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Reaction of Epoxyaldonolactones with HF–Amine Complexes

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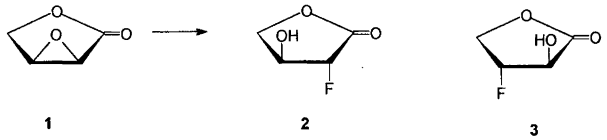
The opening of 2,3-epoxyaldonolactones with trialkylamine·3HF gave 2-deoxy-2-fluoroaldonolactones regio- and stereo-selectively, while collidine·3HF gave a mixture of 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-lactones in a 2:1 ratio. Pyridine·3HF and Olah's reagent gave complex mixtures. 5,6-Epoxyhexonolactones were opened exclusively at C-6, using the tris(hydrogen fluoride) complex of either triethylamine, collidine or pyridine. The following fluorolactones were prepared: 6-bromo-2,6-dideoxy-2-fluoro-D-glucono-1,4-lactone (**5**), 2,3,6-trideoxy-6-fluoro- (**12**), 2,6-dideoxy-6-fluoro- (**13**) and 3,6-dideoxy-6-fluoro-D-*arabino*-hexono-1,4-lactone (**14**), together with the following fluoro deoxy sugars: 1,3,4-tri-*O*-acetyl-6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranose (**7**), 1,2,4-tri-*O*-acetyl-6-bromo-3,6-dideoxy-3-fluoro-α-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-*arabino*-hexopyranose (**16**) and 1,2,4-tri-*O*-acetyl-3,6-dideoxy-6-fluoro-D-*arabino*-hexopyranose (**17**).

Fluorinated carbohydrates have gained much importance for the evaluation of biochemical mechanisms, and thus the synthesis of such compounds is of great interest.[1,2] The most commonly method used is the nucleophilic displacement of an activated hydroxy group,[3] but, owing to the low nucleophilicity and high basicity of the fluoride ion,[3] 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 bromodeoxyaldonolactones,[5] we decided to continue our study[6] on the opening of such epoxylactones with HF-reagents. Previously, we have shown[6] that 2,3-anhydrotetrono- and -pentono-lactones yielded 2-fluoro-2-deoxyaldonolactones when treated with triethylamine – tris(hydrogen fluoride). A similar regioselective opening of these epoxides was observed when tetrabutylammonium dihydrogentrifluoride was used as the fluorinating agent.[7] On the other hand, Ourari *et al.*[8] have observed that glycid esters, on reaction with HF–pyridine (Olah's reagent, 70% HF) gave only β-fluoro-α-hydroxy esters. In order to investigate whether this difference in regioselectivity could be obtained in epoxyaldonolactones, as a model compound, the opening of the 2,3-anhydro-L-erythrono-1,4-lactone (**1**) with different HF–amine complexes was studied. The $Et_3N·3HF$ and the HF–pyridine complexes were chosen first, since they are both commercially available and easy to handle.

Results and discussion

The epoxylactone **1** was reacted with $Et_3N·3HF$ 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



1 **2** **3**

Reaction time/temp.	Reagent	Product ratio (**2:3**)
3 d/70°C	$Et_3N·3HF$	1:0
3 d/70°C	$Oct_3N·3HF$	1:0
1 d/70°C	Olah's reagent	destruction
3 d/30°C	Olah's reagent	destruction
3 d/70°C	pyridine·3HF	complex mixture
6 d/70°C	collidine·3HF	2:1

Scheme 1.

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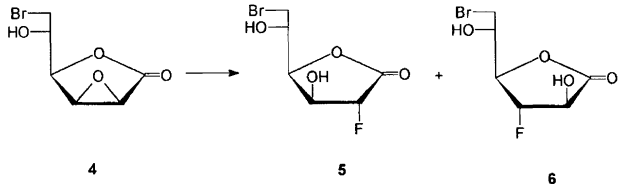
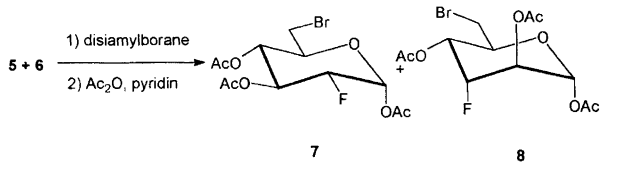


