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Reaction of 1,2-Dideoxy-glyc-1-enopyranoses and 2-Deoxyglycopyranoses with Hydrogen Fluoride. VI *

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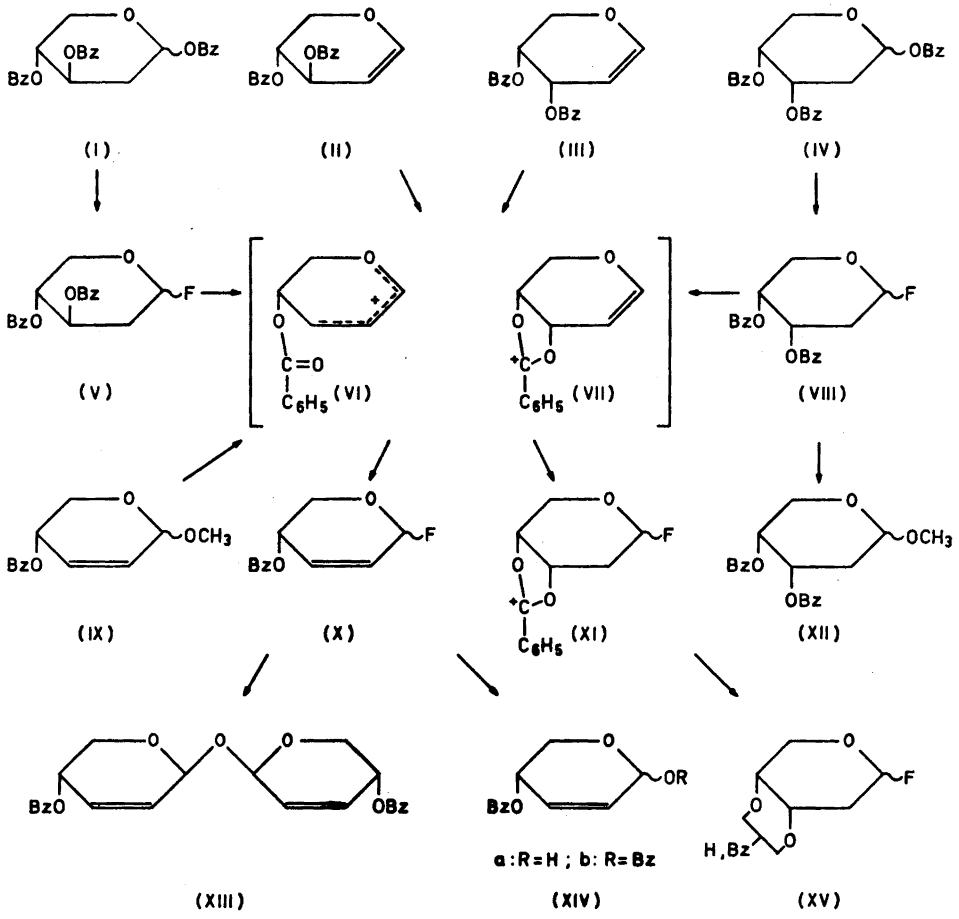
Reaction of 1,3,4-tri-*O*-benzoyl-2-deoxy-D-*threo*- and D-*erythro*-pentopyranose, (I) and (IV), with hydrogen fluoride in benzene gave the corresponding 3,4-di-*O*-benzoyl-2-deoxy-D-pentosyl fluorides (V) and (VIII), respectively. Similar treatment of 3,4-di-*O*-benzoyl-1,2-dideoxy-D-*threo*- or D-*erythro*-pent-1-enopyranose, (II) and (III), yielded 4-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pent-2-enopyranosyl fluoride (X), isolated as the corresponding methyl glucoside (IX). With anhydrous hydrogen fluoride (I), (II), (III), and (IV) were all converted to the same dioxolanylium ion (XI) which, by hydrolysis, benzoylation and treatment with methanol, yielded the methyl 3,4-di-*O*-benzoyl-2-deoxy-D-*erythro*-pentopyranosides (XII). The mechanisms of the reactions were studied through experiments with deuterium fluoride.

In previous papers,[1–3] the reaction of derivatives of 1,2-dideoxy-hex-1-enopyranoses and of 2-deoxy-hexopyranoses with hydrogen fluoride was investigated. The reaction of the corresponding pentose derivatives with hydrogen fluoride has now been studied.

