 70°C in a polyethylene tube for 3 days, then worked up as described above. The crude product was purified by column chromatography (toluene–EtOAc 2:1) to give 5 (0.74 g, 68%). $\left[\alpha\right]_D^{29}$ + 48.7$^\circ$ (c 0.3, EtOH). Anal. C$_9$H$_9$BrFO$_4$·C, H, Br. $^{13}$C NMR (CDCl$_3$): $\delta$ 170.3 (d, C-1, $J_{CF}$ 21.3 Hz), 91.5 (d, C-2, $J_{CF}$ 197.1 Hz), 80.5 (d, C-4, $J_{CF}$ 8.7 Hz), 70.5 (d, C-3, $J_{CF}$ 20.8 Hz), 69.3 (C-5), 38.6 (C-6).

6-Bromo-3,6-dideoxy-3-fluoro-D-altroono-1,4-lactone (6). The 6-bromo-2,3-epoxy lactone 4 (1.0 g, 4.48 mmol) was treated with trimethylpyridine·3HF as described above. Purification by chromatography (toluene–EtOAc 2:1) gave a mixture of 5 and 6 (0.78 g). $^{13}$C NMR (CDCl$_3$): $\delta$ 168.4 (s, C-1), 88.4 (d, C-3, $J_{CF}$ 198.5 Hz), 80.2 (d, C-4, $J_{CF}$ 23.5 Hz), 79.5 (d, C-2, $J_{CF}$ 22.1 Hz), 68.4 (C-5), 37.1 (C-6).

1,3,4-Tri-O-acetyl-6-bromo-2,6-dideoxy-2-fluoro-D-glucopyranose (7). A solution of disiamylborane$^2$ was prepared by adding 2-methyl-2-butenes (3 ml) to borane–dimethyl sulfide (1.4 ml) in THF (10 ml) under an N$_2$ atmosphere, keeping the mixture at room temperature for 5 h. Then 5 (200 mg, 0.82 mmol) in THF (5 ml) was added at 0°C, and the mixture was allowed to reach room temperature overnight. Water (10 ml) was then added and the mixture was refluxed for 1 h, concentrated to half its volume and extracted with CHCl$_3$ (3 x 20 ml). The aqueous phase was concentrated and co-evaporated three times with toluene. Then Ac$_2$O (10 ml) and 1 drop of aqueous HClO$_4$ (60%) were added. After completion of the reaction (TLC:toluene–EtOAc 3:1) the mixture was diluted with CHCl$_3$, washed with H$_2$O, dried (MgSO$_4$) and concentrated. Flash chromatography of the residue gave the α-anomer as a syrup (135 mg, 44%). $^1$H NMR (CDCl$_3$): $\delta$ 5.74 (dd, 1 H, J$_{2,3}$ 3.9, J$_{2F,3F}$ 1.0 Hz, H-3, 5.17 (m, 1 H, J$_{2,3}$ 9.6, J$_{3,4}$ 9.7, J$_{3F,4F}$ 12.7 Hz, H-3), 5.10 (m, 1 H, J$_{3,4}$ 9.7 Hz, H-4), 4.80 (ddd, 1 H, J$_{3,4}$ 49.3 Hz, H-3), 4.27 (ddd, 1 H, J$_{5,6a}$ 4.3, J$_{5,6b}$ 1.9 Hz, H-5), 3.59 (dd, J$_{6a,6b}$ 11.8 Hz, H-6a, 3.40 (dd, H-6b).

1,2,4-Tri-O-acetyl-6-bromo-3,6-dideoxy-3-fluoro-D-altro- pyranose (8). The mixture (500 mg) of 5 and 6 obtained from the reaction of 4 with trimethylpyridine·3HF, was reduced with disiamylborane as described above. Purification by flash chromatography (toluene–EtOAc 4:1) gave the α-anomer, 8 (43 mg) as an almost pure syrup. $^1$H NMR (CDCl$_3$): $\delta$ 5.71 (dd, 1 H, J$_{1,2}$ 1.3, J$_{1F}$ 4.6 Hz, H-1), 5.20 (ddd, 1 H, J$_{1,2}$ 2.4, J$_{1,3}$ 4.5, J$_{1F,2F}$ 49.5 Hz, H-3), 5.09 (ddd, 1 H, J$_{1,2}$ 10.2, J$_{1F}$ 24.5 Hz H-4), 4.24 (ddd, 1 H, J$_{1,2F}$ 10.1 Hz, H-2), 4.20 (m, 1 H, J$_{6a,6b}$ 3.4, J$_{5,6b}$ 4.6 Hz, H-5), 3.64 (dd, 1 H, J$_{6a,6b}$ 11.2 Hz, H-6a, 3.44 (dd, H-6b).

2,5,6-Trideoxy-6-fluoro-D-arabinono-hexono-1,4-lactone (12). The 5,6-anhydro-2,3-dideoxy lactone$^9$ (1.0 g, 7.75 mmol) was treated with Et$_3$N·3HF as described above. Purification by flash chromatography (toluene–EtOAc 1:1) gave 12 as a syrup (0.64 g, 55%). $\left[\alpha\right]_D^{29}$
+ 18.4° (c 0.4, EtOAc). Anal. C₅₀H₇₀FO₂; C, H, 13C NMR (CDCl₃): δ 177.3 (C-1), 82.3 (C, C-, J_CF = 169.9 Hz), 78.2 (C, C, J_CF = 5.6 Hz), 70.5 (C, C, J_CF = 20.5 Hz), 28.1, 22.5 (C-2, C-3).

