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Reaction of Sugar Esters with Hydrogen Fluoride

X. Derivatives of D-Glucofuranose and D-Mannofuranose

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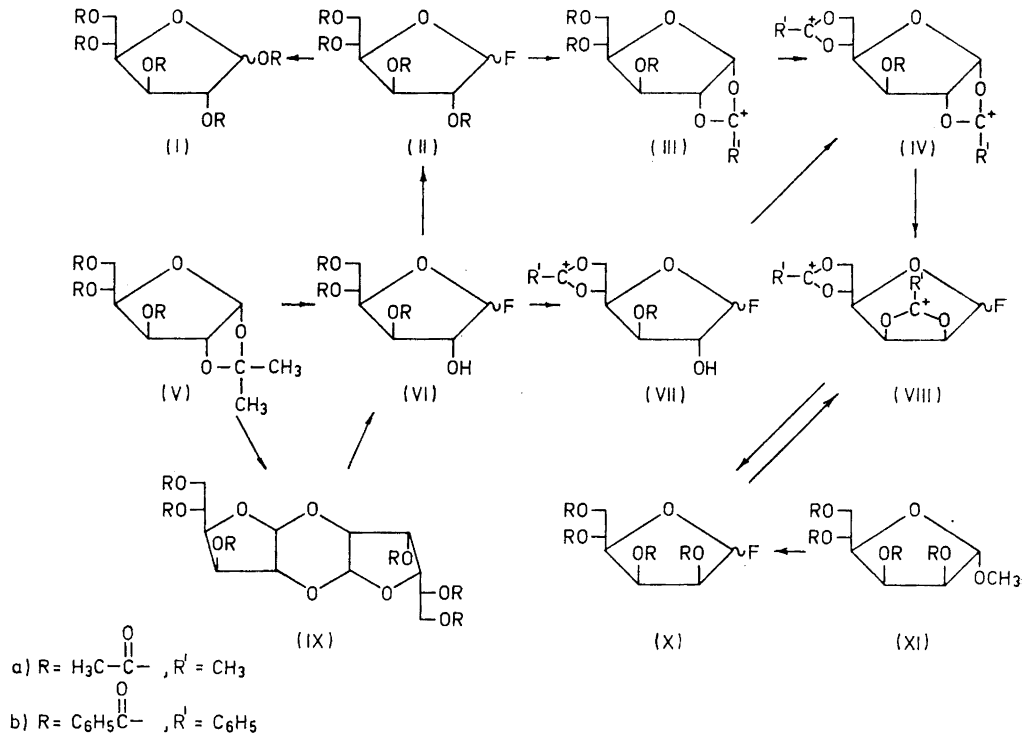
When tetra-*O*-acetyl-D-glucofuranosyl fluoride (IIa), or the corresponding tetrabenzoate (IIb), are treated with anhydrous hydrogen fluoride inversion takes place at C-2 and D-mannofuranose derivatives (VIII) are formed *via* the dioxolanylium ions (III) and (IV). The ions (VIII) are also formed when acetylated mannofuranosyl fluorides (X) are treated with hydrogen fluoride. Reaction of tri-*O*-acetyl-1,2-isopropylidene-α-D-glucofuranose (Va) with hydrogen fluoride at −70°C yields 3,5,6-tri-*O*-acetyl-α,β-D-glucofuranosyl fluoride (VIa). If the reaction is carried out at 0° C a dimeric compound (IXa) is formed in addition to (VIa). Similar results were obtained with the tribenzoate (Vb). NMR data of a number of derivatives of D-glucofuranose and D-mannofuranose are given.

Treatment of acylated arabinofuranose derivatives with anhydrous hydrogen fluoride led to epimerization at C-2 and formation of ribofuranose derivatives.[1] The same ribofuranoses were also formed when ribopyranose or arabinopyranose tetrabenzoates were treated with hydrogen fluoride for several days.[2] Hydrogen fluoride induced ring-contraction of pyranoses to furanoses has also been observed with 2-*O*-methyl-xylopyranose derivatives [3] and with tetra-*O*-benzoyl-2-*O*-methyl-D-glucopyranose.[4]

It was found previously that treatment of acylated glucopyranoses and mannopyranoses with hydrogen fluoride led to inversion at C-2 and (or) C-3 with formation of derivatives of mannopyranose and altropyranose;[5,6] no furanose derivatives were found. However, a reinvestigation of these reactions using NMR technique has now shown that furanose derivatives may be formed to some extent.[7] It was therefore of interest to investigate the behaviour of gluco- and manno-furanose derivatives towards hydrogen fluoride.