Treatment of 3,4-di-*O*-benzoyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (II), or the corresponding D-*erythro*-compound (III) with hydrogen fluoride in benzene presumably gave the 2,3-unsaturated fluoride (X), in analogy with the results described previously.[1,2] This fluoride was, however, very unstable, and it was therefore immediately treated with methanol in the presence of a catalytic amount of boron trifluoride. This resulted in the formation of the anomeric methyl 4-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pent-2-enopyranosides (IX), which were separated and characterized through their NMR spectra (Table 1).[4] 3,4-Di-*O*-benzoyl-1,2,-dideoxy-D-*erythro*-pent-1-enopyranose (III) gave, in addition to the 2,3-unsaturated methyl glycosides (IX), small amounts of the anomeric methyl 3,4-di-*O*-benzoyl-2-deoxy-D-*erythro*-pentopyranosides (XII), resulting from direct addition of hydrogen fluoride to the double bond

* For previous papers in this series, see Refs. 1–3.

of (III). Corresponding products were not observed when (II) was treated with hydrogen fluoride. This difference between (II) and (III) is analogous to the difference observed in the behaviour of the 1,2-dideoxy-D-*arabino*- and D-*lyxo*-hex-1-enopyranoses towards hydrogen fluoride.[1,2] The D-*lyxo*-compound gave small amounts of products resulting from 1,2-addition, whereas the D-*arabino*-compound gave rearranged products only. Apparently, com-



pounds with *trans*-substituents at C-3 and C-4 lose the group at C-3 very rapidly, giving only rearranged products. Glyc-1-enopyranoses with *cis*-substituents loose the C-3-group more slowly, allowing the addition of hydrogen fluoride to the 1,2-double bond to compete.

Attempts to isolate the 2,3-unsaturated fluoride (X) resulted in hydrolysis with formation of 4-*O*-benzoyl-2,3-dideoxy-D-*glycero*-pent-2-enopyranose (XIVa). Besides, a low yield of the disaccharide (XIII) was obtained. The formation of the latter is in agreement with previous results.[5] Treatment of crude

(X) with calcium benzoate gave 1,4-di-*O*-benzoyl-2,3-dideoxy-*β*-D-*glycero*-pent-2-enopyranose (XIVb).

Similar treatment of tri-*O*-benzoyl-2-deoxy-D-*threo*-pentopyranose (I) and the corresponding *erythro*-compound (IV) with hydrogen fluoride in benzene gave 3,4-di-*O*-benzoyl-2-deoxy-D-*threo*- and D-*erythro*-pentopyranosyl fluorides (V) and (VIII), respectively, as mixtures of anomers. The anomers were separated by chromatography and the structures were determined by NMR spectroscopy.

Treatment of (II) or (III) with anhydrous hydrogen fluoride at low temperature would be expected to give the ions (VI) or (VII) as the initial product.[1] However, the reactions of (II) and (III) with anhydrous hydrogen fluoride was fast, as found with derivatives of 1,2,6-trideoxy-L-*arabino*-hex-1-enopyranose,[1] and (VI) or (VII) were therefore not detected, even at −70°C. The final dioxolanylium ion (XI), arising from addition of hydrogen fluoride to (VII), was the only product which could be detected in the NMR spectra of the hydrogen fluoride solutions. The conversion of (II) or (III) to the dioxolanylium ion (XI) was completed in the course of *ca.* 90 min at −30°C.

When the hydrogen fluoride solution which contained the ion (XI) was worked up, the monobenzoylated fluorides (XV) were obtained. These were unstable and they were therefore immediately benzoylated, to give a low yield of the anomeric 3,4-di-*O*-benzoyl-2-deoxy-D-*erythro*-pentopyranosyl fluorides (VIII). Since the crude fluorides (VIII) are also somewhat unstable, they were treated with methanol and boron trifluoride, in order to convert them into the methyl glycosides (XII), which were obtained in *ca.* 40 % yield from either (II) or (III).

The mechanism of the conversion of (II) or (III) into the ion (XI) with hydrogen fluoride is undoubtedly the same as that described previously.[1,2] Thus the first step in the reaction is probably a rapid loss of the *O*-benzoyl group at C-3 with formation of (VI), which is in equilibrium with the unsaturated dioxolanylium ion (VII). Addition of hydrogen fluoride to (VII) then gives (XI). This was confirmed by the fact that the unsaturated methyl glycoside (IX), when treated with hydrogen fluoride under the same conditions, also gave the anomeric glycosides (XII) as the final products.