2.6-Dideoxy-6-fluoro-D-arabino-hexono-1,4-lactone (13). The 5,6-anhydro-2-deoxy lactone 10⁵ (1.0 g, 6.94 mmol) was treated with Et₃N·3HF as described above. Purification by flash chromatography (toluene-EtOAc 1:1) gave 13 as a syrup (0.74 g, 65%), [α]D²⁰ = 21.6° (c 0.3, EtOAc). Anal. C₅₀H₇₀FO₂; C, H, 13C NMR (CDCl₃): δ 176.1 (C-1), 73.5 (C-3), 82.4 (C, C, J_CF = 178.6 Hz), 78.2 (C, C, J_CF = 7.8 Hz), 72.1 (C, C, J_CF = 22.9 Hz), 28.3 (C-2).

3.6-Dideoxy-6-fluoro-D-arabino-hexono-1,4-lactone (14). The 5,6-anhydro-3-deoxy lactone 11²⁰ (1.0 g, 6.94 mmol) was treated with Et₃N·3HF as described above. Purification by chromatography (toluene-EtOAc 2:1) gave 14 as a syrup (0.64 g, 56%), [α]D²⁰ = 12.9° (c 0.3, EtOAc). Anal. C₅₀H₇₀FO₂; C, H, 13C NMR (CDCl₃): δ 179.5 (C-1), 80.1 (C, C, J_CF = 164.8 Hz), 79.5 (C, C, J_CF = 8.5 Hz), 68.8 (C-2), 68.6 (C, C, J_CF = 21.0 Hz). 32.9 (C-3).

1.4-Di-O-acetyl-2,3,6-trideoxy-6-fluoro-D-erythro-hexopyranos (15). The 6-fluorolactone 12 (200 mg, 1.34 mmol) was reduced with disiamylborane and acetylated as described above. Purification by column chromatography (toluene-EtOAc) gave the acetylated sugar as an amorphous mixture (124 mg, 41%). H NMR (CDCl₃): δ 6.08 (m, J₁₂₂₃₂₄ = 3.4 Hz, H-1a), 5.78 (dd, J₁₈₂₅₉ = 9.8, J₁₈₃₈₄ = 2.5 Hz, H-1β), 5.05 (m, 1 H, J₃₄₄₅ = 9.7, J₃₄₅ = 4.9, J₄₅ = 9.6 Hz, H-4), 4.45 (m, 2 H, J₆₅ = 47.0 Hz, H₆₆, H-6b), 3.89 (ddd, 1 H, J₅₆₅ = 5.4, J₅₆₆ = 3.5, J₆₅ = 21.8 Hz, H-5), 2.28 (m, 1 H, H-2e), 2.24 (m, 1 H, H-3e), 1.98 (m, 2 H, H₃a, H-2a), 2.13, 2.08 (2 OAc).

1.3.4-Tri-O-acetyl-2,6-dideoxy-6-fluoro-D-arabino-hexopyranos (16). The 6-fluorolactone 13 (200 mg, 1.22 mmol) was reduced and worked up as described above to give the acetylated α,β-pyranoses 16 as a colorless syrup (186 mg, 56%). H NMR (CDCl₃): δ 6.10 (m, J₁₂₂₃₂₄ = 3.4, J₁₂₃₂₄ = 1.2 Hz, H-1a), 5.86 (dd, J₁₈₂₅₉ = 9.8, J₁₈₃₈₄ = 2.5 Hz, H-1β), 5.38 (m, J₃₄ = 9.6, J₄₅ = 9.6, H-1β), 5.12 (dd, H-2a), 5.30 (m, 1 H, J₃₄ = 11.1, J₃₅ = 5.4, H-3), 4.44-4.46 (m, 4 H, J₆₅ = 47.0 Hz, H₆₆, H-6b), 4.10 (m, J₆₅ = 4.5, J₆₆ = 3.7, J₆₅ = 23.1 Hz, H-5a), 3.85 (m, J₅₆ = 21.8 Hz, H-5b), 2.33 (m, 1 H, J₃₄ = 12.9 Hz, H-2e), 2.28 (m, H-2e), 1.97 (ddd, H-2a), 1.86 (ddd, H-2b), 2.10, 2.09, 2.07 (3 OAc).

1.2.4-Tri-O-acetyl-3,6-dideoxy-6-fluoro-D-arabino-hexopyranos (17). The 6-fluorolactone 14 (200 mg, 1.22 mmol) was reduced and acetylated as described above. Chromatographic purification (toluene-EtOAc) gave 17 (164 mg, 49%), as a syrup containing an excess of the α-acetate. H NMR (CDCl₃): δ 6.00 (m, J₁₂₂ = 1.1 Hz, H-1a), 5.92 (dd, J₁₂₂ = 2.2 Hz, H-1β), 5.24 (ddd, J₂₃ = 5.0, J₂₃ = 3.3 Hz, H-2β), 5.01 (m, 1 H, J₃₄ = 11.2, J₃₄ = 5.2, J₄₅ = 10.4 Hz, H-4), 4.99 (ddd, H-2a), 4.45 (ddd, 1 H, J₄₅ = 6.0, J₄₅ = 1.2, J₆₅ = 49.2 Hz, H-6a), 4.34 (ddd, 1 H, J₆₅ = 2.8 Hz, H-6b), 3.90 (ddd, 1 H, J₇₆ = 22.1 Hz, H-5), 2.20 (m, 1 H, H-3e), 1.97 (m, H-3a), 2.12, 2.11, 2.0 (3 OAc).

Acknowledgements. Support of this work by the Danish National Research Council, the Fonds der Chemischen Industrie and the NATO Science Programme including a travel allowance to J. J., are gratefully acknowledged.

References

Received September 24, 1993.