The reaction of tetra-*O*-acetyl-α,β-D-glucofuranosyl fluoride (IIa) with hydrogen fluoride was studied by NMR spectroscopy. NMR spectra of (IIa) in hydrogen fluoride solution at −45°C showed that the dioxolanylium ion (IIIa) was formed immediately. Thus an acetoxonium ion signal was found



at 2.9 ppm in addition to signals corresponding to three acetoxy groups. The anomeric proton of (IIIa) gave a doublet a 7.42 ppm with a splitting of 4.5 Hz (J_{12}), clearly showing that a fluoride is not present. Further data are given in Table 1. When the temperature of the hydrogen fluoride solution was allowed to rise to 0°C the ion (IIIa) rapidly disappeared and a new ion was formed which contained two acetoxonium groups, as seen from the spectrum (Table 1). At the same time one equivalent of acetic acid was formed. This ion is undoubtedly (IVa). It is rather stable in hydrogen fluoride at 0°C, but at room temperature it was converted into a third ion in the course of *ca.* 24 h. The latter ion also contained two acetoxonium groups (Table 1), but it was at the same time a glycosyl fluoride as seen from the signal of H-1, which was a doublet with a coupling of 54 Hz (J_{1F}). On the basis of this and of the other spectral data (Table 1) this ion is assumed to be the mannofuranose derivative (VIIIa).

When the hydrogen fluoride solution containing (VIIIa) was poured into water hydrolysis should yield a mixture of diacetylated D-mannofuranosyl fluorides. These were, however, unstable and decomposed. In order to show that a mannose derivative was present, the crude product, resulting from the hydrolysis, was boiled with methanol and acid. This gave methyl α-D-mannopyranoside.

Table 1. NMR spectra of D-glucofuranose and D-mannofuranose derivatives in anhydrous hydrogen fluoride.

Compound	H_1	H_2	H_3	H_5	H_4	H_6	H_6'	J_{1F}	J_{12}	J_{2F}	J_{23}	J_{34}	J_{45}	J_{56}	J_{56}'	J_{66}'	CH_3 / C^+	J_{4F}	HOAc	OAc
IIIa	7.42	6.11	5.86	5.75	4.6	—	5.2		4.5		~0	3.5					2.90			2.50(3H) 2.35(6H)
IIIb		6.38	6.50	6.15	5.50	5.25	4.95		4.5		~0	3.8	7.5	3.0	5.0	13.5	2.90			
IVa	7.43	6.08	5.92	6.10	5.4	—	5.7		4.5		~0	4.0					2.85		2.60	2.35
VIIIa	6.12	6.15	6.34	5.96	5.08	5.2—	5.5	56.0	~0	5.0	6.5	3.0	6.0	8.5	8.0		2.90 2.81	6.0	2.50	
VIIIb	6.52	6.50	6.77	6.50	5.4	—	5.9	55.0	~0	5.0	6.5	3.0	6.0	8.5						

Table 2. NMR spectra of D-glucofuranose and D-mannofuranose derivatives in deuteriochloroform.