In analogy with the results obtained in the 2-deoxy-D-*arabino*-hexose series,[3] treatment of tri-*O*-benzoyl-2-deoxy-D-*threo*-pentopyranose (I) with anhydrous hydrogen fluoride at −30°C led to inversion at C-3 with formation of the ion (XI), as seen from the NMR spectra. Work up of the hydrogen fluoride solution, as described above, gave the methyl glycosides (XII) in 70 % yield. Treatment of (IV) with hydrogen fluoride also gave the ion (XI), analogous to the results obtained with tri-*O*-benzoyl-2-deoxy-D-*lyxo*-hexose.[1]

In view of the results obtained previously [1] with deuterium fluoride, this reagent was also investigated in the present case. Treatment of the unsaturated compounds (II) and (III) with deuterium fluoride gave, by the procedure described above, the methyl glycosides (XII). This product contained *ca.* 1 equiv. of deuterium at C-2, in agreement with the mechanism proposed. The deuterium was not introduced in a stereospecific manner, as seen from the fact that the hydrogen remaining at C-2 was placed in both the axial and in the equatorial position. The tribenzoates (I) and (IV) were also treated with

Table 1. δ-Values and coupling constants (Hz) in deuteriochloroform of compounds shown in Fig. 1.

Compound	δ-Values							Coupling constants													Predominant conformation
	H_1	H_{2a}	H_{2e}	H_3	H_4	H_{5a}	H_{5e}	J_{1F}	J_{1a2}	J_{1e2}	J_{a2F}	J_{e2F}	J_{a2e}	J_{a2a}	J_{a2e}	J_{34}	J_{45a}	J_{45e}	J_{5a5e}	
α-V	5.77	2.10	2.65	5.75	5.46	4.00	4.18	50.7	2.6	1.8	36.4	5.0	13.8	10.8	5.0	9.2	10.0	5.5	10.6	$^4C_1$
β-V	5.77	2.2–2.8		5.41	5.22	4.54	4.05	51.0	3.2	3.2			15.0		3.2		3	2.0	12.5	$^1C_4$
α-VIII	5.70	2.1–2.6		5.75	5.45	4.45	3.98	51.0	3	2						3	10.2	5.2	11.2	$^4C_1$
β-VIII	5.91	2.2–2.7		5.5–5.8		4.18	4.30	51.0	2	2							2	1	13	$^1C_4$
β-VIII[a]	5.53	1.7–2.4		5.57	5.50	3.70	3.80	51.0	2.1	2.1			13.0	11.0	6.0	3.0	2.0	1.0	13.0	$^1C_4$
α-XII	4.59	2.1–2.3		5.4–5.6		4.77	3.78		4.5	4.5							4.2	2.5	12.2	
β-XII	4.96	2.40	2.12	5.66	5.55	3.93	4.07		3.2	2.0			12.4	11.0	5.0	3.0	2.6	1.8	12.8	$^1C_4$
	H_1	H_2	H_3	H_4	H_{5e}	H_{5a}		J_{12}	J_{13}	J_{14}	J_{23}	J_{24}	J_{34}	J_{45e}	J_{45a}	J_{5e5a}	J_{35e}			
β-IX	4.95	6.08	6.20	5.20	4.00	4.25		2.4	0.8		10.3		4.2	1.3	2.8	13.0	1.2			^5H_O
α-IX	4.88	5.90	6.06	5.56	3.9–4.1			2.1	0.6	1.5	10.1	1.5	1.8	6	8		0.6			$^OH_5$
XIII	5.52	6.10	6.25	5.23	4.07	4.27		2.6	0.8		10.2		4.8	1.0	2.8	13.1	1.0			^5H_O
β-XIV, R=Bz	6.65	6.23	6.40	5.30	4.20	4.38		2.7	0.8		10.0		5.0	1.0	2.6	12.5	1.0			^5H_O

[a] Solvent: benzene-d_6

deuterium fluoride and thereby gave (XII), in which 1 equiv. of hydrogen at C-2 was replaced by deuterium.

From these experiments it may be concluded that (I) and (IV) first form the fluorides (V) and (VIII), respectively, when treated with hydrogen fluoride. These fluorides then lose benzoic acid to give (VI) or (VII), which subsequently add hydrogen fluoride to give the dioxolanylium ion (XI). The latter ion is the final product in hydrogen fluoride, and it is converted into the methyl glycosides (XII) by the procedure used when the hydrogen fluoride solution is worked up. Prolonged treatment of (I) or (II) with deuterium fluoride did not increase the amount of deuterium incorporated into (XII), showing that the addition of deuterium fluoride to (VII) is not reversible.