4 5 6

Reaction time	Reagent	Yield/product ratio	
(70°C)		5	6
3 d	$Et_3N \cdot 3HF$	68%	0
3 d	collidine · 3HF	2:1	



7 8

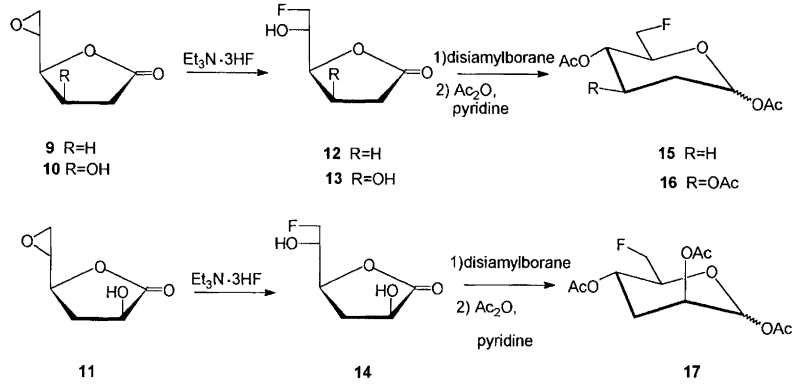
Scheme 2.

^{13}C NMR spectra. After 3 days the 2-fluoro-lactone **2**[6] 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 prominant 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 trioctylamine. 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 ration 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**)[5] was investigated (Scheme 2). Reaction of **4** with $Et_3N \cdot 3HF$ 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 ^1H and ^{13}C NMR spectroscopy to be acetylated 6-bromo-2,6-dideoxy-2-fluoro-α-D-glucopyranose (**7**) and 6-bromo-3,6-dideoxy-3-fluoro-α-D-altropyranose derivatives (**8**), respectively.

The regioselectivity of the opening of primary epoxylactones by amine·HF complexes was further investigated with the three 5,6-epoxyhexonolactones **9**,[5] **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.

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

Having shown that $Et_3N{\cdot}3HF$ 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-mannono-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 fluorolactone 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'. $Et_3N{\cdot}3HF$ is a distillable complex with no excess of HF[11] capable of acting as a source of nucleophilic fluoride, in contrast with the acidic Olah's reagent. The difference in the regioselectivity of trihydrogenfluoride complexes of the aliphatic and aromatic amines cannot be interpreted at the moment.

In summary, it was shown that both $Et_3N{\cdot}3HF$ and $Oct_3N{\cdot}3HF$ regioselectively open 5,6-anhydrohexono-1,4-lactones to give 6-fluoro-6-deoxylactones, whereas 2,3-anhydrolactones yield 2-fluoro-2-deoxylactones exclusively. Attempts to obtain 3-fluoro-3-deoxylactones by opening the 2,3-epoxylactones using Olah's reagent as described by Ourari for simple epoxy esters,[8] led to complex mixtures. With milder reagents, such as aromatic amine·3HF, no regioselectivity was observed and mixtures of 2- and 3-fluorolactones were obtained.