Compound	H_1	H_2	H_3	H_4	H_5	H_6	H_6'	J_{1F}	J_{12}	J_{2F}	J_{23}	J_{34}	J_{4F}	J_{45}	J_{56}	J_{56}'	J_{66}'	ϕF
αIIa	5.99	5.64	5.56	4.60	5.28	4.56	4.13	60.8	3.9	14.4	3.0	5.2	~1	8.3	2.5	5.5	12.4	−64.0
β-IIa	5.70	5.17	5.47	4.65	5.33	4.63	4.20	60.3	~0	4.4	~0	5.1	5.7	9.4	2.4	4.6	12.5	−44.9
α-IIb	6.22	5.54	6.22	5.15	5.84	4.97	4.67	60.8	3.7	16.5	5.0	6.0	~1	8.6	2.6	5.1	12.3	−61.8
β-IIb	5.99	5.64	6.03	5.19	5.88	5.00	4.78	60.0	~0	4.4	~0	5.2	5.2	9.0	2.5	4.6	12.3	−44.6
α-Xa	5.81	5.43	5.66	4.60	5.33	4.60	4.15	64.0	2.0	14.0	5.2	4.8	2.0	8.5	2.5	5.6	12.5	−48.6
β-Xa	5.80	5.07	5.70	4.47	5.46	4.62	4.21	65.8	3.8	22.4	5.8	5.1	7.6	9.8	2.6	4.5	12.5	−53.1
α-Xb	6.05	5.85	6.19	5.12	5.96	5.04	4.70	59.9	0.8	9.0	5.4	6.0	2.4	8.2	2.5	5.1	12.5	−47.4
β-Ia	6.14	5.14	5.46	4.58	5.32	4.63	4.10		~0		0.8	4.8		9.2	2.5	5.2	12.3	$J_{13}=0.4$
α-Ib	6.99	5.84	6.25	5.14	5.86	5.00	4.68		4.4		4.0	5.6		8.5	2.6	5.3	12.3	
β-Ib	6.72	5.79	6.02	5.18	5.94	5.00	4.68		~0		~0	4.8		9.0	2.6	5.0	12.4	
XIb	5.25	5.66	6.11	4.89	5.93	5.00	4.76		1.7		5.3	5.3		8.9	2.5	5.4	12.4	
IXa	5.21	3.89	5.46	4.53	5.25	4.58	4.13		3.8		0.6	3.2		9.0	2.4	6.0	12.0	
IXb	5.38	4.14	5.74	5.04	5.87	5.01	4.67		3.6		0.7	3.3		9.0	2.4	6.0	12.1	

Brief treatment of methyl α-D-mannofuranoside tetraacetate (XIa) with hydrogen fluoride gave tetra-*O*-acetyl-D-mannofuranosyl fluoride (Xa) as a mixture of anomers which could be separated. A solution of this product in hydrogen fluoride initially gave complicated NMR spectra. However, after *ca.* 24 h at room temperature the ion (VIIIa) was formed, the spectra being identical with those described above.

Similarly, penta-*O*-benzoyl-D-glucofuranose (Ib) gave tetra-*O*-benzoyl-β-D-glucofuranosyl fluoride (β-IIb) by brief reaction with hydrogen fluoride. A solution of this product in hydrogen fluoride gave NMR spectra which were less resolved than those obtained from the acetate, but the ion (IIIb) could be detected. This slowly underwent further changes and after *ca.* 2 weeks at room temperature it was converted into the mannofuranose ion (VIIIb), as seen from the spectra (Table 1). When this solution was hydrolyzed and the product benzoylated a 70 % yield of tetra-*O*-benzoyl-α-D-mannofuranosyl fluoride (Xb), was obtained. The ion (VIIIb) was also obtained when tetra-*O*-benzoyl-D-mannofuranosyl fluoride (Xb) was kept in hydrogen fluoride for *ca.* 4 days at room temperature.

The rearrangement of the glucofuranosyl fluoride (II) into the ion (VIII), *via* (III) and (IV), is analogous to the rearrangement of arabinofuranose derivatives to ribofuranose derivatives[1] except that in the present case a 5,6-dioxolanylium ion is formed simultaneously. The formation of the latter ion and of the 2,3-ion from the mannofuranose derivative (X) probably takes place through the mechanism by which *cis* 1,2-diacyloxycyclohexanes give dioxolanylium ions in anhydrous hydrogen fluoride.[7,8]

It was found that treatment of 1,2-isopropylidene-α-D-glucofuranose tribenzoate (Vb) with hydrogen fluoride for 10 min at −70°C gave a mixture of the anomeric 3,5,6-tri-*O*-benzoyl-D-glucofuranosyl fluorides (VIb). Benzoylation of this mixture yielded the anomeric tetrabenzoylated fluorides (IIb) which could be separated. It may be noted that brief reaction of the pentabenzoate (Ib) with hydrogen fluoride gave the β-anomer (β-IIb) only. Analogous treatment of the triacetate (Va) with hydrogen fluoride gave (VIa), which by acetylation yielded the anomeric tetra-*O*-acetyl-D-glucofuranosyl fluorides (IIa). Treatment of (IIa) with hydrogen bromide in glacial acetic acid gave the corresponding bromide, which by subsequent reaction with silver acetate, furnished penta-*O*-acetyl-β-D-glucofuranose (β-Ia).