The four fluorides, (α and β V) and (α and β VIII) were prepared by brief treatment of the corresponding tribenzoates, (I) and (IV), with hydrogen fluoride in benzene. Under these conditions, rearrangement would not be expected, and the only structural problem was that of the anomeric configuration. From the NMR spectra, and especially from the coupling constants, $J_{4,5}$, the predominant conformation of these four compounds could be determined (Table 1). The coupling constants, J_{12}, are small in all four cases, showing that H-1 and H-2 are *gauche*, and hence, that the fluorine is axially oriented. Apparently, the conformation is determined predominantly by the anomeric effect, the importance of which has been demonstrated for other glycosyl fluorides.[6]

The mixture of anomeric methyl glycosides (XII) was prepared following the method of Lemieux *et al.*[7] The two anomers thus obtained were separated, and the pure products were found to be identical with those obtained from the reactions described above. The anomeric structures of those two products were also determined by NMR spectroscopy (Table 1). The α-anomer is probably a mixture of the two chair conformations, as seen from J_{45a}, which was found to be 4.2 Hz. In the ideal $^4C_1$ conformation, this coupling constant should be *ca.* 10 Hz, as found for the corresponding fluoride (α-VIII).

EXPERIMENTAL

Melting points are uncorrected. For details of thin layer chromatography (TLC) and NMR spectra, see Ref. 2.

*Methyl-3,4-di-*O*-benzoyl-2-deoxy-*α,β-D-erythro-*pentopyranoside* (XII) was prepared by the method of Lemieux *et al.*[7] To 3,4-di-*O*-acetyl-1,2-dideoxy-D-*erythro*-pent-1-enopyranose (3.80 g) in methanol (100 ml) was added silver acetate (4.40 g) and the suspension was cooled to 0°C. Bromine (1.37 ml) was then added over a period of 10 min with stirring and cooling. After an additional 30 min, the silver salts were removed by filtration through charcoal, and the solvent was evaporated. The residue was dissolved in methylene chloride and washed twice with aqueous sodium hydrogen carbonate and twice with 5 % sodium thiosulfate and dried. Evaporation gave a syrup (5.53 g, 93 %) which contained several products, as seen by NMR. The product was dissolved in 125 ml of a mixture of methanol, water, and triethylamine (10:9:1) and hydrogenated at 1 atm and room temperature for 12 h in the presence of 5 % palladium on carbon (500 mg). The catalyst was then filtered off and the solvent was evaporated. After reevaporation with pyridine (20 ml) the residue was benzoylated in the usual manner with benzoyl chloride (20 ml) in pyridine (30 ml). The product (5.0 g, 75 %) was a syrup which consisted of a mixture of the anomeric glycosides (XII). A sample was separated into two fractions by preparative TLC, using ether:pentane (1:1) as eluent. The fastest moving

fraction gave pure methyl 3,4-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentopyranoside (β-XII) as a syrup, $[\alpha]_D^{23} = -221°$ (*c* 1.8, $CHCl_3$). (Found: C 67.27; H 5.73. Calc. for $C_{20}H_{20}O_6$: C 67.39; H 5.66.) The next fraction gave the syrupy α-anomer (α-XII), $[\alpha]_D^{23} = -25.0°$ (*c* 4.6, $CHCl_3$). (Found: C 67.60; H 5.80.)

Reactions with hydrogen fluoride in benzene

3,4-Di-*O*-benzoyl-1,2-dideoxy-D-*threo*-pent-1-enopyranose (II)[8] (527 mg) was dissolved in 10 ml of a saturated solution of hydrogen fluoride in benzene and kept at 0 – 5° for 15 min. Methylene chloride (25 ml) was then added and the solution was washed with aqueous sodium hydrogen carbonate, dried and evaporated. The product was separated into several fractions by preparative TLC using ether:pentane (1:1) as eluent. Most of these fractions could not be identified. One fraction was obtained pure after recrystallization from ether:pentane, 50 mg (15 %), m.p. 125 – 126°C, $[\alpha]_D^{23} = +263°$ (*c* 1.2, $CHCl_3$). (Found: C 68.30; H 5.32. Calc. for $C_{24}H_{22}O_7$: C 68.24; H 5.26.) An NMR spectrum showed that the product was the disaccharide (XIII) (Table 1). Another fraction gave 111 mg (31 %) of 4-*O*-benzoyl-2,3-dideoxy-D-*glycero*-hex-2-enopyranose (XIVa) as a syrup. The product was a mixture of the pyranose and the aldehyde form in a ratio of 4:1, as seen from the NMR spectrum.