Experimental

General methods. Optical rotations were determined on a Perkin Elmer 241 polarimeter. ^1H 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_2SO_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**)[6] (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 ($CDCl_3$): **2**: δ 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.[6] **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**[5] (1.0 g, 4.48 mmol) in $Et_3N{\cdot}3HF$ (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%) as a syrup. $[\alpha]_D^{20}$ +48.7° (*c* 0.3, EtOAc). Anal. $C_6H_8BrFO_4$: C, H, Br. ^{13}C NMR ($CDCl_3$): δ 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-altrono-1,4-lactone (**6**).* The 6-bromo-2,3-epoxylactone **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 ($CDCl_3$) (**6**): δ 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-α-D-glucopyranose (**7**).* A solution of disiamylborane[9] was prepared by adding 2-methyl-2-butene (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 CH_2Cl_2 (3 × 20 ml). The aqueous phase was concentrated and co-evaporated three times with toluene. Then Ac_2O (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_2O, dried ($MgSO_4$) and concentrated. Flash chromatography of the residue gave the α-anomer **7** as a syrup (135 mg, 44%). ^1H NMR ($CDCl_3$): δ 5.74 (dd, 1 H, $J_{1,2}$ 3.9, $J_{1,F}$ 1.0 Hz, H-1), 5.17 (m, 1 H, $J_{2,3}$ 9.6, $J_{3,4}$ 9.7, $J_{3,F}$ 12.7 Hz, H-3), 5.10 (m, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 4.80 (ddd, 1 H, $J_{2,F}$ 49.3 Hz, H-2), 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-α-D-altropyranose (**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. ^1H NMR ($CDCl_3$): δ 5.71 (dd, 1 H, $J_{1,2}$ 1.3, $J_{1,F}$ 4.6 Hz, H-1), 5.20 (ddd, 1 H, $J_{2,3}$ 2.4, $J_{3,4}$ 4.5, $J_{3,F}$ 49.5 Hz, H-3), 5.09 (ddd, 1 H, $J_{4,5}$ 10.2, $J_{4,F}$ 24.5 Hz H-4), 4.24 (ddd, 1 H, $J_{2,F}$ 10.1 Hz, H-2), 4.20 (m, 1 H, $J_{5,6a}$ 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).

*2,3,6-Trideoxy-6-fluoro-D-*arabino*-hexono-1,4-lactone (**12**).* The 5,6-anhydro-2,3-dideoxylactone **9**[5] (1.0 g, 7.75 mmol) was treated with $Et_3N{\cdot}3HF$ as described above. Purification by flash chromatography (toluene–EtOAc 1:1) gave **12** as a syrup (0.64 g, 55%). $[\alpha]_D^{20}$

+ 18.4° (*c* 0.4, EtOAc). Anal. $C_6H_9FO_3$: C, H. ^{13}C NMR ($CDCl_3$): δ 177.3 (C-1), 82.3 (d, C-6, J_{CF} 169.9 Hz), 78.2 (d, C-4, J_{CF} 5.6 Hz), 70.5 (d, C-5, 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-deoxylactone **10**[5] (1.0 g, 6.94 mmol) was treated with $Et_3N{\cdot}3HF$ as described above. Purification by flash chromatography (toluene–EtOAc 1:1) gave **13** as a syrup (0.74 g, 65%). $[\alpha]_D^{20}$ +21.6° (*c* 0.3, EtOAc). Anal. $C_6H_9FO_4$: C, H. ^{13}C NMR ($CDCl_3$): δ 176.1 (C-1), 73.5 (C-3), 82.4 (d, C-6, J_{CF} 178.6 Hz), 78.2 (d, C-4, J_{CF} 7.8 Hz), 72.1 (d, C-5, 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-deoxylactone **11**[10] (1.0 g, 6.94 mmol) was treated with $Et_3N{\cdot}3HF$ as described above. Purification by chromatography (toluene–EtOAc 2:1) gave **14** as a syrup (0.64 g, 56%). $[\alpha]_D^{20}$ −12.9° (*c* 0.3, EtOAc). Anal. $C_6H_9FO_4$: C, H. ^{13}C NMR ($CDCl_3$): δ 179.3 (C-1), 80.1 (d, C-6, J_{CF} 164.8 Hz), 79.5 (d, C-4, J_{CF} 8.5 Hz), 68.8 (C-2), 68.6 (d, C-5, J_{CF} 21.0 Hz), 32.9 (C-3).

1,4-Di-O-*acetyl-2,3,6-trideoxy-6-fluoro-D*-erythro-*hexopyranose* (**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 anomeric mixture (124 mg, 41%). ^1H NMR ($CDCl_3$): δ 6.08 (m, $J_{1\alpha,2a\alpha}$ 3.4 Hz, H-1α), 5.78 (dd, $J_{1\beta,2a\beta}$ 9.8, $J_{1\beta,2e\beta}$ 2.5 Hz, H-1β), 5.05 (m, 1 H, $J_{3a,4}$ 9.7, $J_{3e,4}$ 4.9, $J_{4,5}$ 9.6 Hz, H-4), 4.45 (m, 2 H, $J_{6,F}$ 47.0 Hz, H-6a, H-6b), 3.89 (dddd, 1 H, $J_{5,6a}$ 5.4, $J_{5,6b}$ 3.5, $J_{5,F}$ 21.8 Hz, H-5), 2.28 (m, 1 H, H-2e), 2.24 (m, 1 H, H-3e), 1.98 (m, 2 H, H-3a, H-2a), 2.13, 2.08 (2 OAc).