Reaction of (Va) with hydrogen fluoride at 0°C for 15 min gave, in addition to (VIa), the dimeric compound (IXa) in *ca.* 40 % yield. Similar treatment of the tribenzoate (Vb) gave a lower yield of the dimeric benzoate (IXb). The structures of (IXa and b) were proposed on the basis of their NMR spectra (Table 2) and of their molecular weights. They are probably formed by dimerization of the C-1 carbonium ion, corresponding to (VIa or b). Treatment of (VIa) with boron trifluoride in methanol gave, in addition to the expected methyl glycoside, a small amount of (IXa).

When (Va) or (IXa) were kept in hydrogen fluoride solution for 24 h at room temperature they both gave the ion (VIIIa). NMR spectra showed that the ion (IVa) was an intermediate in this reaction. Presumably (Va) and (IXa), *via* (VIa), will form the 5,6-acetoxonium ion (VIIa) and acetic acid in hydrogen fluoride. It has been shown that acetic acid will acetylate alcohols in an-

hydrous hydrogen fluoride [7] and (VIIa) could therefore be acetylated and the resulting 2-*O*-acetate would then yield (IVa).

The NMR spectra of the compounds prepared during this investigation are in accordance with the proposed structures (Table 2). It may be noted that a long range coupling, J_{4F}, of *ca.* 2 Hz is found in all the α-furanosyl fluorides in which H-4 and F-1 are *cis*-oriented. The corresponding coupling constant in the β-fluorides is *ca.* 6 Hz. This is in agreement with results found in the pentofuranosyl fluoride series.[9]

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were obtained on Varian A-60 and HA-100 instruments using tetramethylsilane (TMS) as internal reference. NMR spectra in anhydrous hydrogen fluoride were measured in Teflon sample tubes. Positions of signals in hydrogen fluoride are given in ppm relative to $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$. ^{19}F Spectra were measured at 94.1 MHz. Positions of signals (ϕF) are given in ppm relative to internal methyl trifluoroacetate. Thin layer chromatography (TLC) was performed on silica gel PF_{254} (Merck); for preparative work 1 mm layers were used on 20 × 40 cm plates. Spots were visualized under UV light or by charring with a hot wire.

Brief treatment of (Ib) with hydrogen fluoride

Penta-*O*-benzoyl-α,β-D-glucofuranose [10,11] (Ib) (800 mg) was dissolved in anhydrous hydrogen fluoride (3 ml) and kept at 0°C for 15 min. Methylene chloride (20 ml) was then added and the mixture was poured onto ice. The organic layer was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue (690 mg, 100 %) consisted of almost pure tetra-*O*-benzoyl-β-D-glucofuranosyl fluoride (β-IIb), as seen from an NMR spectrum. Preparative TLC (benzene-chloroform 7:3) gave the pure product (390 mg) as a syrup, $[\alpha]_D^{23} = -3.4°$ (*c* 1.3, $CHCl_3$). (Found: C 68.14; H 4.66. Calc. for $C_{34}H_{27}FO_9$: C 68.24; H 4.52.) Only traces of the α-anomer could be found.

Reaction of (Vb) with hydrogen fluoride at −70°C

Tri-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (Vb) (1.02 g) was kept in hydrogen fluoride (2 ml) at −70°C for 10 min. Work up as described above gave 950 mg of crude (VIb) as a mixture of anomers in an α-β ratio of 1:1 as seen from an NMR spectrum. The product was benzoylated with benzoyl chloride (1 ml) in pyridine (2 ml) to give 1.20 g (100 %) of (IIb) as a mixture of anomers. A portion of this (300 mg) was separated into two fractions by preparative TLC (benzene-chloroform 7:3). The fast running fraction gave 122 mg of (β-IIb), identical with the product described above. The next fraction gave 120 mg of tetra-*O*-benzoyl-α-D-glucofuranosyl fluoride (α-IIb) as a syrup, $[\alpha]_D^{23} = +22.2°$ (*c* 0.8, $CHCl_3$). (Found: C 68.14; H 4.59. Calc. for $C_{34}H_{27}FO_9$: C 68.24; H 4.52.)