In a separate experiment (II) (593 mg) was treated with hydrogen fluoride in benzene as described above. The crude product was dissolved in methylene chloride (7 ml), and 3 ml of a mixture of methanol, boron trifluoride etherate, and methylene chloride (2:1:17) was added. After 20 min at room temperature the solution was diluted with methylene chloride and washed with sodium hydrogen carbonate, dried and evaporated. The product (450 mg) was separated into two fractions by preparative TLC (ether:pentane 1:1). The fast running fraction gave 90 mg (19 %) of methyl 4-*O*-benzoyl-2,3-dideoxy-α-D-*glycero*-pent-2-enopyranoside (α-IX) as a syrup, $[\alpha]_D^{23} = +169°$ (*c* 6, $CHCl_3$). (Found: C 66.72; H 6.10. Calc. for $C_{13}H_{14}O_4$: C 66.60; H 6.02.) The next fraction gave 250 mg (59 %) of the corresponding β-anomer (β-IX). The product was recrystallized from ethanol, m.p. 56 – 58°C, $[\alpha]_D^{23} = +173°$ (*c* 2.6, $CHCl_3$). (Found: C 66.60; H 6.06.) The corresponding L-enantiomers have been prepared by Lemieux *et al.*,[7] who obtained higher numerical values for the specific rotations of their products. It is possible that our products contain small amounts of the L-enantiomers, since some epimerization might occur at the allylic C-4.

In a third experiment (II) (497 mg) was kept in a saturated solution of hydrogen fluoride in benzene (10 ml) for 20 min at 0°. Calcium benzoate (2.0 g) suspended in acetonitrile (20 ml) was then added, and the mixture was stirred at room temperature for 2 h. It was then filtered through activated carbon and evaporated. The residue was dissolved in methylene chloride and washed twice with aqueous sodium hydrogen carbonate. The solution was dried and evaporated, leaving 243 mg of crude product. Crystallization from ether:pentane gave 120 mg (41 %) of 1,4-di-*O*-benzoyl-2,3-dideoxy-β-D-*glycero*-pent-2-enopyranose (β-XIV, R = benzoyl), m.p. 150 – 153°C. Two recrystallizations gave the pure product, m.p. 157 – 158°C, $[\alpha]_D^{23} = +227°$ (*c* 1.1, $CHCl_3$). (Found: C 70.31; H 5.10. Calc. for $C_{19}H_{16}O_5$: C 70.36; H 4.98.)

3,4-Di-O-*benzoyl-1,2-dideoxy*-D-erythro-*pent-1-enopyranose (III)* (535 mg) was treated with hydrogen fluoride in benzene, followed by reaction with methanol and boron trifluoride as described above. The crude product (457 mg) was separated into four fractions by preparative TLC (ether:pentane 1:1). The fastest running fraction gave 62 mg (16 %) of (α-IX). This was followed by 164 mg (43 %) of (β-IX), 57 mg (9.5 %) of (β-XII), and 19 mg (3.5 %) of (α-XII).

1,3,4-Tri-O-*benzoyl-2-deoxy-α,β*-D-erythro-*pentopyranose* (IV)[8] (436 mg) was dissolved in 10 ml of a solution of hydrogen fluoride in benzene and kept at 0 – 5°C for 5 min. The solution was then diluted with methylene chloride, washed with aqueous sodium hydrogen carbonate, dried and evaporated *in vacuo* at 25°C. The product was a rather unstable syrup which was separated into two fractions by preparative TLC (ether: pentane 1:1). The fast running fraction gave 262 mg (78 %) of 3,4-di-*O*-benzoyl-2-deoxy-β-D-*erythro*-pentopyranosyl fluoride (β-VIII), which was recrystallized from ether: pentane, m.p. 77 – 78.5°C, $[\alpha]_D^{23} = -199°$ (*c* 1.7, $CHCl_3$). (Found: C 66.59; H 5.09. Calc. for $C_{19}H_{17}FO_5$: C 66.27; H 4.98.) The second fraction was also crystallized from ether:

pentane and yielded 44 mg (13 %) of the α-anomer (α-VIII), m.p. 112°C (dec.), $[\alpha]_D^{23} = +59.2°$ (*c* 0.8, $CHCl_3$). (Found: C 66.35; H 5.06.)