1,3,4-Tri-O-*acetyl-2,6-dideoxy-6-fluoro-D*-arabino-*hexopyranose* (**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%). ^1H NMR ($CDCl_3$): δ 6.10 (m, $J_{1\alpha,2a\alpha}$ 3.4, $J_{1\alpha,2e\alpha}$ 1.2 Hz, H-1α), 5.86 (dd, $J_{1\beta,2a\beta}$ 9.8, $J_{1\beta,2e\beta}$ 2.5 Hz, H-1β), 5.38 (m, $J_{3,4}$ 9.6, $J_{4,5}$ 9.6, H-4β), 5.12 (dd, H-4α), 5.30 (m, 1 H, $J_{2a,3}$ 11.1, $J_{2e,3}$ 5.4, H-3), 4.44–4.46 (m, 4 H, $J_{6,F}$ 47.0 Hz, H-6a, H-6b), 4.10 (m, $J_{5,6a}$ 4.5, $J_{5,6b}$ 3.7, $J_{5\alpha,F}$ 23.1 Hz, H-5α), 3.85 (m, $J_{5\beta,F}$ 21.8 Hz, H-5β), 2.33 (m, 1 H, $J_{2e,2a}$ 12.9 Hz, H-2eα), 2.28 (m, H-2eβ), 1.97 (ddd, H-2α), 1.86 (ddd, H-2β), 2.10, 2.09, 2.07 (3 OAc).

1,2,4-Tri-O-*acetyl-3,6-dideoxy-6-fluoro-D*-arabino-*hexopyranose* (**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. ^1H NMR ($CDCl_3$): δ 6.00 (m, $J_{1\alpha,2}$ 1.1 Hz, H-1α), 5.92 (dd, $J_{1\beta,2}$ 2.2 Hz, H-1β), 5.24 (ddd, $J_{2,3a}$ 5.0, $J_{2,3e}$ 3.3 Hz, H-2β), 5.01 (m, 1 H, $J_{3a,4}$ 11.2, $J_{3e,4}$ 5.2, $J_{4,5}$ 10.4 Hz, H-4), 4.99 (ddd, H-2α), 4.45 (ddd, 1 H, $J_{5,6a}$ 6.0, $J_{6a,6b}$ 1.2, $J_{6,F}$ 49.2 Hz, H-6a), 4.34 (ddd, 1 H, $J_{5,6b}$ 2.8 Hz, H-6b), 3.90 (dddd, 1 H, $J_{5,F}$ 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).

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References

1. Card, P. J. *J. Carbohydr. Chem. 4* (1985) 451.
2. Mann, J. *Chem. Soc. Rev. 16* (1987) 381.
3. Penglis, A. A. *Adv. Carbohydr. Chem. Biochem. 38* (1981) 1195.
4. Sheppard, R. and Sharts, P. *Organic Fluorine Chemistry*, Benjamin, New York 1969, pp. 52–184.
5. Lundt, I. and Pedersen, C. *Synthesis* (1992) 669.
6. Bols, M. and Lundt, I. *Acta Chem. Scand. 44* (1990) 252.
7. Lundt, I., Albanese, D., Landini, D. and Penso, M. *Tetrahedron 49* (1993) 7295.
8. Ourari, A., Condom, R. and Guedi, R. *Can. J. Chem. 60* (1982) 2707.
9. Bock, K., Lundt, I. and Pedersen, C. *Carbohydr. Res. 90* (1981) 7.
10. Bock, K., Lundt, I. and Pedersen, C. *Acta Chem. Scand., Ser. B 40* (1986) 163.
11. Franz, R. *J. Fluorine Chem.* (1980) 423.

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