Reaction of (Vb) with hydrogen fluoride at 0°C

A solution of (Vb) (690 mg) was kept in hydrogen fluoride (1.5 ml) at 0°C for 15 min. Work up as described above followed by benzoylation with benzoyl chloride and pyridine gave 700 mg of product which was separated into two fractions by preparative TLC (ether–pentane 1:1). The fast running fraction gave 500 mg (64 %) of (IIb) as a mixture of anomers. The slower running fraction gave 100 mg (16 %) of the dimeric compound (IXb) as a syrup, $[\alpha]_D^{23} = -32.2°$ (*c* 1.43, $CHCl_3$) (Found: C 68.16; H 4.66. Calc. for $C_{54}H_{44}O_{16}$: C 68.30; H 4.56.) Molecular weight, found: 929; calc.: 948.

Prolonged treatment of (IIb) with hydrogen fluoride

Tetra-*O*-benzoyl-α,β-D-glucofuranosyl fluoride (IIb) (1.05 g) was kept in hydrogen fluoride (3 ml) for 10 days at room temperature. The solution was then worked up to give 883 mg of a product which was benzoylated with benzoyl chloride in pyridine. The product thus obtained (1.1 g) was crystallized from ether giving 500 mg of tetra-*O*-benzoyl-α-D-mannofuranosyl fluoride (Xb), m.p. 85–88°C. Preparative TLC (ether–pentane 1:1) gave an additional 220 mg of the same product, bringing the total yield to 720 mg (68.5 %). Recrystallization from ether gave pure (α-Xb), m.p. 90–91°C, $[\alpha]_D^{23} = -115.6°$ (*c* 2.0, $CHCl_3$). (Found: C 68.16; H 4.49. Calc. for $C_{34}H_{27}FO_9$: C 68.24; H 4.52.)

Methyl tetra-*O*-benzoyl-α-D-mannofuranoside (XIb)

Methyl α-D-mannofuranoside [12] (2.6 g) was benzoylated with benzoyl chloride (9 ml) in pyridine (20 ml). Crystallization of the crude product from ethanol gave 5.9 g (72 %) of (XIb), m.p. 102–111°C. Two recrystallizations from methanol gave the pure product, m.p. 114–115°C, $[\alpha]_D^{25} = -79.0°$ (*c* 1.18, $CHCl_3$). (Found: C 68.74; H 5.03. Calc. for $C_{35}H_{30}O_{10}$: C 68.89; H 4.96.)

Brief treatment of (XIb) with hydrogen fluoride

Treatment of methyl tetra-*O*-benzoyl-α-D-mannofuranoside (XIb) (150 mg) with hydrogen fluoride (0.5 ml) at 0°C for 15 min gave 140 mg of product. Crystallization from ether gave 100 mg (68 %) of (Xb), m.p. 84–87°C. NMR spectra showed that the product was identical with that described above.

Reaction of (Va) with hydrogen fluoride at –70°C

Tri-*O*-acetyl-1,2-isopropylidene-α-D-glucofuranose (Va) (720 mg) was dissolved in anhydrous hydrogen fluoride (2 ml) at –70°C. After 5 min the solution was worked up as described above and the crude (VIa) (680 mg) was immediately acetylated with acetic anhydride (2 ml) in pyridine (3 ml). This gave a syrup (660 mg, 91 %) which, as seen from an NMR spectrum, consisted of a mixture of the anomeric fluorides (IIa) in an α to β ratio of 1:1. These were separated by preparative TLC using two elutions with ether–pentane (1:1). The fast running fraction gave 252 mg (35 %) of tetra-*O*-acetyl-α-D-glucofuranosyl fluoride (α-IIa) as a syrup, $[\alpha]_D^{23} = +86.0°$ (*c* 3.6, $CHCl_3$). (Found: C 47.98; H 5.41. Calc. for $C_{14}H_{19}FO_9$: C 48.00; H 5.43.) The slower running fraction gave 350 mg (48 %) of the almost pure β-anomer (β-IIa). A small amount of the α-anomer was removed by preparative TLC (ether–pentane 1:2). This gave pure (β-IIa), m.p. 86–88°C, $[\alpha]_D^{23} = +17.0°$ (*c* 4.0, $CHCl_3$). (Found: C 47.94; H 5.52.)