Tri-O-*benzoyl-2-deoxy*-β-D-threo-*pentopyranose* (I)[8] (116 mg) was treated with hydrogen fluoride in benzene, as described above, giving 84 mg (90 %) of crude product. An NMR spectrum indicated that the product was a mixture of the anomeric fluorides (V) in an α- to β-ratio of 7:3. Crystallization from ether:pentane gave the pure β-anomer (β-V), m.p. 126–127°C (dec.), $[\alpha]_D^{23} = -146°$ (*c* 1.8, $CHCl_3$). (Found: C 66.11; H 5.19.) Attempts to obtain pure (α-V) by chromatography were unsuccessful. The NMR data (Table 1) of this anomer were obtained from the mixture.

Reactions with anhydrous hydrogen fluoride

Tri-O-*benzoyl-2-deoxy*-β-D-threo-*pentopyranose* (I) (525 mg) was dissolved in anhydrous hydrogen fluoride (2 ml) and kept at −30°C for 4 h. Cold methylene chloride was then added, and the solution was washed with ice water and aqueous sodium hydrogen carbonate, dried and evaporated. The product was immediately benzoylated with pyridine (5 ml) and benzoyl chloride (1 ml). Work up in the usual way gave 343 mg of a rather unstable product which was separated into four fractions by preparative TLC (ether:pentane 1:1). The fastest running fraction gave 110 mg (28 %) of (β-VIII). The second fraction gave 22 mg (5 %) of (α-VIII). NMR spectra proved the identity of these two products with those described above. The third fraction gave 93 mg (18 %) of the tribenzoate (β-IV), m.p. 156–157°C, $[\alpha]_D^{23} = -187°$ (*c* 1.7, $CHCl_3$), and the last fraction yielded 50 mg (10 %) of (α-IV), m.p. 147–148°, $[\alpha]_D^{23} = +34.2°$ (*c* 0.8, $CHCl_3$). The latter two products were identical with those described previously,[9] and their structures were further confirmed by their NMR spectra.[10]

In a separate experiment (I) (544 mg) was treated with hydrogen fluoride, and the product was benzoylated as described above. The product thus obtained was dissolved in methylene chloride (10 ml), and 3 ml of a mixture of methanol, boron trifluoride etherate, and methylene chloride (2:1:17) was added. The solution was kept for 30 min at room temperature, washed, dried, and evaporated. The product was separated into two fractions by preparative TLC (ether:pentane 1:1). The fast moving fraction gave 240 mg (54 %) of (β-XII), and the next fraction gave 73 mg (16 %) of (α-XII). The products were identical with those described above.

1,3,4-Tri-O-*benzoyl-2-deoxy*-D-erythro-*pentopyranose* (IV) (388 mg) was treated with hydrogen fluoride, benzoylated and then reacted with methanol and boron trifluoride as described above. The product (300 mg) was separated into 175 mg (56 %) of (β-XII) and 57 mg (18 %) of (α-XII).

3,4-Di-O-*benzoyl-1,2-dideoxy*-D-threo-*pent-1-enopyranose* (II) (714 mg) gave, by the same procedure, 577 mg of crude product. Chromatography yielded 250 mg (32 %) of (β-XII) and 90 mg (11 %) of (α-XII).

An analogous treatment of (III) gave 25 % of (β-XII) and 9.5 % of (α-XII).

Reactions with deuterium fluoride

A solution of (I) (632 mg) in deuterium fluoride [1] (1.5 ml) was kept at −30°C for 8 h. It was then worked up and treated with methanol and boron trifluoride as described above. The product (460 mg) was separated into two fractions by preparative TCL (ether:pentane 1:1) to give 212 mg (42 %) of (β-XII) and 88 mg (17 %) of (α-XII). The integrated NMR spectra showed that the two products contained 0.7 equiv. of deuterium at C-2.

Treatment of the isomeric tribenzoate (IV) with deuterium fluoride gave 47 % of (β-XII) and 23 % of (α-XII). The unsaturated compound (II) gave 13 % of (β-XII) by the same procedure. These products also contained 0.7 equiv. of deuterium at C-2. Apart from this, their NMR spectra were identical with those of the compounds described above.

Microanalyses were carried out by Mr. Preben Hansen.

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