Penta-O-acetyl-β-D-glucofuranose (β-Ia). A crude mixture of the anomeric fluorides (IIa) (1.5 g), obtained as described above, was dissolved in 10 ml of a 30 % solution of hydrogen bromide in glacial acetic acid. The solution was kept at 0°C for 2 h. Methylene chloride was then added and the solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The residue was dissolved in acetonitrile (30 ml) and stirred with silver acetate (3.0 g) over night. The suspension was then filtered through activated carbon and the solvent was evaporated. The residue was dissolved in methylene chloride, washed with aqueous sodium hydrogen carbonate and dried. Evaporation of the solvent gave 1.42 g of a product which was separated into two fractions by preparative TLC (ether–pentane 2:1). The fast running fraction gave 527 mg (31 %) of penta-*O*-acetyl-β-D-glucofuranose (β-Ia) as a syrup $[\alpha]_D^{23} = -21.2°$ (*c* 1.46, $CHCl_3$). (Found: C 49.11; H 5.66. Calc. for $C_{16}H_{22}O_{11}$: C 49.30; H 5.65.) The slow running fraction yielded 435 mg (29 %) of 2,3,5,6-tetra-*O*-acetyl-D-glucofuranose, as seen from the NMR spectrum.

Reaction of (Va) with hydrogen fluoride at 0°C

A solution of (Va) (1.19 g) in hydrogen fluoride (2 ml) was kept at 0°C for 5 min. Work up as described above gave a product which crystallized from ether–pentane to give 250 mg (27 %) of the dimeric acetate (IXa) with m.p. 143–148°C. Two additional recrystallizations gave the pure product, m.p. 159–161°C, $[\alpha]_D^{23} = +72.4°$ (*c* 1.1, $CHCl_3$). (Found: C 50.26; H 5.51. Calc. for $C_{24}H_{32}O_{16}$: C 50.00; H 5.56.) Molecular weight found: 553; calc.: 576.

The material in the mother liquor was acetylated with acetic anhydride in pyridine. The product (600 mg) was separated into 3 fractions by preparative TLC (benzene–ether 1:1). The fast running fraction gave 200 mg (17 %) of a mixture of the anomeric fluorides (IIa) in an $\alpha:\beta$ ratio of 1:1. The next fraction gave 180 mg (13 %) of the pentaacetate (Ia) as a mixture of anomers. The third gave an additional 200 mg (21 %) of (IXa), m.p. 152–155°C.

Prolonged treatment of (Va) with hydrogen fluoride. A solution of (Va) (1.28 g) in hydrogen fluoride (3 ml) was kept at room temperature for 48 h. Most of the hydrogen fluoride was then evaporated with a stream of dry air. The residue was then dissolved in methanol (30 ml) and the solution was boiled under reflux for 5 h. It was then neutralized with Amberlite IR-4B and the solvent was evaporated. The residue was crystallized from ethanol to give 200 mg (25 %) of methyl-α-D-mannopyranoside, m.p. 175–180°C. The material in the mother liquor (300 mg) was acetylated with acetic anhydride in pyridine to give 500 mg of a product which, as seen from an NMR spectrum, contained *ca.* 30 % methyl tetra-*O*-acetyl-α-D-mannopyranoside.

Tetra-O-acetyl-α-β-D-mannofuranosyl fluoride (Xa). Methyl tetra-*O*-acetyl-α-D-mannofuranoside (XIa) (650 mg) was dissolved in hydrogen fluoride (1.5 ml) and kept for 5 min at 0°C. Work up gave 488 mg of a product which was separated into two fractions by preparative TLC (ether–pentane 1:1). The fast running fraction gave 180 mg (29 %) of the α-fluoride (α-Xa) which was recrystallized from ether, m.p. 96–97.5°C, $[\alpha]_D^{25} = +68.5°$ (*c* 2.1, $CHCl_3$). (Found: C 48.08; H 5.44. Calc. for $C_{14}H_{19}FO_9$: C 48.00; H 5.43.) The next fraction gave 187 mg (30 %) of (β-Xa). Recrystallization from ether gave the pure product, m.p. 91–92.5°C, $[\alpha]_D^{25} = -13.8°$ (*c* 2.5, $CHCl_3$). (Found: C 48.24; H 5.56.)

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